Normal Kidney Function

1. Extra Cellular Fluid Volume control
2. Electrolyte balance
3. Waste product excretion
4. Drug and hormone elimination/metabolism
5. Blood pressure regulation
6. Regulation of haematocrit regulation of calcium/phosphate balance (vitamin D3 metabolism)
The Nephron: Basic Kidney Functional Unit

- GFR: 125 ml/min (180 l/day)
- 99% reabsorbed
- Kidney uses active + passive transport to achieve this
A) Glomeruli:
Hydrostatic pressure in Afferent Arteriole = + 75 mm Hg-
Osmotic pressure of plasma Albumin = -- 25 mm Hg
Hydrostatic pressure in Bowman’s Capsule = -- 5 mm Hg
Net filtering pressure = + 45 mm Hg
Renal Blood Flow (RBF) = 1300 ml / min = 1/4 C.O.P.
Glomerular Filtration Rate (G.F.R.) = 125 ml / min = 180 Liter / day.
Only 1 -2 liters of urine is excreted / day = About 99% of filtrate is reabsorbed.
So the kidney can be considered as a Reabsorbing organ mainly.
1. **Site I**: Most of filtered NaCl (About 65%) is **Actively reabsorbed**
2. **Site II**: Some Na+ is reabsorbed in exchange for H+ under the effect of Carbonic Anhydrase Enzyme (CA.E.)
3. Na+ is reabsorbed with its iso-osmotic water = Obligatory water reabsorption.
4. Filtrate is isotonic.
5. Most of filtered K+, Glucose & amino-acids are reabsorbed.
6. Organic acids & bases are **Reabsorbed & Secreted** in P.C.T. e.g. Uric acid, penicillin, Diuretics & Probenecid.
Descending Limb

- No active transport
- Water permeable

odal limb loses $\text{H}_2\text{O}$ due to hypertonicity of interstitial fluid
- Concentrates the urine
- Ascending limb dilutes – only loses salt
**Distal Convoluted Tubule**

- **Site IV:** Early part of D.C.T.  
  = Cortical Diluting Segment →  
  Active Reabsorption of about 10% of Filtered NaCl.

- **Late part of D.C.T.** → Compensatory Na+ Reabsorption →  
  Limited Capacity (3-5%):  
  **Site V:** Na+ / H+ Exchange under the effect of C.A.E.  
  **Site VI:** Na+ / K+ Exchange under the effect of Aldosterone

Late Part of D.C.T. & Collecting tubules → Reabsorb water under the effect of A.D.H. = Facultative water reabsorption.
Collecting Duct

Permeability to water, salt under hormonal control

**Aldosterone (mineralocorticoid)**
- Increases sodium reabsorption
- Increases potassium excretion

**Antidiuretic hormone (ADH, Vasopressin)**
- Increases water permeability
- Increases urine osmolality

**Active transport sodium**

**Passive movement water**

**Important site for K⁺ balance**
- Na⁺ transport – lumen –ve potential
- Higher urine flow washes K⁺ away – increased [ ] gradient
Major functions of the kidney

Ultra filtration 1.

It removes fluid volume from the circulating blood, substances dissolved in this fluid are also removed.

Fluid and Electrolyte Control 2.

It maintains correct balance of fluid and electrolytes within a normal range by excretion, secretion, and reabsorption.

Acid-Base Balance 3.

It maintains pH at normal range by directly excreting hydrogen ions and forming bicarbonate for buffering.
Excretion of Waste Products 4.
Direct removal of metabolic waste products contained in the glomerular filtrate.

Blood Pressure Regulation 5.
It regulates blood pressure by controlling circulating volume and rennin secretion.

RBCs Production 6.
Erythropoietin secreted by kidneys stimulates bone marrow to produce RBCs.

Regulation of Calcium Phosphate Metabolism 7.
Vitamin D activation is regulated by kidneys.
Clinical Estimation of renal function

Clinical examination
pallor, volume status, blood pressure measurement, urinalysis

Blood tests
Routine Tests
haemoglobin level
electrolyte measurement (Na, K, Ca, PO$_4$)
urea
creatine normal range 70 to 140 μmol/l
Serum Creatinine and GFR

- concentration  Muscle metabolite proportional to muscle mass
  - High: muscular young men
  - Low: conditions with muscle wasting
    - elderly
    - muscular dystrophy
    - Anorexia
    - malignancy

70 to 140 μmol/litre  “Normal” range
Serum Creatinine (40 to 120 Micromoles/Litre)  

**Increased by:**
- Large muscle mass, dietary intake
- Drugs
- Interfere with analysis (Jaffe reaction) e.g. methyldopa, levodopa, dexamethasone, cephalosporins
- Inhibit tubular secretion e.g. cimetidine, trimethoprim, aspirin
- Ketoacidosis

**Decreased by:**
- Reduced muscle mass (elderly)
- Severe renal disease (increased secretion)
- Cachexia / starvation
- Immobility
- Pregnancy
S. creatinine approx. = 1/GFR

Serum Creatinine (mg/dL) vs. GFR (ml/min/1.73 m²)
Serum Urea (BUN – blood urea nitrogen) (2.5 – 7.5 mmoles/Litre)

Limitations as a marker:
It varies with the dietary protein intake •
Reabsorbed by the tubules •
Reabsorption varies with urine flow. Its clearance is independent of GFR at low urine flow rates •

Factors increasing serum urea
High protein diet •
Hypercatabolic conditions e.g. severe infection, burns, hyperthyroidism •
Gastrointestinal bleeding •
Muscle injury •
Drugs e.g. Glucocorticoids (with catabolism) Tetracycline •
Hypovolaemia •

Factors decreasing serum urea
Malnutrition •
Liver disease •
Sickle cell anaemia •
Other biochemical abnormalities seen in renal impairment

a) Raised Serum Potassium (3.5 to 5 mmol/L)
   When GFR < 5 ml/min – hyperkalaemia develops
   When serum potassium > 7 mmol/L – life threatening

b) Raised Serum Phosphate (0.8 to 1.2 mmol/L)
   Chronic Renal Failure leads to hyperphosphataemia

c) Decreased Serum Calcium (2.2 to 2.6 mmol/L)
   Linked to vitamin D production
   Patients with CRF are typically hypocalcaemic
Clinical Assessment  1(a).

<table>
<thead>
<tr>
<th>Basic Function</th>
<th>Sign</th>
<th>Symptom</th>
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<tbody>
<tr>
<td>Fluid Balance</td>
<td>Oedema, Raised JVP</td>
<td>Breathlessness</td>
</tr>
<tr>
<td>Electrolyte</td>
<td>Abnormal ECG</td>
<td>None</td>
</tr>
<tr>
<td>Regulation especially K⁺, Na⁺, PO₄ and calcium</td>
<td>Absent P waves</td>
<td>None</td>
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<td>Broad QRS complex</td>
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<td></td>
<td>Peaked T waves</td>
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<tr>
<td>EPO production</td>
<td>Pallor</td>
<td>Fatigue</td>
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<tr>
<td>Vitamin D3</td>
<td>Osteomalacia</td>
<td>Bone Pain</td>
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<tr>
<td>Excretion</td>
<td>Raised urea concentration in blood</td>
<td>Pruritis Nausea and vomiting</td>
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<td></td>
<td>Low pH and bicarb.</td>
<td>Deep and rapid respiration</td>
</tr>
</tbody>
</table>
The nephron and electrolyte handling

- **Na⁺-Cl⁻**
  - Gitelman's syndrome
  - *Thiazide sensitive*

- **Na⁺-K⁺, H⁺**
  - Liddle’s syndrome
  - Pseudohypoaldosteronism type-I
  - *Amiloride sensitive*

- **Na-K-2Cl**
  - ROMK
  - Bartter’s syndrome
  - *Bumetanide sensitive*
Diuretics
Drugs that increase the volume of urine by increasing water & solute excretion

I- Extra-Renal (Pre-Renal):
1. Water & Ethyl Alcohol $\rightarrow \downarrow$ Release of ADH $\rightarrow \downarrow$ Facultative water reabsorption.
2. Digitalis ONLY in cases of Heart Failure $\rightarrow$ +ve Inotropic $\rightarrow \uparrow$ C.O.P. $\rightarrow \uparrow$ R.B.F.
3. Albumin ONLY in cases of Hypoalbuminemia $\rightarrow$ Restore osmotic pressure of plasma $\rightarrow \uparrow$ Blood volume $\rightarrow \uparrow$ R.B.F.
4. Dobutamine ($\uparrow$ C.O.P.) & Dopamine ($\uparrow$ C.O.P. & Renal V.D. $\rightarrow \uparrow$ R.B.F.).
5. Methylxanthines eg Theophylline $\rightarrow \uparrow$ COP & Renal VD $\rightarrow \uparrow$ RBF + Renal effect.

II- Renal:

A) Natriuretics = Saluretics:
B) Osmotic Diuretics e.g. Mannitol
C) Acidifying Diuretics e.g. Ammonium Chloride.
Osmotic Diuretics

- Main example: Mannitol
- Filtered at glomerulus but not reabsorbed
- Increases urine osmolality
- Decreases water reabsorption
- Only diuretic acting outside nephron lumen
- Given IV (orally – osmotic diarrhoea)
- Uses: treatment of renal failure reducing intracranial, intraocular pressure (nb not a renal mechanism)
A) Natriuretics = Saluretics:

They ↓ Na+ reabsorption from the nephron → ↑ Na+ excretion in urine with its iso-osmotic (obligatory) water → Volume of urine.

**High Efficacy (High Ceiling) = Loop Diuretics:**
They act mainly on the Medullary part of thick ascending loop of Henle → ↓ C.C.M.S.
Examples: Frusemide & Ethacrynic acid.

**Moderate Efficacy Diuretics:**
They act mainly on the cortical diluting segment.
Examples: Thiazide diuretics & Thiazide analogues.

**Low Efficacy Diuretics:**
Carbonic Anhydrase Inhibitors e.g. Acetazolamide.
Potassium Retaining (Sparing or Conserving) Diuretics:
Aldosterone Antagonists e.g. Spironolactone.
Non-Aldosterone Antagonists e.g. Triamterene & Amiloride.
Hyperosmolar Medulla

Cortex

Thiazide diuretic (-)

Ca^{2+}  
Na^+  
K^+  
Cl^-

Lumen

Cl^-  
Na^+  
K^+

K retaining diuretic (-)

Spironolactone

Na^+  
K^+

Lumen

K^+  
-30 mV

Amiloride, Triamterene

Na^+  
K^+

Lumen

K^+  
-30 mV

Loop diuretic

Na^+K^+  
Cl^-

Lumen

2Cl^-  
K^+

2Cl^-/Na,K

ADH
Diuretics: general considerations

- All except osmotic diuretics act from inside lumen
- Pattern of electrolyte excretion varies with class
- Maximal response depends on site of action
- Effects can be additive or synergistic
**Carbonic anhydrase inhibitors:**

- **Azetazolamide**
  - Can trigger metabolic acidosis
  - Not in use as diuretic anymore
  - Primary indications is glaucoma (prevents production of aequous humor)

- **Dorzolamide**
  CA-inhibitors are sulfonamides => cross-allergenic with antibiotics etc.
Pharmacodynamics

III Anti-diuretic Effect:
1. Only in Nephrogenic Diabetes Insipidus = Insensitivity to A.D.H.
2. May be due to ↓ G.F.R.

IV Hyperglycemia: Open K+-channel → Hyperpolarization → ↓ Insulin release.

V Hyperlipidemia: ↑ Blood Cholesterol & Triglycerides.

VI Hyperuricemia: ↓ Uric acid excretion via competition in P.C.T.
II Antihypertensive Effect:
Thiazides are effective Anti-hypertensives even in sub-diuretic doses.
Mainly due to Direct Arteriolar V.D.:
K+-channel opener → Hyperpolarization.

NB) Diazoxide → Thiazide → Non-diuretic BUT Direct Arterial V.D.
Depletion of Na+ & Water from arteriolar wall →↓ Edema & ↓ Pressor effect of
noradrenaline & angiotensin.

Prostaglandins may play a role. NSAID # Antihypertensive effect of Thiazides
Diuretic → ↓ Blood volume → Temporary effect & NOT Essential.
**Therapeutic Uses of Thiazide Diuretics**

**Edema**: *Cardiac*, Hepatic or Renal. Thiazides are useful in Congestive Heart Failure (C.H.F.) due to:

Diuresis $\rightarrow$ ↓ Blood volume $\rightarrow$ ↓ V.R. $\rightarrow$ ↓ E.D.V. $\rightarrow$ ↓ Pre-load.

Arterial V.D. $\rightarrow$ ↓ T.P.R. $\rightarrow$ ↓ After-load.

Mild & Moderate **Hypertension**:
Useful even in use sub-diuretic doses.
Direct V.D. & ↓ Blood volume.
Antagonize edema induced by other Direct V.D. e.g. Hydralazine.

**Nephrogenic Diabetes Insipidus.**

**Premenstrual Syndrome** (P.M.S.) & Premenstrual Migraine.

**Idiopathic hypercaluria** & Renal calcium calculi (stones).
Useful in Hypocalcemia & Osteoporosis.
Pharmacodynamics

Diuretic Effect (cont.)

3- Some Thiazides e.g. Chlorothiazide → Weak ↓ Carbonic Anhydrase enzyme by their sulfonamide radical (*Not essential for the diuretic effect*).

4- Excess NaCl will reach the late part of D.C.T., where **PART** of Na+ is reabsorbed in exchange for K+ mainly & some H+. The remaining Na+ will be excreted in urine with its iso-osmotic water.

5- Thiazides ↓ R.B.F. & ↓ G.F.R. → They *NOT* indicated in renal insufficiency. Thiazides lose their diuretic effect when G.F.R. < 20 ml / minute.
**Adverse Effects & Toxicity of Thiazide Diuretics:**

*Hypokalemia* → Worsens Digitalis Toxicity, Liver & Kidney insufficiency. Hypokalemia can be avoided by:
- Intermittent use of least effective dose of the diuretic.
- Fruit juice.
- KCl supplement. Oral solution is less irritant than tablets.
- Add K+-retaining diuretic e.g. Spironolactone.
  - Hyponatremia.
  - Hypochloremic Alkalosis.
- Hypomagnesemia.
- Hypovolemia.
**Hypokalemic diuretic**

\[ \uparrow \text{Na in D.T} \rightarrow \uparrow \text{Na/K exchange} \]

<table>
<thead>
<tr>
<th>Thiazide</th>
<th>Loop diuretic (ceiling)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibit</strong> Na/Cl reabsorption in early D.T.</td>
<td><strong>Inhibit</strong> Na/K/Cl cotransport in thick asc. Part of loop of henle.</td>
</tr>
<tr>
<td>less</td>
<td>potent</td>
</tr>
<tr>
<td><strong>Delayed onset (1 h)</strong></td>
<td><strong>Rapid onset (20 m)</strong></td>
</tr>
<tr>
<td>longer</td>
<td><strong>Short duration</strong></td>
</tr>
<tr>
<td><em>NO</em></td>
<td>[ \uparrow \text{GFR} (\text{act at GFR}&lt;20\text{ml/m}) ]</td>
</tr>
<tr>
<td>arteriolodilator</td>
<td>No</td>
</tr>
<tr>
<td>Thiazide</td>
<td>Loop diuretic (ceiling)</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>- ↑serum Ca</td>
<td>- ↓serum Ca (↓ excretion)</td>
</tr>
<tr>
<td>- ↓K, Mg, Na &amp; potency.</td>
<td>- More</td>
</tr>
<tr>
<td>- ↑ glucose, uric acid, lipid, allergy, oto/nephrotoxicity</td>
<td>- More</td>
</tr>
<tr>
<td></td>
<td>&amp; hypovolaemia</td>
</tr>
<tr>
<td>2-hypocalcemia, idiopathic hypercalcuria</td>
<td>2-renal failure</td>
</tr>
<tr>
<td>3-diabetes insipidis</td>
<td>3-hypercalcemia</td>
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<td></td>
<td>4-hypertension (Th. tolerance, Renal impairment)</td>
</tr>
<tr>
<td>e.g: Hydrochlorothiazide (6h), clorthalidone, indapamid (2 4h)</td>
<td>frusemide, bumetanide, ethacrynic acid, Indacrynic acid (uricosuric)</td>
</tr>
<tr>
<td>Condition</td>
<td>CIRRHOSIS</td>
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<tr>
<td>Furosemide</td>
<td>40 to 80</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>1 to 2</td>
</tr>
<tr>
<td>Torsemide</td>
<td>10 to 20</td>
</tr>
</tbody>
</table>

Protein Binding Increases Ceiling Dose
Impaired Delivery Increases Ceiling Dose
IMPORTANT DRUG INTERACTIONS

**NSAIDS**
- Salt
- Decongestants
- Probenecid

**Hyperkalemia** - Induced by K-Sparing Diuretics

**Diminished Diuretic Response**

**ACE Inhibitors**
- Beta-Blockers
- K Supplements
- K-Sparing Diuretics
- Heparin

**Hyperkalemia-Induced by K-Sparing Diuretics**

**Ototoxic Drugs**

**Enhanced Ototoxicity of Loop Diuretic**
DROP Thiazide & ADD Loop Diuretic:
1) Titrate Single Daily Dose to Ceiling
2) Optimize Frequency of Ceiling Dose
   - Furosemide: up to 4X daily
   - Bumetanide: up to 6X daily
   - Torsemide: up to 3X daily

ADD Thiazide:
- If CrCl > 50, use 50 to 100 mg/d HCTZ

ADD K-Sparing Diuretic:
- If CrCl > 75
- If Urinary [Na]:[K] ratio is < 1
  (Note: May add K-Sparing Diuretic to Loop and/or Thiazide Diuretic at any point in algorithm for K homeostasis.)

ADD Thiazide Diuretic:
- CrCl > 50, use 25 to 50 mg/d HCTZ
- CrCl 20 to 50, use 50 to 100 mg/d HCTZ
- CrCl < 20, use 100 to 200 mg/d HCTZ

While Maintaining Other Diuretics, Switch Loop Agent to Continuous Infusion

Spironolactone Titrated to 400 mg Daily.
Results of dietary protein deficiency, hypo-albuminemia and insufficient plasma oncotic pressure can vary from subtle to extreme.

Would a diuretic help these kids appreciably?
Hypokalaemia (low potassium levels)

- Major problem with loop diuretics, thiazides
- Increased NaCl passed on to collecting duct increases transport across PRINCIPAL cells
- Increases lumen –ve potential leading to K⁺ loss
- Increased volume of urine: increased flushing of K⁺
K. sparing diuretics (hyperkalemic)

- Act on distal tubule → increase exchange diuretic, combination with thiazide.

- Precaution in R. impairment and added ACEIs

- Classified into:
  
  A) Aldestrone antagonists (spironolactone)

  - Delayed onset (2-3 days)
  
  - Used only in presence of hyperaldosteronemia

    e.g: Heart failure, hepatic failure

    - Side effect: gynecomastia in male, change of voice and irregular menses in female, antagonise digitalise and carbenoxalole,
Potassium Sparing Diuretics

- General mechanism: decrease trans-principal cell Na\(^+\) movement, decrease –ve lumen potential

- Main examples: Spironolactone, amiloride, triamterene
B) Na channel blockers:

- Rapid onset, Not dependent on aldosterone
- Decrease of Ca, H in urine
- Usually used in combination with hypokalemic diuretics

E.g. *Triametrine (uricosuric), not used in hepatic impairment or renal stones

*amiloride
INDICATIONS FOR K+ SPARING DIURETICS

• Primary hyper-aldosteronism, or that secondary to various other causes: e.g. congestive heart failure

• Can be effective in edema or ascites from hepatic disease in some patients; however, ascites with advanced cirrhosis is not easily treated

• Available in combination tablet with K+ wasting thiazide diuretics for opposing, counteracting hyper-kalemic and hypo-kalemic side effects.

• Aldosterone excess might also have direct unexplained pathogenic effect on heart (speculative).

• Eplerenone: newer ALDO receptor antagonist. Good for CHF and improvement in survival after MI.
VOLUME SIGNALS: NATRIURETIC PEPTIDE AND ANTIDIURETIC HORMONE.

A. Natriuretic peptides are covered elsewhere (see text). Nesiritide is a recombinant NP approved for decompensated CHF.

B. Anti-diuretic hormone, or vasopressin, is secreted by the hypothalamus in response to volume depletion or increased osmolality. ADH causes increased cAMP and insertion of aquaporin water channels into luminal membrane. This permits outflow of water down osmolar gradient into the interstitium. and venous return.
• ADH normally increases CD permeability to water (but not Na+), permitting H₂O outflow driven by trans-epithelial osmotic driving force (1,200 milliosmolar outside the tubule) (P. 313).

• The cortico-medullary osmolar gradient is driven by the Na⁺ /K⁺ /2Cl co-transporter in ascending limb, and the counter-current exchange.

• Failure to secrete vasopressin from pituitary prevents water reabsorption and causes large volumes of dilute urine.

• DESMOPRESSIN is analogue of ADH, and is ADH receptor agonist, causing anti-diuresis or decreased urine flow.

• Lithium in psychiatric practice causes large diuresis of 1 liter/day excess dilute urine by cAMP-related mechanism.
Diuretics are widely used with *or* without good evidence for benefits versus risks.

Some say they are over prescribed. However, in controlled trials side effects are being found acceptable, e.g. moderate K+ abnormalities.

NHLBI website provides summary of sound medical practice.

Here, and in your text, several of the conditions for diuretic use are summarized (there are many others):

1. ”Essential” hypertension (various causes)
2. Heart failure
3. Nephrotic syndrome
4. Edema and ascites of cirrhosis
5. Brain edema (above)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Uses</th>
<th>Side Effects/Toxicities</th>
<th>Interactions/Contraindications</th>
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</thead>
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<td><strong>OSMOTIC DIURETICS</strong></td>
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<tr>
<td><em>Mechanism—Act as an osmole, opposing water reabsorption along the nephron</em></td>
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<tr>
<td>Mannitol</td>
<td>↑ Intracranial pressure</td>
<td>Hypernatremia</td>
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<td></td>
<td>↑ Intraocular pressure</td>
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<tr>
<td><strong>LOOP DIURETICS</strong></td>
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<tr>
<td><em>Mechanism—Competitively inhibit Na⁺-K⁺-2Cl⁻ cotransporter (thick ascending limb of Henle; apical membrane)</em></td>
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<tr>
<td>Furosemide</td>
<td></td>
<td>All loop diuretics can be used in:</td>
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<tr>
<td></td>
<td></td>
<td>CHF, acute renal failure</td>
<td>All loop diuretics can cause:</td>
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<tr>
<td>Bumetanide</td>
<td></td>
<td>Edematous states (see Notes)</td>
<td>Volume contraction</td>
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<td>Torsemide</td>
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<td>Hypercalcemia</td>
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<td>Ethacrynic acid</td>
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<td>Hyperkalemia</td>
<td>Ototoxicity</td>
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<td>Hypokalemia</td>
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<td>Hyperuricemia</td>
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<tr>
<td><strong>THIAZIDE DIURETICS</strong></td>
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<tr>
<td><em>Mechanism—Competitively inhibit Na⁺-Cl⁻ co-transporter (distal convoluted tubule; apical membrane)</em></td>
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<td>Hydrochlorothiazide</td>
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<td>All thiazide diuretics can be used in:</td>
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<tr>
<td>Hydroflumethiazide</td>
<td></td>
<td>CHF and hypertension</td>
<td>All thiazide diuretics can cause:</td>
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<tr>
<td>Chlorothalidone</td>
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<td>Osteoporosis (rare)</td>
<td>Hypokalemia metabolic alkalosis</td>
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<td>Bendroflumethiazide</td>
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<td>Nephrogenic diabetes insipidus</td>
<td>Impaired glucose tolerance</td>
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<td>Polyzide</td>
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<td>Hyperuricemia</td>
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<td>Metolazone</td>
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<td>Indapamide</td>
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<td><strong>POTASSIUM-SPARING DIURETICS</strong></td>
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<td><em>Mechanism—Decrease collecting duct Na⁺ reabsorption; see Notes.</em></td>
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<tr>
<td>Spironolactone</td>
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<td>CHF, liver failure</td>
<td>Hyperkalemia</td>
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<td>Metabolic acidosis</td>
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<td>Gynecomastia</td>
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<td>Eplerenone</td>
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<td>tion, hypertension</td>
<td>Metabolic acidosis</td>
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<td>Amiloride</td>
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<td>CHF, Liddle syndrome</td>
<td>Hyperkalemia</td>
<td></td>
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<tr>
<td>Triamterene</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### INHIBITORS OF ANGIOTENSIN-CONVERTING ENZYME (ACE)
*Mechanism—Inhibit conversion of AT1 to ATII; also increase bradykinin by ↓ degradation*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Uses</th>
<th>Side Effects/Toxicities</th>
<th>Interactions/Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>All ACE inhibitors can be used in:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension (especially in diabetes)</td>
<td>All ACE inhibitors can cause: Cough</td>
<td>Hyperkalemia can occur with K+-sparing diuretics</td>
</tr>
<tr>
<td>Enalapril</td>
<td>CHF</td>
<td>Angioedema</td>
<td>All ACE inhibitors are contraindicated in: Pregnancy</td>
</tr>
<tr>
<td>Benazepril</td>
<td>Myocardial infarction</td>
<td>Hypotension</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Fosinopril</td>
<td></td>
<td>Acute renal failure (bilateral renal artery stenosis)</td>
<td>Bilateral renal artery stenosis</td>
</tr>
<tr>
<td>Trandolapril</td>
<td></td>
<td>Hyperkalemia</td>
<td></td>
</tr>
<tr>
<td>Quinapril</td>
<td></td>
<td>Rash</td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moexipril</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perindopril</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### INHIBITORS OF ANGIOTENSIN RECEPTORS
*Mechanism—Competitive antagonists of AT1 receptor*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Uses</th>
<th>Side Effects/Toxicities</th>
<th>Interactions/Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>All AT1-antagonists can be used in hypertension</td>
<td></td>
<td>All AT1-antagonists are contraindicated in: Pregnancy</td>
</tr>
<tr>
<td>Losartan</td>
<td></td>
<td></td>
<td>Bilateral renal artery stenosis</td>
</tr>
<tr>
<td>Irbesartan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telmisartan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valsartan</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### NATRIURETIC PEPTIDE
*Mechanism—Multiple, including vascular smooth muscle relaxation and antagonism of ADH*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Uses</th>
<th>Side Effects/Toxicities</th>
<th>Interactions/Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nesiritide</td>
<td>Decompensated CHF</td>
<td>Hypotension</td>
<td>Caution when used in combination with ACE inhibitors</td>
</tr>
</tbody>
</table>

### CARBONIC ANHYDRASE INHIBITORS
*Mechanism—Noncompetitively inhibit carbonic anhydrase II and IV (proximal tubule; apical membrane and cytoplasm)*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Uses</th>
<th>Side Effects/Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>CHF, glaucoma, gout</td>
<td>Metabolic acidosis</td>
</tr>
</tbody>
</table>
Normal glucose homeostasis¹,²

Net balance ~0 g/day

Glucose input ~250 g/day:
- Dietary intake ~180 g/day
- Glucose production ~70 g/day
- Gluconeogenesis
- Glycogenolysis

Glucose uptake ~250 g/day:
- Brain ~125 g/day
- Rest of the body ~125 g/day

The kidney filters circulating glucose
Glucose filtered ~180 g/day

The kidney reabsorbs and recirculates glucose
Glucose reabsorbed ~180 g/day

Existing and novel mechanisms to reduce hyperglycaemia in Type 2 diabetes

**Insulin-dependent mechanisms**

1. **Insulin action**
   - Thiazolidinediones
   - Metformin
   - Adipose tissue, muscle and liver

2. **Insulin release**
   - Sulphonylureas
   - GLP-1R agonists*
   - DPP4 inhibitors*
   - Meglitinides

3. **Insulin replacement**
   - Insulin

**Glucose utilisation**

*In addition to increasing insulin secretion, which is the major mechanism of action, GLP-1 agonists and DPP4 inhibitors also act to decrease glucagon secretion. DDP4, dipeptidyl peptidase-4; GLP-1R, glucagon-like peptide-1 receptor.

**Insulin-independent mechanism**

SGLT2 inhibition

**Glucose excretion/caloric loss**

Glucose transporters SGLT1 and SGLT2:

**Glucose**

- **Site**
  - SGLT1: Intestine, kidney
  - SGLT2: Kidney

- **Sugar specificity**
  - SGLT1: Glucose or galactose
  - SGLT2: Glucose

- **Glucose affinity**
  - SGLT1: High $K_m=0.4 \text{ mM}$
  - SGLT2: Low $K_m=2 \text{ mM}$

- **Gl. transport capacity**
  - SGLT1: Low
  - SGLT2: High

- **Role**
  - SGLT1: Dietary absorption of glucose and galactose, Renal glucose reabsorption
  - SGLT2: Renal glucose reabsorption

**Equation:**

$$(180 \text{ L/day}) \times (900 \text{ mg/L}) = 162 \text{ g/day}$$

**Diagram:**

- SGLT1 at S1 and S3
- SGLT2 at S1
- No glucose at S3
Dapagliflozin: A novel insulin-independent approach to remove excess glucose

Dapagliflozin selectively inhibits SGLT2 in the renal proximal tubule

*Increases urinary volume by only ~1 additional void/day (~375 mL/day) in a 12-week study of healthy subjects and patients with Type 2 diabetes.4

Treatment with an SGLT2 inhibitor: clinical benefits in type 2 diabetes mellitus

**Sustained glucose lowering**
- Potential prevention of microvascular morbidity
- Decrease in glucotoxicity

**Insulin-independent mechanism**
- Efficacy at all stages of the disease
- Possibility of combination with antihyperglycaemics of other classes
- Stable control in combination with insulin and insulin secretagogues

**Osmotic diuresis**
- Initial weight loss
- Decrease in blood pressure

**Loss of excess calories**
- Sustained weight loss
- Mitigation of weight gain caused by antihyperglycaemics of other classes

---

Nephrotoxic Drugs

• Dose dependant toxicity
  – NSAIDs including COX 2
  – Aminoglycosides
  – Radio opaque contrast materials

• Idiosyncratic Renal Damage
  – NSAIDs
  – Penicillins
  – Gold, penicillamine
NSAIDs (Non-steroidal anti-inflammatory drugs)

• Commonly used
  – Interfere with prostaglandin production, disrupt regulation of renal medullary blood flow and salt water balance

• Chronic renal impairment
  – Habitual use
  – Exacerbated by other drugs (anti-hypertensives, ACE inhibitors)
  – Typical radiological features when advanced
Examples of Nephrotoxicants

I) Nephrotic syndrome (glomerular filtration injury & proteinuria) e.g. lead

II) Nephritic syndrome (glomerular filtration injury & haematuria) e.g. amphetamine

III) Tubular necrosis e.g. Lead, Cadmium, Mercury, CCl4, CHCL3, radiocontrast, aminoglycosides, cephalosporines

VI) Obstructive Uropathies:
   - Intrarenal (toxicant crystal deposition) e.g. sulphonamide
   - Extrarenal (due to retroperitoneal fibrosis) e.g. methysergide.
Diabetic Nephropathy

Result of these hemodynamic changes is increased pressures and flows in the glomerulus or hyperfiltration.
# Summary of use of ACEIs and ARBs in CKD

1. **Indications**
   - Diabetic kidney disease
   - Nondiabetic kidney disease with spot urine total protein-to-creatinine ratio >200 mg/g
   - Consider in kidney transplant recipients with spot urine total protein-to-creatinine ratio >500-1,000 mg/g

2. **Doses Used in Controlled Trials (mg/d)**
   - ACE inhibitors (benazepril 30, captopril 100, lisinopril 20, perindopril 4, ramipril 10, trandolapril 3)
   - ARBs (candesartan 16, irbesartan 300, losartan 100, valsartan 160)

3. **Side-Effects**
   - Hypotension, early decrease in GFR, hyperkalemic, cough, angioneurotic edema, rash, contraindicated in 2nd and 3rd trimesters of pregnancy (recommend contraception to women of child-bearing age)

4. **Causes of Early Decrease in GFR**
   - ECF volume depletion, hypotension, renal artery disease (bilateral or unilateral with a solitary kidney)

5. **Causes of Hyperkalemia**
   - Increased potassium intake (high potassium foods, supplements, herbal supplements, transfusions, salt substitutes)
   - Metabolic acidosis
   - Acute GFR decline
   - Drugs (beta-blockers, heparin, NSAID, Cox 2 inhibitors, heparin, digoxin overdose, potassium supplements, herbal supplements, potassium-sparing diuretics, cyclosporine, tacrolimus, pentamidine, trimethoprim, lithium.
   - Laboratory error

6. **Frequency of Monitoring for Side Effects (Blood Pressure, GFR, Serum Potassium)**
   - If SBP <120 mm Hg, GFR <60 mL/min/1.73 m², change in GFR ≥15%, or serum potassium >4.5 mEq/L,
     - ≤4 weeks after initiation or increase in dose, or
     - 1-6 months after blood pressure is at goal and dose is stable.

7. **Conditions in which ACE Inhibitors or ARBs Should Not be Used or Used with Caution**
   - Pregnancy
   - History of cough, angioedema or other allergic reaction
   - Bilateral renal artery stenosis
   - Serum potassium >5.5 mEq/L despite treatment
   - GFR decline >30% within 4 months without explanation
Electrolyte correction

<table>
<thead>
<tr>
<th>GFR (ml/min/1.73 m²)</th>
<th>Stage of CKD</th>
<th>Phosphorus (mg/dl)</th>
<th>Corrected Calcium (mg/dl)</th>
<th>Ca × P**</th>
<th>Monitoring Frequency of Calcium, Phosphorus and Ca × P</th>
<th>iPTH (pg/ml)</th>
<th>Monitoring of iPTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–59</td>
<td>3</td>
<td>2.7–4.6</td>
<td>Within normal limits</td>
<td>&lt; 55</td>
<td>Every year</td>
<td>35–70</td>
<td>Every year</td>
</tr>
<tr>
<td>15–29</td>
<td>4</td>
<td>2.7–4.6</td>
<td>Within normal limits</td>
<td>&lt; 55</td>
<td>Every 3 months</td>
<td>70–110</td>
<td>Every 3 months</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>5</td>
<td>3.5–5.5</td>
<td>8.4–9.5</td>
<td>&lt; 55</td>
<td>Every month</td>
<td>150–300</td>
<td>Every 3 months</td>
</tr>
</tbody>
</table>

*Target ranges and monitoring frequency of biochemical parameters based on stage of CKD. Once pharmacotherapy is initiated, monitoring may be performed more frequently to assess treatment safety and efficacy.

**Calcium × phosphorus product calculated by multiplying the corrected calcium concentration by the phosphorus concentration
Examples of Phosphate-Binding Medications and Initial Dosing Information (Tomasello, 2008)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage Form</th>
<th>Initial Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcium-Containing Phosphate Binders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium acetate (prescription only)</td>
<td>667-mg capsules</td>
<td>667–1,334 mg</td>
</tr>
<tr>
<td>Calcium carbonate (nonprescription products; not preferred)</td>
<td>250- to 1,000-mg tablets</td>
<td>500–1,000 mg</td>
</tr>
<tr>
<td><strong>Aluminum-Containing Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aluminum hydroxide (nonprescription products)</td>
<td>300 mg/5 ml suspension</td>
<td>1,200–1,800 mg</td>
</tr>
<tr>
<td></td>
<td>600 mg/5 ml suspension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>300- to 600-mg tablets</td>
<td></td>
</tr>
<tr>
<td><strong>Newer Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sevelamer hydrochloride (prescription only)</td>
<td>400- and 800-mg tablets</td>
<td>800–1,600 mg</td>
</tr>
<tr>
<td>Lanthanum carbonate (prescription only)</td>
<td>250-, 500-, 750-, and 1,000-mg chewable tablets</td>
<td>500–1,000 mg</td>
</tr>
</tbody>
</table>

All doses should be administered three times a day with meals and also with snacks if necessary.
### Summary of the Pharmacotherapeutic Management of Chronic Renal Failure

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adult dose</th>
<th>Onset</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ca</strong>&lt;sup&gt;++&lt;/sup&gt; Gluconate</td>
<td>Up to 9.4 mEq of Ca&lt;sup&gt;++&lt;/sup&gt; (20 mL) iv over 3 min.</td>
<td>Immediate</td>
<td>5 - 20 min</td>
<td>Contraindicated in pts receiving digoxin. Don't mix with HCO&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;-&lt;/sup&gt;. May use an equivalent amount of CaCl&lt;sub&gt;2&lt;/sub&gt;.</td>
</tr>
<tr>
<td><strong>Insulin + glucose</strong></td>
<td>5 U + 50 mL D50W or multiple thereof (ratio is 1 unit per 5 g)</td>
<td>30 - 60 min</td>
<td>3 - 4 hrs</td>
<td>Monitor glucose level. This treatment should be preceded by the administration of Ca salt.</td>
</tr>
<tr>
<td><strong>NaHCO&lt;sub&gt;3&lt;/sub&gt;</strong> (1 mEq/mL)</td>
<td>50 mEq over 2 - 5 min</td>
<td>30 - 60 min</td>
<td>0.5 - 3 hrs</td>
<td>large Na load</td>
</tr>
<tr>
<td><strong>Albuterol</strong> (β-agonist)</td>
<td>0.5 mg iv over 15 min</td>
<td>&lt;30 min</td>
<td>2 - 6 hrs</td>
<td>May use nebs in place of iv; watch for tachycardia and tremor.</td>
</tr>
<tr>
<td><strong>Na polystyrene sulfonate</strong></td>
<td>Up to 60 g PO or Rectally. May repeat after 3 hrs.</td>
<td>2 - 3 hrs</td>
<td>---</td>
<td>Each gram of resin removes 1 mEq of K and adds 2 mEq of Na. Preparation contains sorbitol to prevent constipation.</td>
</tr>
<tr>
<td><strong>Dialysis</strong></td>
<td>---</td>
<td>Hours</td>
<td>Variable</td>
<td>---</td>
</tr>
</tbody>
</table>
Thank you
Hypomagnesemia

Metabolic Alkalosis

Hypokalemia

Profound ECFV Depletion

Hypocalcemia

Ototoxicity

Hyperuricemia

Hypomagnesemia

Hyperglycemia

Increase Na Excretion to 5% of Filtered Load

Treatment for Hypertension

Treatment for Nephrogenic Diabetes Insipidus

Decrease Ca Excretion

Treatment for Calcium Nephrolithiasis

Treatment for Mild Edema
6. Hypercalcemia.
8. Hyperlipidemia.
10. Hypersensitivity & Cross allergy with other sulfonamides e.g. Antibacterial.
13. Fetotoxic.
Contraindications of Thiazide Diuretics:

Digitalis toxicity (Hypokalemia, Hypomagnesemia & Hypercalcemia).
With corticosteroids (Hypokalemia).
Advanced liver disease.
Advanced renal disease. Thiazides $\rightarrow \downarrow$ R.B.F. & $\downarrow$ G.F.R.
Diabetes mellitus (Hyperglycemia).
Gout (Hyperuricemia).
Pregnancy (Fetotoxic).
* Preparations of Thiazide Diuretics:

All → Absorbed Orally & Excreted in P.C.T. # Probenecid.

500-1000 mg/day
- Water soluble

1- Chlorothiazide

25-100 mg/day
- Rapid excretion

2- Hydrochlorothiazide (Hydrex)

3- Hydroflumethiazide

25-100 mg/day
- Onset 1 hour

4- Bendroflumethiazide

2.5-15 mg /day
- Short duration 6-12 hs.

5- Trichlormethiazdie

1-4 mg/day
- Lipid soluble

6- Polythiazide

1-4 mg/day
- Slow excretion → Long duration 24 hs

7- Cyclothiazide

1-2 mg/day
- Onset 1 hour.
* Thiazide Analogues:
Differ from thiazide chemically but similar pharmacology + Long Duration

1- **Chlorthalidone** *(Hygroton)*: 50 mg/day Long duration
2- **Indapamide** *(Natrilix)*: 2.5 mg/day

a- Calcium channel blocker → Direct arterial V.D.
b- Used in sub-diuretic dose in treatment of hypertension.
c- Minimal effect on electrolytes, glucose & uric acid.
d- Depends on *Biliary* excretion → Safe in renal patients.
e- Long duration → Effective in a single Oral dose (2.5 mg/day)

3- **Clopamide** *(Brinerdin)*
4- **Xipamide** *(Epitens)*.
5- **Quinethazone**
6- **Metolazone** → Effective even G.F.R. < 20 ml/min
II- Loop Diuretics

“High Efficacy or High Ceiling Diuretics”

1- Sulfonamides: Frusemide, Torsemide, Bumetanide, Piretanide & Mefruside.

2- Non-Sulfonamides: Ethacrynic acid, Indacrinone & Tienilic acid.
1- Furosemide (Furosemide, *Lasix*):

*Pharmacokinetics:*

1- Well absorbed Orally.

2- Extensively bound to plasma proteins → Displaces Warfarin.

3- Hepatic metabolism.

4- Active excretion in P.C.T. # Probenecid → Antagonize its diuretic effect.

5- Prompt (quick) onset & Short Duration:

a- Orally (20 – 80 mg) → Onset 15 - 30 minutes & Duration 4 - 6 hours

b- I.V. (20 – 40 mg) → Onset 2 – 10 minutes & Duration 2 - 3 hours.
Nephrotoxic Drugs

Dose dependant toxicity

- NSAIDs including COX 2 –
- Aminoglycosides –
- Radio opaque contrast materials –

Idiosyncratic Renal Damage

- NSAIDs –
- Penicillins –
- Gold, penicillamine –
* **Pharmacodynamics:**

1- **Diuretic Effect:**
   1- Powerful (High efficacy), Prompt onset & Short Duration.
   2- Frusemide *Must* be excreted in PCT to act from inside Nephron # Probenecid.

3- Acts *Mainly* on the Medullary Part of Thick Ascending Loop of Henle → ↓ Na⁺ / K⁺ / 2 Cl⁻ Symport (Co-transport, about 25% of filtered Na⁺) → ↓ Osmolarity of the Medulla → Interfere with Counter-current Multiplier System → Excess water excretion.

4- Large dose → Mild ↓ Carbonic Anhydrase Enzyme (Sulfonamide radical).

5- Excess Na⁺ will reach the late part of D.C.T. where a part of Na⁺ is reabsorbed in exchange with some H⁺ & MAINLY K⁺. The remaining Na⁺ will be excreted in urine with its iso-osmotic water.
6- The **URINE** will contain

**Blood**

→ Hypovolemia  → High Efficacy Diuresis  → Hypoalbuminemia → Hypocalcemia

→ Hyponatremia  → Natriuretic effect  → Hypochloremia  → Chloruretic effect

→ Alkalosis  → Acid urine  → Hypokalemia  → Kaluretic effect

→ Hypomagnesemia  → Hypomagnesemia  → Hypocalcemia

→ Frusemide ↑ R.B.F. may be via Prostaglandins # N.S.A.I.D.

7- Frusemide ↑ R.B.F. may be via Prostaglandins # N.S.A.I.D.

It is effective as a diuretic even when G.F.R. < 10 ml/min.
2- Antihypertensive effect: By its diuretic effect, NO direct arterial V.D.
3- Hyperglycemia $\rightarrow$ ↓ Release of Insulin.
4- Hyperlipidemia $\rightarrow$ ↑ Plasma Cholesterol & Triglycerides.
5- Hyperuricemia $\rightarrow$ ↓ Excretion of Uric acid.
* **Therapeutic Uses of Frusemide:**

Powerful & Prompt → Useful in Emergency, Severe & Resistant (Refractory) cases.

Used Orally & Injection.

1- **Edema:**

a- Emergency Acute Pulmonary Edema = Acute Left Ventricular Failure.

I.V. Frusemide → ↓ Blood volume & \textit{Veno-dilatation} → ↓ V.R. → ↓ EDV → ↓ Preload & ↓ Pulmonary congestion.

b- Cerebral edema. I.V. Frusemide → ↓ Edema & ↓ Pressure on vital centers.

c- Severe or Refractory edema e.g. C.H.F., Liver cirrhosis & Nephrotic syndrome.

Use Oral Frusemide either Alone or + Other diuretic (Thiazide or K+-Retaining).
2- **Hypertension:**
a- Frusemide lowers Bl.p. by its diuretic effect ONLY, it has NO direct V.D.
b- Emergency Hypertensive Encephalopathy → I.V. Frusemide.
c- Severe & Resistant Hypertension → Oral Frusemide.
d- Hypertension + renal Impairment → Oral Frusemide.

3- **Acute Renal Failure** → Use Large Dose of Frusemide either Oral or I.V.

4- **Hypercalcemia**.
* Adverse Effects & Toxicity of Frusemide:

1- **Hypokalemia** → Worsens Digitalis Toxicity, and Liver & Kidney insufficiency.
Hypokalemia can be avoided by:
a- Intermittent use of least effective dose of the diuretic.
b- Fruit juice.
c- KCl supplement. Oral solution is less irritant than tablets.
d- Add K+-retaining diuretic e.g. Spironolactone.
4- 3- Hypochloremic Alkalosis.
5- Hypomagnesemia.
6- Hypovolemia, Hypotension & Dehydration.
7- Hyperglycemia → Worsen Diabetes mellitus.
8- Hyperlipidemia.
9- Hyperuricemia → Worsens Gout.
10- Hypersensitivity & Cross allergy with other sulfonamides e.g. Antibacterial.
11- Bone marrow depression.
12- **Ototoxicity**: Frusemide is toxic to hair cells of inner ear → Hearing defect & **Deafness** especially in patients with Renal insufficiency or taking concurrent ototoxic drugs e.g. Gentamicin.
13- G.I.T. disturbances.
14- Fetotoxic
* Contraindications of Furosemide Diuretics:

1- Digitalis toxicity (Hypokalemia).
2- With corticosteroids (Hypokalemia).
3- Advanced liver disease.
4- Diabetes mellitus (Hyperglycemia).
5- Gout (Hyperuricemia).
6- Pregnancy (Fetotoxic).
* Drug Interactions of Furosemide:

1- Frusemide displaces Warfarin from plasma protein binding sites.
2 - Frusemide ↓ Renal clearance of Lithium carbonate.
3 - Probenecid ↓ Renal tubular excretion of Frusemide.
4 - N.S.A.I.D. → ↓ Diuretic effect of Frusemide.
5- Frusemide → Hypokalemia → ↑ Digitalis toxicity.
6 - Frusemide → ↑ Ototoxicity of Aminoglycosides e.g. Gentamicin.
7 - Frusemide → ↑ Nephrotoxicity & Aminoglycosides & Cephalosporins.
2- Torsemide (*Demadex*): 10-20 mg/day Orally & I.V.

1- Stronger than Frusemide 3 times.
2- Less excretion of K+ & Ca2+.
3- Metabolic elimination.

3- Bumetanide (*Burinex, 0.5–1 mg Oral & I.V.*) → Stronger than Frusemide.

4- Piretenide (*Arelix, 6 mg Orally*) → Similar to Frusemide + Direct V.D.
50-150 mg Orally or I.V.  5- *Ethacrynic acid* (*Edecrin*):

1- Similar to Frusemide, But:
   a- *NOT* sulfonamide derivative:
      - *NOT* Carbonic anhydrase enzyme
      - *No* cross allergy with other sulfonamides.
   b- Has a uricosuric effect.
   c- More gastric irritation.
   d- More *Deafness*, may be permanent.

2- Useful in Emergency, Severe & Refractory Edema & Hypertension.

Similar to *Ethacrynic acid*

6- *Indacrinone*:

Uricosuric effect  7- *Tienilic Acid* (*Ticrynafen*):
Pharmacodynamics

I Diuretic Effect:

Thiazide diuretics **MUST** be secreted in P.C.T. to act from inside the nephron. Probenecid inhibits this secretion → Antagonize the diuretic effect of thiazides.

They act **MAINLY** on the early part of **D.C.T.** (Cortical Diluting Segment) → Inhibit NaCl reabsorption (About 10%).