Therapeutic and diagnostic uses of hormones in non endocrine patients
Essay

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ABBREVIATIONS

ABPA: Allergic bronchopulmonary aspergillosis.
ACE: angiotensin-converting enzyme.
ACTH: Adreno corticotrophic hormone.
AD: Alzheimer disease.
ADT: Androgen deprivation therapy.
AIHA: Autoimmune hemolytic anemia.
AIS: Aromatase inhibitors.
ALT: Alanine transamiase.
ASD: Autism spectrum disorders.
AST: Aspartate transaminase.
ATL: Adult T-cell lymphoma.
AVP: Arginine vasopressin.
BBB: Blood brain barrier.
BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone.
BIM 23014: lanreotide.
BMD: Bone marrow density.
BPD: Bronchopulmonary dysplasia.
BPH: Benign prostatic hyperplasia.
CA: Coronary artery aneurysm.
CABG: Coronary artery bypass grafting.
CACs: cancer cachexia.
Camp: cyclic adenosine monophosphate.
CBC: Complete blood count.
CBG: Corticosteroid-binding globulin.
CE: Ciliary epithelium.
CEA: Carcino embryonic antigen.
CFU-E: erythroid colony-forming units.
CIDP: Chronic inflammatory demyelinating polyneuropathy.
CKD: Chronic kidney disease.
CME: Cystoid macular edema.
COPD: Chronic obstructive pulmonary disease.
COX: Cyclo oxygenase.
CPB: Cardiopulmonary bypass.
CRF: Chronic renal failure.
CRS: Chronic rhinosinusitis.
CSF: cerebrospinal fluid.
CSS: Churg-Strauss syndrome.
CT: calcitonin.
CT: Cat scan.
CTR: calcitonin receptor.
CTS: Carpal tunnel syndrome.
CYP2D6: cytochrome P450 2D6.
DDAVP: 1-deamino-8-D-arginine vasopressin.
DHEA: Dehydroepiandrosterone.
DHT: dihydrotestosterone.
DITPA: 3,5-diiodothyropropionic acid.
DNA: Double strand ribonucleic acid.
DNA: Double strand ribonucleic acid.
DOX: Doxorubicin (chemotherapeutic drug).
DR: Detachment of retena.
DTC: Differentiated thyroid cancer.
DVT: Deep venous thrombosis.
E2: Estradiol.
EF: Ejection fraction.
ERC: European Resuscitation Council.
ERCP: Endoscopic retrograde cholangiopancreatography.
ERE: Estrogen response element.
ESAs: Erythropoiesis-stimulating agents.
FAH: Functional adrenal hyperandrogenism.
FSH: Follicle-stimulating hormone.
GABA: Gamma amino butyric acid.
GCs: Glucocorticoids.
GFR: Glomerular filtration rate.
GH: Growth hormone.
GI: Gastro intestinal.
GIO: Glucocorticoid induced osteoporosis.
GnRH: Gonadotropin releasing hormone.
HCC: Hepatocellular Carcinoma.
HCG: Human chorionic gonadotropin.
HDL: High density lipoprotein.
HES: Hypereosinophilic syndromes.
HF: Heart failure.
HGB: hemoglobin.
HHT: Hereditary hemorrhagic telangectasia.
HHT: hereditary hemorrhagic telangectasia.
HPA: Hypothalamo pituitary adrenal.
HUS: Hemolytic uremic syndrome.
I.M: intra muscular.
I.V: intravenous.
ICP: Intracranial presser.
ICS: Inhaled glucocorticoids.
ICU: Intensive care units.
IFN: Interferon.
IGF-I: Insulin like growth factor I.
IH: Intracranial hypertension.
IIT: Intensive insulin therapy.
IIT: Intensive insulin therapy.
ITP: Idiopathic thrombocytopenic purpura.
IVIG: Intravenous immune globulin.
KD: Kawasaki disease.
LAR: long acting repeatable.
LDL: low-density-lipoprotein.
LFTs: Liver function tests.
LH: luteinizing hormone.
LHRH: luteinizing hormone releasing hormone.
LV: Left ventricular.
MAP: mean arterial pressure.
MBC: metastatic breast cancer.
MCD: Minimal change disease.
MCTD: Mixed connective tissue disease.
MG: Myasthenia gravis.
MI: Myocardial infarction.
MK 678: Seglitide.
MPA: Medroxyprogesterone acetate.
MPGN: Membranoproliferative glomerulonephritis.
MRI: Magnetic resonance imaging.
MS: Multiple sclerosis.
MTCs: Medullary thyroid carcinomas.
NHLs: Non-Hodgkin’s lymphomas.
NK: Natural killer
NO: Nitric oxide.
NPC: Nasopharyngeal Carcinomas.
NSAIDs: Non steroidal anti inflammatory drugs.
NTIS: Non-thyroidal illness syndrome.
OC: Osteoclast.
OC: Oral contraceptive pills.
OCs: Oral contraceptives.
OPC-21268: a vasopressin V1 antagonist.
OT: oxytocin.
PACNS: Primary angitis of the central nervous system.
Pas: progesterone antagonists.
PCL: primary central nervous system lymphoma.
PCOs: polycystic ovary syndrome.
PEP: Post ERCP Pancriatits.
PKD: Polycystic kidney.
PNH: paroxysmal nocturnal hemoglobinuria.
PRCA: Pure red cell aplasia.
PSA: prostatic specific antigen.
PTH: Parathyroid hormone.
RA: Rheumatoid Arthritis.
RAAS: renin-angiotensin-aldosterone system.
RC-160: Vapreotide.
SAPS II: Simplified Acute Physiology Score II.
SCLCs: Small-cell lung cancers.
SERM: selective estrogen receptor modulator.
SIADH: syndrome of inappropriate antidiuretic hormone.
SLE: Systemic lupus erythematosus.
SNS: single nucleotide polymorphism.
SR: Slow release.
SR121463B: satavaptan.
SRIF: Somatotropin release inhibitory factor.
SSR-149415: orally active V3-receptor antagonist.
SST: Somatostatin.
SSTR: Somatostatin receptor.
ABBREVIATIONS

SubQ; sub cutaneus.
T3: Triiodothyronine.
TB: Tuberculosis.
TP: Terlipressin.
TPN: Total parenteral nutrition.
TR: Thyroid receptor.
TSH: Thyroid stimulating hormone.
TTP: Thrombotic thrombocytopenic purpura.
VCAP: vincristine, cyclophosphamide, doxorubicin, prednisone, ranimustine, vindesine, etoposide, and carboplatin.
VEGF: vascular endothelial growth factor.
VIP: Vasoactive intestinal polypeptide.
VP: arginine vasopressin.
VP: Vasopressin.
Vwf: von Willebrand factor.
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INTRODUCTION

In the last two decades, great advance had been reached in the use of hormones, hormone analogues and hormone antagonists not only in the treatment but also in diagnosis of non endocrine diseases (Bang et al., 2008).

Cancer prostate can be treated with LHRH agonists, LHRH antagonist, anti androgens, Somatostatin analogues, Bombesin and GRP antagonists (Van Aken et al., 2008).

Approximately 30% of unselected pre menopausal patients with breast cancer, have oestrogen dependent tumors and can be treated with hormonal approaches, such as anti estrogen, Tamoxifen and LHRH agonists. FDA approved the uses of Tamoxifen for chemoprevention of breast cancer in women at high risk, and uses of selective estrogen receptor modulator (Raloxifen) for chemoprevention of breast and endometrial cancer (Rivera et al., 2005).

Radiolabeled Somatostatin analogues, make feasible the treatment of Somatostatin receptor positive tumors by delivering therapeutic doses by delivering therapeutic doses of radioactive isotope to the cancer (Lambert B, et al., 2004).

Randomized control trials have established the efficacy of octreotides for malignant bowel obstruction, for chemotherapy induced diarrhea and in variety of pancreatic disorders, including: acute pancreatitis, in prevention of post operative and post ERCP pancreatitis (Povoski et al., 2009).

Recently vasopressin analogue has been added to the advanced cardiac life support for resuscitation of VT and VF (Prvulovich EM, 2008).

Potential therapeutic uses of AVP receptor antagonists include: the blockade of V1 vascular AVP receptors in arterial hypertension, congestive heart failure and peripheral vascular disease. The blockade of V2 renal AVP receptors in the SIADH,
chronic heart failure, nephritic syndrome and liver cirrhosis. The blockade of V3 pituitary AVPreceptors in ACTH secreting tumors (Critichey M., 2008).

Attempts are being made to use Somatostatin analogues (labeled with radionuclide) such as $^{111}$Indium for cancer localization (Bang et al., 2008).
AIM OF THE WORK

The aim of this essay is to:

Study the uses of hormones, hormone analogues and hormone antagonists in the treatment and diagnosis of non endocrine diseases.
THYROIDHORMONE

A. physiology

Thyroid hormones are critical determinants of brain and somatic development in infants and of metabolic activity in adults; they also affect the function of virtually every organ system. Thyroid hormones must be constantly available to perform these functions. To maintain their availability, there are large stores of thyroid hormone in the circulation and in the thyroid gland. Furthermore, thyroid hormone biosynthesis and secretion are maintained within narrow limits by a regulatory mechanism that is very sensitive to small changes in circulating hormone concentrations (Oetting, et al. 2007).

B. Mechanism of action

Thyroid hormone, in the form of triiodothyronine (T3), acts by modifying gene transcription in virtually all tissues to alter rates of protein synthesis and substrate turnover. These actions are the net result of the presence of T3 and of multiple other factors that amplify or reduce its action. (Oetting, et al. 2007).

C. Pharmacodynamics/Kinetics:

Liothyronine: Thyroid Product

Onset of action: 2-4 hours.
Peak response: 2-3 days.
Absorption: Oral: Well absorbed (95% in 4 hours).
Half-life elimination: 2.5 days.
D. DOSAGE and Dosage Forms

Injection, solution: 10 mcg/mL (1 mL)


I.V. Administer doses at least 4 hours, and no more than 12 hours, apart. Resume oral therapy as soon as the clinical situation has been stabilized and the patient is able to take oral medication. (Watts NB, 1989).

E. Monitoring Parameters


F. Therapeutic uses in non-endocrine patients

1. Thyroid hormone and cardiac remodeling

Treatment with T3 for 3 weeks (starting 1 week after myocardial infarction) resulted in improved cardiac function. Thyroid hormone administration at doses producing nearly twofold increase in T3 plasma levels significantly improved the myocardial ejection fraction (EF). More importantly, the ratio of wall thickness to chamber diameter (which is negatively related to wall tension) was increased with thyroxin treatment as compared to non-treated post-infarcted hearts. This effect is thought to be due to the unique changes induced in cell shape and geometry by thyroid hormone (Thomas, et al. 2005).

In fact, changes in cell morphology are translated in the whole heart to an increased wall thickness and decreased chamber diameter with subsequent wall stress normalization. (Friberg L, et al. 2002).

Its clinical application is mainly due to the thyroid hormone positive inotropic and vasodilatory effect. (Naito, et al. 2006).
T3 administration increased cardiac output and decreased systemic vascular resistance without episodes of ischemia or arrhythmias in patients with heart failure. Similarly, in patients with dilated cardiomyopathy, thyroxine improved haemodynamic parameters without any adverse effects (Ojamaa, et al. 2000).

More importantly, thyroid hormone administration after on pump bypass surgery has recently shown to increase cardiac index and reduce tissue injury as this was assessed with troponin release. (Ranasinghe, et al. 2006).

2. Thyroid hormone in left ventricular dysfunction

Treatment with T3 might be a useful therapeutic adjunct by preserving responsiveness to conventional B-adrenergic agonist therapy in the setting of chronic LV dysfunction and after cardioplegic arrest. There are numerous studies on the intravenous use of the thyroid hormone in heart surgery for its inotropic effects, but the oral use for this purpose is highly limited (Murai N, et al. 1999).

Oral T3 improved postoperative cardiovascular performance and resulted in decreased inotropic requirement. Oral T3 treatment was achieved safely without any untoward changes in blood pressure, heart rate or cardiac rhythm. There was no adverse cardiovascular affects such as anginal symptoms and supraventricular arrhythmias. But atrial fibrillation rate was present as side effect. (Klemperer JD, et al. 1996).

3. Thyroid hormone in cardiac surgery

The use of thyroid hormone therapy in cardiac surgery still remains one of debate. Investigators have been unable to demonstrate any significant benefit in terms of either major morbidity or mortality with correction of the NTIS in cardiac surgery (Cerillo, et al. 2003).

Of great interest is the recent animal data suggesting that T3 is able to attenuate myocardial injury. Although the currently available evidence suggests that thyroid hormone supplementation may be beneficial in the setting of
adult cardiac surgery the routine use of thyroid hormone supplementation cannot yet be recommended. Studies in the paediatric population again exhibit encouraging initial results, but none as yet is sufficiently large to recommend routine use of thyroid hormone supplementation (Chowdhury et al. 2001).

Different regimens with earlier and longer T3 administration may potentially be beneficial and the crucially the administration of T3 in this setting may well have a beneficial outcome with respect to recipient heart function in the immediate post-operative period (Dimmick et al. 2004).

4. Thyroid hormone analogs for treatment of hypercholesterolemia and heart failure

Thyroid hormone analogs may be useful in treating patients who are intolerant to ‘statins’, or who do not respond to this type of medication (Wada Y et al. 2000).

Thyroid analogs have now developed for lowering cholesterol in plasma and controlling body weight or for treating heart failure without influencing the heart rhythm. DIPTA, a thyroid analogue which displays an inotropic effect without chronotropic action, is tried in humans (Pantos et al. 2005).

5. Thyroid-hormone suppressive therapy in benign thyroid nodules

There is controversy surrounding thyroid-hormone-suppressivetherapy in benign thyroid nodules, and notes that the most recent meta-analysis did not show a benefit for suppressive therapy with no significant difference between suppression of thyroid-stimulating hormone (TSH), non-suppressive levothyroxin treatment, and no treatment at all (Castro MR et al. 2002).

6. Thyroid hormone and human astrocytomas

The identification of the various TRs and the association of the various isoforms to the degree of tumor malignancy may open up an area for exciting
research. Not only may these isoforms in themselves be targets for therapy, but manipulation of the patients' thyroid status may be an adjunct to treatment. Therefore, it will be interesting to investigate the effect of T3 on the astrocytomas that over express the thyroid hormone receptors. Because the hormonal treatment may be an alternative strategy for malignant astrocytomas and TR isoforms determines the binding capacity of thyroid hormone, the effect of the differential regulation of TR isoforms, should not be overlooked. (Strojnik T, et al. 2007).

G. Side effects

• Unexplained change in appetite. • Unexplained change in weight.

• Nervous and excitable. • Shakiness.

• Sensitive to heat. • Excessive sweating.

• Headache. • Diarrhea.

• Nausea or vomiting. Small frequent meals, frequent mouth care, sugar-free candy, or chewing sugar-free gum may help.

• Irritable. • Leg cramps.

• Inability to sleep.

(Sanders LR, 1990).

Precautions

• Adrenal insufficiency: Use with caution in patients with adrenal insufficiency.

• Cardiovascular disease: Use with caution and reduce dosage in patients with angina pectoris or other cardiovascular disease.

• Myxedema: Use with caution in patients with myxedema.

• Elderly: Use with caution in elderly patients; they may be more likely to have compromised cardiovascular function.

• Weight reduction: Thyroid supplements are ineffective and potentially toxic for weight reduction. (Johnson DG and Campbell S, 1993).

H. Contraindications

Hypersensitivity to liothyronine sodium or any component of the formulation; undocumented or uncorrected adrenal insufficiency; recent myocardial infarction or thyrotoxicosis (Dahlberg PA, et al. 1979).

I. Drug Interactions

Bile Acid Sequestrants: May decrease the absorption of Thyroid Products. Risk C.

Calcium Polystyrene Sulfonate: May decrease the serum concentration of Thyroid Products. Risk D.

Calcium Salts: May diminish the therapeutic effect of Thyroid Products. Risk C.

Estrogen Derivatives: May diminish the therapeutic effect of Thyroid Products. Risk C.

Phenytoin: May increase the metabolism of Thyroid Products. Phenytoin may also displace thyroid hormones from protein binding sites. Risk C.

Rifampin: May decrease the serum concentration of Thyroid Products. Risk C.
Theophylline Derivatives: Thyroid Products may increase the metabolism of Theophylline Derivatives. Risk C.

Vitamin K Antagonists (eg, warfarin): Thyroid Products may enhance the anticoagulant effect of Vitamin K Antagonists. Risk D (Dahlberg PA, et al. 1979).
GnRH

A. PHYSIOLOGY

Control of the reproductive axis originates in the hypothalamus with the periodic pulsatile release of gonadotropin-releasing hormone (GnRH). In response to GnRH (also called luteinizing hormone releasing hormone or LHRH), the pituitary releases pulses of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) into the bloodstream. These hormones then induce gonadal production of a variety of hormones, such as estradiol, progesterone, and testosterone, that play an important role in the regulation of reproduction (Schwanzel-Fukuda, et al. 1992).

B. MECHANISM OF ACTION:

Goserelin (a gonadotropin-releasing hormone [GnRH] analog) causes an initial increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH), chronic administration of goserelin results in a sustained suppression of pituitary gonadotropins. Serum testosterone falls to levels comparable to surgical castration. The exact mechanism of this effect is unknown, but may be related to changes in the control of LH or down-regulation of LH receptors. (Schwanzel-Fukuda, et al. 1992).

C. PHARMACODYNAMICS/ KINETICS

ABSORPTION: SubQ: Rapid and can be detected in serum in 10 minutes; 3.6 mg: released slowly in first 8 days, then rapid and continuous release for 28 days.

DISTRIBUTION: Male: 44.1 L; Female: 20.3 L.

Protein binding: 27%.
TIME TO PEAK, SERUM: SubQ: Male: 12-15 days, Female: 8-22 days.

HALF-LIFE ELIMINATION: SubQ: Male: ~4 hours, Female: ~2 hours; Renal IMPAIRMENT: Male: 12 hours.

EXCRETION: Urine (>90%; 20% as unchanged drug). (Brogden RN and Faulds D.1995).

D. Dosing:

Dosage Forms: Implant.

1. Prostate cancer, treatment: SubQ:

Combination monthly/3-month implant: 3.6 mg implant, followed in 28 days by 10.8 mg implant.

Monthly implant (alternate dosing): 3.6 mg; repeated every 28 days for a total of 4 doses.

2. Breast cancer: SubQ: Monthly implant: 3.6 mg every 28 days.

3. Endometriosis: SubQ: Monthly implant: 3.6 mg every 28 days for 6 months. (Brogden RN and Faulds D.1995).

E. Monitoring Parameters

Bone mineral density, serum calcium.

F. Therapeutic uses in non endocrine patients

1. Metastatic prostate cancer

- **GONADOTROPIN RELEASING HORMONE AGONISTS:**

  Synthetic GnRH analogs have greater receptor affinity and reduced susceptibility to enzymatic degradation compared to the natural GnRH molecule, and are approximately 100-fold more potent. GnRH agonists bind to the GnRH receptors on pituitary gonadotropin-producing cells, causing an initial release of both luteinizing hormone (LH) and follicle stimulating hormone (FSH), which causes a subsequent increase in testosterone production from testicular Leydig cells. GnRH receptors are down-regulated on the gonadotropin-producing cells, with a decline in the pituitary production of LH and FSH. The fall in serum LH leads to a decrease in serum testosterone to castrate levels within three to four weeks after the start of treatment. The decrease in testosterone production is generally reversible. GnRH agonist used daily subcutaneous administration (Limonta, et al, 2001).

  Despite the high price of GnRH agonists compared to the one-time procedure of orchiectomy, GnRH agonists are given to the majority of American prostate cancer patients for initial ADT (Loblaw, et al, 2007).

- **GnRH antagonists**

  Pure GnRH antagonists have been developed to suppress testosterone while avoiding the flare phenomenon of GnRH agonists (an increase in bone pain, bladder obstruction, or other symptoms due to prostate cancer). These GnRH antagonists bind to the GnRH receptors on pituitary gonadotropin-producing cells, but do not cause an initial release of luteinizing hormone or follicle stimulating hormone (FSH). (Loblaw, et al, 2007).
2. Therapy in Breast Cancer

GnRH agonists provide an alternative method for estrogen deprivation in premenopausal women who do not wish to undergo surgery. GnRH agonists such as goserelin and leuprolide are peptide analogs of luteinizing hormone releasing hormone (LHRH) that are 50 to 100-fold more potent than the natural hormone. Although no initial rise in serum estrogen has been detected in women with MBC treated with GnRH agonists, breast cancer flare reactions may occur (as have been seen with tamoxifen and estrogen therapy), which have been attributed to gonadotropin release. Randomized trials support the view that in premenopausal women, GnRH agonists are as efficacious for MBC as oophorectomy or tamoxifen (Chia, et al. 2008).

3. Therapy in Fibroid

Gonadotropin-releasing hormone (GnRH) agonists are the most effective medical therapy for uterine myomas. These drugs work by initially increasing the release of gonadotropins, followed by desensitization and downregulation to a hypogonadotropic, hypogonadal state that clinically resembles menopause. Most women will develop amenorrhea, improvement in anemia (if present), and a significant reduction (35 to 60 percent) in uterine size within three months of initiating this therapy, thus achieving improvement in both categories of myoma symptomatology. Because of the rapid rebound in symptoms and side effects, GnRH agonists are primarily used as preoperative therapy. (Viswanathan, et al. 2007).

Gonadotropin-releasing hormone antagonists: Similar clinical results have been achieved with GnRH antagonists, which compete with endogenous GnRH for pituitary binding sites. The advantage of antagonists over agonists is the rapid onset of clinical effects without the characteristic initial flare-up observed with GnRH agonist treatment (Felberbaum, et al. 2001).
4. Therapy in Endometriosis

GnRH agonists can be prescribed for adolescents, with laparoscopically confirmed endometriosis, who are at least 16 years old as an alternative GnRH agonist; however, compliance is often unpredictable in the adolescent population (Hornstein et al, 1998).

G. Adverse Reactions:

- **>10%:**
  
  **CARDIOVASCULAR**: Edema.
  
  **CENTRAL NERVOUS SYSTEM**: Headache, emotional lability, depression, pain, insomnia.
  
  **DERMATOLOGIC**: Acne.
  
  **ENDOCRINE & METABOLIC**: Hot flushes, sexual dysfunction, breast atrophy, breast enlargement, erections decreased, libido disturbance.
  
  **GENITOURINARY**: Vaginitis, dyspareunia, lower urinary symptoms.
  
  **NEUROMUSCULAR & SKELETAL**: Weakness.
  
  **MISCELLANEOUS**: Diaphoresis, infection.

- **1% TO 10%:**
  
  **CARDIOVASCULAR**: Heart failure, arrhythmia, cerebrovascular accident, hypertension, MI, peripheral vascular disorder, chest pain, palpitation, edema.
  
  **CENTRAL NERVOUS SYSTEM**: Lethargy, dizziness, abnormal thinking, anxiety, chills, fever, malaise, migraine, nervousness, somnolence.
  
  **DERMATOLOGIC**: Hirsutism, rash, alopecia, bruising, pruritus.
ENDOCRINE & METABOLIC: Breast pain, breast swelling/tenderness, dysmenorrhea, gout, hyperglycemia.

GASTROINTESTINAL: Anorexia, nausea, appetite increased, constipation, diarrhea, flatulence, dyspepsia, ulcer, vomiting, weight gain/loss, xerostomia.

GENITOURINARY: Renal insufficiency, urinary frequency, urinary obstruction, urinary tract infection, vaginal hemorrhage.

HEMATOLOGIC: Anemia, hemorrhage.

LOCAL: Application site reaction.

NEUROMUSCULAR & SKELETAL: Back pain, arthralgia, bone mineral density decreased, hypertonia, joint disorder, leg cramps, myalgia, paresthesia.

OCULAR: Amblyopia, dry eyes.

RESPIRATORY: Upper respiratory tract infection, COPD, pharyngitis, bronchitis, cough, epistaxis, rhinitis, sinusitis.

MISCELLANEOUS: Allergic reaction, voice alteration.

POSTMARKETING AND/OR CASE REPORTS: ALT increased, anaphylaxis, AST increased, lipids increased, glucose tolerance decreased, hypersensitivity reactions, hypotension, ovarian cyst, pituitary apoplexy, psychotic disorders, urticaria. (Levine GN, et al. 2010).

Precautions

• Cervical resistance: Cervical resistance may be increased; use caution when dilating the cervix.

• Decreased bone density: Has been reported in women and may be irreversible; use caution if other risk factors are present.
• Hypercalcemia: Has been reported in prostate and breast cancer patients with bone metastases.

• Hyperglycemia: Hyperglycemia has been reported in males and may manifest as diabetes or worsening of pre-existing diabetes.

• Hypersensitivity reactions: Allergic hypersensitivity reactions (including anaphylaxis) and antibody formation may occur; monitor.

• Pituitary apoplexy: May present as sudden headache, vomiting, visual or mental status changes, and infrequently cardiovascular collapse; immediate medical attention required.

• Spinal cord compression: Has been reported when used for prostate cancer.

• Tumor flare: Transient worsening of signs and symptoms (tumor flare) may develop during the first few weeks of treatment.

• Urinary tract obstruction: Has been reported when used for prostate cancer; closely observe patients for urinary tract obstruction in first few weeks of therapy.

• Cardiovascular disease: Androgen-deprivation therapy may increase the risk for cardiovascular disease. (Levine GN, et al. 2010).

H. Drug Interactions

GROWTH HORMONE

A. PHYSIOLOGY

Growth hormone (GH), the most abundant anterior pituitary hormone, is produced by the pituitary somatotroph cells. GH production begins early in fetal life and continues throughout life, although at a progressively lower rate (Herrington, et al. 2001).

B. MECHANISM OF ACTION

Somatropin is a purified polypeptide hormones of recombinant DNA origin; somatropin contains the identical sequence of amino acids found in human growth hormone; human growth hormone assists growth of linear bone, skeletal muscle, and organs by stimulating chondrocyte proliferation and differentiation, lipolysis, protein synthesis, and hepatic glucose output; stimulates erythropoietin which increases red blood cell mass; exerts both insulin-like and diabetogenic effects; enhances the transmucosal transport of water, electrolytes, and nutrients across the gut. (Cohen P, et al. 2008).

C. PHARMACODYNAMICS/KINETICS

DURATION: Maintains supraphysiologic levels for 18-20 hours.

ABSORPTION: I.M., SubQ: Well absorbed.

DISTRIBUTION: ~1 L/kg.

METABOLISM: Hepatic and renal (~90%).

BIOAVAILABILITY: SubQ: ~70% to 90%; Note: Variable; product-dependent.

HALF-LIFE ELIMINATION: Preparation and route of administration dependent; SubQ: ~2-4 hours.

D. Dose and Dosage Forms:

Injection, powder for reconstitution and injection, solution.

Short-bowel syndrome: Zorbtive®: SubQ: 0.1 mg/kg once daily for 4 weeks (maximum: 8 mg/day) (Grunfeld C, et al. 2007).

E. Monitoring Parameters

Growth curve, Tanner staging (children), periodic thyroid function tests, bone age (annually), periodical urine testing for glucose, somatomedin C (IGF-I) levels; funduscopic examinations at initiation of therapy and periodically during treatment; serum phosphorus, alkaline phosphatase and parathyroid hormone (Molitch ME, et al. 2006).

F. Therapeutic uses in non endocrine patients

1. As performing enhancing drug by athletes (malpractice)

Athletes take recombinant human growth hormone because of its demonstrated effects on body composition (more muscle, less fat). Administration of growth hormone alone (2 mg/day) to men and women, and growth hormone (2 mg/day) plus a blend of four different testosterone esters (250 mg/week) to men increased anaerobic work capacity on a cycle ergometer in both groups. Neither treatment increased jump height or strength on a dynamometer. The clinical significance of the increase in one physical performance parameter but not others in spite of supraphysiologic doses of both drugs is uncertain (Liu, et al. 2008).

It would be expected to cause acromegaly if given in high doses long enough, but no such cases have been reported. In addition, epidemiologic data
suggest an association between serum concentrations of insulin-like growth factor 1 (IGF-1) and cancer risk. A review of studies in which growth hormone was administered to normal men and women showed an increased incidence of soft tissue edema compared to those not treated (Liu, et al. 2008).

2. Therapy in osteoporosis

Growth hormone (GH) and insulin-like growth factor-I (IGF-I) increase bone collagen and DNA synthesis in vitro, and they stimulate bone growth and osteoblast activity in vivo. Patients with growth hormone deficiency have low bone density. Trials of growth hormone in women with osteoporosis who did not have growth hormone deficiency have been conflicting, and side effects were common. These conflicting results plus the necessity for administration by injection make it unlikely that growth hormone will become a therapeutic option for patients with osteoporosis who are not growth hormone-deficient. IGF-1 therapy does not appear to be effective (Friedlander, et al. 2001).

3. Therapy in short gut syndrome

Reports have suggested that the combination of glutamine, growth hormone, and a diet high in complex carbohydrates and fiber enhanced the adaptation process and allowed enteral nutrition in patients who had been dependent upon parenteral nutrition. In randomized, controlled crossover trials in adults given glutamine and growth hormone with various dietary maneuvers, there was modest improvement in electrolyte absorption but no effect on small bowel morphology, stool losses, or macronutrient absorption occurred (Weiming, et al. 2004).

G. Adverse Reactions

Acne, ALT increased, AST increased, arthralgia, back pain, bronchitis, carpal tunnel syndrome, chest pain, cough, depression, diabetes mellitus (type
2), diaphoresis, dizziness, edema, fatigue, flu-like syndrome, gastritis, headache, hypertension, hypoesthesia, hypothyroidism, infection, insomnia, insulin resistance, joint disorder, leg edema, muscle pain, myalgia, nausea, paresthesia, peripheral edema, pharyngitis, retinopathy, rhinitis. (Cohen P, et al. 2008).

H. Contraindications

Hypersensitivity to growth hormone or any component of the formulation; growth promotion in pediatric patients with closed epiphyses; progression or recurrence of any underlying intracranial lesion or actively growing intracranial tumor; acute critical illness due to complications following open heart or abdominal surgery; multiple accidental trauma or acute respiratory failure; evidence of active malignancy; active proliferative or severe nonproliferative diabetic retinopathy. (Cohen P, et al. 2008).

Precautions

• Fluid retention: May occur frequently in adults during use.

• Intracranial hypertension (IH): IH with headache, nausea, papilledema, visual changes, and/or vomiting has been reported with somatropin.

• Neoplasm: An increased risk of second neoplasm as meningiomas in patients treated with radiation to the head for their first neoplasm.

• Slipped capital epiphyses: may occur

• Acute critical illness: Initiation of somatropin is contraindicated with acute critical illness due to complications.

• Diabetes: Use with caution in patients with diabetes or with risk factors for impaired glucose tolerance; may decrease insulin sensitivity.
• Hypoadrenalism: Excessive glucocorticoid therapy may inhibit the growth promoting effects of somatropin in children; monitor and adjust glucocorticoids carefully.

• Hypopituitarism: Closely monitor other hormonal replacement treatments in patients with hypopituitarism.

• Hypothyroidism: Untreated/undiagnosed hypothyroidism may decrease response to therapy; monitor thyroid function test.

• Obesity: Increased incidence of adverse events may occur when using a weight-based dosing regimen.

• Scoliosis: Progression of scoliosis may occur in children experiencing rapid growth.

• Turner syndrome: increased risk for otitis media and other ear/hearing disorders, cardiovascular disorders, and thyroid disease, monitor carefully. (Molitch ME, et al. 2006).

I.Drug Interactions

Antidiabetic Agents: Somatropin may diminish the hypoglycemic effect of Antidiabetic Agents. Risk D.

Cortisone: Somatropin may diminish the therapeutic effect of Cortisone. Growth hormone may reduce the conversion of cortisone to the active cortisol metabolite. Risk D.

Estrogen Derivatives: May diminish the therapeutic effect of Somatropin. Risk D.

SOMATOSTATIN

A. PHYSIOLOGY

Somatostatin originally discovered as an inhibitor of growth hormone release, it is now known to inhibit a variety of gastrointestinal processes. Somatostatin is produced by paracrine cells that are scattered throughout the gastrointestinal tract and inhibits gastrointestinal endocrine secretion. Somatostatin is also found in various locations in the nervous system and exerts neural control over many physiological functions. (Lamberts, et al. 1996).

<table>
<thead>
<tr>
<th>Hormones inhibited by somatostatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
</tr>
<tr>
<td>Arginine vasopressin</td>
</tr>
<tr>
<td>Cholecystokinin</td>
</tr>
<tr>
<td>Epidermal growth hormone</td>
</tr>
<tr>
<td>Glucagon</td>
</tr>
<tr>
<td>Gastrin</td>
</tr>
<tr>
<td>Gastric inhibitory polypeptide</td>
</tr>
<tr>
<td>Growth hormone</td>
</tr>
<tr>
<td>Insulin</td>
</tr>
<tr>
<td>Motilin</td>
</tr>
<tr>
<td>Neurotensin</td>
</tr>
<tr>
<td>Pancreatic polypeptide</td>
</tr>
<tr>
<td>Secretin</td>
</tr>
<tr>
<td>Serotonin</td>
</tr>
<tr>
<td>Substance P</td>
</tr>
<tr>
<td>Thyrotropin</td>
</tr>
<tr>
<td>Vasoactive intestinal polypeptide</td>
</tr>
</tbody>
</table>

Table 1 (Lamberts, et al. 1996).

Somatostatin is distributed throughout the entire body, although it is particularly abundant in nervous tissue of the cortex, hypothalamus, brainstem, and spinal cord. It has also been localized in nerves of the heart, thyroid, skin, eye, and thymus. Somatostatin is abundant in the gastrointestinal tract and
pancreas. Both S-14 and S-28 are expressed throughout regions of the gastrointestinal tract (Broglio, et al. 2007).

At present there are five known subtypes of the somatostatin receptor (designated subtypes 1 to 5). These receptors do not differ appreciably in their binding of somatostatin 14 or 28; however, there is significant variation in binding of synthetic somatostatin peptides (Kidd, et al. 2008).

**Distribution of somatostatin receptor subtypes**

<table>
<thead>
<tr>
<th>Subtype 1</th>
<th>Brain, pancreas, liver, GI tract, lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtype 2</td>
<td>Brain, kidney</td>
</tr>
<tr>
<td>Subtype 3</td>
<td>Brain, pancreas</td>
</tr>
<tr>
<td>Subtype 4</td>
<td>Brain, lung</td>
</tr>
<tr>
<td>Subtype 5</td>
<td>Brain, heart, adrenal, pituitary, GI tract, skeletal muscle</td>
</tr>
</tbody>
</table>

Table (2) (Lamberts, et al. 1996).

Somatostatin secretion occurs in response to a variety of stimuli. Meal ingestion and gastric acid secretion increase somatostatin output from gastric D-cells. Gut somatostatin production is regulated by the autonomic nervous system with catecholamines inhibiting and cholinergic mediators stimulating peptide release (Chiba, et al. 1994).

**B. MOLECULAR FORMS**

SST analogues such as SMS 201-955 (octreotide), RC-160 (vapreotide), MK 678 (seglitide), BIM 23014 (lanreotide), and SOM 230. (Epelbaum Jetal, 1994).
1. Short-Acting Formulations

The first commercially available SST analogue, octreotide, was synthesized and formulated for subcutaneous (sc) administration with half-life approximately 80 times greater than native SST. The compound has the highest affinity for SSTR2 and SSTR5, with the affinity for SSTR2 approximately 10 times greater than for SSTR5 (Bevan JS, et al. 2005).

The SC formulation, administered by two to four injections daily, is the shortest acting of the available SST analogues. A medium-acting SST analogue, lanreotide SR, whose structure and binding profile are similar to octreotide with the exception of three amino acid substitutions. This compound is longer acting than the sc octreotide because the drug is encapsulated in microspheres that provide release over 10–14 days after intramuscular (IM) administration. Lanreotide SR is provided in a 30-mg dose only, and the pharmacological effect is manipulated by changing the dosing interval between 7 and 14 days (Bevan JS, et al. 2005).

2. Long-Acting Formulations

Octreotide long acting repeatable (LAR). After an IM injection, drug levels begin to rise over 7–14 days and plateau for 20–30 days. The development of depot formulation of octreotide administered up to 30–60 mg once every 4 weeks has, to a large extent, eliminated the need for daily injections. A new slow-release depot preparation of lanreotide, Lanreotide Autogel, which is administered subcutaneously at doses of up to 120 mg once monthly, has recently been introduced. Like octreotide LAR, Lanreotide Autogel also has a monthly administration schedule. The active agent is the same as lanreotide SR and as such exhibits a higher affinity for SSTR2 than SSTR5. (Lightman, et al. 2002).
The most recently synthesized SST analogue, SOM 230, is a compound with high affinity for SSTR1, SSTR2, SSTR3, and SSTR5. In binding experiments, SOM 230 has a higher affinity to SSTR1, SSTR3, and SSTR5 and a slightly lower affinity to SSTR2 compared with octreotide. In addition, this semi-universal ligand has a 30- to 40-fold higher affinity for SSTR1 and SSTR5 than octreotide or lanreotide and has a >7-fold longer plasma half-life than octreotide. (Schmid H, et al. 2005).

3. Peptide Receptor Radionuclide Therapy

The technique involves the coupling of a radioisotope to an SST analogue such that the conjugate may then bind to tumor cells that express specific surface receptors and thereafter undergo endocytosis. The principal is to provide a focal and effective dose of radiation that can be administered to tumor or peritumoral cells only, leaving the majority of surrounding non-neoplastic tissue intact. In addition, by using individual isotopes with different emission wavelengths, the extent of local irradiation can be “tailored” to the size range of the lesions. Although renal exposure is of some concern, kidney irradiation can be substantially decreased (20–50%) by a pre-therapy IV infusion of positively charged amino acids (L-lysine and L-arginine) and intratherapy IV fluid loading to “flush” the system. The use of lanreotide as the parent molecule for isotopic therapy causes 25% less renal exposure than noted with octreotide analogues (Lambert B, et al. 2004).
### Human Somatostatin Receptor (SSTR) - Binding Affinities

<table>
<thead>
<tr>
<th>Ligand</th>
<th>SSTR1</th>
<th>SSTR2</th>
<th>SSTR3</th>
<th>SSTR4</th>
<th>SSTR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin-14</td>
<td>1.1</td>
<td>1.3</td>
<td>1.6</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Somatostatin-28</td>
<td>2.2</td>
<td>4.1</td>
<td>6.1</td>
<td>1.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Octreotide</td>
<td>&gt;1000</td>
<td>2.1</td>
<td>4.4</td>
<td>&gt;1000</td>
<td>5.6</td>
</tr>
<tr>
<td>Vapreotide</td>
<td>&gt;1000</td>
<td>5.4</td>
<td>30.9</td>
<td>45.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>&gt;1000</td>
<td>1.8</td>
<td>43.0</td>
<td>66.0</td>
<td>0.6</td>
</tr>
<tr>
<td>SOM230(128)</td>
<td>9.3</td>
<td>1.0</td>
<td>1.5</td>
<td>&gt;100</td>
<td>0.16</td>
</tr>
<tr>
<td>(^{111})InDTPA-(\beta)-Phe(^1)-octreotide (OctreoScan)</td>
<td>&gt;1000</td>
<td>1.5</td>
<td>30</td>
<td>&gt;1000</td>
<td>1</td>
</tr>
<tr>
<td>([^{90})y]DOTA-Tyr(^3)-octreotate (DOTATOC)</td>
<td>&gt;10,000</td>
<td>1.6</td>
<td>&gt;1000</td>
<td>523</td>
<td>187</td>
</tr>
<tr>
<td>([^{90})y]DOTA-lanreotide (DOTALAN)</td>
<td>215</td>
<td>4.3</td>
<td>5.1</td>
<td>3.8</td>
<td>10</td>
</tr>
</tbody>
</table>

*Table (3) (Oberg K. 2004)*

### B. Mechanism of Action

Inhibiting serotonin release, and the secretion of gastrin, VIP, insulin, glucagon, secretin, motilin, and pancreatic polypeptide. Decreases growth hormone and IGF-1 in acromegaly. Octreotide provides more potent inhibition of growth hormone, glucagon, and insulin as compared to endogenous somatostatin. Also suppresses LH response to GnRH, secretion of thyroid-stimulating hormone and decreases splanchnic blood flow (Erstad BL, et al. 2001).

#### Antitumor effects of somatostatin

They inhibit pituitary GH release and sst2 and sst5 are the subtypes primary involved in this effect. They also inhibit hepatic GH-induced IGF-I production via sst2- and/or sst3-mediated activation of a tyrosine phosphatase leading to dephosphorylation of STAT5b and to a decrease in IGF-I gene transcription (Murray, et al. 2004).

Somatostatin also inhibits endothelial cell invasion and monocyte migration and these effects are related to its antiangiogenic effect (Zatelli, et al. 2007).

Somatostatin also help in induction of cell cycle arrest (Arena, et al. 2007).
Somatostatin is a potent anti-migrative and anti-invasive agent for various tumor cells including pancreatic cancer, neuroblastoma and glioma cells. (Cattaneo, et al. 2006).

Somatostatin and analogs can promote apoptosis in normal and tumor cells by regulating the two main signaling pathways, cell-extrinsic pathway (triggered by death receptors) and the cell-intrinsic pathway (also called the mitochondrial pathway). Somatostatin-induced apoptosis can be signaled through sst3 and sst2. When sst3 is transfected into previously sst-free cell lines, the addition of octreotide causes the up-regulation of the tumor suppressor protein p53, which is associated with a dephosphorylation-dependent conformational change of p53 as well as induction of Bax. (Teijeiro, et al. 2002).

C. Pharmacodynamics/Kinetics

DURATION: SubQ: 6-12 hours.

ABSORPTION: SubQ: Rapid and complete; I.M. (depot formulation): Released slowly (via microsphere degradation in the muscle).

DISTRIBUTION: 14 L (13-30 L in acromegaly).

PROTEIN BINDING: 65%, primarily to lipoprotein (41% in acromegaly).

METABOLISM: Extensively hepatic.

BIOAVAILABILITY: SubQ: 100%; I.M: 60% to 63% of SubQ dose.

HALF-LIFE ELIMINATION: 1.7-1.9 hours; Increased in elderly patients; Cirrhosis: Up to 3.7 hours; Fatty liver disease: Up to 3.4 hours; Renal impairment: Up to 3.1 hours.

TIME TO PEAK, plasma: SubQ: 0.4 hours (0.7 hours acromegaly); I.M.: 1 hour.

EXCRETION: Urine (32% as unchanged drug) (Carr R and Zed PJ. 2002).
D. Dosage

Therapy with octreotide is usually started with a dose of 300 mg/d subcutaneously of octreotide LAR 10 mg/4 weeks intramuscularly or lanreotide LA 30 mg/7–10 days intramuscularly. The dose is then adjusted according to the clinical and biochemical response. Octreotide and lanreotide are equally effective in controlling clinical symptoms. After the start of the long-acting formulations, subcutaneous octreotide has to be added for up to 2 months until steady-state concentrations are achieved. The dose for symptomatic treatment has to be titrated individually. Subcutaneous octreotide is used in the event of a carcinoid crisis or for prevention of a carcinoid crisis during surgical procedures (Erstad, et al. 2001).

E. Monitoring Parameters

Chronic therapy: Thyroid function (baseline and periodic), vitamin B12 level, blood glucose, glycemic control and antidiabetic regimen (patients with diabetes mellitus), cardiac function (heart rate, ECG), zinc level (patients with excessive fluid loss maintained on TPN) (Erstad, et al. 2001).

F. INDICATIONS: NON HORMONAL USES

F.1. Diagnostic applications

(SCINTIGRAPHY AND AUTORADIOGRAPHY)

1. Non-Functioning Islet Cell Tumors

SRS identifies 84% of these lesions (Marcos, et al. 2002).

2. Other Neuroendocrine Tumors

a. Medullary thyroid carcinomas
The sensitivity of SRS in detecting MTC lesions is variable (50–70%) and may be related to loss of SSTRs as the tumor becomes less differentiated. The addition of SST analogue imaging to the detection of MTChas, however, not been demonstrated to significantly increase detection of metastatic lesions. In addition, scintigraphy is more frequently positive with high serum tumor markers and large tumors and therefore seems less suitable for showing microscopic disease. *(Stokkel, et al. 2004)*.

b. Small-cell lung cancers

SSTRs are found in 50–75% of SCLCs, and SRS detects between 63 and 100% of primary tumors, but the degree of uptake is variable and independent of lesion size. Regional and distant metastases were detected in 60 and 45%, respectively. As SST uptake by the primary tumor was noted to be affected by chemotherapy, it has been suggested that SRS may be used to follow the course of SCLC. Inclusion of SRS in the staging protocol of patients with SCLC may also lead to upstaging in some of the patients with limited disease *(Reisinger, et al. 1998)*.

c. Pheochromocytomas

Seventy-three percent of pheochromocytomas were SSTR positive. There was no correlation between thereceptor status and tumor size, benign versus malignant tumors or urinary metanephrine excretion *(Reubi, et al. 1992)*.

d. Neuroblastomas

Receptor analysis with radiolabeled ligands concluded that SST-14 mainly binds to SSTR2 in human neuroblastomatous tumors *(Manil, et al. 1996)*.

e. Paragangliomas
SRS was also used to detect local recurrence or residual tumor following surgery that may occur in 15–30%. In vitro autoradiography on surgically removed tissue sections from 14 paragangliomas demonstrated 93% to be SSTR positive (Ellison, et al. 2001).

3. CNS Tumors

Large percentage of low-grade tumors express SSTRs (80%) compared with rare expression in high-grade lesions. With minimal expression of SSTR1 and SSTR2 in diffuse and anaplastic tumors (Mawrin, et al. 2004).

One hundred percent of meningiomas were detected, and the intensity of the scintigraphic signal correlated well with the tumor SSTR density (Safford, et al. 2004).

Medulloblastomatous tumor cells expressed SSTR2 and SSTR3 transcripts at high levels in comparison with gliomas, where SSTR expression was restricted to endothelial cells on proliferating vessels. A high somatostatin receptor density in all patients with newly diagnosed, residual or recurrent cranial meningiomas was detected by \(^{111}\)Indium DTPA-octreotide scintigraphy. Therefore isotope-labelled octreotide represents a radiopharmaceutical which may be used several hours after the labeling procedure (Cervera, et al. 2002).

4. Pituitary Adenomas

Virtually all GH-producing pituitary adenomas express SSTRs (particularly SSTR2). TSH-secreting pituitary tumors can also be visualized with nearly 100% sensitivity. Non-functioning pituitary tumors also express SSTRs, and 75% can be visualized by SRS (Legovini, et al. 1997).

5. Adenocarcinomas

a. Gastrointestinal cancers
Low affinity, high-capacity SST binding to the plasma membranes was observed in 79% of the gastric cancers and 74% of the colorectal cancers. In comparison, colon carcinomas expressed SSTRs only in a minority of cases (8%) and at low density. (Reubi, et al. 1999).

b. Hepatocellular Carcinoma

SSTR expression in 41% of HCC with high affinity for SST and octreotide, but their density was low compared with that found in liver metastases of neuroendocrine tumors (Reubi, et al. 1999).

c. Breast carcinomas

As many as 50% of breast carcinomas demonstrate SSTR positivity in vitro. In a study of 52 patients with stages I and II breast cancers (lesions <2 cm and between 2 and 5 cm, respectively), SRS localized 75% (39/52) of tumors (van Eijck CH, et al. 1994).

d. Renal Cell carcinomas

The SSTR status of 39 surgically removed human renal cell carcinomas was evaluated using $^{123}$I-labeled octreotide. Although 72% were SSTR positive, there was no correlation between the SSTR profile and the histopathological type or grade of the tumor or the tumor node metastasis stage of the disease (Reubi, et al. 1992).

e. Prostate cancers

Primary human prostate cancers, express a different SSTR subtype than benign prostate tissue (Halmos, et al. 2000).
f. ovarian cancer

Transcript for SSTR1 and SSTR2 was detected in 65% of the ovarian cancer specimens, whereas the incidence of SSTR3 and SSTR5 was 41 and 24%, respectively. (Halmos, et al. 2000).

g. Nasopharyngeal Carcinomas

Seventy-five percent of NPC samples demonstrated moderate to high expression of SSTRs, predominantly SSTR2 (Kouroumalis, et al. 1998).

h. Other Tumors and Para neoplastic Syndromes

Lymphomas

The overall sensitivity of SRS for detecting HD is between 70 and 100%. The overall detection sensitivity of SRS in NHL was less than that for HD (35–62%). In these B-cell lymphomas, SSTR positivity was 10/11 in the low-grade group, 8/8 intermediate grade, and 7/10 high grade. Although SRS was positive in a large proportion of low-grade NHL, in most patients, only part of the lesion could be visualized, limiting the role of SRS in NHL (Lugtenburg, et al. 2001).

Melanomas

SSTR1 expression in 96% of tumors, SSTR2 in 83%, SSTR3 in 61%, SSTR4 in 57%, and SSTR5 in 9%. A separate study demonstrated 16/19 positive octreotide scintigrams in melanomas. However, the exact impact of SRS on staging and management remains to be determined (Lum, et al. 2001).

Thymic Tumors

High uptake of indium-labeled octreotide has been noted in tumors of the thymus. In contrast to neuroendocrine tumors, thymic tumors express high
levels of SSTR3 in vitro. This may be relevant to the future use of receptor-specific ligands for these lesions (Modlin et al. 2003).

**Mesenchymal Tumors**

The receptors were located on neoplastic cells and had high affinity and high specificity for SST-14 and SST-28 as well as for octreotide, indicating the expression of the SSTR2 (Lugtenburg et al. 2001).

**Merkel Cell Tumors**

The overall detection of tumor sites was 80% by SRS although small lesions (<0.5 cm) were not detected (Lugtenburg et al. 2001).

**Thyroid malignancy**

**SSTR scintigraphy in differentiated thyroid cancer**

There is possibility of using radiolabelled octreotide for diagnosis and radiation therapy of SSTR-positive tumours. Few data are available concerning differentiated thyroid cancer (DTC) imaging with Octreoscan. Octreoscan could be useful for visualising metastatic DTC, especially when $^{131}$I scan is not able to localise the disease (Gorges et al. 2001).

**SSTR scintigraphy in medullary thyroid cancer**

Octreoscan is useful in persistent MTC for the localization of metastatic tumour sites, especially neck lymph nodes, but is not very sensitive in detecting liver metastases and intrathyroidal tumour (Gorges et al. 2001).

6. **Granulomatous Disease**

There was no correlation between the degree of radioactive accumulation in the thorax and specific patterns of pathological uptake with disease severity or
clinical course. Thedegree of uptake ofradioactivity in the parotid glands, however, was correlated withsignificantly higher serum angiotensin-converting enzyme level (Kwekkeboom, et al. 1998).

**F.2. Therapeutic applications**

1. Nervous System

a. Antipsychotic effect

Sst3 receptors might play a role in behavior, and more specifically, a role in the antidepressant effects of somatostatin. Somefindings suggest that the sst2 and sst3 receptoragonists do not produce significant behavioral effects at doses below 27 µg, test doses higher than 27 µg was difficult because our sst4 and sst5 agonists appeared toproduce seizures in some animals at doses of 27 and even 9 µg (non-systematic observations). This seizure-like activityseems counterintuitive considering that somatostatin itself has anticonvulsant-like actions. However, it should be noted that in rats, the anticonvulsant activity of somatostatin is mediated by sst2 receptors (Qiu, et al. 2008).

somatostatin has both anxiolytic and pro-cognitive effects (Engin, et al. 2008).

Specific agonism of sst4 receptor function, results in an enhancement of at least some forms of memory function (Gastambide, et al. 2009).

The inhibitory role of somatostatin interneurons in limbic areas such as the hippocampus, the co-localization of somatostatin within GABAergic terminals in several brain areas and the inhibition of glutamate release followingsst2 receptor activation could all contribute to the anxiolytic-like effects of somatostatin (Baraban, et al..2004).
b. Retinal disorders

SST-28 or a SST-28-like material is detected in tissue extracts from the ciliary processes, and in aqueous humor. SST appears to exert multiple, and probably overlapping effects in the bovine CE including the attenuation of the Na+/H+-exchanger in the CE is the inhibition of aqueous humor secretion and presumably the lowering of intraocular pressure. (Fidzinski, et al., 2004).

Octreotide reduces vitreous hemorrhage and loss of visual acuity in patients with high-risk proliferative DR after full scatter laser coagulation. In patients with nonproliferative DR, eight weeks of octreotide administration improved visual acuity and had only partial effect on GH levels while concurrent improvement in retinopathy level was also evident in two out of six subjects studied. One-year treatment with octreotide had modest effects on GH, IGF-1, and glucose metabolism and no significant effects on early retinopathy in Type I (insulin-dependent) DM, while daily administration of octreotide for six months reduced the plasma levels of thrombomodulin, a marker of endothelial cell damage, in patients with Type I DM. (Spranger et al., 2000, 2001).

The effectiveness of SRIF analogues in diabetic retinopathy could possibly be due to a direct neuroprotective and antiangiogenic effect of these compounds in the retina (Baldysiak, et al. 2004).

Sandostatin-LAR had an edema-reducing effect in patients with chronic uveitic CME with successful responses to the drug being related to the duration of CME before the beginning of the treatment. (Hogewind, et al. 2008).

c. Epilepsy

Intra cerebroventricular and intra hippocampal injections of SS and SS analogues have been shown to modulate seizure activity in animal models. SS was directly injected into the hippocampus, have demonstrated inhibitory
effects on electrical seizures recorded in vivo. Therapeutical options in epilepsy therefore seems to be still far ahead (Baraban, et al. 2004).

2. Gastrointestinal tract

a. Treatment of active variceal hemorrhage

Somatostatin inhibits the release of vasodilator hormones such as glucagon, indirectly causing splanchnic vasoconstriction and decreased portal inflow. Following a bolus injection of somatostatin or octreotide, portal venous inflow, portal pressures, azygos flow, and intravariceal pressures decrease within seconds. Of these effects, the most consistently observed is the decrease in collateral flow (azygos flow). Octreotide caused a marked but transient decrease in portal pressure and azygos blood flow and an increase in mean arterial pressure. These effects lasted only five minutes, even with the addition of continuous infusions. Repeated bolus injections had shorter, less marked effects, while continuous infusion did not decrease portal pressure, suggesting that there was rapid desensitization (Garcia-Tsao, et al. 2007).

Variceal hemorrhage is associated with an increase in intestinal blood flow, presumably mediated by pathways that are activated by the presence of blood, a high protein substance, in the gut. Octreotide can blunt this response for at least 48 hours. In addition, activation of somatostatin receptors may decrease the rebound increase in portal venous pressure that occurs when blood enters the gastrointestinal tract and during correction of hypovolemia (Fernandez, et al. 2006).

Trials have compared somatostatin or octreotide to either vasopressin or placebo in the management of active bleeding:
Somatostatin versus vasopressin: Somatostatin is also superior to vasopressin and balloon tamponade, due in part to the virtual absence of side effects (Imperiale, et al. 1995).

Somatostatin versus sclerotherapy: Sclerotherapy was not superior to somatostatin or octreotide for any outcome (D'Amico, et al. 2003).

Somatostatin plus sclerotherapy: Treatment with somatostatin or octreotide infusions when used in addition to sclerotherapy is superior to sclerotherapy alone or somatostatin alone for the prevention of early rebleeding and possibly survival (D'Amico, et al. 1998).

Somatostatin plus endoscopic variceal ligation: Combination therapy improved the five-day success rate compared with endoscopic variceal ligation alone. However, no mortality benefit could be demonstrated (D'Amico, et al. 2002).

b. Angiodysplasia

There are several potential ways in which somatostatin analogues like octreotide could impact on rebleeding rates in patients with gastrointestinal angiodysplasia. The hypothesized mechanisms include inhibition of angiogenesis, decreased splanchnic bloodflow, increased vascular resistance and improved platelet aggregation (Szilagyí, et al. 2006).

There is no evidence that somatostatin analogues would be effective for patients with hereditary hemorrhagic telangiectasia (HHT), an autosomal-dominant disorder characterized by systemic arteriovenous malformations (Grand, et al. 2009).

Octreotide have a role especially in lesions that have failed endoscopic therapy or are inaccessible and in patients in whom multiple co-morbidities make endoscopic interventions risky. Ahead-to-head comparison of endoscopic
approaches and octreotide is also needed to help rationalize treatment decisions in these patients (Junquera, et al. 2007).

c. Pancreatitis

Octreotide was able to down-regulate the secretions of many human organs in the gastrointestinal tract, including the pancreas, its applications on acute pancreatitis were soon suggested. Many drugs have, therefore, been introduced, first of all octreotide (SMS201-995), lameotide (BIM-23014) and, more recently, long-acting octreotide. The inhibiting effect of these hormones depends on their capacity to bind to the somatostatin receptor (Raulf, et al. 1994).

The main benefits of these drugs in pancreatic diseases are postulated to be:

a) treatment of acute pancreatitis.

b) prevention of complications secondary to elective pancreatic surgery, particularly fistulae.

c) prevention of complications secondary to endoscopic manoeuvres on the papilla of Vater.

d) treatment of endocrine tumours.

e) treatment of pain in chronic pancreatitis.

No positive controlled clinical trials have shown evidence of their usefulness in patients with acute pancreatitis and similar results have emerged with these drugs used for prophylactic purposes (Hardt, et al. 2000).

Octreotide was not found to be beneficial in patients suffering from severe acute pancreatitis, either in the intention-to-treat or in the valid for efficacy analysis. Vapreotide, a potent synthetic analogue of somatostatin, is a cyclic octapeptide with a high affinity for somatostatin receptor subtypes 2 and 5.
and some affinity for subtype 4. This somatostatin analogue has been shown to decrease pancreatic exocrine secretion by more than 75%. Patients with chronic pancreatitis (Shan, et al. 2003).

d. Post endoscopic retrograde cholangiopancreatography

In a recent systematic survey of 21 studies involving 16,855 patients, the incidences of ERCP-associated complications and mortality were 6.85% and 0.33%, respectively. Increases in serum amylase and lipase activities after ERCP are common, occurring in about 25–75% of all patients. Acute pancreatitis is a major complication of ERCP (Andriulli, et al. 2007).

Based on the potent inhibition of pancreatic exocrine secretion, somatostatin and octreotide may be useful for treatment of acute pancreatitis and prophylaxis against PEP. The effects of somatostatin and octreotide for acute pancreatitis and prevention of PEP have been controversial despite extensive clinical studies (Lee, et al. 2008).

Somatostatin given as a bolus seemed to be an efficacious and applicable measure for PEP prevention. In the most recent randomized, multicenter, and controlled study with continuous infusion of somatostatin 3 mg for 12 hours or placebo was given to 391 patients undergoing therapeutic ERCP. Somatostatin could significantly reduce the incidence of PEP. Short-term administration of somatostatin (2.5 and 6.5 hours) was ineffective for the prevention of PEP trials evaluating the prophylactic effect of somatostatin as a bolus-plus-continuous infusion for 12 hours and as a bolus alone for prevention of PEP (Chan, et al. 2008).
e. Post pancreatectomy

Prophylactic octreotide may be useful in patients in whom a pancreaticojejunostomy is to be performed, or in those patients with a pancreatic duct diameter of less than 3 mm, or both (Shan, et al. 2003).

The efficacy of somatostatin analogues for protection against anastomotic leaks may be affected by several factors:

1. Fluctuations in enzyme concentrations after administration of octreotide, which resulted in production of low volumes of pancreatic juice with high enzyme concentrations, which could be detrimental for fistula prevention or closure.

2. The inhibitory effects of octreotide on pancreatic secretion have been reported to diminish with repeat applications.

3. Somatostatin and its synthetic analogues cause a decrease in splanchnic blood flow that theoretically may interfere with anastomotic healing.

4. Somatostatin and its analogues have been shown to alter T cell function, which may also affect postoperative immune function (Talme, et al. 2004).

In addition, some authors have suggested that the benefits of somatostatin analogues may be more evident in patients undergoing resection at low-volume centers with higher leak rates (Suc, et al. 2003).

The use of somatostatin analogues preoperatively and for 5–7 days postoperatively in an attempt to prevent pancreas-related complications after pancreatic resection remains at best controversial and cannot be recommended as routine therapy. Solid evidence for its efficacy is lacking; however, its use in patients with a soft pancreatic parenchyma, in whom the risk...
of a pancreatic leak is greater, may be justified, but the cost/benefit ratio remains unproven (Talme et al. 2004).

f. Liver diseases

Schistosomiasis

Somatostatin might play an important role in disrupting host–parasite interactions responsible for schistosomiasis:

(1) by directly effecting fibrosis, portal hypertension and variceal bleeding.

(2) by influencing the immunomodulatory mechanisms in the intestines. (Reynaert, et al. 2001).

Somatostatin could prevent the degranulation of inflammatory mast cells, thereby preventing the release of histamine and other inflammatory mediators known to cause GI motility disturbances. This implies a positive therapeutic effect of somatostatin on the inflammatory cells surrounding the GI tract granulomas (Reynaert, et al. 2001).

Hepatocellular Carcinoma

Although limited antitumor activity has been suggested in nonrandomized studies, a randomized trial of lanreotide versus placebo in 272 patients with advanced HCC failed to show any advantage for drug treatment in terms of progression-free or overall survival, and treatment was associated with worse quality of life. Thus, routine administration of octreotide or lanreotide cannot be recommended, particularly in view of the high cost of these drugs (Barbare, et al. 2009).
g. Diabetic nephropathy

Recent studies show that octreotide therapy could potently enhance filtration fraction, glomerular filtration rate, proximal tubular fluid reabsorption, and decreased vascular resistance induced by diabetes in streptozotocin diabetic rat model. Somatostatin agonists possess therapeutic promise for diabetic nephropathy, further research is necessary to define the roles of somatostatin and its receptor subtypes in diabetic renal complications (Bak, et al. 2007).

3. Oncology

a. Pituitary tumors

Several reports suggest that in human tumors, somatostatin analog treatment can be effective in the control of tumor growth. Octreotide and lanreotide are clinically used to control hormonalsymptoms of pituitary adenomas. They reduce or normalize excessive growth hormone and insulin-like growth factor (IGF-1) levels associated with acromegaly. In addition, somatostatin analog therapy is associated with tumor shrinkage in 37–82% of patients receiving somatostatin analog as primary medical therapy (Cattaneo, et al. 2006).

b. Thyroid malignancies

Therapeutic applications: SST analogs in differentiated thyroid cancer

SST analogs can change the biological activity of metastatic thyroid cancer lesions that express SSTRs (Robbins RJ, et al. 2000).

Therapeutic applications: SST analogs in medullary thyroid cancer

It has not been demonstrated that octreotide reduces the tumour mass. An interesting tool for the treatment of refractory tumours may be the combined
treatment with two different biologic agents, like octreotide and interferon (IFN). Taken together, these studies show that SST analogs that are currently used in the clinical field are very effective in controlling the symptoms, but are not able to reduce neoplastic C cell growth. This could be due to the particular expression pattern of SSTRs in MTC, where SSTR2, an octreotide-sensitive receptor, is not always expressed. (Zatelli MC, et al. 2002).

c. Gall bladder cancer

DOX had been reported to display a cell cycle-dependent cytotoxicity: cells synchronized in S phase were more sensitive to DOX than those in G1 phase. GBC cells treated with SST and DOX gained obviously larger lethal effect when compared to the other groups. This could explain one of the mechanisms that SST enhanced the cytotoxicity of DOX on GBC-SD cells. The target enzyme of DOX is Topo IIa which plays essential role in DNA metabolic process (McClendon AK, et al. 2007).

Exploring the relations of SST, Topo IIa (as one of the target enzymes for drug-resistance cancer cells) and enhanced chemosensitivity, it is found that SST had significantly up-regulated Topo IIa protein in the GBC-SD cells line when compared to that of control group. This may be the other effective pathway that SST strengthens chemosensitivity to DOX in GBC-SD cells line. Our results showed that SST might increase the ratio of cells in S phase, which is sensitive to DOX, and up-regulate the expression of Topo IIa protein in GBC-SD cells line (Arpino G, et al. 2005).

d. Cancer prostate

Somatostatin analogues were much less effective in prostate cancer than they do in neuroendocrine tumors. All somatostatin analogues on the market have highest affinity to SSTR2, but SSTR2 is not dominant in prostate cancer (adenocarcinoma) (Sciarra A., et al. 2004).
In addition to SSTR2 gene therapy to amplify the biologic effect of genetic transduction events, there are some additional possible combined therapies with somatostatin analogues in prostate cancer (SciarrA., et al. 2004).

Steroid was used as combination therapy to down-regulate GHindependent IGF-I, whereas somatostatin analogues suppresses the level of GH dependent IGF-I. This combination yielded objective response and major improvement of bone pain in prostate cancer. Rationale for this combination is that some studies have shown that the number of neuroendocrine tumor cells increase during hormone therapy in prostate adenocarcinoma (SciarrA., et al. 2004).

e. Cervical and Endometrial carcinoma

Subgroup of receptor-positive uterine carcinomas may be a potential target for treatment with somatostatin analogs. Given the recent development of subtype-selective ligands it is particularly important to determine the precise pattern of somatostatin receptor protein expression for each tumor in order to select one or more somatostatin analogs for an optimal therapeutic effect (Bruns C, et al. 2002).

4. Polycystic kidney

Somatostatin may reduce renal and liver cyst fluid accumulation among patients with PKD. In a pilot study comparing somatostatin to placebo in patients with PKD, active therapy was associated with a smaller increase in cyst size and total kidney volume after six months of treatment. Glomerular filtration rate (GFR) was decreased to the same degree in both groups at one year. Octreotide was associated with improved perception of pain and physical activity (Caroli, et al. 2010).
G. Adverse Reactions

- **>16%:**

Cardiovascular: Sinus bradycardia, chest pain.

Central nervous system: Fatigue, headache, malaise and dizziness.

Dermatologic: Pruritus.

Endocrine & metabolic: Hyperglycemia.

Gastrointestinal: Abdominal pain, loose stools, nausea, diarrhea, flatulence, cholelithiasis, biliary sludge, constipation, vomiting, biliary duct dilatation.

Local: Injection site pain.

Neuromuscular & skeletal: Back pain, arthropathy and myalgia.

Respiratory: Upper respiratory infection and dyspnea.

Miscellaneous: Antibodies to octreotide and flu symptoms.

- **5% to 15%:**

Cardiovascular: Hypertension, conduction abnormalities, palpitation and peripheral edema.

Central nervous system: Pain, anxiety, confusion, hypoesthesia and insomnia.

Dermatologic: Rash, alopecia.

Endocrine & metabolic: Hypothyroidism, goiter.

Gastrointestinal: Anorexia, cramping, tenesmus, dyspepsia and steatorrhea.

Hematologic: Anemia.

Neuromuscular & skeletal: Arthralgia, myalgia, paresthesia, rigors, weakness.
Renal: Renal calculus.

Respiratory: Cough, pharyngitis, sinusitis, rhinitis.

Miscellaneous: Allergy, diaphoresis.

- 1% to 4%:

Cardiovascular: Angina, cardiac failure, edema, flushing, hematoma, phlebitis.

Central nervous system: Abnormal gait, amnesia, depression, dysphonia, hallucinations, nervousness, neuralgia, somnolence, vertigo.

Dermatologic: Acne, bruising, cellulitis.

Endocrine & metabolic: Hypoglycemia, hypokalemia, hypoproteinemia, gout, cachexia, breast pain, impotence.

Gastrointestinal: Colitis, diverticulitis, dysphagia, fat malabsorption, gastritis, gastroenteritis, gingivitis, glossitis, melena, stomatitis, taste perversion, xerostomia.

Genitourinary: Incontinence, pollakuria (non-depot formulations), urinary tract infection.

Local: Injection site hematoma.

Neuromuscular & skeletal: Hyperkinesia, hypertonia, joint pain, neuropathy, tremor.

Ocular: Blurred vision, visual disturbance.

Renal: Albuminuria, renal abscess.

Respiratory: Bronchitis, epistaxis.

Miscellaneous: Bacterial infection, cold symptoms, moniliasis.
<1% (Limited to important or life-threatening): Anaphylactic shock, anaphylactoid reaction, aneurysm, aphasia, appendicitis, arthritis, ascending cholangitis, ascites, atrial fibrillation, basal cell carcinoma, Bell's palsy, biliary obstruction, breast carcinoma, cardiac arrest, cerebral vascular disorder, CHF, cholecystitis, cholestatic hepatitis, CK increased, creatinine increased, deafness, diabetes insipidus, diabetes mellitus, facial edema, fatty liver, galactorrhea, gallbladder polyp, GI hemorrhage, GI ulcer, glaucoma, gynecomastia, hearing loss, hematuria, hemiparesis, hemorrhoids, hepatitis, hyperesthesia, hypertensive reaction, hypoadrenalism, hypoxia (children), intestinal obstruction, intracranial hemorrhage, intraocular pressure increased, ischemia, jaundice, joint effusion, lactation, LFTs increased, libido decreased, malignant hyperpyrexia, menstrual irregularities, MI, migraine, necrotizing enterocolitis (children), nephrolithiasis, neuritis, orthostatic hypotension, pancreatitis, pancytopenia, paresis, petechiae, pituitary apoplexy, pleural effusion, pneumonia, pneumothorax, pulmonary embolism, pulmonary hypertension, pulmonary nodule, Raynaud’s syndrome, rectal bleeding, renal failure, renal insufficiency, retinal vein thrombosis, scotoma, seizure, status asthmaticus, suicide attempt, syncope, tachycardia, thrombocytopenia, thrombophlebitis, thrombosis, urticaria, visual field defect, weight loss (Broglio, et al. 2007).

Precautions

• Abnormal Schillings test: Chronic treatment has been associated with abnormal Schillings test; monitor vitamin B12 levels.

• Cholelithiasis: May impair gallbladder function (inhibits gallbladder contractility and decreases bile secretion); monitor patients for cholelithiasis.

• Glucose regulation: Somatostatin analogs may affect glucose regulation. In type I diabetes, severe hypoglycemia may occur; in type II diabetes or patients without diabetes, hyperglycemia may occur.
• Hypothyroidism: Suppresses secretion of TSH; monitor for hypothyroidism.

• Pancreatitis: May alter absorption of dietary fats; monitor for pancreatitis.

• Cardiovascular disease: Use with caution in patients with heart failure or concomitant medications that alter heart rate or rhythm. Cardiovascular medication requirements may change.

• Excessive fluid loss: May reduce excessive fluid loss in patients with conditions that cause such a loss; periodic monitoring for elevations in zinc levels is recommended in such patients that are maintained on total parenteral nutrition (TPN).

• Hepatic impairment: Use caution in patients with hepatic impairment.


**H. Drug Interactions:**

Codeine: Somatostatin Analogs may decrease the metabolism of Codeine. Risk C.

CycloSPORINE: Somatostatin Analogs may decrease the serum concentration of CycloSPORINE. Risk D.

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. Risk C.

# VASOPRESSIN

## A. PHYSIOLOGY

### Vasopressin Receptor Distribution and Function

<table>
<thead>
<tr>
<th>Receptor Subtype</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td>Vascular smooth muscle</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>Platelet aggregation</td>
</tr>
<tr>
<td></td>
<td>Adrenal gland</td>
<td>Aldosteron and cortisol release</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>Glycogenolysis and glucose release</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal tract</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myometrium</td>
<td>Peristalsis</td>
</tr>
<tr>
<td></td>
<td>Brain</td>
<td>Uterine contraction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Regulation of blood pressure and heart rate</td>
</tr>
<tr>
<td>V2</td>
<td>Kidney</td>
<td>Efferent arteriolar constriction</td>
</tr>
<tr>
<td></td>
<td>Vascular smooth muscles</td>
<td>Vasodilatation</td>
</tr>
<tr>
<td></td>
<td>Vascular endothelium</td>
<td>Release of von willebrand factor and factor8</td>
</tr>
<tr>
<td>V3</td>
<td>Vascular smooth muscles</td>
<td>Vasodilatation</td>
</tr>
<tr>
<td></td>
<td>Vascular endothelium</td>
<td>Release of von willebrand factor and factor8</td>
</tr>
<tr>
<td></td>
<td>Anterior pituitary</td>
<td>Neuromodulation</td>
</tr>
<tr>
<td></td>
<td>Brain</td>
<td>Stress adaptation</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>Insulin synthesis and release</td>
</tr>
<tr>
<td></td>
<td>Heart</td>
<td>Atrial natriuretic peptide synthesis and release</td>
</tr>
</tbody>
</table>

Table (4) ([Lauzier F, et al. 2006](#)).
B. Mechanism of Action

Increases cyclic adenosine monophosphate (cAMP) which increases water permeability at the renal tubule resulting in decreased urine volume and increased osmolality; causes peristalsis by directly stimulating the smooth muscle in the GI tract; direct vasoconstrictor without inotropic or chronotropic effects (Dunser MW, et al. 2001).

C. Pharmacodynamics/Kinetics

Onset of action: Nasal: 1 hour.

Duration: Nasal: 3-8 hours; I.M., SubQ: 2-8 hours.

Metabolism: Nasal/Parenteral: Hepatic, renal.

Half-life elimination: Nasal: 15 minutes; Parenteral: 10-20 minutes.

Excretion: Nasal: Urine; SubQ: Urine (5% as unchanged drug) after 4 hours (Rosendale JD, et al. 2003).

D. Synthetic Vasopressin Analogs: Forms

Terlipressin

Relative to VP, it exhibits a greater degree of V1-receptor specificity (2.2:1 compared with 1:1 for AVP). When compared with VP, TP has a longer duration of action that allows for bolus injection. However, because bolus dosing has been linked to a higher frequency of systemic side effects, continuous infusion therapy is favored. Like VP, TP is only available for parental use. Of note, TP, but not VP, has been shown to dilate intrahepatic vessels, thereby enhancing blood flow through the hepatic artery in patients with cirrhotic liver disease and portal hypertension. (Ertmer C, et al. 2008).
Deamino-D-arginine vasopressin

DDAVP (1-deamino-8-D-arginine vasopressin) was the first and remains the only clinically available VP agonist with V2-receptor specificity (V2:V1 receptor affinity approximately 2,000-3,000 times that of VP). DDAVP increased the release of vWF and factor VIII. This led to the use of prophylactic DDAVP to reduce perioperative bleeding in patients with some types of von Willebrand disease as well as hemophilia and uremia-induced platelet dysfunction (Franchini M, et al. 2007).

Vasopressin Antagonists

Several nonpeptide vasopressin antagonists, also called vaptans, were developed to oppose VP-induced free water conservation. Conivaptan is a parenterally formulated vaptan and the only vaptan with substantial activity at both V1 and V2 receptors. Several other vaptans including tolvaptan, lixivaptan, mozavaptan, and satavaptan are specific V2-receptor antagonists and are available in oral form (Decaux G, et al. 2008).

E. Dose:

I.V.: Use extreme caution to avoid extravasation because of risk of necrosis and gangrene.

Usual concentration: 100 units in 500 mL D5W. More dilute solution (eg, 20 units in 500 mL D5W) was employed.

Vasodilatory shock: Administration through a central catheter is recommended.

Intranasal (topical administration on nasal mucosa): Administer injectable vasopressin on cotton plugs, as nasal spray, or by dropper. Should not be inhaled.

F. Therapeutic uses in non endocrine patients

DISORDERS OF PLASMA OSMOLALITY

1-Hyponatremia

1.1. Congestive Heart Failure and Cirrhosis

Hyponatremia has been found to be an independent predictor of major complications, rehospitalization, and mortality in patients with congestive heart failure. Baseline and persistent hyponatremia were found to be independent predictors of hospitalization for heart failure and mortality over a 6-month follow-up period. Among these patients, suppression of VP release that would be expected because of hyponatremia is overridden by baroreceptor activation in the aortic arch and carotid sinus resulting from low cardiac output. Enhanced activity of the renin-angiotensin-aldosterone system (RAAS) also may promote VP secretion (Oghlakian G, et al. 2009).

Gheorghiade et al studied the impact of 3 doses of tolvaptan in a double-blind placebo-controlled trial of 254 patients with chronic heart failure. Over the 25-day study period, reductions in body weight and edema, as well as normalization of serum sodium concentration in hyponatremic patients, were observed in patients treated with tolvaptan but not placebo. Tolvaptan therapy was well tolerated and produced no appreciable changes in heart rate, systemic blood pressure, or renal function. (Gheorghiade M, et al. 2007).

Other trials of V2 antagonists have been conducted among patients with hyponatremia from cirrhosis, SIADH, and congestive heart failure. All have shown efficacy in terms of normalization of serum sodium concentration. Many have reported symptomatic benefits including reduced edema and increased ease of breathing. In animal models of congestive heart failure, V1/V2 antagonist therapy
has been shown to improve fluid regulation and reduce cardiac hypertrophy. Studies in humans have exhibited mixed results (Bishara B, et al. 2008).

In a 12-week placebo-controlled trial of oral conivaptan therapy in patients with class III heart failure, no impact on functional capacity or exercise tolerance was shown. In a 1-year follow-up, tolvaptan-treated patients exhibited statistically nonsignificant increases in left ventricular ejection fraction; in addition, there was a trend toward lower rates of mortality and heart failure–related hospitalizations (Udelson J, et al. 2007).

However, in the Efficacy of Vasopressin Antagonist in Heart Failure Study with Tolvaptan trial, the largest study to date, investigators were unable to identify improvement in heart function, physical health, or overall mortality over a median 9.9-month follow-up period. BALANCE trial will study the safety and efficacy of oral lixivaptan for increasing serum sodium concentration and will assess the impact of therapy on rehospitalization as well as all-cause and cardiovascular mortality (Oghlakian G, et al. 2009).

**DISORDERS OF HEMOSTASIS**

1-von Willebrand Disease and Disorders of Coagulation

DDAVP enhanced the release of factor VIII, vWF, and plasminogen activator, thereby promoting platelet aggregation and coagulation. This effect is mediated via V2 receptors present on the vascularendothelium. Since then, DDAVP has achieved widespread use in the perioperative management of patients with von Willebrand disease type 1, which results from a partial quantitative reduction in vWF (Sadler JE, et al. 2006).

DDAVP is transiently effective in most patients with von Willebrand disease types, which are caused by qualitative vWF defects, although its prophylactic use in these patients is more controversial. DDAVP is also used to reduce perioperative
bleeding in patients with hemophilia A and other conditions associated with coagulation dysfunction, such as uremia and cirrhosis (Franchini M, et al. 2007).

In addition, it has proven effective at improving platelet function and reducing blood loss in patients treated with antiplatelet agents such as aspirin and ticlopidine. The mechanism of this effect appears to involve more than stimulation of procoagulant release but remains to be fully explained. Prophylactic DDAVP administration might help reduce blood loss in patients without intrinsic bleeding disorders who were undergoing complex surgical procedures at risk for large blood loss (Cattaneo M, et al. 2008).

2-Variceal Bleeding

Both VP and TP are first-line therapies in the management of variceal hemorrhage because both have powerful vasoconstrictive effects in splanchnic vascular beds. Compared with VP, TP appears to have a wider safety profile and is also the only drug that has shown a survival benefit compared with placebo. However, TP remains unavailable in the United States (Döhlerand Meyer 2008).

Terlipressin has similar efficacy in control of acute bleeding. A study comparing the acute hemodynamic effects of terlipressin to octreotide in stable patients with cirrhosis found a sustained effect of terlipressin on portal pressure and blood flow compared with only a transient effect from octreotide, suggesting that terlipressin might have more sustained hemodynamic effects in patients with bleeding varices. A randomized controlled trial comparing variceal ligation in combination with terlipressin or octreotide found that terlipressin was not inferior to octreotide for control of esophageal variceal bleeding and in-hospital survival (Abid, et al. 2009).

3-Severe gastrointestinal bleeding in Crohn's disease

Typically, vasopressin therapy involves an initial 20-minute infusion at a rate of 0.2 U/min followed by repeated arteriography to determine whether bleeding has
stopped. Higher infusion rates (0.3–0.4 U/min) can be used but each increment requires a waiting period and repeat angiogram for reassessment. Though the overall intra-procedural time is similar for both procedures, vasopressin infusion needs to be continued for a total 12–24 h (Girona E, et al. 2007).

**Hypertension**

Arginine vasopressin stimulates or inhibits the proliferation of vascular smooth muscle cells. This finding provides new insights into the role of vasopressin in pathophysiological conditions including hypertension and atherosclerosis. Vasopressin may play an important role in the modulation of vascular functions in an autocrine or paracrine fashion as a local factor, through the proliferation of vascular smooth muscle cells. Arginine vasopressin stimulates both growth promoting signals and prostanoid production through the V receptor in vascular smooth muscle cells. The balance between them may determine the final growth state of vascular smooth muscle cells (Spatz, et al. 1994).

**DISORDERS OF HYPOPERFUSION**

1- **Hepatorenal Syndrome**

TP has been found to reduce portal venous pressure and blood flow through portosystemic shunts as well as to dilate intrahepatic blood vessels, leading to increased hepatic blood volume (Solanki, et al. 2003).

TP is now under active investigation in the management of patients with HRS as a bridge therapy to liver transplant. In clinical trials, treatment has been shown to improve both renal and cardiovascular function and possibly confer survival benefit. Current evidence supports early intervention to maximize treatment benefits (Döhler and Meyer, 2008).

2- **Cardiac Arrest**
The exogenous administration of VP in cardiac arrest improved vital organ perfusion, neurologic outcomes, and short-term survival. Studies in human cardiac arrest patients have not consistently shown benefit from VP therapy; however, there also has not been convincing evidence of demonstrable harm. Guidelines of the European Resuscitation Council (ERC) support the use of VP in all cases of pulseless cardiac arrest (Aung, et al. 2005).

As with research in the treatment of septic shock, interest in the potential benefit of combination therapy to treat cardiac arrest soon followed. Initial studies suggested a possible survival benefit with the combined use of epinephrine and VP. These results may be biased by the tendency for VP to be used as a “last resort” among patients with prolonged arrest and those with more significant underlying pathology (Duncan, et al. 2009).

‘Triple drug’ therapy, consisting of epinephrine, vasopressin and nitroglycerin, provides significantly greater vital organ blood flow and coronary perfusion pressures compared with the epinephrine alone. Moreover, the previously observed negative side effect of decreased cerebral perfusion when combining epinephrine and vasopressin did not occur with addition of nitroglycerin. Both epinephrine and vasopressin are currently recommended by the American Heart Association and European Resuscitation Council for use in patients in shock refractory cardiac arrest. However, there are potential problems when each therapy is used alone. the combination of vasopressin with epinephrine rendered successful defibrillation likely (Mayr, et al. 2004).

3- Heart failure

It has been shown that conivaptan improves cardiac function, reduces preload and after load, and exerts aquauretic effects in congestive heart failure. In a clinical study in heart failure patients with hyponatraemia, conivaptan reduced urine osmolality, increased free water clearance and corrected hyponatraemia (Udelson, et al. 2001).
AVP antagonism with conivaptan in advanced heart failure significantly decreased pulmonary capillary wedge pressure and right atrial pressure. These findings and the present results suggest that conivaptan, which is able to block the activity of AVP at both V1a and V2 receptors, may offer significant clinical benefit to patients with heart failure. Further study is needed to evaluate the effect of long-term conivaptan administration for the treatment of heart failure. In conclusion, cardiac and haemodynamic disorders due to i.v. infusion of AVP. These results suggest the potential usefulness of conivaptan as a neuro hormonal antagonist for the treatment of congestive heart failure (Udelson, et al. 2001).

4-Septic Shock

In the early phase of sepsis, VP levels are acutely elevated and then decline rapidly as the condition progresses. The depletion of endogenous VP appears to contribute to the vasodilation associated with advanced sepsis, and an inverse relationship between patient survival and endogenous serum VP levels in the late stage of shock has been observed (Sharshar, et al. 2008).

High levels of circulating catecholamines and NO also have been shown to suppress VP release. VP exhibited treatment benefit among patients with less severe sepsis (based on norepinephrine infusion) as well as in those at risk of renal dysfunction. Acting on the knowledge that VP enhances corticotropin responsiveness and that patients in shock states often exhibit relative adrenal insufficiency, there is reduction in mortality at 28 days among patients treated with the combination of corticosteroids and VP as opposed to corticosteroids and norepinephrine. Equally interesting was the finding that among patients who did not receive corticosteroid therapy, those treated with VP had a higher rate of mortality compared with those who received norepinephrine. It was found that patients treated with corticosteroids had a substantially greater increase in plasma VP levels relative to those who did not receive steroid therapy (Russell, et al. 2009).
TP used in septic patients with refractory hypotension despite traditional therapies. A recent trial has been conducted comparing continuous infusion TP with norepinephrine or VP as first-line therapy in the treatment of patients with resuscitated septic shock. Preliminary reports suggest no harm and possibly some benefit from TP treatment. VP deficiency appears to play a lesser role in the pathophysiology of septic shock in the pediatric population compared with adults; however, VP and its analogs have in select cases resulted in some benefit. (Morelli, et al. 2007).

Reported doses have varied widely. For TP, boluses as low as 7 micro g/kg every 12 hours and 2 to 20 micro g/kg every 4 hours have been used; however, continuous infusions using doses as high as 10 to 20 micro g/kg/h also have been reported. When VP has been used, bolus doses of 0.1 to 0.3 U/kg (Dellinger, et al. 2008).

NB: Evidence from case reports has offered the use of VP or its analogs as rescue therapy in other conditions associated with refractory hypotension including overdoses of calcium channel blockers and tricyclic antidepressants as well as traumatic brain injury (Salluh, et al. 2007).

5-Hemorrhagic Shock

Several case reports have acknowledged a favorable impact with VP as a temporizing measure to support blood pressure during triage of trauma victims. However, some research suggests that although VP may help restore blood pressure and reduce resuscitative fluid requirements, this benefit may come at the expense of adverse metabolic and hemodynamic consequences, including lactic acidemia and a decline in cardiac index with definitive recommendations on the use of VP in the context of hemorrhagic shock (Lienhart, et al. 2008).
6-Anesthesia-Induced Hypotension

Much of the hypotension induced by anesthetics is catechol responsive, as shown by the effective use of vasopressors such as phenylephrine and ephedrine to treat anesthesia-induced vasodilation. However, clinical experience suggests that at least some of the hypotension induced by anesthesia is refractory to catecholamines. The exogenous administration of VP has been used successfully to treat catechol-resistant hypotension (Jochberger, et al. 2008).

VP appears to be particularly useful in treating hypotension in anesthetized patients who also are treated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (Lange, et al. 2008).

7-Post cardiotomy/Cardiopulmonary Bypass–Induced Hypotension

Patients undergoing cardiac surgery also experience significant fluctuations in serum VP concentrations. The initiation of cardiopulmonary bypass (CPB) is associated with a dramatic rise in serum VP levels; this is followed by a gradual return to baseline in the postoperative period. In some patients, VP levels are inappropriately low relative to the degree of postoperative hypotension and contribute to refractory vasodilatory shock. Risk factors for the development of post-CPB vasodilatory hypotension include low presurgical ejection fraction and the use of ACE inhibitors. In these patients, exogenous VP infusion has been found to effectively increase mean arterial pressure (MAP) and reduce catecholamine requirements (Singh Ranger, et al. 2002).

Prophylactic VP infusion begun before the initiation of CPB was shown to improve hemodynamic stability in patients undergoing coronary artery bypass graft surgery or valvular surgery who also were treated with ACE inhibitors. Decreases in time to extubation and length of intensive care unit stay also were observed (Morales, et al. 2003).
VP infusion was associated with significant increases in MAP, left ventricular stroke work index, and systemic vascular resistance along with a decrease in heart rate and no change in cardiac index or stroke volume index. The unique benefits and risks of VP therapy to treat vasodilatory hypotension remain to be fully established. Some groups have identified a reduction in markers of myocardial ischemia associated with VP infusion (Masetti, et al. 2002).

VP improved coronary artery blood flow and did not increase coronary vascular resistance. However, high-dose VP therapy such as that used to control bleeding has been known to cause coronary vasoconstriction and produce a substantial negative inotropic effect. The use of VP in patients with cardiogenic as opposed to vasodilatory hypotension is likely to pose the most risk of exacerbating myocardial dysfunction. There is also evidence to suggest that VP therapy may confer a renal-protective effect (Mayr, et al. 2004).

VP also increases platelet aggregation, which could promote thrombogenesis and impair microcirculation. However, no data suggest that these complications are common. Several vasopressors in addition to VP, including norepinephrine, phenylephrine, and methylene blue, have been shown to increase MAP in postcardiotomy hypotension. (Egi, et al. 2007).

**Nocturnal Polyurea**

Causes of polyuria include diabetes mellitus and, lithium induced polydipsia/polyuria and primary thirst disorders. While polyuria causes increased nocturnal urine volume, like nocturnal polyuria. Desmopressin has been proved effective and well tolerated to treat neurogenic diabetes insipidus and enuresis in children and adults. Desmopressin also reduced or eliminated nocturnal voiding in patients with autonomic dysfunction and Parkinson’s disease (Sugaya, et al. 2001).

Patients with nocturia due to multiple sclerosis have been successfully treated with desmopressin, with a decrease in the number of voids per night and
corresponding increase in nights free from voiding and hours of uninterrupted sleep. In addition, patients previously diagnosed with BPH had fewer voids when treated with desmopressin, particularly those with high nocturnal urine output (Valiquette, et al. 1996).

Desmopressin therapy has also been successful for treating women with nocturia after antispasmodic medication failed. The success of desmopressin for these indications and an increased awareness of the use of voiding diaries for the diagnosis of voiding dysfunction in general have led to its use to treat nocturia specifically due to nocturnal polyuria. Desmopressin intranasally or 0.1 mg. orally increased by increments of 10 mg. or 0.1 mg., respectively, every third night until the desired effect is reached, to a maximum dose of 40 mg. or 0.4 mg., respectively, every bedtime. The aforementioned protocol may be prescribed to appropriately selected patients with nocturia due to nocturnal urine overproduction who are 21 years old or older. It is important to remind patients receiving desmopressin that they should sharply curtail evening water intake to minimize fluid retention (Asplund, et al. 1993).

A recent study indicates the general lack of side effects resulting from treatment of elderly men and women (mean age 72 and 73 years, respectively) with nocturnal polyuria using 40 mg. desmopressin during a 2-month interval ((Sugaya, et al. 2001).

**Aggressive behavior**

SRX251 is the first example of an orallyactive V1a antagonist with central nervous system activity. However, it is possible that the anti-aggressive effect of oral SRX251 was due, in part, to the blockade of V1a receptors in peripheral tissues like the liver and blood vessels. To control for this possibility, MC a selective V1a antagonist with reduced brain penetrance, was tested for anti-aggressive activity at doses exceeding that reported to block peripheral V1a receptors (Ferris, et al. 2006).

**vasopressin in affective disorders**
Affective disorders comprise mood disorders such as unipolar depression and anxiety disorders, including generalized anxiety, post-traumatic stress disorder, panic, phobia and obsessive–compulsive disorder. The etiology of these disorders is related to stress. Further, they are characterized by alterations of the hypothalamus–pituitary–adrenal (HPA) axis function, controlling the endocrine response to stress. (Alonso, et al. 2004).

It has been suggested that vasopressin may be involved in affective disorders. Several studies show an increased plasmatic level of vasopressin in anxiety disorders as well as in unipolar depression. Further, a single nucleotide polymorphism (SNP) of the vasopressin V1b receptor has been found to protect against depression. Preclinical data are convergent with the clinical findings. Antagonism of the V1b receptor decreases anxiety and depressive-like behaviors in rodents, as well as HPA responsivity to stress. Taken together, these data indicate that affective disorders may be related to excessive vasopressin function and consequently that a treatment with vasopressin receptor antagonists may be an effective treatment (Griebel, et al. 2005).

**Vasopressin in chronic fatigue syndrome**

Several neuroendocrine studies have suggested hypoactivation of the hypothalamic–pituitary–adrenal axis in chronic fatigue syndrome. One possible determinant of this neuroendocrine abnormality, as well as the primary symptom of fatigue, is reduced hypothalamic secretion of corticotropin-releasing hormone (CRH). Because CRH and vasopressin secreted from the hypothalamus act synergistically at the pituitary to activate ACTH secretion, the ACTH response to peripheral infusion of vasopressin can provide an indirect measure of hypothalamic CRH secretion. The ACTH and cortisol response to a one hour infusion of arginine vasopressin in 19 patients with chronic fatigue syndrome and 19 age and sex matched healthy volunteers. Patients with chronic fatigue syndrome had a reduced ACTH response to the vasopressin infusion and a more rapid cortisol response to the infusion. These
results provide further evidence of reduced hypothalamic CRH secretion in patients with chronic fatigue syndrome (Heim, et al. 2000).

**Autism spectrum disorders**

Autism spectrum disorders (ASD) are male-biased and characterized by deficits in social behavior and social communication, excessive anxiety or hyperreactivity to stressful experiences, and a tendency toward repetitiveness. Evidence for a role for two sexually dimorphic neuropeptides, oxytocin (OT) and arginine vasopressin (VP), in these features of ASD is present. Both VP and OT play a role in normal development. VP is of particular importance to male behavior. Excess VP or disruptions in the VP system could contribute to the male vulnerability to ASD. Alternatively, protective processes mediated via OT or the OT receptor might help to explain the relatively rare occurrence of ASD in females. Disruptions in either OT or VP or their receptors could result from genetic variation or epigenetic modifications of gene expression, especially during early development. Deficits in other developmental growth factors, such as reelin, which may in turn regulate or be regulated by OT or VP, are additional candidates for a role in ASD (Bielsky, et al. 2005).

**Renal malignancies**

Application of the selective V2-R antagonist SR121463B (satavaptan) prevent cellular proliferation, presumably the consequence of specific V2-R blockage. On the other hand, the presence of V2-R may also have a paradoxically positive aspect if used as a target for specific and alternative anticancer therapies. Different controlled trials are currently underway worldwide to assess the potential extension of this new therapeutical approach to human models, thus holding the hope of finally providing a pathogenic cure for a disease that is still treated only for its symptoms. Endogenous AVP may trigger the same growth effects on human renal carcinoma due to the acquired capacity of cancer cells to express V2-R, it is reasonable to explore the
possibility of another new therapeutic application of aquaretic agents as antitumoral drugs (Schally, et al. 2008).

**Nerve cell growth**

AVP4–9 caused a significant increase in filopodial length following 96 h of exposure at concentrations higher than 300 nM. AVP4–9 was more potent than AVP. AVP4–8 also induced an increase in filopodial length, but this effect was less than that of AVP. The selective V1 agonist vasopressin caused a significant increase in filopodial length, whereas the selective V2 agonist vasopressin showed no such effect. OPC-21268, a vasopressin V1 antagonist, blocked AVP and AVP fragment-induced increases in filopodial length. However, the V2 antagonist OPC-31260 showed no such effect. A23187, a representative Ca ionophore, also increased filopodial length, and the A23187-induced increase in filopodial length was potentiated by AVP and AVP fragments. These results indicated that AVP4–9 and AVP4–8 increased filopodial length in cultured hippocampal neurons by activating V1 receptors (Mihara, et al. 1999).

**Trials**

Several nonpeptide VP antagonists are in various stages of clinical trials for a wide assortment of clinical indications. V1-receptor antagonists including relcovaptan are under investigation for the management of Raynaud’s disease, premature labor, dysmenorrhea, and Meniere’s disease (Steinwall, et al. 2005).

The finding that cyclic adenosine monophosphate promotes renal epithelial cell growth has prompted investigations on the utility of V2-receptor antagonist therapy for slowing the progression of renal dysfunction in patients with polycystic kidney disease. Studies of V2-receptor antagonists for other indications including the reduction of intraocular pressure in patients with glaucoma and the minimization of cerebral edema and infarct size after ischemic brain injury are also underway (Torres, et al. 2008).
V3 antagonist therapy has shown promise in reducing stress-induced cortisol secretion and exerting anxiolytic and mood-elevating effects in rodent models. SSR-149415, the only orally active V3-receptor antagonist, is currently in phase II clinical trials to evaluate its efficacy in humans (Dempster, et al. 2007).

In vitro evidence suggests that increased intracellular cyclic AMP plays a significant role in cystogenesis in polycystic kidney disease and vasopressin V2 receptor antagonists can lower renal epithelial cell intracellular cAMP levels (Calvet, et al. 2008).

G. Adverse Reactions

CARDIOVASCULAR: Arrhythmia, asystole (>0.04 units/minute), blood pressure increased, cardiac output decreased (>0.04 units/minute), chest pain, MI, vasoconstriction, venous thrombosis (Obritsch, et al. 2004).

VP may worsen postresuscitation acidemia and increase the risk of reperfusion injury-induced multiorgan system dysfunction, depression of cardiac index has been observed. (Morelli, et al. 2005).

CENTRAL NERVOUS SYSTEM: Pounding in head, fever, vertigo.

DERMATOLOGIC: Ischemic skin lesions, circumoral pallor, urticaria

GASTROINTESTINAL: Abdominal cramps, flatulence, mesenteric ischemia, nausea, vomiting.

GENITOURINARY: Uterine contraction.

NEUROMUSCULAR & SKELETAL: Tremor.

RESPIRATORY: Bronchial constriction.

MISCELLANEOUS: Diaphoresis (Kahn, et al. 2002).
Precautions

- I.V. infiltration: May lead to severe vasoconstriction and localized tissue necrosis; also, gangrene of extremities, tongue, and ischemic colitis.

- Water intoxication: May cause water intoxication; early signs include drowsiness, listlessness, and headache, these should be recognized to prevent coma and seizures.

- Asthma: Use with caution in patients with asthma.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease, including arteriosclerosis.

- Goiter: Use with caution in patients with a goiter with cardiac complications.

- Migraine: Use with caution in patients with a history of migraines.


- Seizures: Use with caution in patients with a history of seizure disorder.


- Elderly: Caution elderly patients not to increase their fluid intake beyond that sufficient to satisfy their thirst (Rosendale, et al. 2003).

H.Contraindications

Hypersensitivity to vasopressin or any component of the formulation.

I.Drug Interactions

There are no known significant interactions.(Dellinger, et al. 2008).
PARATHYROID HORMONE

A. PHYSIOLOGY

Parathyroid hormone (PTH) is one of the two major hormones modulating calcium and phosphate homeostasis, the other being calcitriol (1,25-dihydroxyvitamin D). The minute-to-minute regulation of serum ionized calcium is exclusively regulated through PTH, maintaining the concentration of this cation within a narrow range, through stimulation of renal tubular calcium reabsorption and bone resorption. On a more chronic basis, PTH also stimulates the conversion of calcidiol (25-hydroxyvitamin D) to calcitriol in renal tubular cells, thereby stimulating intestinal calcium absorption (Potts, et al. 1996).

B. MECHANISM OF ACTION

Teriparatide is a recombinant formulation of endogenous parathyroid hormone (PTH). The pharmacologic activity of teriparatide, which is similar to the physiologic activity of PTH, includes stimulating osteoblast function, increasing gastrointestinal calcium absorption, and increasing renal tubular reabsorption of calcium. Treatment with teriparatide results in increased bone mineral density, bone mass, and strength. (Potts, et al. 1996).

C. PHARMACODYNAMICS/KINETICS: TERIPARATIDE

Distribution: ~0.12 L/kg.

Metabolism: Hepatic (nonspecific proteolysis).

Bioavailability: 95%.

Half-life elimination: I.V.: 5 minutes; SubQ: ~1 hour.

Time to peak, serum: ~30 minutes.

D. Dosing and dosage forms

Osteoporosis: SubQ: 20 mcg once daily; Note: Initial administration should occur under circumstances in which the patient may sit or lie down, in the event of orthostasis.

Dosage Forms: Injection, solution (Reeve.2002).

E. Monitoring Parameters

Serum calcium, serum phosphorus, uric acid; blood pressure; bone mineral density. (Potts, et al.1996).

F. Therapeutic uses in non endocrine patients

1. Treating bone marrow depletion in cancer patients caused by chemotherapeutic drugs and ionizing radiation

Since then, it has been shown that the hematopoietic stemcell niche consists of PTH receptor-bearing, osteoblastic trabecular bone-lining cells that maintain the stem cells proliferatively quiescent ‘stemness’ by various gene up-regulating and down-regulating signals caused by the tight adhesion of the HSCs to the osteoblastic niche-lining cells (Suzuki, et al.2005).

Stimulating the osteoblastic lining cells with recombinant human PTH-(1-34) causes acyclic AMP-mediated enlargement of the HSC pool and promotes bone marrow transplant engraftment and growth and the survival of lethally irradiated mice. It is for safely promoting the engraftment of peripherally harvested HSCs in cancer patients whose bone marrows have been ‘emptied’ by chemotherapeutic drugs or ionizing radiation (Whitfield.2005).

2. Therapy in Osteoporosis

PTH 1-34 (teriparatide, Forteo) and PTH 1-84 (PreOs) belong to a new class of anti-osteoporosis drugs, the so-called "anabolic" agents. These drugs, in
contrast to antiresorptive agents, stimulate bone formation, activate bone remodeling and are administered subcutaneously as daily injections. Other agents in this class include growth hormone (GH), IGF-I and PTH-related peptide (PTHrp). PTH 1-34, teriparatide, at a dose of 20 mcg/day is available in the United States and Europe for the treatment of severe osteoporosis in both men and women (Rosen, 2003).

Markers of bone turnover indicate that bone resorption in patients on PTH begins at about six months and peaks after 12 months of treatment. It is thought that increased bone formation in the first three months precedes bone resorption and places the remodeling unit in a positive balance. But, long-term PTH treatment leads to a re-equilibration of the bone remodeling unit, such that resorption catches up to formation, resulting in coupling of the remodeling sequence, and a subsequent plateau in the acquisition of new bone (Dobnig, et al., 2005).

PTH enhances bone turnover by initiating greater bone formation. Most of the gains in BMD occur in the first few months, although antifracture efficacy is evident only after six months or more of treatment. Patients on bisphosphonates will often have incremental improvement in BMD even after 10 years of treatment, while it appears that the BMD changes with PTH begin to level off after 18 months (McClung, et al., 2005).

Patients treated with PTH have increased bone formation rates on cancellous, endocortical, and periosteal surfaces compared with untreated patients. Enhanced mineralization and greater numbers of both osteoblasts and osteoclasts have also been demonstrated (Lindsay, et al., 2007).

The effects of PTH are dose-dependent, such that higher daily doses result in greater increases in formation, and subsequently higher BMD with treatment. During the first month of treatment, formation occurs distinct from remodeling.
sites and hence there is little osteoclast activation. Later, remodeling is stimulated, resulting in increased bone formation and resorption (Dobnig, et al. 2005).

PTH increases spine and hip BMD in a dose-dependent manner. But, relative percent change in BMD per individual may vary considerably for the following reasons:

• There is significant heterogeneity in skeletal responsiveness for a given subject treated with PTH.

• Skeletal sites differ in their response to PTH due to inherent remodeling activity.

• The type and biologic activity of PTH in clinical trials differ; some trials used teriparatide (PTH 1-34), others used a commercial preparation of PTH 1-84, still others made their own preparation of PTH (Bauer, et al. 2006).

In addition to improvements in BMD, PTH reduces fracture risk. PTH treatment for at least 18 months markedly reduces the risk of spine fractures in postmenopausal women with osteoporosis. The risk reduction becomes apparent after eight months of treatment, and the effect is not dose dependent nor does it depend upon the type of PTH. Greenspan, et al. 2007).

COMBINATION THERAPY

PTH PLUS BISPHOSPHONATES: Because PTH stimulates bone formation and bisphosphonates reduce bone resorption, it has been hypothesized that combining the two therapies would increase bone density more than either therapy alone. But no additional benefit for spine or hip BMD compared with PTH alone (Finkelstein, et al. 2006).
PTH AFTER BISPHOSPHONATES: PTH is a treatment option in patients who cannot tolerate or who fail bisphosphonate therapy. PTH (teriparatide) increases BMD in women previously treated with bisphosphonates, although the improvement may be less than in women not previously exposed to bisphosphonates (Obermayer-Pietsch et al. 2008).

PTH PLUS SERMS: Prior or concurrent treatment with raloxifene does not appear to compromise the effect of teriparatide on BMD and markers of bone turnover as alendronate. These results suggest that treatment with raloxifene (prior to or concurrent with teriparatide) does not suppress BMD response as much as alendronate. In patients who are taking raloxifene but require additional therapy, it is unclear whether teriparatide should be added to or replace raloxifene. Combination therapy with raloxifene and teriparatide was not recommended. However, in patients not adequately treated with raloxifene, there is no need to delay teriparatide therapy once raloxifene is discontinued (Cosman et al. 2005).

PTH PLUS HORMONE THERAPY: Combined estrogen plus PTH therapy appears to be more effective than hormone therapy alone. Patients receiving combination therapy had a greater increase in spine and hip BMD than those receiving hormone therapy alone. A slightly larger study reported similar increases in spine BMD with the same dose of PTH combined with hormone therapy (Cosman et al. 2005).

ANTiresorptive Therapy: Treatment with an antiresorptive agent after PTH preserves the gains in BMD achieved with PTH. Women randomized to receive alendronate following PTH discontinuation had a further increase in areal BMD of nearly 6 percent, coupled with a 6 percent increase during the first year. Treatment with alendronate during that year following PTH 1-84, preserved the increase of 30 percent in trabecular BMD gained in the first year.
by PTH 1-84 alone. After PTH treatment is discontinued, an antiresorptive, preferably a bisphosphonate, should be used to preserve or increase gains in BMD acquired with PTH alone. Raloxifene is an alternative for women who are unable to tolerate oral or intravenous bisphosphonates. A persistent reduction in fracture risk with the use of antiresorptive therapy after PTH is discontinued has not yet been firmly established (Finkelstein, et al. 2006).

RETREATMENT WITH PTH: PTH results in significant increases in bone mineral density and a reduction in fracture risk. However, due to the potential risk of carcinogenicity, teriparatide treatment should be limited to a maximum of two years. Nevertheless, there is interest in studying the efficacy of retreatment with teriparatide, after a drug-free interval, to determine if the initial response can be replicated. Thus, retreatment with teriparatide does appear to increase spine BMD, but the increase is less than that of initial treatment (Obermayer-Pietsch, et al. 2008).

ALTERNATIVES TO DAILY ADMINISTRATION: PTH treatment requires daily injection and is expensive. In one analysis, daily PTH therapy, when compared to alendronate, was less cost-effective as a first-line drug for severe osteoporosis in women. Hence alternative approaches have been considered (Liu, et al. 2006).

Intermittent PTH: One randomized trial reported that intermittent administration of teriparatide for 15 months, ie, once daily for three months, followed by three months off and then a return to three months daily, in postmenopausal women treated with long-term alendronate, was as effective for increasing BMD as daily teriparatide and alendronate (Cosman, et al. 2005).

PTH once weekly: Another randomized trial showed that once weekly teriparatide administered to postmenopausal women with fractures, at doses of
60 mcg/dose/week, was as good as daily teriparatide with respect to changes in spine BMD (Black, et al. 2008).

**Glucocorticoid-induced osteoporosis (GIO):**

Parathyroid hormone (PTH) stimulates bone formation as well as resorption, and intermittent administration stimulates formation more than resorption. Initial studies show that it is beneficial in patients with osteoporosis. The bisphosphonates are considered standard therapy to prevent or treat GIO. However, PTH is also effective, and teriparatide has been approved for the treatment of GIO. The role of PTH in the treatment of GIO is reviewed in detail separately (Saag, et al. 2009).

**Male osteoporosis:**

There are three trials using PTH in men with osteoporosis. All show that teriparatide can increase spine and hip BMD in doses of 20 to 40 ug/day. There are no trials for fracture outcome in men, but teriparatide is approved for the treatment of this condition in men (Finkelstein, et al. 2003).

**Combination therapy:**

1- Bisphosphonates with teriparatide (Kurland, et al. 2004).

2- Raloxifene: Raloxifene, a selective estrogen receptor modulator that improves bone mineral density in women, may also be effective in men (Smith, et al. 2004).

3- Other anabolic agents, including growth hormone and insulin-like growth factor-1, are in evaluation for the treatment of men with osteoporosis. Growth hormone is effective in men with growth hormone deficiency who have osteoporosis (Boonen, et al. 2009).
G. Adverse Reactions:

- **>10%:**

  **ENDOCRINE & METABOLIC:** Hypercalcemia [women 11%; men 6%].

- **1% to 10%:**

  **CARDIOVASCULAR:** Orthostatic hypotension (5%; transient), chest pain (3%), syncope (3%).

  **CENTRAL NERVOUS SYSTEM:** Dizziness (8%), insomnia (4% to 5%), anxiety (≤4%), depression (4%), vertigo (4%).

  **DERMATOLOGIC:** Rash (5%).

  **ENDOCRINE & METABOLIC:** Hyperuricemia (3%).

  **GASTROINTESTINAL:** Nausea (9% to 14%), gastritis (≤7%), dyspepsia (5%), vomiting (3%), tooth disorder (2%).

  **NEUROMUSCULAR & SKELETAL:** Arthralgia (10%), weakness (9%), leg cramps (3%).

  **RESPIRATORY:** Rhinitis (10%), pharyngitis (6%), dyspnea (4% to 6%), pneumonia (4% to 6%).

  **MISCELLANEOUS:** Antibodies to teriparatide (3% of women in long-term treatment; hypersensitivity reactions or decreased efficacy were not associated in preclinical trials), herpes zoster (≤3%). *(Harper, et al. 2007)*.

**Precautions:**

- Orthostatic hypotension: use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular...
disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Osteosarcoma: In animal studies, teriparatide has been associated with an increase in osteosarcoma; risk was dependent on both dose and duration.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

- Urolithiasis: Use with caution in patients with active or recent urolithiasis.

- Appropriate use: Use of teriparatide for longer than 2 years is not recommended. (Reeve, et al., 2002).

**H. Contraindications**

Hypersensitivity to teriparatide or any component of the formulation. (Reeve, et al., 2002).

**I. Drug Interactions**

There are no known significant interactions.

CALCITONIN

A. PHYSIOLOGY

Calcitonin inhibits osteoclasts and therefore bone resorption in pharmacologic doses. However, its physiologic role is minimal in the adult skeleton. Its effects are transient, probably because of receptor downregulation. As a result, it is only transiently effective in treating hypercalcemia due to excessive bone resorption (Austin, et al. 1981).

B. MECHANISM OF ACTION

Peptide sequence similar to human calcitonin; functionally antagonizes the effects of parathyroid hormone. Directly inhibits osteoclastic bone resorption; promotes the renal excretion of calcium, phosphate, sodium, magnesium, and potassium by decreasing tubular reabsorption; increases the jejunal secretion of water, sodium, potassium, and chloride. (Fatemi, et al. 1992).

C. PHARMACODYNAMICS/KINETICS:

ONSET of action:

Hypercalcemia: I.M., SubQ: ~2 hours.

Paget’s disease: Within a few months; may take up to 1 year for neurologic symptom improvement.

DURATION: Hypercalcemia: I.M., SubQ: 6-8 hours.

DISTRIBUTION: 0.15-0.3 L/kg.

METABOLISM: Metabolized in kidneys, blood and peripheral tissue.

BIOAVAILABILITY: I.M. 66%; SubQ: 71%; Nasal ~3-5% (relative to I.M.).
Half-life elimination (terminal): I.M. 58 minutes; SubQ 59-64 minutes; Nasal: ~18 minutes.

Time to peak, plasma: SubQ ~23 minutes; Nasal: ~13 minutes.

**EXCRETION:** Urine (as inactive metabolites) *(Pontiroli, et al. 1994).*

**D. Dosage Forms and Administration**

Injection solution: May be administered I.M. or SubQ. I.M route is preferred if the injection volume is >2 mL. SubQ route is preferred for outpatient self-administration unless the injection volume is >2 mL *(Reginster, et al. 1998).*

Nasal spray *(Reginster, et al. 1998).*

**E. Monitoring Parameters**

Serum electrolytes and calcium; alkaline phosphatase and 24-hour urine collection for hydroxyproline excretion (Paget's disease), urinalysis (urine sediment); bone mineral density. Nasal formulation: Visualization of nasal mucosa, turbinate, septum, and mucosal blood vessels *(Austin, et al. 1981).*

**F. Therapeutic uses in non endocrine patients**

1. **Calcitonin In Paget disease therapy**

Salmon calcitonin, given subcutaneously, is the only preparation approved in the United States for the treatment of patients with Paget disease who cannot tolerate bisphosphonates. The usual initial dose is 50 to 100 units daily, as tolerated; the usual maintenance regimen is 50 units daily or 50 to 100 units every one to three days. Therapy is often continued indefinitely, since cessation typically results in recurrent disease activity. Parenteral salmon calcitonin was evaluated and markers of bone turnover, such as serum alkaline phosphatase or urine hydroxyproline excretions, were initially reduced by about 50
percent. Almost all of these patients developed high titer anti-calcitonin antibodies. In addition to the reduction in markers of bone turnover, other clinical benefits that have been described with parenteral calcitonin therapy include relief of bone pain, improvement or stabilization of hearing loss and other neurologic deficits, and decreased bone vascularity (De Lange, et al. 2006).

2. Calcitonin in the treatment of pain

It has analgesic properties, primarily through receptor mediated modulation of serotonergic pain pathways in the central nervous system. Salmon calcitonin has greater physiological and analgesic potency than mammalian forms of the hormone and is therefore reproduced as a synthetic drug for clinical use. Calcitonin was effective in the treatment of complex regional pain syndrome and systematic reviews reported benefit in the treatment of acute vertebral fracture pain and metastatic bone pain (Martinez, et al. 2004).

3. Expression and function of the calcitonin receptor by myeloma cells in their osteoclast-like activity

Previous clinical observations demonstrated relative inefficacy of the hormone to arrest the progression of osteolytic lesions in patients undergoing long-term treatment. This discrepancy between the in vitro suppression of the OC-like activity of malignant plasma cells and the minor efficacy of CT therapy in myeloma may be explained by the down-regulating effect of CT on the CTR expression. It has been reported that OCs repeatedly treated in vitro with CT undergo a gradual inhibition of the CTR expression as an effect of parallel activation of inhibitory kinases by the receptor. Therefore, it is conceivable that a similar inhibition of the CTR expression by these kinases could have occurred in vivo in patients unsuccessfully treated with the hormone (Zhang, et al. 2002).
4. Central calcitonin and its anorectic effects

CT-induced satiety is not mediated via the HPA axis. The findings suggest that CT is a potent regulator of the chick's appetite, with some similarities and differences between mammalian systems (Paxinos et al. 2004).

5. Therapy in osteoporosis

Bone mineral density in the calcitonin group increased by 2.7 percent in the first year, while in the group receiving calcium alone it decreased by 2.8 percent. Calcitonin prevented more bone loss during the second year, while the calcium group continued to lose bone (Cranney et al. 2000).

Calcitonin has not been found to reduce the risk of fractures in glucocorticoid-treated patients. Calcitonin is not considered first line therapy for the treatment or prevention of GIO. Calcitonin could be considered in patients who cannot tolerate oral or intravenous bisphosphonates (Cranney et al. 2000).

6. Therapy in medullary thyroid cancer

Serum calcitonin and CEA should be measured six months after surgery to detect the presence of residual disease. Patients who have normal serum CEA and serum calcitonin values are considered biochemically cured and have the best prognosis. Among those in one large series who were biochemically cured, the five-year recurrence rate was only 5 percent (Modigliani et al. 1998).

7. Therapy in hypercalcemia

Pharmacologic doses of calcitonin reduce the serum calcium concentration by increasing renal calcium excretion and, more importantly, by decreasing bone reabsorption via interference with osteoclast maturation. Salmon calcitonin (4 international units/kg) is usually administered intramuscularly or subcutaneously every 12 hours; doses can be increased up to 6 to 8 international
units/kg every 6 hours. Nasal application of calcitonin is not efficacious for
treatment of hypercalcemia. It works rapidly, lowering the serum calcium
concentration by a maximum of 1 to 2 mg/dL (0.3 to 0.5 mmol/L) beginning
within four to six hours (Fatemi, et al. 1992).

G. Adverse Reactions

Unless otherwise noted, frequencies reported are with nasal spray.

- **>10%**:

  Respiratory: Rhinitis (≤12%, including ulcerative) 1% to 10%.

  Cardiovascular: Flushing (nasal spray: <1%; injection: 2% to 5%), angina (1%
to 3%), hypertension (1% to 3%).

  Central nervous system: Depression (1% to 3%), dizziness (1% to 3%), fatigue
(1% to 3%).

  Dermatologic: Erythematous rash (1% to 3%).

  Gastrointestinal: Nausea (injection: 10%; nasal spray: 2%), abdominal pain (1%
to 3%), constipation (1% to 3%), diarrhea (1% to 3%), dyspepsia (1% to 3%).

  Genitourinary: Cystitis (1% to 3%).

  Local: Injection site reactions (injection: 10%).

  Neuromuscular & skeletal: Back pain (5%), arthrosis (1% to 3%), myalgia (1%
to 3%), paresthesia (1% to 3%).

  Ocular: Conjunctivitis (1% to 3%), lacrimation abnormality (1% to 3%).

  Respiratory: Nasal ulcerations (3%), bronchospasm (1% to 3%), sinusitis (1% to
3%), upper respiratory tract infection (1% to 3%).
Miscellaneous: Flu-like syndrome (1% to 3%), infection (1% to 3%), lymphadenopathy (1% to 3%).

- **<1%** (Limited to important or life-threatening):

Agitation, allergic rhinitis, alopecia, anaphylactoid reaction, anaphylaxis/anaphylactic shock, anemia, anorexia, anxiety, arthralgia, arthritis, blurred vision, bronchitis, bundle branch block, cerebrovascular accident, cholelithiasis, cough, diaphoresis, dyspnea, earache, eczema, edema, eye pain, fever, flatulence, gastritis, goiter, hearing loss, hematuria, hepatitis, hypersensitivity, hyperthyroidism, insomnia, migraine, mucosal excoriation, myocardial infarction, nasal congestion, neuralgia, nocturia, palpitation, parosmia, periorbital edema, pharyngitis, pneumonia, polymyalgia rheumatica, polyuria, pruritus, pyelonephritis, rash, renal calculus, skin ulceration, sneezing, stiffness, tachycardia, taste perversion, thirst, thrombophlebitis, tinnitus, urine sediment abnormality, vertigo, visual disturbances, vitreous floater, vomiting, weight gain, xerostomia. *(Austin, et al. 1981).*

**Precautions**

Hypersensitivity reactions: Salmon-derived products: A skin test should be performed prior to initiating therapy of calcitonin salmon in patients with suspected sensitivity. *(Stevenson, et al. 1988).*

**H.Contraindications**

Hypersensitivity to calcitonin salmon or any component of the formulation. *(Austin, et al. 1981).*

**I.Drug Interactions**

Lithium: Calcitonin may decrease the serum concentration of Lithium. Risk C.

**J. Dietary Considerations**

Recommended amounts of vitamin D and calcium intake is essential for preventing/treating osteoporosis. Patients with Paget's disease and hypercalcemia should follow a low calcium diet as prescribed. (Austin, et al. 1981).
INSULIN

A. PHYSIOLOGY

Insulin is a 51-amino acid peptide hormone that is synthesized and secreted by pancreatic beta cells. (Stumvoll, et al. 1997).

B. MECHANISM OF ACTION

Insulin action begins with the binding of insulin to a heterotrimeric receptor on the cell membrane of the target cells. Insulin directly or indirectly affects the function of virtually every tissue in the body. However, in this brief overview we will focus on insulin's metabolic effects on the three tissues most responsible for energy storage: liver, muscle, and adipose tissue (Stumvoll, et al. 1997).

C. PHARMACODYNAMICS/kinetics

Rate of absorption, onset, and duration of activity affected by type, site of injection, exercise, presence of lipodystrophy, local blood supply, and/or temperature, also according type of insulin. (Edgerton, et al. 2006).

D. DOSAGE FORMS AND ADMINISTRATION:

Forms:

Rapid acting.

Short acting.

Intermediate acting.

Long acting.

Mixed.
Administration:

SubQ and I.V administration. (Edgerton, et al., 2006).

E. Monitoring Parameters

Plasma glucose, electrolytes, Hb A1c. (Edgerton, et al., 2006).

F. Therapeutic uses in non endocrine patients

1. Intensive insulin therapy during critical illness

Hyperglycemia associated with critical illness (also called stress hyperglycemia or stress diabetes) is a consequence of many factors, including increased cortisol, catecholamines, glucagon, growth hormone, gluconeogenesis, and glycogenolysis. Recent evidence indicating that uncontrolled hyperglycemia is associated with poor outcomes has prompted efforts to routinely correct and prevent hyperglycemia in critically ill patients (Saberi, et al., 2008).

Hyperglycemia is also associated with worse neurologic outcomes and increased intracranial pressure in patients with traumatic brain injury. Critically ill medical and surgical patients who are hyperglycemic have a higher mortality rate than patients who are normoglycemic (Falciglia, et al., 2009).

GLYCEMIC CONTROL: IIT was defined as a target blood glucose level ≤150 mg/dL. Patients who received IIT had significantly lower mortality than those who received less stringent glycemic control (Finfer, et al., 2009).

Hypoglycemia is the most common adverse effect of IIT. It occurs in up to 19 percent of patients when defined as a blood glucose <40 mg/dL, or up to 32 percent of patients when defined as a blood glucose <60 mg/dL. Its frequent occurrence is problematic because hypoglycemia can lead to seizures, brain
damage, depression, and cardiac arrhythmias. Hypoglycemia is also a risk factor for death (Hermanides, et al. 2010).

Recommend a blood glucose target is of 140 to 180 mg/dL in most critically ill patients. This range avoids marked hyperglycemia, while minimizing the risk of both iatrogenic hypoglycemia and other harms associated with a lower blood glucose target (Marik, et al. 2010).

2. Effects of High-Dose Insulin Treatment in Aortic Valve and Coronary Surgery

The high-dose glucose-insulin treatment led to faster normalization of lactate levels and to lower serum free fatty acid levels after combined aortic valve and coronary artery bypass surgery. Besides, there was lesser need for inotropic medication and temporary pacing and a trend towards higher cardiac indices. The glucose-insulin treatment led to higher respiratory quotient, slightly elevated CO2 production and to a higher core temperature after the surgery, but it did not have a remarkable effect on systemic O2 consumption and the energy expenditure (Bothe, et al. 2004).

3. Alzheimer disease

An area of active research is investigating a possible relationship between insulin and beta amyloid metabolism. One study has shown that increased peripheral insulin levels are associated with reduced brain atrophy and cognitive impairment in patients with early AD, suggesting a role for insulin signaling in the pathophysiology of AD (Burns, et al. 2007).

4. As enhancing drug by athletes

Athletes have also begun to use insulin because of its anabolic effects on muscle. In one survey of 20 men who were recruited from gyms and admitted to using androgens, 5 reported that they also used insulin. They reported ingesting
large amounts of sugar after insulin injection, but there have been reports of hypoglycemia in athletes who have taken insulin (Rich, et al. 1998).

5. Treatment and prevention of hyperkalemia

Insulin with glucose: Insulin administration lowers the serum potassium concentration by driving potassium into the cells, primarily by enhancing the activity of the Na-K-ATPase pump in skeletal muscle. Glucose is usually given with insulin to prevent the development of hypoglycemia. However, insulin should be given alone if the serum glucose is ≥250 mg/dL. The serum glucose should be measured one hour after the administration of insulin (Mount, et al. 2008).

One commonly used regimen for administering insulin and glucose is 10 units of regular insulin in 500 mL of 10 percent dextrose, given over 60 minutes. Another regimen consists of a bolus injection of 10 units of regular insulin, followed immediately by 50 mL of 50 percent dextrose (25 g of glucose). However, hypoglycemia occurs in up to 75 percent of patients treated with the bolus regimen, typically about one hour after the infusion. The effect of insulin begins in 10 to 20 minutes, peaks at 30 to 60 minutes, and lasts for four to six hours. In almost all patients, the serum potassium concentration drops by 0.5 to 1.2 meq/L (Allon, et al. 1990).

Precautions

• Hypoglycemia: The most common adverse effect of insulin is hypoglycemia.

• Hypokalemia: Insulin (especially I.V. insulin) causes a shift of potassium from the extracellular space to the intracellular space, possibly producing hypokalemia.

• Hepatic impairment: Use with caution in patients with hepatic impairment.
• Renal impairment: Use with caution in patients with renal impairment. Dosage requirements may be reduced.

• Administration: Insulin NPH and insulin regular combination products are NOT intended for I.V. or I.M. administration.

• Patient education: Diabetes self-management education is essential to maximize the effectiveness of therapy. (Morley and Perry, 1991).

G. Drug Interactions

Antidiabetic Agents (Thiazolidinedione): Insulin may enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). Risk C.

Beta-Blockers: May enhance the hypoglycemic effect of Insulin. Exceptions: Levobunolol; Metipranolol. Risk C.

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. Risk C.

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. Risk C.

Edetate CALCIUM Disodium: May enhance the hypoglycemic effect of Insulin. Risk C.

Edetate Disodium: May enhance the hypoglycemic effect of Insulin. Risk C.

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. Risk C.

Hypoglycemic Agents: May enhance the adverse/toxic effect of other Hypoglycemic Agents. Risk C.
Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. Risk C.

Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. Risk C.

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. Risk D.

ERYTHROPOITIN

A. PHYSIOLOGY

Erythropoietin (EPO) is the primary stimulus to erythropoiesis, promoting the terminal differentiation of CFU-E into normoblasts and then erythrocytes. Erythropoietin is produced by the kidney and to a much lesser degree (<10 percent) by the liver (Porter, et al. 1993).

B. MECHANISM OF ACTION

Induces erythropoiesis by stimulating the division and differentiation of committed erythroid progenitor cells; induces the release of reticulocytes from the bone marrow into the bloodstream, where they mature to erythrocytes. There is a dose response relationship with this effect. This results in an increase in reticulocyte counts followed by a rise in hematocrit and hemoglobin levels. (Porter, et al. 1993).

C. PHARMACODYNAMICS/KINETICS

Onset of action: Several days.

Peak effect: Hemoglobin level: 2-6 weeks.

Distribution: 9 L; rapid in the plasma compartment; concentrated in liver, kidneys, and bone marrow.

Metabolism: Some degradation does occur.

Bioavailability: SubQ: ~21% to 31%; intraperitoneal epoetin: 3%.

Half-life elimination: Cancer: SubQ: 16-67 hours; Chronic renal failure: I.V.: 4-13 hours.
Time to peak, serum: Chronic renal failure: SubQ: 5-24 hours.

Excretion: Feces (majority); urine (small amounts, 10% unchanged in normal volunteers) (Rizzo, et al. 2008).

D. Dosing and dosage forms:

1. CHRONIC RENAL FAILURE PATIENTS: I.V. (preferred for hemodialysis patients), SubQ: Initial dose: 50-100 units/kg 3 times/week.

Dialysis patients: Median dose: 75 units/kg 3 times/week.

Nondialysis patients: Dosing range: 75-150 units/kg/week.

2. CANCER PATIENT ON CHEMOTHERAPY:

SubQ: Initial dose: 150 units/kg 3 times/week or 40,000 units once weekly; commonly used doses range from 10,000 units 3 times/week to 40,000-60,000 units once weekly.

3. SURGERY PATIENTS: Prior to initiating treatment, measure hemoglobin to establish that it is >10 g/dL and ≤13 g/dL: SubQ: Initial dose: 300 units/kg/day for 10 days before surgery, on the day of surgery, and for 4 days after surgery.

Alternative dose: 600 units/kg in once weekly doses plus a fourth dose on the day of surgery.


E. Monitoring Parameters

F. Therapeutic uses in non endocrine patients

1. Erythropoietin for the anemia of chronic kidney disease

Subcutaneous EPO is highly effective in raising hemoglobin levels in dialysis patients with anemia due to CKD. Compared with the intravenous route, which is often used for reasons of convenience in hemodialysis patients, subcutaneous administration of EPO is preferred for convenience for the treatment of anemia in patients undergoing maintenance peritoneal dialysis (Pergola, et al. 2010).

Other forms:

EPO mimetics

Continuous Erythropoiesis Receptor Activator (Macdougall, et al. 2008).

2. As erythropoiesis-stimulating agents in the treatment of anemia in patients with cancer

ESAs were effective in raising HGB levels and decreasing transfusion requirements in a substantial number of patients with cancer-related and chemotherapy-induced anemia. Use of these agents has become controversial because of data linking ESA use to an excess of thromboembolic events, inferior survival, and worse cancer outcomes, particularly when used in patients whose anemia is unrelated to chemotherapy and in those receiving myelosuppressive chemotherapy with the intent of cure. While there is general agreement that ESAs are not indicated in anemic cancer patients who are not receiving chemotherapy, whether ESAs should be avoided in patients who are receiving myelosuppressive chemotherapy with the intent of cure remains controversial (Glaspy, et al. 2010).
Therapy be discontinued once the hemoglobin is ≥10 g/dL. ESAs be withheld if hemoglobin exceeds a level needed to avoid transfusion but do not specify a specific hemoglobin value (Ludwig, et al. 2009).

3. As hematopoietic growth factors

Erythropoietin (EPO) is essential for the terminal maturation of erythroid cells. Recombinant preparations are as effective as the natural hormone. EPO and its receptor may also contribute to wound healing responses, angiogenesis, and the response to brain and heart injury (Merchionne, et al. 2009).

INDICATIONS:
- Transient bone marrow failure following chemotherapy.
- Bone marrow transplantation.
- Myelodysplastic syndrome.
- Chronic bone marrow failure and aplastic anemia.
- Human immunodeficiency virus infection.
- Inherited bone marrow failure syndromes.
- Chronic anemias (eg, renal failure, prematurity, anemia of chronic disease, anemia associated with HIV infection).
- Stem cell and progenitor cell mobilization (in vitro and ex vivo).
- Gene transfer (Smith, et al. 2006).

G. Adverse Reactions

- >10%:
  Cardiovascular: Hypertension (5% to 24%), thrombotic/vascular events (23%), edema (6% to 17%), deep vein thrombosis (≤11%).

  Central nervous system: Fever (29% to 51%), dizziness (5% to 21%), insomnia (13% to 21%), headache (10% to 19%).
Dermatologic: Pruritus (14% to 22%), skin pain (4% to 18%), rash (≤16%).

Gastrointestinal: Nausea (11% to 58%), constipation (42% to 53%), vomiting (8% to 29%), diarrhea (6% to 21%), dyspepsia (7% to 11%).

Genitourinary: Urinary tract infection (3% to 12%).

Local: Injection site reaction (<10% to 29%).

Neuromuscular & skeletal: Arthralgia (≤11%), paresthesia (≤11%).

Respiratory: Cough (≤18%), congestion (≤15%), dyspnea (13% to 14%), upper respiratory infection (≤11%).

- **1% to 10%:**
  
  Central nervous system: Seizure (1% to 3%).

  Local: Clotted vascular access (7%).

  - **<1% (Limited to important or life-threatening):**

    Allergic reaction, anemia associated with neutralizing antibodies (severe; with or without other cytopenias), CVA, flu-like syndrome, hyperkalemia, hypersensitivity reactions, hypertensive encephalopathy, microvascular thrombosis, MI, myalgia, neutralizing antibodies, pulmonary embolism, pure red cell aplasia (PRCA), renal vein thrombosis, retinal artery thrombosis, stroke, tachycardia, temporal vein thrombosis, thrombophlebitis, thrombosis, TIA, urticaria (Henry and Thatcher.1996).

**Precautions:**

- Cardiovascular events/mortality/thromboembolic events/stroke: Erythropoiesis-stimulating agents (ESAs) increased the risk of serious cardiovascular events, thromboembolic events, stroke, and mortality in clinical studies; a rapid rise in hemoglobin (>1 g/dL over 2 weeks) or maintaining
higher hemoglobin levels may contribute to these risks. Patients treated with epoetin may require increased heparinization during dialysis to prevent clotting of the artificial kidney.

- Pure red cell aplasia (PRCA): Cases of severe anemia and PRCA have been reported, predominantly in patients with CRF receiving SubQ epoetin (the I.V. route is preferred for hemodialysis patients); cases have also been reported in patients with hepatitis C who were receiving ESAs, interferon, and ribavirin. Patients with a sudden loss of response (with severe anemia and a low reticulocyte count) should be evaluated for PRCA with associated neutralizing antibodies to erythropoietin; discontinue treatment in patients with PRCA secondary to neutralizing antibodies to erythropoietin. Antibodies may cross-react; do not switch to another ESA in patients who develop antibody-mediated anemia.

- Cancer patients: A shortened overall survival and/or increased risk of tumor progression or recurrence has been reported in studies with breast, cervical, head and neck, lymphoid, and nonsmall cell lung cancer patients. It is of note that in these studies, patients received ESAs to a target hemoglobin of ≥12 g/dL; although risk has not been excluded when dosed to achieve a target hemoglobin of <12 g/dL.

- Chronic renal failure patients: An increased risk of death, serious cardiovascular events, and stroke was reported in patients administered ESAs to target hemoglobin levels ≥13 g/dL; dosing should be individualized to achieve and maintain hemoglobin levels within 10-12 g/dL range. Hemoglobin rising >1 g/dL in a 2-week period may contribute to the risk.

- Hematologic diseases: Safety and efficacy in patients with underlying hematologic diseases have not been established, including hypercoagulation disorders and sickle cell disease.
• Perisurgery patients: Epoetin alfa increased the rate of DVT in patients not receiving anticoagulant prophylaxis; consider DVT prophylaxis in surgery patients.

• Porphyria: Use caution with porphyria, exacerbation of porphyria has been reported in patients with chronic renal failure.

• Seizures: Seizures have been reported in clinical trials for chronic renal failure; use with caution in patients with a history of seizures.

• Severe anemia or acute blood loss: Due to the delayed onset of erythropoiesis, epoetin is not recommended for acute correction of severe anemia or as a substitute for emergency transfusion.

• Factors impairing erythropoiesis: Prior to treatment, correct or exclude deficiencies of iron, vitamin B12, and/or folate, as well as other factors which may impair erythropoiesis.

• Iron supplementation: Prior to and periodically during therapy, iron stores must be evaluated. Supplemental iron is recommended if serum ferritin <100 mcg/L or serum transferrin saturation <20%. (Hershman, et al. 2009).

H. Contraindications

Hypersensitivity to albumin (human) or mammalian cell-derived products; uncontrolled hypertension. (Corbo, et al. 1992).
GLUCOCORTICOIDS

A. PHYSIOLOGY

Pharmacologic doses of glucocorticoids are used to treat patients with inflammatory, allergic, immunological disorders. A number of factors that influence both the therapeutic and adverse effects of glucocorticoids (Pensabeni-Jasper, et al. 1996).

STRUCTURES OF COMMON SYNTHETIC: The introduction of a double bond between the 1 and 2 positions of hydrocortisone (cortisol) yields prednisolone (delta-1-hydrocortisone), which has about four times more glucocorticoid activity than cortisol (Pensabeni-Jasper, et al. 1996).

B. MECHANISM OF ACTION

Decreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability; suppresses the immune system by reducing activity and volume of the lymphatic system (Frey and Frey, 1990).

C. PHARMACOKINETICS: Most of the cortisol in serum is bound to proteins, primarily corticosteroid-binding globulin (CBG) and albumin. In addition, much of the biologically available cortisol may be bound to erythrocytes. Because they have little or no affinity for CBG, synthetic steroids other than prednisolone circulate either bind weakly to albumin (two-thirds) or as free steroid (one-third) (Yokoyama, et al. 1992).

Plasma disappearance half-life: The half-lives of synthetic glucocorticoids are generally longer than that of cortisol, which is about 80 min at concentrations within the binding capacity of CBG. The half-lives of the synthetic steroids range from about one hour for prednisolone to over four hours.
for dexamethasone, with considerable interindividual variation, clearance in older adults may be slower than in younger adults (Ng, et al. 1998).

**Activation and Inactivation in Target Cells:** The 11-beta-hydroxysteroid dehydrogenase type 1 isoenzyme, which converts inactive cortisone to cortisol, is expressed in many glucocorticoid target tissues. The type 2 isoenzyme, which converts cortisol to cortisone, is found mainly in mineralocorticoid target tissues (kidney, colon, salivary glands) and in the placenta, in which it protects the cell from glucocorticoid action via the corticosteroid type 1 (mineralocorticoid) receptor. Glucocorticoids that are fluorinated at the 6-alpha or 9-alpha position (dexamethasone, fludrocortisone, betamethasone) or methylated at the 6-alpha position (methylprednisolone), or methyloxazoline at position 16,17 (deflazacort), are protected from oxidation inactivation by the type 2 isoenzyme. Prednisone is more effectively oxidized by 11 beta-hydroxysteroid dehydrogenase type 2 than is cortisol, which may explain why prednisone has less salt-retaining activity than cortisol (Pensabeni-Jasper, et al. 1996).

**Metabolism:** Exogenous glucocorticoids are subject to the same reduction, oxidation, hydroxylation, and conjugation reactions as endogenous steroids. Like cortisone, which must be converted to cortisol by hepatic 11ß-hydroxysteroid dehydrogenase, prednisone must be converted to prednisolone to exert any glucocorticoid action (Pensabeni-Jasper, et al. 1996).

**Assays of Biologic Activity:** Classic bioassays test the ability of the glucocorticoid to lower the circulating eosinophil count in humans, and to stimulate hepatic glycogen deposition and inhibit inflammation after subcutaneous oil injection in rats. The last two assays presumably measure directly the "glucocorticoid" and "antiinflammatory" potency of the test compound, respectively (Kuperman, et al. 2001).
D. Criteria for initiating therapy

Medical emergencies: High doses of glucocorticoids can be administered for a few days with little risk.

Chronic therapy: In less urgent circumstances, more careful consideration must be given to the evidence for glucocorticoid efficacy. (Pensabeni-Jasper, et al. 1996).

E. Route of administration and doses: Dosage and route of administration depend on the disorder being treated:

Parenteral therapy.

Oral administration.

Nonsystemic administration: Intraarticular injection for joint inflammation, inhalation therapy for asthma, and topical application for inflammatory skin disorders are examples. (Christy, et al. 1988).

Usual dose (range): Oral: 5-60 mg/day.

Rheumatoid arthritis: Oral: Initial: 5-7.5 mg/day, adjust dose as necessary.

Multiple sclerosis: Oral: 200 mg/day for 1 week followed by 80 mg every other day for 1 month.

Conjunctivitis: Ophthalmic (suspension/solution)

Acute asthma: Oral: 1-2 mg/kg/day in divided doses 1-2 times/day for 3-5 days.

Anti-inflammatory or immunosuppressive dose: Oral: 0.1-2 mg/kg/day in divided doses 1-4 times/day.

Nephrotic syndrome: Oral: Initial (first 3 episodes): 2 mg/kg/day or 60 mg/m2/day (maximum: 80 mg/day) in divided doses 3-4 times/day until urine is
protein free for 3 consecutive days (maximum: 28 days); followed by 1-1.5 mg/kg/dose or 40 mg/m2/dose given every other day for 4 weeks. Maintenance (for frequent relapses): 0.5-1 mg/kg/dose given every other day for 3-6 months.

Alternate-day administration: Alternate-day regimens were devised in an attempt to alleviate the undesirable side effects of chronic high-dose daily glucocorticoid therapy. Approximately twice the usual daily dose is given on alternate days, the rationale being that the patient is not exposed to high glucocorticoid concentrations every day and therefore has less chance of developing Cushing's syndrome or pituitary suppression. Unfortunately, alternate-day therapy is unsuccessful in virtually all adult patients who require high doses of glucocorticoids. (Christy, et al. 1988).

F. Monitoring Parameters

Blood pressure; blood glucose, electrolytes; intraocular pressure (use >6 weeks); bone mineral density and blood picture. (Christy, et al. 1988).

G. Therapeutic uses in non endocrine patients

G. GLUCOCORTICIOIDS IN ALLERGIC CONDITIONS

1. Treatment of Churg-Strauss syndrome (allergic granulomatosis and angiitis)

For patients with evidence of systemic vasculitis, treatment is initiated with prednisone (or the equivalent) at a dose of 0.5 to 1.5 mg/kg per day. The higher dose is used for patients with more severe vasculitis (eg, impending respiratory failure, cardiac involvement, glomerulonephritis, neuropathy). With acute multiorgan disease, intravenous glucocorticoid (eg, methylprednisolone 1 g daily for three days) is used for initial therapy, followed by oral glucocorticoid therapy as noted. The majority of patients with CSS achieve a remission with glucocorticoid therapy alone (Sinico, et al. 2009).
2. Medical management of chronic rhinosinusitis

**Nasal sprays:** Topical intranasal glucocorticoids (intranasal GCs) (Scadding, et al. 2008).

Also used in occupational rhinitis (Moscato, et al. 2009).

Also in allergic disease during pregnancy as rhinitis, urticaria and atopic dermatitis (Schatz, et al. 2009).


3. Treatment of atopic dermatitis (eczema)

Higher potency topical corticosteroids can be used for up to 10 days in some patients with acute flares, and then replaced with lower potency preparations until the lesions resolve (Green, et al. 2005).

Maintenance therapy that includes intermittent use of a topical corticosteroid may help prevent relapse. (Glazenburg, et al. 2009).

N.B: Treatment of poison ivy (Toxicodendron) dermatitis:

Topical glucocorticoids and Systemic glucocorticoids (Hershko, et al. 2005).

4. Treatment of eosinophilic esophagitis

**Systemic glucocorticoids:** Systemic glucocorticoids are effective in eosinophilic esophagitis. Patients were treated with methylprednisolone 1.5 mg/kg per day, divided into twice daily dosing for four weeks with significant improvement in symptoms within four weeks with histologic improvement. But withdrawal of glucocorticoids and thus their role as a long-term management strategy is unclear (Rothenberg, et al. 2009).
Topical glucocorticoids: No formulation of topical glucocorticoids has been approved specifically for eosinophilic esophagitis. However, both fluticasone and budesonide have been studied (Remedios, et al. 2006).

5. Anaphylaxis

The onset of action of glucocorticoids takes hours; therefore, these medications do not relieve the initial symptoms and signs of anaphylaxis. They are given on an empirical basis with the rationale that they may help to prevent the biphasic or protracted reactions that occur in up to 23 percent of individuals, although there is no satisfactory published evidence that they actually have this effect. If given, a dose of methylprednisolone of 1 to 2 mg per kilogram per day is sufficient. If glucocorticoid treatment is instituted, it can be stopped after three or four days without a taper (Tole, et al. 2007).

6. Allergic bronchopulmonary aspergillosis

Glucocorticoids are effective for controlling ABPA but are associated with significant immunosuppressive and metabolic side effects. The glucocorticoid dose varies with the stage of disease. Inhaled steroids may help control symptoms of asthma but do not have documented efficacy in preventing acute episodes of ABPA. (Riscili, et al. 2009).

7. Asthma management

Patients with continued wheezing and shortness of breath despite intensive bronchodilator therapy most likely have persistent airflow obstruction on the basis of airway inflammation and intraluminal mucus plugging. Among patients with significant airflow obstruction despite intensive treatment with bronchodilators, systemic glucocorticoids speed the rate of improvement. Current guidelines encourage early systemic glucocorticoids for all patients who have a moderate (peak expiratory flow <70 percent of baseline) or severe
exacerbation (peak expiratory flow <40 percent of baseline; in the urgent care setting, the criterion for a severe asthmatic attack changes from the <50 percent used for decision-making at home to <40 percent), or in whom inhaled short-acting beta agonists do not fully correct the decrement in peak flow (Rodrigo, et al. 2004).

Treatment with regular inhaled glucocorticoids constitutes an important method to prevent recurrent asthma attacks after discontinuation of oral glucocorticoids and to prevent the potential decline in lung function associated with any future severe asthma exacerbation. Virtually every patient who has suffered an asthma attack severe enough to require urgent care should receive an inhaled glucocorticoid as part of their discharge medication plan (Oborne, et al. 2009).

8. Role of systemic glucocorticoid therapy in COPD

Both systemic and inhaled glucocorticoids are widely prescribed for patients with COPD as an extension of their use in asthma based on hypotheses that glucocorticoids might suppress inflammatory processes unique to COPD. Systemic glucocorticoids have been shown to be beneficial in both acute and chronic asthma, and inhaled glucocorticoids have become a cornerstone in the management of persistent asthma. Although most experts regard asthma and COPD as distinct diseases, some patients with obstructive lung disease cannot be clearly categorized even after careful clinical evaluation. Whenever asthma remains a diagnostic possibility, glucocorticoids therapy may have an important role (De Jong, et al. 2007).

Acute exacerbations: systemic (oral or intravenous) glucocorticoids reduced treatment failure and increased the rate of improvement in lung function and symptoms. The benefits of glucocorticoids appear to be greatest in the first 72 hours after administration (Wood-Baker, et al. 2005).
9. Role of inhaled glucocorticoid therapy in COPD

The data suggest that ICS therapy decreases exacerbations and modestly slows the progression of respiratory symptoms, exacerbations, but has minimal or no impact on lung function and mortality. ICS therapy using doses of 1200 mcg per day or higher was associated with a dose-dependent decrease in the incidence of lung cancer. Smaller doses had no effect (Agarwal, et al. 2010).

10. Treatment of the hypereosinophilic syndromes

The mechanism of action of glucocorticoids in HES patients is not entirely clear. Glucocorticoids interfere with eosinophilopoiesis, but this is unlikely to account for the observation that eosinopenia may occur as early as four hours after glucocorticoid administration. Accelerated apoptosis and/or sequestration of eosinophils may also play a role. Although a small number of steroid-refractory patients appear to have decreased glucocorticoid receptor expression, the mechanisms of glucocorticoid resistance in most patients with HES have not been defined (Ogbogu, et al. 2009).

G.2. GLUCOCORTICOID AN IMMUNOLOGAL AND VASCULITIC DISORDERS

1. Treatment of Churg-Strauss syndrome

See before

2. Treatment of dermatomyositis and polymyositis in adults

Although older studies were unable to demonstrate an improvement in survival with glucocorticoids, there is a general consensus that glucocorticoid therapy improves strength and preserves muscle function. In a National Institutes of Health series, for example, 39 percent of 113 glucocorticoid-treated
patients had complete normalization of serum enzymes and 25 percent regained full muscle strength. The outcome of patients in community hospital settings may be better than those presumably more ill patients in tertiary care settings (Hoogendijk, et al. 2004).

3. Initial immunosuppressive therapy in Wegener's granulomatosis and microscopic polyangiitis

When initiating glucocorticoid therapy, there is disagreement among experts and among the authors as to whether therapy should begin with pulse methylprednisolone (7 to 15 mg/kg to a maximum dose of 500 to 1000 mg/day for three days) in all patients or only in those with necrotizing or crescentic glomerulonephritis or more severe respiratory disease. Oral glucocorticoid therapy, either from day 1 or from day 4 if pulse methylprednisolone is given, typically consists of 1 mg/kg per day (maximum of 60 to 80 mg/day) of oral prednisone (or its equivalent) (Merkel, et al. 2005).

4. Use of glucocorticoids in Rheumatoid Arthritis

Glucocorticoids are effective in suppressing the symptoms of RA and may have an impact upon disease progression. However, because of their associated toxicities, they are not ideal for the long-term management of RA (Katchamart, et al. 2009).

5. Treatment of Behcet's disease

Glucocorticoids are the mainstay of Behcet's disease treatment for patients with moderately severe to severe disease. High doses may be required for acute life- or organ-threatening disease; lower doses are appropriate for less acute or severe disease. Although general clinical experience with Behcet's disease and extrapolation from the treatment of related conditions suggest that glucocorticoids are effective for this disorder (Hatemi, et al. 2009).
6. Treatment of acute cardiac allograft rejection:

The mechanism of action of steroids in reversing acute rejection is incompletely understood. The major immunosuppressive action of corticosteroids is to inhibit the synthesis of almost all known cytokines. Steroids appear to act by inducing the synthesis of IkBa, a protein that traps free nuclear factor kappa B, an activator of cytokine genes and mediator of the proinflammatory action of tumor necrosis factor. Pulse corticosteroids may more effectively impair cytokine generation (Stewart, et al. 2005).

In transplant rejection, steroids act in part by suppressing the production of interleukin-1 by macrophages. This in turn leads to diminished production of IL-2 by activated T cells, thereby lessening the entire cellular immune response. Inhibition of IL-6, tumor necrosis factor alpha, and interferon gamma may also be important. In addition, they induce lymphocytolysis in some animal species; it is not known if this occurs in humans (Dinarello, et al. 1987).

7. Treatment of mixed connective tissue disease

Since MCTD was considered to be a steroid responsive disease, there is often a tendency to assume that all patients with MCTD should be treated with long-term corticosteroids. This mistake is compounded by the assumption that all medical problems are related to MCTD. As an example, apparent flares of discomfort and pain in MCTD may instead be due to myofascial pain syndrome or fibromyalgia and are therefore unresponsive to corticosteroids. In addition, malaise and easy fatiguability may be due to a reactive depression or lack of conditioning. As a result, the management of patients with MCTD requires continuing reassessment of the changing pattern of disease activity and a constant alertness to the emergence of new problems (Jais, et al. 2008).

8. Initial treatment and prognosis of Kawasaki disease
Although glucocorticoids have been reported to be beneficial in patients with KD who fail to respond to IVIG, it remains unknown whether they have a role in initial therapy. However, the results of two clinical trials suggest that the addition of a single pulsed dose of intravenous methylprednisolone to a single dose regimen of IVIG (2 mg/kg) does not significantly reduce the incidence of CA abnormalities in children receiving routine initial therapy for KD (Inoue, et al. 2006).

9. Primary angiitis of the central nervous system

High-dose glucocorticoids are required to achieve disease control in PACNS. Start therapy with prednisone at a dose of 1 mg/kg per day to a maximum of 80 mg/day, or its equivalent. Some experts begin with intravenous methylprednisolone, 15 mg/kg each day for three days. Daily prednisone is begun on day four (Guillevin, et al. 2003).

10. Autoimmune pancreatitis

In most reports, one-half to two-thirds of patients responded to glucocorticoids but about 25 percent required a second course of treatment, while a smaller proportion needed continuous treatment. The time to response is variable, usually occurring within two weeks to four months. Unfavorable events (sclerosing cholangitis, distal bile duct stenosis, and retroperitoneal fibrosis) were significantly less common in the patients treated with prednisolone (32 versus 70 percent). This finding supports the recommendation that AIP patients, especially those with obstructive jaundice and bile duct strictures, should be treated and maintained on glucocorticoids (Sahani, et al. 2009).

11. Treatment of autoimmune hepatitis
Glucocorticoids are the mainstay of antiinflammatory/immunosuppressive therapy in autoimmune hepatitis. However, steroid-sparing with azathioprine is frequently used. Combination regimens permit the use of lower doses of glucocorticoids thereby reducing glucocorticoid-related side effects. A regimen of glucocorticoids alone may be preferred in settings in which there is a concern related to exposing the patient to azathioprine such as in patients with preexisting cytopenias, malignancy, and thiopurine methyltransferase deficiency (Manns, et al. 2010).

12. Therapy in systemic lupus erythematosus in adults

Systemic glucocorticoids (eg, high doses of 1 to 2 mg/kg/day of prednisone or equivalent or as intermittent intravenous "pulses" of methylprednisolone) used alone or in combination with immunosuppressive agents are generally reserved for patients with significant organ involvement, particularly renal and central nervous system disease. There are a paucity of data to support the use of intravenous "pulse" versus daily oral glucocorticoids. Patients with organ-threatening disease (eg, cardiopulmonary, hepatic, renal, hemolytic anemia, immune thrombocytopenia) usually are given the above-mentioned oral doses, whereas non-organ-threatening disease (eg, cutaneous, musculoskeletal, constitutional) patients usually respond to 5 to 15 mg of prednisone equivalent a day until a steroid-sparing agent or antimalarial can take effect. Immunosuppressive agents such as mycophenolate, azathioprine, or cyclophosphamide are given with glucocorticoids to patients with more than mild lupus nephritis, and cyclophosphamide to those with alveolar hemorrhage, systemic vasculitis, and to most patients with significant central nervous system involvement. Lower doses of glucocorticoids (eg, ≤10 mg/day of prednisone) may be used for symptomatic relief of severe arthralgia, arthritis, or serositis while awaiting a therapeutic effect from other medications (Parker, et al. 2007).
13. Management of the vasculitides in adults

Systemic vasculitis: Patients with systemic vasculitic involvement usually require at least glucocorticoid therapy. As an example, glucocorticoid therapy usually leads to remission in giant cell arteritis. In most patients, the dose can be reduced and eventually discontinued, but some require chronic therapy with low dose prednisone. By comparison, patients with rapidly progressive vasculitic diseases, such as Wegener granulomatosis or polyarteritis nodosa, are likely to require combination therapy consisting of a cytotoxic drug (usually cyclophosphamide) and steroids. Both oral or pulse cyclophosphamide have been utilized based upon physician experience and disease severity; after one or two months of combined therapy, the steroid dose may be reduced; therapy is usually continued for 6 to 12 months to diminish the risk of relapse. Azathioprine and Methotrexate have been used in less severe forms of vasculitis and as maintenance therapy after remission has been induced by cyclophosphamide (Mahr, et al. 2008).

14. Myasthenia gravis

Oral prednisone is usually recommended as initial therapy for most patients with MG who require chronic immunotherapy. Glucocorticoids are most often started in high doses only in hospitalized patients who are receiving concurrent plasmapheresis or IVIG for myasthenic crisis. These latter therapies have a quick onset of action that precludes the transient worsening of MG that would otherwise occur due to the glucocorticoids (SchneiderGold, et al. 2005).

Some have used pulsed intravenous (IV) methylprednisolone (2 g over 12 hours) for exacerbations of MG, followed by 30 mg of oral prednisone, and a
case series suggested that there is a faster onset of action and less in the way of transient worsening than with oral prednisone alone (Hart, et al. 2007).

15. Treatment of immune (idiopathic) thrombocytopenic purpura

Corticosteroids have been used for many years for the management of ITP in all age groups. Steroids are presumed to reduce the risk of symptoms in ITP patients by:

• Reducing antibody production.
• Reducing reticuloendothelial system phagocytosis of antibody-coated platelets.
• Improving vascular integrity.

A variety of dose regimens have been used ranging from prednisone at a dose of 2 mg/kg per day for two to four weeks, to high pulse doses of intravenous or oral methylprednisolone (50 mg/kg per day) for three to seven days. Some evidence suggests that time of response and rate of response are dose-related, but comparative studies among the multiple regimens are few and involve only small numbers of patients (Beck, et al. 2005).

16. Treatment and prognosis of IgA nephropathy

Most nephrologists do not treat mild, stable, or very slowly progressive IgA nephropathy. Glucocorticoid therapy should only be attempted in patients with clinical and histologic evidence of active inflammation (e.g., hematuria and/or proliferative or necrotizing glomerular changes). Glucocorticoid therapy for 6 to 24 months or more may be associated with a reduction in proteinuria and perhaps improved renal survival with preserved kidney function.
Glucocorticoids plus ACE inhibitors or ARBs also used in treatment (Floege, et al. 2005).

17. Amyloidosis

Melphalan with or without prednisone, Melphalan and dexamethasone, Dexamethasone and interferon alpha, Thalidomide and dexamethasone, Cyclophosphamide thalidomide and dexamethasone and Bortezomib with or without dexamethasone are the most common therapies used in treatment (Landau, et al. 2009).

18. Treatment of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome in adults

If the patient has idiopathic TTP/HUS (ie, no evidence for a drug-induced etiology, no bloody diarrheal prodrome), it is likely that the disorder has an autoimmune etiology. Immunosuppressive treatment with prednisone (1 mg/kg per day by mouth) or methylprednisolone (125 mg IV twice daily) is reasonable for patients with a poor response to initial treatment with plasma exchange. In patients whose platelet counts do not increase within several days of treatment with plasma exchange, or those in whom thrombocytopenia recurs when plasma exchange treatments are diminished or discontinued, addition of glucocorticoids is also appropriate (George, JN. 2006).

19. Treatment of paroxysmal nocturnal hemoglobinuria

Prednisone may act by diminishing complement activation, thereby halting hemolysis. The effective dose of prednisone is generally higher than can be easily tolerated if given on a daily basis. As a result, moderate doses (15 to 30 mg) are usually administered on alternate days. During marked hemolytic episodes, however, higher doses given daily may help allay the paroxysm. Since activation of complement may be involved in thrombotic episodes, moderate to
high doses of prednisone (0.5 to 1 mg/kg per day) can be given, although the effectiveness of this agent has been questioned (Brodsky, et al. 2008).

20. Treatment of autoimmune hemolytic anemia

Corticosteroids are frequently used as the first therapy for warm AIHA, as they induce remission of antibody production in about 60 to 70 percent of patients. The initial doses used are usually quite high. Doses in children are generally similar. The minimal prednisone dose capable of inducing remission has never been established (Petz, et al. 2001).

When successful, the effect on antibody production, manifest by a rising hemoglobin concentration, is usually seen within one to three weeks. How corticosteroids act in this setting is not clear; some have suggested that the simultaneous presence of steroid in its receptor and the antigen in its receptor induces apoptosis of specifically-programmed T-cells (King, et al. 2005).

21. Eales' disease

Glucocorticoids have an important role in the inflammatory phase of Eales' disease. Periocular glucocorticoid injections into the posterior subtenon region are particularly helpful in the setting of cystoid macular edema, and may be used in addition to systemic glucocorticoids (Biswas, et al. 2002).

22. Treatment of minimal change disease of kidney in adults

There are no randomized trials comparing prednisone to other agents for the initial therapy of idiopathic MCD in adults. In adults, numerous retrospective observational studies have demonstrated a high response rate in patients treated with relatively long courses of high dose daily or alternate day steroids. (Meyrier, et al. 2009).
23. Treatment of primary focal segmental glomerulosclerosis

The optimal dose and duration of therapy are unknown. In many cases, an overall course of treatment of at least six to eight months is required, and complete remission may not be attained for 12 months or longer. Shorter courses (≤two months) result in much lower remission rates (20 to 30 percent) and may have led to the earlier belief that this condition was not steroid responsive. It is preferred, daily dosing for initial therapy in patients with no contraindications, since failure to respond to alternate day dosing would necessitate conversion to daily dosing and result in prolongation of the steroid course. Despite this general recommendation, alternate day dosing may be a better option in patients at higher risk of complications from glucocorticoids (Duncan, et al. 2004).

24. Treatment of membranoproliferative glomerulonephritis

Early therapy was emphasized (mean duration of disease five months), a setting in which active inflammation was most likely to be present. Pulse intravenous methylprednisolone (30 mg/kg daily times three) being used initially if the creatinine clearance were below 50 mL/min per 1.73 m2 body surface area. Better response to corticosteroid therapy may be observed among patients with type I compared with type III disease (Jones, et al. 2004).

G.3. ANTI INFLAMMATORY THERAPEUTIC APPLICATIONS

1. Treatment of pulmonary sarcoidosis with glucocorticoids

The optimal dose of glucocorticoids is not known, so that choosing a dose requires balancing the risk of adverse effects with the likelihood of response. Daily oral glucocorticoids therapy is initiated with relatively high doses of oral
prednisone. This is followed by a slow taper to the lowest effective dose for a total duration of therapy between six and 12 months (Paramothayan, et al. 2005).

**Other forms of therapy:**

Alternate day therapy with oral glucocorticoids.

High-dose oral glucocorticoids therapy.


### 2. Treatment of chronic inflammatory demyelinating polyneuropathy:

**Oral:** Weather to use daily or alternate-day oral glucocorticoids is determined by the individual nature of the patient's medical health and the severity and pattern of CIDP. Weekly pulse methylprednisolone (500 mg once a week) is also an effective option for long-term treatment of CIDP. Alternate-day glucocorticoid therapy may reduce the incidence of side effects, but some experts believe it is less effective than a daily dosing regimen. Oral regimen is to start prednisone at 1 to 1.5 mg/kg daily (usually around 50 to 80 mg daily; no more than 100 mg). (Muley, et al. 2008).

**Intravenous:** As with oral glucocorticoid therapy, there is no standard regimen for pulse IV glucocorticoids. One suggested regimen is an initial dose of IV methylprednisolone (1000 mg/day) for three days, followed by 1000 mg one day a week. Tapering is accomplished by slowly decreasing the frequency of dosing to once every 2 to 12 weeks (Muley, et al. 2008).

### 3. Treatment of acute gout

Glucocorticoid therapy can be injected into the affected joint(s) or given systemically, either orally or parenterally:
Intraarticular glucocorticoids are a reasonable option in patients with only one or two actively inflamed joints with systemic glucocorticoids in patients who cannot take NSAIDs or colchicine. (Zhang, et al. 2006).

Systemic glucocorticoids may be administered orally in patients who cannot take NSAIDs or colchicine and who are not candidates for intraarticular glucocorticoid injection because of polyarticular disease (Janssens, et al. 2008).

4. Treatment of acute exacerbations of multiple sclerosis in adults

Acute attacks of MS are usually treated with glucocorticoids. Three to seven day courses of intravenous methylprednisolone, 500 to 1000 mg daily, with or without a short prednisone taper, are used most commonly. The bioavailability of oral prednisone (1250 mg) appears to be equal to that of intravenous methylprednisolone (1000 mg) (Murray, TJ. 2006).

5. Postnatal use of glucocorticoids in bronchopulmonary dysplasia

Recommendations was NOT to use postnatal systemic glucocorticoid therapy to prevent BPD. In practice, use systemic glucocorticoid therapy will be only in infants greater than three weeks of age with severe BPD who require maximal ventilatory and oxygen support. In practice, inhaled beclomethasone or fluticasone used in selected infants with severe BPD who are dependent upon substantial pulmonary support (Bassler, et al. 2009).

6. Dexamethasone to prevent neurologic complications of bacterial meningitis in children

Administration of dexamethasone did not affect mortality, but reduced the incidence of severe hearing loss in children with bacterial meningitis, particularly those with Haemophilus influenzae meningitis (van de Beek, et al. 2007).
Glucocorticoid therapy appears to be beneficial in selected children and adults with tuberculous meningitis (Feigin, et al. 2009).

7. Treatment of carpal tunnel syndrome

Injection of glucocorticoids into the region of the carpal tunnel is intended to reduce tissue inflammation and aid recovery. Its value relative to conservative treatment has been controversial because no well-controlled comparative studies have been performed, and because a prominent histological inflammatory response is not usually seen with CTS. Glucocorticoids can be injected proximal or distal to the carpal tunnel. Injections appear to be safe; although cases of median nerve injury after injections have been reported (Gooch, et al. 2005).

8. Nonspecific interstitial pneumonia

Prednisone at 1 mg/kg ideal body weight per day up to a maximum of 60 mg/day for one month followed by 40 mg/day for an additional two months is the recommended dose. For patients with severe disease requiring hospitalization, some authors have used pulse intravenous methylprednisolone. The usual regimen is 1000 mg/day for three days followed by oral prednisone as dosed above. Rarely, patients need additional pulse doses (Kondoh, et al. 2005).

9. Treatment of ankylosing spondylitis

Injection by long-acting corticosteroid may be helpful as found in some, but not all studies. A beneficial effect may even be observed when the injected corticosteroid is placed near the sacroiliac joints. In practice, a blind injection can be recommended; if ineffective, fluoroscopic, CT, or MRI-guided injection can be performed (Hanly, et al. 2000).
10. Acute pericarditis

The 2004 guidelines recommended that systemic steroid therapy be restricted to patients with the following conditions:

• Acute pericarditis due to connective tissue disease.

• Autoreactive (immune-mediated) pericarditis.

• Uremic pericarditis. (Maisch, et al. 2004).

The guidelines recommend use of high doses of glucocorticoids (e.g., prednisone 1 mg/kg/day) when indicated with rapid tapering to reduce the risk of systemic side effects. In patients with a co-existing pericardial effusion, intrapericardial steroids is an option that limits systemic toxicity (Maisch, et al. 2004).

11. Management of ulcerative proctitis, proctosigmoiditis, and left-sided (distal) colitis

Hydrocortisone foam and enemas reach the proximal sigmoid colon and splenic flexure in virtually all patients who are able to retain them. hydrocortisone foam preparations generally reach only the mid-sigmoid colon, while suppositories are effective only in the distal 5 to 8 cm of the rectum. (Lichtenstein, et al. 2006).

For patients who do not tolerate or who have an inadequate response to the above treatments, oral corticosteroids (e.g., prednisone 40 to 60 mg every morning) are highly effective. A gradual taper can begin after the patient has been stable for two to four weeks. Decreasing the dose by 5 mg every one to two weeks down to a dose of 20 mg/day helps reduce the acute side effects. Oral corticosteroids should not be used for maintenance of remission since they have
not been proven to be beneficial and are associated with many side effects (Regueiro, et al. 2006).

The mainstay of treatment of patients with severe disease is parenteral corticosteroids. Steroid enemas (one hydrocortisone enema twice daily) or steroid foam preparations (1 gram three times daily) are commonly given as adjunctive treatment, particularly for patients with urgency and tenesmus. (Regueiro, et al. 2006).

12. Treatment of retroperitoneal fibrosis

Glucocorticoids have been the mainstay of therapy based on observed benefit. If surgery is not absolutely necessary, some investigators have advocated using glucocorticoids alone, since procedures may be associated with significant risks and complications. The dose is prednisone 1 mg/kg per day (maximum dose 80 mg/day) for approximately six weeks. If improvement is observed, the dose is then tapered over approximately two to three months to 10 mg/day, and maintained for an additional 6 to 18 months (Magrey, et al. 2009).

13. As therapy to prevent restenosis following percutaneous coronary intervention

Single dose treatment with corticosteroids is ineffective in reducing restenosis after balloon angioplasty. Steroid therapy may be effective if it is given for a longer period, and if it is targeted to patients who have evidence of an active inflammatory response after stent placement. The combined end point of death, MI, or repeat revascularization at one year occurred at a lower rate in patients treated with prednisone (7 versus 35 percent), mostly because of a lesser requirement for repeat revascularization (Kakio, et al. 2004).
14. Treatment of miliary tuberculosis

There has never been a study of adjunctive corticosteroids in patients with miliary tuberculosis, although corticosteroids are used in some forms of extrapulmonary TB, particularly meningitis. Results of case reports and small clinical series using corticosteroids in miliary TB are conflicting (Sharma, et al. 2005).

15. Emerging therapies for hepatic fibrosis

Corticosteroids have been a mainstay of therapy for many inflammatory liver diseases. As an example, they can induce clinical remission and improve hepatic histopathology in patients with autoimmune hepatitis, even those with advanced histologic features. However, the incomplete suppression of fibrogenesis and undesirable side effects after prolonged administration limit its use (Friedman, SL. 2008).

16. Subacute and chronic low back pain

Epidural glucocorticoid injections involve the administration of steroids via a catheter inserted in the space between the dura and the spine. (Chou, et al. 2009).

Epidural injections have been used in patients with radiculopathy, spinal stenosis, and nonspecific low back pain. More than three injections at the same site within 12 months are usually not recommended because of concerns about potential suppression of the hypothalamic-pituitary-adrenal axis (Riew, et al. 2006).

Intradiscal injection: There is no convincing evidence that intradiscal glucocorticoids are effective for low back pain. In patients with MRI evidence of degenerative disc disease and a positive response to discography (Staal, et al. 2008).
Facet joint injection and medial branch block: No clear differences between facet joint glucocorticoid and placebo injections. (Chou, et al. 2009).

Sacroiliac joint injection: The sacroiliac joints are thought to be the source of low back pain in some patients. Periarticular sacroiliac joint glucocorticoid injection more effective than local anesthetic injection for pain relief in patients with chronic pain in the sacroiliac joint area. There are no randomized trials of intra-articular sacroiliac joint steroid injection in patients without spondyloarthropathy. (Luukkainen, et al. 2002).

17. Corticosteroid therapy in septic shock

Randomized trials have important differences that may, at least in part, explain their conflicting results:

• The French trial enrolled patients within eight hours after the onset of shock and included patients with a greater severity of illness. The mean Simplified Acute Physiology Score II (SAPS II) was 55.5 and septic shock was defined as a systolic blood pressure <90 mmHg for more than one hour despite adequate fluid resuscitation and vasopressor administration (Annane, et al. 2002).

• The CORTICUS trial enrolled patients within 72 hours of the onset of shock and included patients with a lower severity of illness. The mean SAPS II was 49 and septic shock was defined as a systolic blood pressure <90 mmHg despite adequate fluid resuscitation, or the need for vasopressor administration for more than one hour (Sprung, et al. 2008).

These differences imply that corticosteroid therapy is most likely to benefit patients with severe septic shock. This was supported by two meta-analyses that looked at the effects of long courses of low-dose steroids (≤300 mg per day of hydrocortisone or an equivalent for ≥5 days) in patients with septic shock (Annane, et al. 2009).
Dose: 50 mg of hydrocortisone every six hours or 100 mg of hydrocortisone every eight hours. Hydrocortisone alone has sufficient mineralocorticoid effect and absorption of the enterally administered drug is questionable in situations of compromised splanchnic perfusion (Annane, et al. 2002).

18. Antenatal use of glucocorticoids in women at risk for preterm delivery

Two regimens of antenatal glucocorticoid treatment have evolved and are effective for accelerating fetal lung maturity:

- Betamethasone (two doses of 12 mg given intramuscularly 24 hours apart).
- Dexamethasone (four doses of 6 mg given intramuscularly 12 hours apart).

Studies have consistently shown that both betamethasone and dexamethasone are effective in reducing most morbidities and mortality related to prematurity. Dexamethasone has the advantage of having a lower cost and wider availability, but there are concerns over risk of neurotoxicity. Currently, there is insufficient high quality evidence on possible adverse effects on which to base a strong recommendation for use of one drug over the other (Brownfoot, TA. 2008).

19. Cancer pain management: Adjuvant analgesics (coanalgesics)

In palliative care, glucocorticoids are often used to alleviate symptoms such as pain, nausea, fatigue, anorexia, and malaise, and improve overall quality of life. Glucocorticoids may be beneficial for a variety of types of pain, including neuropathic and bone pain, pain associated with capsular expansion or duct obstruction, pain from bowel obstruction, pain caused by lymphedema, and headache caused by increased intracranial pressure. The mechanism of analgesia probably relates to reduction of tumor-related edema,
antiinflammatory effects, and direct effects on nociceptive neural systems (Mercadante, et al. 2007).

20. Adjuvant therapy in acute pain management in adults with sickle cell disease

The participants who received methylprednisolone had a significant (approximately a 50 percent) reduction in the length of hospitalization for pain when compared with the placebo group. Despite this immediate benefit, approximately 25 percent of the patients who received methylprednisolone were re-admitted within a week of discharge, greatly attenuating the benefit of treatment with methylprednisolone for inpatient management of vasooclusive pain. (Lottenberg, et al. 2005).

21. Pharmacologic management of cancer anorexia/cachexia

The mechanism of action of corticosteroids in CACS has not been established. Euphorogenic and antiinflammatory effects, and perhaps stimulation of orexigenic hormones within the hypothalamus, may be responsible for an increase in appetite. At one time, corticosteroids were first-line therapy for appetite stimulation in CACS. A reasonable dose of dexamethasone in this setting is 4 mg/day, although lower doses may also be effective (Yavuzsen, et al. 2005).

22. Glucocorticoids in Brain Tumors

Most patients with brain tumors and peritumoral edema can be adequately managed with glucocorticoids. Reduction of intracranial pressure and improvement in neurologic symptoms usually begins within hours. A decrease in capillary permeability (ie, improvement in blood-brain barrier function) can be identified within six hours, and changes of diffusion-weighted MRI indicating decreased edema are identifiable within 48 to 72 hours. However,
adequate reduction in elevated ICP resulting from peritumoral edema may take several days with glucocorticoid therapy alone, and additional treatment may be required in the initial management of these patients (Sinha, et al. 2004).

Dexamethasone has recently been shown to upregulate Ang-1, a strong BBB-stabilizing factor, whereas it downregulates VEGF, a strong permeabilizing factor, in astrocytes and pericytes. Glucocorticoids may also increase the clearance of peritumoral edema by facilitating the transport of fluid into the ventricular system, from which it is cleared by cerebrospinal fluid (CSF) bulk flow (Kim, et al. 2008).

Dose and schedule: 10 mg loading dose, followed by 4 mg four times per day or 8 mg twice daily. There is some evidence that lower doses (1 to 2 mg four times per day) may be as effective and less toxic in patients without impending herniation (Kim, et al. 2008).

23. Glucocorticoid therapy in hirsutism

Glucocorticoids were more effective than OCs or antiandrogens for suppressing serum adrenal androgen concentrations (dehydroepiandrosterone and dehydroepiandrosterone sulfate [DHEA and DHEAS]), but less effective for decreasing hirsutism scores (Koulouri, et al. 2009).

G.4. GLUCOCORTICOIDS IN BLOOD MALIGNANCIES

1. Treatment of adult T-cell lymphoma-leukemia

The optimal chemotherapy combination for patients with ATL is unclear and many intensive regimens have been investigated. The regimen that appears to result in the longest median survival is VCAP-AMP-VECP, which includes
treatment with vincristine, cyclophosphamide, doxorubicin, prednisone, ranimustine, vindesine, etoposide, and carboplatin (Tsukasaki, et al. 2009).

2. Natural killer (NK) cell large granular lymphocyte leukemia

Since NK lymphocytosis is an indolent disease, therapy is usually not needed. For patients with severe neutropenia, we suggest treatment with agents similar to those used in T-cell LGL leukemia (eg, prednisone plus cyclophosphamide, cyclophosphamide alone, or methotrexate) (Lamy, et al. 2003).

3. Initial treatment of advanced (stage III-IV) Hodgkin lymphoma

BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen is given in standard or escalated doses. BEACOPP produces superior progression-free survival rates, but has increased toxicity (ie, neutropenia and infections) and no clear difference in overall survival rates. Complete response rates with BEACOPP are approximately 80 to 95 percent with five-year progression-free and overall survival rates of 81 and 92 percent, respectively (Johnson, et al. 2005).

4. Treatment of primary central nervous system lymphoma

Dexamethasone is the most commonly used preparation, and is often given at a starting dose of 4 mg PO four times per day. If radiation treatment is contemplated, corticosteroids should be continued at full doses until the radiation course has been completed. The dose can then be tapered. Glucocorticoids increase the metabolism of phenytoin and phenobarbital, which may require dosage adjustments (Laack, et al. 2006).

H. Adverse Reactions

- **OPHTHALMIC FORMULATION:**
Endocrine & metabolic: Hypercorticoidism (rare).

Ocular: Conjunctival hyperemia, conjunctivitis, corneal ulcers, delayed wound healing, glaucoma, intraocular pressure increased, keratitis, loss of accommodation, optic nerve damage, mydriasis, posterior subcapsular cataract formation, ptosis, secondary ocular infection.

- **ORAL FORMULATION:**

Cardiovascular: Cardiomyopathy, CHF, edema, facial edema, hypertension.

Central nervous system: Convulsions, headache, insomnia, malaise, nervousness, pseudotumor cerebri, psychic disorders, vertigo.

Dermatologic: Bruising, facial erythema, hirsutism, petechiae, skin test reaction suppression, thin fragile skin, urticaria.

Endocrine & metabolic: Carbohydrate tolerance decreased, Cushing's syndrome, diabetes mellitus, growth suppression, hyperglycemia, hypernatremia, hypokalemia, hypokalemic alkalosis, menstrual irregularities, negative nitrogen balance, pituitary adrenal axis suppression.

Gastrointestinal: Abdominal distention, increased appetite, indigestion, nausea, pancreatitis, peptic ulcer, ulcerative esophagitis, weight gain.

Hepatic: LFTs increased (usually reversible).

Neuromuscular & skeletal: Arthralgia, aseptic necrosis (humeral/femoral heads), fractures, muscle mass decreased, muscle weakness, osteoporosis, steroid myopathy, tendon rupture, weakness.

Ocular: Cataracts, exophthalmus, eyelid edema, glaucoma, intraocular pressure increased, irritation.

Respiratory: Epistaxis.
Miscellaneous: Diaphoresis increased, impaired wound healing. (Ng, et al. 1998).

I. Contraindications

Hypersensitivity to prednisolone or any component of the formulation; acute superficial herpes simplex keratitis; live or attenuated virus vaccines (with immunosuppressive doses of corticosteroids); systemic fungal infections and varicella. (Ng, et al. 1998).

Precautions

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis. Patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do not provide the systemic steroid needed to treat patients having trauma, surgery, or infections.

- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections) or prolong or exacerbate viral infections. Corticosteroids should not be used for cerebral malaria or viral hepatitis. Use with caution in patients with tuberculosis.

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered (Goedert JJ, et al. 2002).

- Myopathy: Acute myopathy has been reported with high dose corticosteroids, usually in patients with neuromuscular transmission disorders; may involve
ocular and/or respiratory muscles; monitor creatine kinase; recovery may be delayed.

- Ocular effects: Prolonged use of corticosteroids may result in glaucoma; damage to the optic nerve (not indicated for treatment of optic neuritis), defects in visual acuity and fields of vision, and posterior subcapsular cataract formation may occur. - Psychiatric disturbances: Corticosteroid use may cause psychiatric disturbances, including depression, euphoria, insomnia, mood swings, and personality changes. Pre-existing psychiatric conditions may be exacerbated by corticosteroid use.

- Cardiovascular disease: Use with caution in patients with HF; long-term use has been associated with fluid retention and hypertension.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia.

- Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, peptic ulcer, ulcerative colitis) due to perforation risk.

- Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; exacerbation of symptoms has occurred especially during initial treatment with corticosteroids.

- Myocardial infarction (MI): Use with caution following acute MI; corticosteroids have been associated with myocardial rupture.

- Osteoporosis: Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.
• Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur.

• Seizure disorders: Use with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis.

• Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones. (Ng, et al. 1998).

**J. Drug Interactions**

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. Risk C.

Aldesleukin: Corticosteroids may diminish the antineoplastic effect of Aldesleukin. Risk X.

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). Risk C.

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. Risk C.

Antacids: May decrease the bioavailability of Corticosteroids (Oral). Risk D.

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. Risk C.
Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). Risk C.

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). Risk C.

BCG: Immunosuppressants may diminish the therapeutic effect of BCG. Risk X.

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). Risk C.

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. Risk C.

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). Risk C.

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. Risk C.

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). Risk C.

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). Risk C.

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). Risk C.

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. Risk C.
Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. Risk C.

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). Exceptions: Azithromycin; Azithromycin (Systemic); Spiramycin. Risk D.

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. Risk D.

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). Risk C.

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). Risk C.

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. Risk C.

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). Risk C.

Ritonavir: May increase the serum concentration of Prednisolone. Management: Consider prednisolone dose reductions in patients receiving ritonavir, and monitor for increased adverse effects with concomitant use. Risk D.

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. Risk C.
Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. Risk C.

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Risk C.

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinial infections may develop. Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live virus vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. Risk X.

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. Risk C (Frey FJ, et al. 1987).
ANDROGEN

A. PHYSIOLOGY

The mechanism by which the secretion of adrenal androgens, dehydroepiandrosterone (DHEA), DHEA sulfate, and androstenedione, are regulated is unknown. The compounds themselves are largely inactive but, because they are precursors for the active androgens, testosterone and dihydrotestosterone, they are referred to as adrenal androgens. Corticotropin (ACTH) acutely stimulates the secretion of DHEA, but not DHEA sulfate (Cunningham, et al. 1994).

TESTOSTERONE

B. MECHANISM OF ACTION:

Principal endogenous androgen responsible for promoting the growth and development of the male sex organs and maintaining secondary sex characteristics in androgen-deficient males (NAMS Board of Trustees 2005).

C. PHARMACODYNAMICS/KINETICS:

DURATION (route and ester dependent): I.M.: Cypionate and enanthate esters have longest duration, ≤2-4 weeks; gel: 24-48 hours.

ABSORPTION: Transdermal gel: ~10% of applied dose.

PROTEIN BINDING: 98%; bound to sex hormone-binding globulin (40%) and albumin.

METABOLISM: Hepatic; forms metabolites, including dihydrotestosterone (DHT) and estradiol.

HALF-LIFE ELIMINATION: Variable: 10-100 minutes.
**Excretion:** Urine (90%); feces (6%). *(Cunningham, et al. 1994).*

**D. DOSE and Dosage Forms:**

Capsule, gelatin, Gel, topical, Implant, subcutaneous, Injection, Patch and transdermal. *(NAMS Board of Trustees. 2005).*

Inoperable metastatic breast cancer (females): I.M. (testosterone enanthate): 200-400 mg every 2-4 weeks. *(NAMS Board of Trustees. 2005).*

**E. Monitoring Parameters:**

Periodic liver function tests, PSA and prostate exam, cholesterol, hemoglobin and hematocrit, radiologic examination of wrist and hand every 6 months (when using in prepubertal children). Withhold initial treatment with hematocrit >50%, hyperviscosity, untreated obstructive sleep apnea, or uncontrolled severe heart failure. Monitor urine and serum calcium and signs of virilization in women treated for breast cancer. Serum glucose (may be decreased by testosterone, monitor patients with diabetes). *(Cunningham, et al. 1994).*

PSA: Withhold initial treatment if PSA >3 ng/mL, or with palpable prostate nodule or induration without further urological evaluation. Do not treat with severe untreated BPH with IPSS symptom score >19. *(Cunningham, et al. 1994).*

Serum testosterone: Monitor 3 months after initiating treatment, then annually. *(Cunningham, et al. 1994).*

**F. Therapeutic uses in non endocrine patients**

1. Uses of androgen as performing enhancing drugs by athletes

Virtually all androgens produced for human or veterinary purposes have been taken by athletes. These include testosterone esters, which are usually
taken by injection, the 17-alpha-alkylated androgens, which are usually taken orally, and androgen precursors. The testosterone esters include the enanthate and cypionate, which are also used for hormone replacement. (Parkinson et al. 2006).

Synthetic androgens, eg, oral 17-alpha-alkylated androgens or parenteral 19-nortestosterone derivatives, were originally developed to have a greater anabolic to androgenic effect than testosterone. They were therefore given the name "anabolic steroids," which persists today. However, whether these compounds have a higher ratio of anabolic to androgenic activity than testosterone in humans is uncertain. Although there is only one androgen receptor, which is present in many tissues, there are many cofactors that influence the transcriptional activity of the androgen receptor. These factors, called coactivators or corepressors, differ from tissue to tissue, and provide a theoretical basis for a compound to affect the androgen receptor differently in one tissue compared to another (Miller et al. 2005).

Nevertheless, no compound has yet been found to have a greater anabolic effect than androgenic effect in humans, and therefore they will all be referred to here simply as androgens. Stimulation of testosterone secretion by HCG, which acts as LH and stimulates the Leydig cells of the testes to secrete testosterone, has also been used by athletes, because what is produced is native testosterone and in normal ratio to epitestosterone, making its use more difficult to distinguish from normal secretion (Parkinson et al. 2006).

• Androstenedione is available and it is not regulated as are many other androgens. Administration of 300 mg of androstenedione once daily for one week to normal young men increased their mean serum testosterone concentration, but administration of 100 mg three times a day for eight weeks did not. In a third study, in which 100 mg of androstenedione or
placebo was given to normal men three times a day in a double-blind fashion for four weeks, the total testosterone concentration did not increase in the androstenedione-treated men, but free testosterone, dihydrotestosterone, and estradiol did (Leder, et al. 2000).

- DHEA is also available as a "nutritional supplement" as an agent that will increase muscle strength. It is not androgenic itself, but is converted to testosterone (Acacio, et al. 2004).

It seems intuitive that androgens increase muscle mass and muscle strength, given the obvious differences between men and women. While exogenous testosterone administration results in increases in serum testosterone concentrations and muscle strength, there is no evidence that androstenedione increases muscle strength. Testosterone treatment increased fat-free mass and muscle strength, both in men who exercised and in men who did not, but more so in those who exercised simultaneously (Wallace, et al. 1999).

2. Therapy in management of sexual dysfunction in females

Levels of endogenous androgens do not predict sexual function; however, androgen therapy that increases serum concentrations to the upper limit of normal has consistently been shown to improve female sexual function in selected populations of postmenopausal women (Buster, et al. 2005).

Testosterone therapy is the most commonly studied androgen treatment for female sexual dysfunction. The addition of testosterone to postmenopausal estrogen (with or without progestin) therapy in women who undergo menopause naturally or as a result of oophorectomy (surgical menopause) has been shown to improve sexual function. Testosterone is primarily used to treat issues with sexual desire or responsiveness, although all aspects of sexual function generally improve, including arousal and orgasmic response (Billups, et al. 2001).
The testosterone 300 mcg group reported significantly more sexual satisfying events than the placebo group, this was not true for the 150 mcg dose. However, both testosterone doses were associated with significant improvements in desire and reduction in distress about sexual dysfunction. Long-term effects of testosterone, including effects on the breast, remain uncertain (Davis, et al. 2008).

Another androgen, dehydroepiandrosterone (DHEA), has been shown to improve sexual interest and satisfaction in some studies of women with adrenal insufficiency, but was ineffective in women who are perimenopausal or naturally postmenopausal (Barnhart, et al. 1999).

Improvements in satisfying sexual events compared with placebo were found only in women treated with 90 microL, but not with other testosterone doses. There were no significant improvements in any other measure of sexuality, including desire, pleasure or orgasm (Davis, et al. 2008).

3. Alzheimer disease

Epidemiologic studies have shown a correlation between testosterone levels and cognitive functioning in healthy older men and between low testosterone levels and risk of developing Alzheimer disease (AD). Studies examining testosterone supplementation in AD have had mixed results. Two double-blind, placebo-controlled studies found a specific benefit of testosterone therapy in visual-spatial cognitive domains (Lu, et al. 2006).

4. Testosterone treatment in angina

There is some evidence that testosterone improves endothelial dysfunction and may be an effective antianginal agent. Testosterone significantly increase the time to 1 mm ST segment depression on treadmill exercise testing compared to placebo. Given the potential for side effects, further trials are warranted.
before testosterone can be considered as a therapy for angina (English, et al., 2000).

5. Endothelial dysfunction

Testosterone may also improve endothelial dysfunction. One small series of 13 patients with coronary heart disease found that testosterone, at physiologic concentrations, induced coronary artery dilatation and increased coronary blood flow. However, this did not appear to be mediated by endothelium-dependent responses, since acetylcholine-induced changes in coronary artery blood flow were not affected by testosterone (Webb, et al., 1999).

6. Therapy in cancer breast

Androgens, including testosterone, fluoxymesterone, and the less virilizing agent testolactone, are rarely used to treat MBC. Although they have response rates of around 20 percent, they are inferior to high dose estrogens for treatment of metastatic disease. The weak androgen danazol, which also inhibits pituitary gonadotropin secretion, has a single agent response rate of 20 percent. If androgen therapy is considered, fluoxymesterone (10 mg by mouth twice daily) is a reasonable choice (Henderson, et al., 1991).

7. Therapy in fibroid and endometriosis

Its mechanisms of action include inhibition of pituitary gonadotropin secretion and direct inhibition of endometriotic implant growth, and direct inhibition of ovarian enzymes responsible for estrogen production. Since it induces amenorrhea and has been shown to have a direct effect on endometriosis implants, danazol likely inhibits autologous endometrium. Danazol may control anemia related to leiomyoma-related menorrhagia, but it does not appear to reduce uterine volume (Coutinho, et al., 1989).
8. Treatment of paroxysmal nocturnal hemoglobinuria

Androgenic hormones are effective in diminishing the anemia of PNH in some cases. Derivitized androgens (such as danacrine or danazol) with less masculinizing effect are also effective. The mechanism by which these agents work is not entirely clear. They may increase hematopoiesis or downregulate the activation of complement (Hill, et al. 2007).

9. Management of cancer anorexia and cachexia

The anabolic steroid fluoxymesterone was shown to be less effective than either dexamethasone or megestrol acetate as an appetite stimulant (Lesser, et al. 2008).

10. Osteoporosis in male

Hypogonadism is among the most commonly identified causes of osteoporosis in men. Many studies have demonstrated that testosterone replacement increases bone mineral density in men with hypogonadism. In contrast, intramuscular testosterone administration did increase spine and hip BMD (Amory, et al. 2004).

G. Adverse Reactions:

Cardiovascular: Deep venous thrombosis, edema, hypertension, vasodilation.

Central nervous system: Aggressive behavior, amnesia, anxiety, blood pressure decreased, depression, dizziness, emotional lability, excitation, headache, insomnia, malaise, memory loss, mood swings, nervousness, seizure, sleep apnea, sleeplessness.
Dermatologic: Acne, alopecia, dry skin, hair discoloration, hirsutism (increase in pubic hair growth), pruritus, rash, seborrhea.

Endocrine & Metabolic: Breast soreness, gonadotropin secretion decreased, growth acceleration, gynecomastia, hot flashes, hypercalcemia, hyperchloremia, hypercholesterolemia, hyper-/hypokalemia, hyperlipidemia, hypernatremia, hypoglycemia, inorganic phosphate retention, libido changes, menstrual problems (including amenorrhea), virilism, water retention.

Gastrointestinal: Appetite increased, GI bleeding, GI irritation, nausea, taste disorder, vomiting, weight gain.

Genitourinary: Bladder irritability, epididymitis, impotence, oligospermia, penile erections (spontaneous), priapism, prostatic carcinoma, prostatic hyperplasia, PSA increased, testicular atrophy, urination impaired (Ruch W and Jenny P. 1989).

Hepatic: Bilirubin increased, cholestatic hepatitis, cholestatic jaundice, hepatic dysfunction, hepatic necrosis, hepatocellular neoplasms, liver function test changes, peliosis hepatis.

Hematologic: Anemia, bleeding, hematocrit/hemoglobin increased, leukopenia, polycythemia, suppression of clotting factors.

Local: Application site reaction (gel), injection site pain.

Transdermal System: Pruritus at application site, burn-like blisters under system, erythema at application site, vesicles at application site, allergic contact dermatitis to system, burning at application site, induration at application site.

Neuromuscular & Skeletal: Hyperkinesias, paresthesia, weakness.

Ocular: Lacrimation increased.
RENAL: Creatinine increased.

RESPIRATORY: Dyspnea.

MISCELLANEOUS: Anaphylactoid reactions, diaphoresis, hypersensitivity reactions, smell disorder. *(Borhan-Manesh F and Farnum JB, 1989).*

**H. Contraindications**

1. Hypersensitivity to testosterone or any component of the formulation; males with known or suspected carcinoma of the breast or prostate; pregnancy or women who may become pregnant; breast-feeding.

2. Depo-Testosterone: Also contraindicated in serious hepatic, renal, or cardiac disease.

3. Andriol: Also contraindicated in hepatic, renal, or cardiac disease; hypercalcemia; nephrosis or nephritic phase of nephritis; prepubertal males; patients who are easily sexually stimulated. *(Moller BB and Ekelund B, 1985).*

**Precautions**

- Hepatic effects: Prolonged use of high doses of androgens has been associated with serious hepatic effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, jaundice).

- Hypercalcemia: in patients with prolonged immobilization or cancer.

- Hypercholesterolemia: May alter serum cholesterol.

- Hypoglycemia: Has both androgenic and anabolic activity, the anabolic action may enhance hypoglycemia.

- Prostate cancer: May increase the risk of prostate cancer.

- Spermatogenesis: Large doses may suppress spermatogenesis.
• Benign prostatic hyperplasia: Urethral obstruction may develop in patients with BPH.

• Edematous conditions: Use with caution in patients with edematous conditions or medications (e.g., corticosteroids); as it may cause fluid retention.

• Sleep apnea: potentiate it in some male patients (obesity or chronic lung disease). (Moller BB and Ekelund B, 1985).

I. Drug Interactions:

CycloSPORINE (Systemic): Androgens may enhance the hepatotoxic effect of it and increase the serum concentration of CycloSPORINE (Systemic). Risk D.

Vitamin K Antagonists (e.g., warfarin): Androgens may enhance the anticoagulant effect of Vitamin K Antagonists. Risk D: Consider therapy modification (Moller BB and Ekelund B, 1985).
ESTERIFIED ESTROGEN

A. PHYSIOLOGY

Estrogens act most importantly on the reproductive organs, but they also act on other organ systems such as cardiovascular, skeletal, immune, gastrointestinal and neural sites. Estrogens act on the reproductive organs, cardiovascular organs and bone. Their major actions are genomic, mediated by nuclear estrogen receptors. (Deroo, et al. 2006).

B. MECHANISM OF ACTION

Esterified estrogens contain a mixture of estrogenic substances; the principle component is estrone. Estrogens are responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Estradiol is the principle intracellular human estrogen and is more potent than estrone and estriol at the receptor level; it is the primary estrogen secreted prior to menopause. In males and following menopause in females, estrone and estrone sulfate are more highly produced. Estrogens modulate the pituitary secretion of gonadotropins, luteinizing hormone, and follicle-stimulating hormone through a negative feedback system; estrogen replacement reduces elevated levels of these hormones. (Deroo, et al. 2006).

C. PHARMACODYNAMICS/KINETICS

ABSORPTION: Readily.

METABOLISM: Rapidly hepatic to estrone sulfate, conjugated and unconjugated metabolites; first-pass effect.

EXCRETION: Urine (as unchanged drug and as glucuronide and sulfate conjugates).
D.Dosing and Dosage Form:

Tablet: 0.3 mg, 0.625 mg, 1.25 mg, 2.5 mg. (Deroo, et al. 2006).

1. Prostate cancer (palliation): Oral: 1.25-2.5 mg 3 times/day.

2. Breast cancer (palliation): Oral: 10 mg 3 times/day for at least 3 months.

3. Osteoporosis in postmenopausal women: Oral: Initial: 0.3 mg/day and increase to a maximum daily dose of 1.25 mg/day. Monitor patients with an intact uterus for signs of endometrial cancer; rule out malignancy if unexplained vaginal bleeding occurs. (Mørch, et al. 2009).

E. Monitoring Parameters

Yearly physical examination that includes blood pressure and Papanicolaou smear, breast exam, mammogram. Monitor for signs of endometrial cancer in female patients with uterus. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Monitor for loss of vision, sudden onset of proptosis, diplopia, migraine; signs and symptoms of thromboembolic disorders; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias; thyroid function in patients on thyroid hormone replacement therapy. Also bone density measurement should be done (Grodstein, et al. 1997).

F. Therapeutic uses in non endocrine patients

1. Osteoporosis in postmenopausal women

**Selective estrogen receptor modulators**: Raloxifene is a tissue selective estrogen receptor modulator (SERM) that is used for the prevention and treatment of osteoporosis. It increases bone mineral density and
reduces the risk of vertebral fractures. Raloxifene also appears to lower the risk of breast cancer, does not stimulate endometrial hyperplasia or vaginal bleeding, and increases the risk of venous thromboembolism. Although it decreases serum total and low-density-lipoprotein (LDL) cholesterol concentrations, raloxifene does not appear to affect the risk of coronary heart disease (Barrett-Connor, et al. 2006).

Tamoxifen is another SERM used primarily for the prevention and management of breast cancer. It is not typically used for osteoporosis, but postmenopausal women who are receiving treatment with tamoxifen for breast cancer are probably receiving effective bone protection. Raloxifene considered one of the first-line drugs for prevention of osteoporosis. However, it is somewhat less effective than estrogen and bisphosphonates, although direct fracture prevention comparisons are lacking (Luckey, et al. 2004).

**Estrogen/progestin therapy**: As noted above, estrogen-progestin therapy is no longer a first-line approach for the treatment of osteoporosis in postmenopausal women because of increased risk of breast cancer, stroke, venous thromboembolism, and perhaps coronary disease (although the risk-benefit profile in the unopposed estrogen trial was different) (Rossouw, et al. 2002).

**2. Estrogen in cognitive function and alzheimer disease**

Several small, randomized clinical trials have evaluated estrogen treatment of women with Alzheimer disease, revealed that, estrogen therapy alone does not appear to be an effective treatment for Alzheimer disease. However, these studies are relatively small and cannot eliminate the possibility of a modest benefit from estrogen therapy (Hogervorst, et al. 2002).
3. Therapy in metastatic breast cancer

a- Selective estrogen receptor modulators

Tamoxifen inhibits the growth of breast cancer cells by competitive antagonism of estrogen at its receptor. However, its actions are complex, and tamoxifen also has tissue-specific partial estrogen agonist activity. The agonist effects can be both beneficial (prevention of bone demineralization) and detrimental (increased risk of uterine cancer and thromboembolic events). Drugs such as tamoxifen that exhibit a selective agonist/antagonist profile depending upon the specific organ or tissue are designated as "selective estrogen receptor modulators" (SERMs) to reflect these properties (Mauri, et al. 2006).

Tamoxifen is effective treatment for both premenopausal and postmenopausal women with hormone-responsive MBC. The duration of response is usually between 12 to 18 months, and in some patients, benefit may persist for several years. Survival benefit with third generation AIs as compared to tamoxifen. Tamoxifen remains a standard first-line agent for premenopausal women and for those postmenopausal women who have relapsed during or within 12 months of completing adjuvant therapy with an Aromatase inhibitors (AIS) (Bonneterre, et al. 2000).

Tamoxifen is well absorbed orally. A single daily 20 mg dose is recommended; higher doses are no more effective and are more toxic. Tamoxifen has a prolonged half-life of seven days. Steady state levels are reached after one month of therapy (Paridaens, et al. 2004).

A transient "flare reaction", as aside effect may occurs. Tamoxifen flare is a transient phenomenon and symptoms should resolve within four weeks (Paridaens, et al. 2004).
Drug resistance is the single biggest limitation of tamoxifen therapy for MBC. Tamoxifen is converted by the hepatic drug-metabolizing enzyme, cytochrome P450 2D6 (CYP2D6), to its active metabolite, endoxifen (Fisher, et al. 2005).

Toxicity: pulmonary embolus, deep venous thrombosis, strokes, cataracts, and endometrial cancer. Less serious but troublesome side effects of tamoxifen included hot flashes, nausea, and vaginal discharge (Fisher, et al. 2005).

Tamoxifen is an appropriate first-line agent in premenopausal women who have never received tamoxifen or who relapse at least 12 months after completion of adjuvant tamoxifen. It is also appropriate for postmenopausal women who have a disease relapse during or within 12 months of receiving adjuvant therapy with an AI. For postmenopausal women who receive an AI for initial endocrine therapy, tamoxifen is also an appropriate option for second-line therapy (Bhide, et al. 2004).

Toremifene is a SERM that is 40-fold less estrogenic than tamoxifen, an effect that might be expected to improve its side effect profile. Several trials and a meta-analysis directly comparing toremifene versus tamoxifen in patients with untreated MBC have concluded that both agents have comparable activity and a similar toxicity profile. Toremifene is cross-resistant with tamoxifen and is ineffective as second-line therapy in patients refractory to tamoxifen (Milla-Santos, et al. 2001).

b-Estrogen deprivation for premenopausal women:

Estrogen deprivation is an alternative to tamoxifen for first-line therapy in premenopausal women who relapse within 12 months of receiving adjuvant tamoxifen. It can be accomplished permanently by ovarian ablation or temporarily by the use of GnRH agonists (Dowsett, et al. 1992).
Ovarian ablation/suppression plus tamoxifen: Combination of oophorectomy or a GnRH agonist plus tamoxifen as first-line endocrine therapy could be recommended to premenopausal women with MBC who have either never received adjuvant tamoxifen or relapsed more than 12 months after completion of such therapy (Klijn, et al. 2001).

c-Sex steroid hormones

Patients who have low volume disease that is restricted to bone or soft tissue, few disease-related symptoms, and a history of a response to either tamoxifen or an AI (or both) may be considered candidates for third or fourth-line endocrine therapy using progestins, androgens, or estrogens. Of these, progestins are the most likely to be considered (Willemse, et al, 1990).

PROGESTINS:

Megestrol acetate and medroxyprogesterone acetate are progestational agents with significant activity in advanced breast cancer. As a group, progestins are associated with an increased risk of thromboembolic events; as a result, their use should be avoided in patients with thromboembolic disorders or other risk factors for thromboembolic disease. Medroxyprogesterone, which requires intramuscular administration, offers no clear advantage in terms of efficacy or safety. The optimal dose of megestrol acetate for the treatment of advanced breast cancer is 40 mg four times daily. Although early studies suggested that higher doses were more active, this was not confirmed in randomized controlled trials. Furthermore, higher doses were associated with more weight gain, fluid retention, and vaginal bleeding, and a lower quality of life (Abrams, et al, 1999).

They may inhibit aromatase activity or increase estrogen turnover, since estrogen levels fall during therapy. They may also act through the glucocorticoid receptor, androgen receptor, or progesterone receptor. Activity
appears to be maintained in patients who are refractory to tamoxifen (Abrams, et al, 1999).

Patients with prior heavy exposure to endocrine therapy (tamoxifen, megestrol acetate, AI) may still respond to estrogens. Although high dose estrogen (estradiol 30 mg daily in divided doses) has typically been used, lower doses (estradiol 6 mg daily in divided doses) may be just as effective with less toxicity. Pharmacologic doses of estrogen are limited by side effects (Ellis, et al, 2009).

4. Therapy in management of sexual dysfunction in females

Estrogens: Treatment with postmenopausal hormone therapy resulted in a significant decrease in dyspareunia and increases in sexual interest, orgasmic response and relationship satisfaction (Gast, et al. 2009).

5. Acne treatment

Combination oral contraceptives: Oral contraceptives containing other progestins are beneficial in acne vulgaris (Arowojolu, et al. 2007).

With anti-androgenic progestins: Oral contraceptives with anti-androgenic progestins are available as therapies for women with acne. These include oral contraceptives that contain cyproterone acetate, chlormadinone acetate, or drospirenone plus an estrogen (Huber, et al. 2006).

6. Therapy in endometriosis

Progestins: Inhibit endometriotic tissue growth by causing initial decidualization and eventual atrophy. They also inhibit pituitary gonadotropin secretion and ovarian hormone production, resulting in a mildly hypoestrogenic state relative to normal (Walch, et al. 2009).
7. Therapy in fibroid

**Estrogen-progestin contraceptives**: Many texts continue to suggest that estrogen-progestin contraceptive pills (OC) are contraindicated in women with uterine leiomyomas. OCs are associated with a decreased risk of leiomyomas and reduced symptoms from other concurrent gynecologic conditions, suggests that a therapeutic trial may be appropriate before proceeding to more invasive therapies. The purported mechanism of action is via endometrial atrophy (Viswanathan, et al., 2007).

**Progestin implants, injections, and pills**: cause endometrial atrophy and thus provide relief of menstrual bleeding-related symptoms. They can be considered for treatment of mild symptoms, especially for women who need contraception (Polatti, et al., 2000).

**Raloxifene**: The efficacy of selective estrogen receptor modulators for treatment of leiomyomas is unclear; while preclinical testing in animal models and treatment of postmenopausal women has been encouraging, clinical trials in reproductive age women have been less convincing (Lingxia, et al., 2007).

8. Hirsutism treatment

Oral contraceptives (Mathur, et al., 2008).

9. Hormonal therapy in Endothelial dysfunction

**Estrogen**: A potential mechanism for this beneficial effect is enhanced endothelial synthesis and release of NO. Another potential mechanism is a reduction in coronary endothelin-1 levels. Concurrent administration of progesterone offsets the beneficial effects of estrogen on endothelial function, without altering its LDL-lowering and antioxidant effects (Thompson, et al., 2000).
Selective estrogen receptor modulators: Tamoxifen and raloxifene have estrogen-like activity on some of the plasma cardiovascular risk factors, for example a decrease in low density lipoprotein and fibrinogen. Tamoxifen therapy produced a significant increase in endothelium-dependent flow mediated vasodilatation. In an animal model, raloxifene improved hypertension-induced endothelial dysfunction by increasing the bioavailability of NO (Wassmann, et al., 2002).

10. Initial hormone therapy for metastatic prostate cancer

Estrogens: Estrogens inhibit the release of luteinizing hormone releasing hormone (LHRH) from the hypothalamus, thus suppressing pituitary luteinizing hormone release and thereby reducing testicular production of testosterone. High estrogen levels thus can lower serum testosterone to castrate levels in one to two weeks by means of this negative feedback on the hypothalamic-pituitary axis. Estrogen may also compete with androgens for steroid hormone receptors and may thereby exert a direct cytotoxic effect on prostate cancer cells (Scherr, et al., 2002).

Parenteral or transdermal administration of estrogen avoids first-pass portal circulation, which may account for most of the toxicity of oral estrogens. Intramuscular estrogen has also been studied (Lycette, et al., 2006).

11. Treatment of retroperitoneal fibrosis

Tamoxifen: Desmoid tumors and retroperitoneal fibrosis are characterized by locally invasive fibroblast proliferation, although the pathobiology, clinical and histologic features differ. Used alone or in combination with corticosteroids, have been reported among patients with retroperitoneal fibrosis (Costanzi, et al., 2008).
12. Mifepristone in Bipolar disorders

Since high cortisol levels are also found in bipolar disorders, treatment with mifepristone has been evaluated in this situation. In a study of 20 bipolar patients treated with mifepristone (600 mg/day) or placebo, selective improvements in neurocognitive function were seen. This included spatial working memory performance, verbal fluency, spatial recognition memory and mood. In contrast to the improvement noted in patients with bipolar disorder, mifepristone had no effect on neurocognitive function or symptoms in patients with schizophrenia (Gallagher, et al. 2005).

13. Mifepristone in malignancies

Many tumors, both benign and malignant, are steroid-dependent. Even non-steroid-dependent tumors may contain steroid receptors. For this reason, PAs may be used in the treatment of some cancers. Studies in animals have suggested that PAs could be used in other tumors, including meningiomas, gliomas, as well as in ovarian and prostate cancer. It has also been reported that mifepristone had a beneficial effect in a woman with a uterine leiomyosarcoma which stained positively for the PR (Koivisto-Korander, et al. 2007).

14. Catamenial epilepsy

Medroxyprogesterone acetate (MPA) is a synthetic progestin-only contraceptive agent that suppresses normal ovulatory functioning. It is not metabolized to allopregnanolone, and its mechanism of action toward reducing seizure frequency may be related to progesterone effects alone. Support for MPA use in catamenial epilepsy comes from uncontrolled observational reports. Injections of MPA every 6 to 12 weeks were associated with an overall reduction in seizure frequency of 39 percent (Herzog, AG. 2008).
G. Adverse Reactions:

Cardiovascular: Edema, hypertension, venous thromboembolism.

Central Nervous System: Dizziness, headache, mental depression, migraine.

Dermatologic: Chloasma, erythema multiforme, erythema nodosum, hemorrhagic eruption, hirsutism, loss of scalp hair, melasma.

Endocrine & Metabolic: Breast enlargement, breast tenderness, libido, increased thyroid-binding globulin, increased total thyroid hormone (T4), increased serum triglycerides/phospholipids, increased HDL-cholesterol, decreased LDL-cholesterol, impaired glucose tolerance, hypercalcemia.

Gastrointestinal: Abdominal cramps, bloating, cholecystitis, cholelithiasis, gallbladder disease, nausea, pancreatitis, vomiting, weight gain/loss.

Genitourinary: Alterations in frequency and flow of menses, changes in cervical secretions, endometrial cancer, increased size of uterine leiomyomata, vaginal candidiasis.

Hematologic: Aggravation of porphyria, decreased antithrombin III and antifactor Xa, increased levels of fibrinogen, increased platelet aggregability and platelet count; increased prothrombin and factors VII, VIII, IX, X.

Hepatic: Cholestatic jaundice.

Neuromuscular & Skeletal: Chorea.

Ocular: Contact lens intolerance, corneal curvature steepening.
RESPIRATORY: Pulmonary thromboembolism.


Precautions:

- Breast cancer: Estrogens may increase the risk of breast cancer. An increase in abnormal mammograms has also been reported with estrogen and progestin therapy. Estrogen use may lead to severe hypercalce mia in patients with breast cancer and bone metastases.

- Dementia: The risk of dementia may be increased in postmenopausal women; increased incidence was observed in women $\geq$65 years of age.

- Endometrial carcinoma

- Lipid effects: As increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased.

- Ovarian cancer: Postmenopausal estrogen therapy and combined estrogen/progesterone therapy may increase the risk of ovarian cancer.


- Cardiovascular disease: Use caution with cardiovascular disease or dysfunction.

- Cholestatic jaundice: Use caution with history of cholestatic jaundice associated with past estrogen use or pregnancy.

- Diseases exacerbated by fluid retention: May be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes or renal dysfunction.

• Hepatic hemangiomas: Use with caution in patients with hepatic hemangiomas.

• Hypocalcemia: Use with caution in patients with severe hypocalcemia.

• Porphyria: Use with caution in patients with porphyria.

• SLE: Use with caution in patients with SLE.

• Osteoporosis use: When used solely for prevention of osteoporosis in women at significant risk, nonestrogen treatment options should be considered.

• Vulvar and vaginal atrophy use: When used solely for the treatment of vulvar and vaginal atrophy, topical vaginal products should be considered. (Grodstein, et al. 1997).

H. Contraindications

Hypersensitivity to estrogens or any component of the formulation; undiagnosed abnormal vaginal bleeding; history of or current thrombophlebitis or venous thromboembolic disorders; active or recent (within 1 year) arterial thromboembolic disease; carcinoma of the breast, except in appropriately selected patients being treated for metastatic disease; estrogen-dependent tumor; hepatic dysfunction or pregnancy. (Grodstein, et al. 1997).

I. Drug Interactions

Anastrozole: Estrogen Derivatives may diminish the therapeutic effect of Anastrozole. Risk X.

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). Risk C.

Somatropin: Estrogen Derivatives may diminish the therapeutic effect of Somatropin. Risk D.
Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. Risk C.

Ursodiol: Estrogen Derivatives may diminish the therapeutic effect of Ursodiol. Risk C.

Ethanol: Avoid ethanol (routine use increases estrogen plasma concentrations and risk of breast cancer). Ethanol may also increase the risk of osteoporosis.

Food: Folic acid absorption may be decreased. (*Mørch, et al. 2009*).
Summary and Conclusion

In the last two decades, great advance had been reached in the use of hormones, hormone analogues and hormone antagonists not only in the treatment but also in diagnosis of non endocrine diseases.

**THYROID HORMONES**

Thyroid hormones are critical determinants of brain and somatic development in infants and of metabolic activity in adults; they also affect the function of virtually every organ system. It has therapeutic uses in:

1. cardiac remodeling.
2. left ventricular dysfunction.
3. cardiac surgery.
5. Benign thyroid nodules.
6. human astrocytomas.
7. breast cancer cell proliferation.

**GnRH**

GnRH (also called luteinizing hormone releasing hormone or LHRH) used as therapy in many diseases as in:

1. Metastatic prostate cancer.
2. Breast Cancer.
3. Hisutism.
4. Fibroid.

5. Endometriosis.

**GROWTH HORMONE**

Growth hormone (GH), the most abundant anterior pituitary hormone recently used in:

1. performing enhancing drugs by athletes.

2. Therapy in Osteoporosis.

3. Therapy in short gut syndrome.

**SOMATOSTATIN**

Somatostatin is distributed throughout the entire body. SST analogues are present in short term and long term formulations. Act through inhibiting serotonin release, and the secretion of gastrin, VIP, insulin, glucagon, secretin, motilin, and pancreatic polypeptide. Also suppresses decreases splanchnic blood flow. Also has antitumor effects.

**Diagnostic applications**

**SCINTIGRAPHY AND AUTORADIOGRAPHY**

1. Non-Functioning Islet Cell Tumors.

2. Neuroendocrine Tumors.

3. CNS tumors.

4. Adenocarcinomas:

   GI cancers, hepatocellular carcinomas, breast carcinoma, renal cell carcinomas, prostate malignancies, ovarian cancer, nasopharyngeal carcinomas, lymphomas, melanomas, thymic tumors, mesenchymal tumorc, mercle cell tumors.
5. Granulomatous Disease.

6. Thyroid malignancy.

**Therapeutic applications**

1. CNS: Antipsychotic effect and Retinal disorders and epilepsy.

2. GIT: Treatment of active variceal bleeding and angiodysplasia.
   - Pancreatitis, post ERCP and post pancreatotomy, Diabetic nephropathy.

3. Liver diseases: Schistosomiasis and HCC.

4. Oncology: pituitary tumors, thyroid malignancies, gallbladder malignancies, cancer prostate and cervical tumor.

5. Polycystic kidney.

**VASOPRESSIN**

Vasopressin analogs and antagonists have a variety of therapeutic applications as:

1. Congestive heart failure and cirrhosis.

2. Von Willebrand Disease and Disorders of Coagulation.

3. Variceal Bleeding.


5. Hypertension.

6. Hepatorenal Syndrome.

7. Cardiac Arrest.

8. Heart failure.

10. Anesthesia-Induced Hypotension.

11. Post cardiotomy/Cardiopulmonary Bypass–Induced Hypotension.


13. Aggressive behavior.


15. Vasopressin in chronic fatigue syndrome.


17. Renal malignancies.

18. Nerve cell growth.

**PARATHYROID HORMONE**

Parathyroid hormone (PTH) is one of the two major hormones modulating calcium and phosphate homeostasis. Used in:

1. Treating bone marrow depletion in cancer patients

2. Therapy in Osteoporosis

**CALCITONIN**

Calcitonin inhibits osteoclasts and therefore bone resorption in pharmacologic doses. PTH used in:

1. Paget disease therapy.

2. Treatment of pain.

3. Myeloma cells in their osteoclast-like activity.

4. Anorectic effects.
5. Osteoporosis.

6. Medullary thyroid cancer.


**ERYTHROPOITIN**

Erythropoietin (EPO) is a glycoprotein growth factor that is the primary stimulus to erythropoiesis. It is mainly used in:

1. Anemia of chronic kidney disease.

2. Treatment of anemia in patients with cancer.

3. As hematopoietic growth factors.

**INSULIN**

Insulin indirectly or indirectly affects the function of virtually every tissue in the body. Its uses out of diabetes are:

1. Intensive insulin therapy during critical illness.

2. Aortic Valve and Coronary Surgery.

3. Alzheimer disease.

4. As enhancing drugs by athletes.

5. Treatment and prevention of hyperkalemia.

**GLUCOCORTICOIDS**

Pharmacologic doses of glucocorticoids are used to treat patients with inflammatory, allergic, immunological disorders. A number of factors that influence both the therapeutic and adverse effects of glucocorticoids.

**Allergic conditions:**
1. Treatment and prognosis of Churg-Strauss syndrome.

2. Chronic rhinosinusitis.

3. Treatment of atopic dermatitis.

4. Treatment of eosinophilic esophagitis.

5. Anaphylaxis.

6. Allergic bronchopulmonary aspergillosis.

7. Asthma management.

8. COPD.


**Glucocorticoids in immunological and vascular disorders**

1. Dermatomyositis and polymyositis in adult.
2. Wegener's granulomatosis and microscopic polyangiitis.
3. Rheumatoid Arthritis .
5. Acute cardiac allograft rejection.
8. Primary angiitis of the central nervous system.
9. Autoimmune pancreatitis.
10. Autoimmune hepatitis.
11. SLE.
12. Vasculitis.
15. IgA nephropathy.
18. Paroxysmal nocturnal hemoglobinuria.
19. Autoimmune hemolytic anemia.
20. Eales' disease.
22. Focal segmental glomerulosclerosis.
23. Membranoproliferative glomerulonephritis.

**Anti inflammatory therapeutic applications**

1. Pulmonary sarcoidosis.
2. Chronic inflammatory demyelinating polyneuropathy.
3. Acute gout.
5. Bronchopulmonary dysplasia.
7. Carpal tunnel syndrome.
10. Acute pericarditis.
11. Ulcerative proctitis, proctosigmoiditis, and left-sided (distal) colitis.
12. Treatment of retroperitoneal fibrosis.
13. To prevent restenosis following percutaneous coronary intervention.
15. Hepatic fibrosis.
16. Low back pain.
17. Septic shock.
18. In women at risk for preterm delivery.
20. Acute pain management in adults with sickle cell disease.


22. Brain tumor.

23. Polycystic ovary.

24. Hirsutism.

**Glucocorticoids in blood malignancies**


2. Natural killer (NK) cell large granular lymphocyte leukemia.


4. Primary central nervous system lymphoma.

**ANDROGEN**

Principal endogenous androgen responsible for promoting the growth and development of the male sex organs and maintaining secondary sex characteristics in androgen-deficient males. Therapeutic uses are:

1. As performing enhancing drugs by athletes.


3. Alzheimer disease.

4. Treatment of angina.


7. Fibroid.

8. Endometriosis.


10. Cancer anorexia and cachexia.
11. Osteoporosis in male.

**ESTROGEN**

Estrogens act most importantly on the reproductive organs, but they also act on other organ systems. Used in:

1. Osteoporosis in postmenopausal women.
2. Estrogen and cognitive function and AD.
3. Therapy in metastatic breast cancer.
4. Therapy in management of sexual dysfunction in females.
6. Therapy in endometriosis.
7. Therapy in fibroid.
9. Hormonal therapy in Endothelial dysfunction.
10. Initial hormone therapy for metastatic prostate cancer.
11. Treatment of retroperitoneal fibrosis.
12. Mifepristone in Bipolar disorders.

**Recommendations:**

Wide therapeutic application of hormones in practical field in Medicine.
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المملح العربي

لقد حدد تقدم هائل في استخدام الهرمونات وشبيهاتها ومضاداتها في إطار عقدين ليس فقط في علاج ولكن أيضا في تشخيص أمراض غير أمراض الغدد الصماء.

هرمونات الغدد الدرقية لها أهمية حيوية لضمان خلايا الخلايا بالعظام وتنظيم العمليات الحيوية للكبار كما أنها تدخل بوظيفة كل عضو بالجسم وتتضمن استخداماتها في غير أمراض الغدد الدرقية في:

1- إعادة كفاءة القلب
2- فشل وظائف القلب
3- ارتفاع نسبة الكوليسترول
4- أورام العظام
5- انتشار خلايا سرطان الثدي

الهرمون يستخدم في:

1- سرطان البروستاتا المنتشر
2- سرطان الثدي
3- مرض غزارة الشعر
4- أورام الرحم الليفيه
5- مرض تداخل خلايا الرحم

هرمون النمو حديثا يستخدم في:

1- كدواء محفز لبناء العضلات
2- في علاج هشاشة العظام
3- متلازمه نقص طويل الجهاز الهضمي

الهرمونات السيوتلينات يوجد في خلايا الجسم وتوجد شبيهاته في صورتين اما قصيره المفعول او طويل المفعول والتي تعمل عن طريق تثبيت هرمونات الجهاز الهضمي وأيضا في تحقيق ضغط الدم بالرغبة البطن الداخليه كما أنها لديها قدره مضادة للأورام
الاستخدامات التشخيصية:
1- أورام البنكرياس، المخ والجهاز الهضمي
2- الورم الحبيبي
3- أورام الغدد الدرقية

الاستخدامات العلاجية:
1- كعلاج أمراض الاكتئاب والصرع وأمراض شبكية العين
2- علاج النزيف الحاد بالجهاز الهضمي
3- التهاب البنكرياس مابعد منظار البنكرياس وبعد استئصال البنكرياس
4- التهاب الكلى المزمن بسبب مرض السكرى
5- البليارسيا وسرطان الكبد
6- تكييف الكلى

مضادات هرمون الفازوبورسين ونظائره للاستخدامات متعددة مثل:

1- فشل القلب والكبد
2- أمراض النزيف بالدم
3- ارتفاع ضغط الدم
4- خلل وظائف الكلى الذي سببه الكبد
5- توقف القلب
6- صدمة العدوى والنزيف
7- انخفاض ضغط الدم بسبب التخدير
8- أمراض الشخصي
9- أمراض التوحد
10- الهومن المزمن
11- أورام الكلى
12- تحفيز نمو الخلايا العصبية

هرمون الغدة الجار دايسي يعمل على تنظيم إيض الكالسيوم والفوسفات ويستخدم أيضاً في
1- علاج ضعف نخاع العظام الناتج عن أورام الجسم
2- علاج هشاشة العظام
3- إعطاء هرمون الكالسيتونين بحافز يساعد في تركيب العظام ويستخدم في:
   1- سرطان العظام
   2- انقطاع الشهية
   3- علاج الالام
4- هشاشة العظام
5- سرطان الغدد الدوائية
6- ارتفاع نسبة الكالسيوم بالدم

هرمون الأريثروبونتين يعمل كمحفز أساسي لتكوين كرات الدم الحمراء ويستخدم أيضا في:

1- علاج الأنيميا المزمنة
2- علاج الأنيميا في مرضى السرطان
3- كمحفز لتنشيط عمل نخاع العظام

هرمون الإنسولين يعمل مباشرة على خلايا الجسم كافه ويستخدم في:

1- كعامل تنظيمي للجسم في جراحات القلب والأمراض الحمراء
2- مرض النسيان (الزهايمر)
3- كعلاج محفز لبناء العضلات
4- علاج ووقاية من ارتفاع نسبة البوتاسيوم بالدم

الكورتيزونات لها استخدامات عديدة:

1- أمراض الحساسية: مرض شيرج، ستراؤز، التهاب الجيوب الانفية المزمن، حساسية الجلد، حساسية الصدر والتهاب الصدر المزمن
2- أمراض المناعة والأوعية الدموية: الزماتويد، الزئبة الحمراء، امراض الأوعية الدموية، التهاب الكبد والبنكرياس، أمراض المناعة بالدم، أمراض التهاب الكلى

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- كمضاف للالتهاب

- أورام الدم: مثل اللوكيميا وأورام الغدد الليمفاوية

- هرمونات الذكور لديها أهمية دون التكاثر مثل:

  1- كمحفز لبناء العضلات

  2- كمحفز للرغبة الجنسية للمرأة

- مرضا النسيان (الزهايمر)

- العلاج الزيادة الصدرية

- الفشل الوظيفي للخلايا المبطنية لجردات الأوعية الدموية

- أورام الثدي

- أورام الرحم الليفي وتداخل الأنسجة

- مرضا تكسير الدم الليلي

- هشاشة العظام

- هرمونات الأنوثة لها أهمية شديدة دون التكاثر للمراء مثل:

  1- هشاشة العظام

- مرضا النسيان (الزهايمر)

- أورام الثدي

- الفشل الوظيفي للخلايا المبطنية لجردات الأوعية الدموية

- فشل الوظائف الجنسية للمرأة

- علاج حب الشباب

- أورام الرحم الليفي وتداخل الأنسجة

- مرضا غزارة الشعر

- سرطان البروستاتا المنتشر
10-التصاقات الغشاء البريتوني
11-امراض الشخصية
12-الصرع
الاستخدامات العلاجية والتشخيصية للهرمونات لغير مرضى الغدد الصماء

رسالة مقدمة من الطبيبة إيمان محمد نجيب السيد إبراهيم

بكايلوس الطب والجراح

توظنه للحصول على درجة الماجستير في الباطنة العامة

تحت إشراف:

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كلية طب بنها
كلية طب بنها

أ. د./ أحمد محمود صالح

استاذ الباطنة العامة
كلية طب بنها
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