Multimodal actions of gabapentin in anaesthesia

Thesis
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AIM OF THE WORK

To evaluate the role of gabapentin in anaesthesia as it has multimodal actions, namely: to decrease cardiovascular response to laryngoscopy and intubation, as a preemptive analgesic and postoperatively to minimize nausea and vomiting.
ABSTRACT

Gabapentin has demonstrated analgesic effects in clinical trials as a preemptive analgesic and in acute postoperative pain management. This study was conducted to evaluate whether the pre-emptive use of gabapentin could reduce postoperative pain and morphine consumption in patients after lower extremity orthopaedic surgery. Methods: 150 ASA I and II patients were randomly assigned to receive 900 mg gabapentin or placebo in a double-blind manner two hours before surgery under general anaesthesia. Postoperatively, the pain was assessed on a visual analogue scale (VAS) at 2, 4, 12, and 24 hours at rest. Morphine 0.05 mg/kg intravenously was used to treat postoperative pain on patients’ demand. Total morphine consumption in the first 24 hours after surgery was also recorded.

Results: Patients in the gabapentin group had significantly lower VAS scores at all time intervals of 2, 4, 12, and 24 hours, than those in the placebo group (respectively, 55.50 [mean] +/- 15.80 [standard deviation], 57.30 +/- 19.30, 45.74 +/- 16.00, 44.60 +/- 17.64, versus 72.30 +/- 14.00, 70.50 +/- 18.13, 62.00 +/- 23.32, 66.50 +/- 25.70; p-value is less than 0.05). The total morphine consumed after surgery in
the first 24 hours in the gabapentin group (15.43 +/- 2.54) was significantly less than in the placebo group (17.94 +/- 3.00; p-value is less than 0.05).

**Conclusion:** Pre-emptive use of gabapentin 900 mg orally significantly decreases postoperative pain and rescue analgesia.

**Summary**

Gabapentin was introduced in 1993 as an adjuvant anticonvulsant drug for the treatment of refractory partial seizures. Subsequently, it was shown to be effective in treating a variety of chronic pain conditions, including post-herpetic neuralgia, diabetic neuropathy, complex regional pain syndrome, inflammatory pain, central pain, malignant pain, trigeminal neuralgia, HIV-related neuropathy, and headaches. In 2002, gabapentin was approved by the US Food and Drug Administration for the treatment of post-herpetic neuralgia. In the UK, gabapentin has a full product licence for treatment of all types of neuropathic pain. Gabapentin use has more recently extended into the management of more acute conditions, particularly in the perioperative period. More than 30 clinical trials evaluating the
potential roles of gabapentin for postoperative analgesia, preoperative anxiolysis, prevention of chronic post-surgical pain, attenuation of haemodynamic response to direct laryngoscopy and intubation, prevention of postoperative nausea and vomiting (PONV), and postoperative delirium have been published within the last 5 yr. These studies reflect many important areas of anaesthesia research and it is interesting that a single drug may have multimodal effects. In this review, various aspects of these perioperative applications will be discussed after a brief description of gabapentin’s pharmacology and anti-nociceptive mechanisms. Pharmacology and anti-nociceptive mechanisms

Gabapentin, \( \text{1-(aminomethyl)cyclohexane acetic acid, is a} \)

structural analogue of the neurotransmitter g-aminobutyric acid (GABA) (Fig. 1) with a molecular formula of \( \text{C}_{9}\text{H}_{17}\text{NO}_2 \) and a molecular weight of 171.24. It is a white crystalline solid, which is highly charged at physiological pH, existing as a zwitterion with a pKa1 of 3.7 and a pKa2 of 10.7. It is freely soluble in water in both basic and acidic aqueous solutions. High performance liquid chromatography 44 and gas chromatography46 can be used for drug assay in plasma and urine. The absorption of gabapentin is dose-dependent due to a saturable L-amino acid transport mechanism.
in the intestine. Thus, the oral bioavailability varies inversely with dose. After a single dose of 300 or 600 mg, bioavailability was approximately 60% and 40%, respectively. Plasma concentrations are proportional with dose up to 1800 mg daily and then plateau at approximately 3600 mg daily. Gabapentin is extensively distributed in human tissues and fluid after administration. It is not bound to plasma proteins and has a volume of distribution of 0.6–0.8 litre kg\(^{-1}\). It is highly ionized at physiological pH; therefore, concentrations in adipose tissue are low. After ingestion of a single 300 mg capsule, peak plasma concentrations (Cmax) of 2.7 mg ml\(^{-1}\) are achieved within 2–3 h. Concentrations of gabapentin in cerebrospinal fluid are approximately 5–35% of those in plasma, whereas concentrations in brain tissue are approximately 80% of those in plasma. In humans, gabapentin is not metabolized and does not induce hepatic microsomal enzymes. It is eliminated unchanged in the urine and any unabsorbed drug is excreted in the faeces. Elimination rate constant, plasma clearance, and renal clearance are linearly related to creatinine clearance. Therefore, dose adjustment I
necessary in patients with compromised renal function. In patients with normal renal function, the elimination half-life of gabapentin when administered as monotherapy is between 4.8 and 8.7 h. Gabapentin is removed by haemodialysis, and a maintenance dose after each treatment should provide steady-state plasma concentrations comparable with those attained in patients with normal renal function. No clinically significant interactions between gabapentin and drugs excreted predominantly by renal mechanisms have been reported. Cimetidine, a H2 receptor blocker, decreases the renal clearance of gabapentin by 12% when administered concomitantly, and antacids reduce the bioavailability of gabapentin from 10% (when given 2 h before gabapentin) to 20% (when given concurrently or 2 h after gabapentin) in healthy individuals. Gabapentin is generally well tolerated with a favourable side-effect profile. When the safety and tolerability of gabapentin were evaluated in 2216 patients undergoing seizure treatment, reported adverse effects were somnolence (15.2%), dizziness (10.9%), asthenia (6%), headache (4.8%), nausea (3.2%), ataxia (2.6%), weight gain (2.6%), and amblyopia (2.1%). Similar side-effects were observed in patients with chronic pain treated with gabapentin. Anti-nociceptive mechanisms
A number of mechanisms may be involved in the actions of gabapentin. Possible pharmacologic targets of gabapentin are selective activation of the heterodimeric GABAB receptors which consist of GABAB1a and GABAB2 subunits; enhancement of the N-methyl-D-aspartate (NMDA) current at GABAergic interneurons; blocking a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor mediated transmission in the spinal cord; binding to the L-a-amino acid transporter; activating adenosine triphosphate sensitive K (KATP) channels; activating hyperpolarization-activated cation current (Ih) channels; and modulating Ca2 current by selectively binding to [3H]gabapentin (a radioligand), the a2d subunit of voltage-dependent Ca2 channels (VGCCs). Currently, VGCC is the most likely anti-nociceptive target of gabapentin. The proposed consequence of gabapentin binding to the a2d subunit is a reduction in neurotransmitter release and hence a decrease in neuronal hyperexcitability. Gabapentin has been shown to inhibit the evoked release of glutamate, aspartate, substance P, and calcitonin gene-related peptide (CGRP) from the spinal cord of rats. Interestingly, recent studies have demonstrated that the descending noradrenergic system, spinal a2 adrenergic receptors and an intact spino-bulbo-spinal circuit are crucial elements influencing the analgesic effects of gabapentin.
Postoperative analgesia

Postoperative pain is not purely nociceptive in nature, and may consist of inflammatory, neurogenic, and visceral components. Therefore, multimodal analgesic techniques utilizing a number of drugs acting on different analgesic mechanisms are becoming increasingly popular.11 Gabapentin may have a role to play in this area and within the past 5 yr, there have been more than 20 well-conducted, randomized controlled trials using perioperative gabapentin as part of a multimodal postoperative analgesic regimen.
Introduction

Gabapentin is an amino acid that exists at physiological pH as a zwitterion, (Both the amino group and the carboxyl group of each amino acid are ionizable) and since it is doubly-charged, its native permeability to membrane barriers within the body is low. However, like several other amino acids, gabapentin is a substrate of the so-called system L transporter of gut, neurons and astrocytes. This property allows gabapentin molecules to cross membrane barriers more easily. In addition to the facilitated transport across cell membranes, there is a smaller non-saturable component of transport that is due to passive diffusion. (1)

These transport properties of gabapentin probably account for the access of gabapentin to brain cytosol, where it is present at about ten-fold higher concentrations than in the brain extracellular space (2).

Numerous reports indicate that g-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in mammalian brain and that seizures occur if GABA synapses are impaired. A variety of GABA-enhancing drugs such as GABA agonists, GABA modulators (e.g. benzodiazepines), drugs converted metabolically to GABA, GABA uptake inhibitors (e.g. tiagabine), and inhibitors of GABA degradation (e.g. vigabatrin) prevent seizures in animal models or in clinical use. The similarity of chemical structures between GABA and gabapentin also suggests a functional relationship (3).
It is likely that its analgesic effects result from an action at the α₂δ₁ subunits of the voltage-dependent Ca²⁺ channel for which it has substantial affinity and which are upregulated in the dorsal root ganglia and spinal cord after peripheral nerve injury as can be produced by surgical incision. Gabapentin may produce analgesia by binding to and inhibiting presynaptic voltage-dependent Ca²⁺ channels, decreasing calcium influx and thereby inhibiting the release of neurotransmitters including glutamate from the primary afferent nerve fibers that synapse on and activate pain responsive neurons in the spinal cord. (4)

A number of mechanisms may be involved in the actions of gabapentin. Currently, VGCC (voltage-dependent Ca²⁺ channels) is the most likely antinociceptive target of gabapentin. The proposed consequence of gabapentin binding to the α₂δ₁ subunit is a reduction in neurotransmitter release and hence a decrease in neuronal hyperexcitability. (4)

Gabapentin has been shown to inhibit the evoked release of glutamate, aspartate, substance P, and calcitonin gene-related peptide (CGRP) from the spinal cord of rats. Interestingly, recent studies have demonstrated that the descending noradrenergic system, spinal α₂ adrenergic receptors and an intact spino-bulbo-spinal circuit are crucial elements influencing the analgesic effects of gabapentin in addition to α₂ interaction. (5)

The versatility of gabapentin in treating a wide array of pain conditions and its favorable side effect profile compared with other drugs or interventions has generated interest in its use as a
The perioperative administration of gabapentin produced significantly better postoperative analgesia. Postoperative analgesia as measured by pain scores and decreased opioid consumption is improved in the immediate postoperative period and for up to 24 hours after a wide range of surgical operations commonly associated with significant postoperative pain. The analgesic benefit of perioperative gabapentin was accompanied by a modest increase in sedation but no other unintended effects. (6)

Oral gabapentin administered within 4 hours before surgery has a significant postoperative analgesic effect. This effect was confirmed by accepted methods to a certain postsurgical pain prevention including reduced opioid requirements and decreased pain scores. The observation that the beneficial effects of gabapentin, a drug with an elimination half-life between 5 and 7 hours, were pronounced 20 to 24 hours after the surgery is suggestive of a preventative effect on postsurgical pain (6).

Gabapentin treatment was not associated with negative outcome such as nausea, vomiting, dizziness, or lightheadedness. It was, however, associated with an increase in perioperative sedation. Sedation can be interpreted as a negative outcome of gabapentin use; however, in the perioperative setting its use may contribute to anxiolysis. (6)

Gabapentin decreases preoperative anxiety. Although 1200 mg gabapentin was less effective in relieving preoperative anxiety than 15
mg oxazepam, 90 significantly lower preoperative visual analogue scale (VAS) anxiety scores have been demonstrated in patients with gabapentin, premedication before knee surgery (7).

The pressor response of tachycardia and hypertension to laryngoscopy and endotracheal intubation may increase perioperative morbidity and mortality, particularly for those patients with cardiovascular or cerebral disease. A variety of drugs have been used to control this haemodynamic response. (7)

It appears that preoperative gabapentin blunts the hypertensive response to intubation. Single and multiple doses have comparable haemodynamic effects. (8)

The mechanism of gabapentin in controlling this haemodynamic response remains unknown. Since gabapentin inhibits membrane VGCCs, it is possible that it have a similar action to calcium channel blockers (8).

Post-operative nausea and vomiting (PONV) are common after anaesthesia and surgery with an overall incidence of 25–30%. It is also one of the most common reasons for poor patient satisfaction ratings in the postoperative period. (8)

Recently, the potential anti-emetic effect of gabapentin was evaluated in the perioperative setting. The mechanism of gabapentin in the prevention of PONV is unknown but it could possibly be due to the indirect effect of opioid sparing or a direct effect on tachykinin activity. A
tendency towards a lower incidence of PONV in patients treated with gabapentin, although statistically insignificant, was noted in several studies on postoperative analgesic effects of gabapentin. (9)
**Patients and methods**

The study will be approved by the ethics committee of benha faculty of medicine and written informed consent will be obtained from each patient. one hundred fifty patients will be randomly allocated into 3 equal groups each group is subdivided into 2 equal subgroups.

**Inclusion Criteria:**

- Hight from 150-190 cm
- Wight from 50-120 kg
- ASA physical status classes I,II.
- Age range between 15 -60 years.
- Methods of randomization: Closed envelope.
- Satisfactory liver functions
- Satisfactory kidney functions.

**Exclusion Criteria:**

- Age>15 or <60years.
- Obese Patients.
- Known to be cardiac patient.
- Known to be Diabetic patient.
- Known to be Hypertensive patient.
Patients receiving any anti-coagulant  

Known allergy to gabapentin.  

Chronic pain or daily intake of analgesics or corticosteroids.  

Impaired renal function.  

Impaired liver functions  

Heavy smoking.  
Technique

patients will be allocated into 3 equal groups: each group will be subdivided into 2 equal subgroups each subgroup is (25 patients each).

1. Group I

Group Ia; control group. Patients in this group will receive oral placebo 2 hours before induction of anaesthesia.

Group Ib; Patients in this group will receive 900 mg oral gabapentin 2 hour before induction of anesthesia.

The patients in these groups will be investigated to assess the effect of gabapentin in cardiovascular pressor response to laryngeoscopy and intubation and its effect on postoperative nausea and vomiting after laparoscopic cholecystectomy.

Data that will be assessed

Heart rate/min, systolic blood pressure, diastolic blood pressure, mean blood pressure just before induction, 1, 5, 10 and 20 minutes after intubation. Serum cortisol level will be estimated preoperatively and 20 minutes postoperatively.

Time elapsed to start vomiting, number of vomitus, receive treatment or not and detection of nausea. Within 24 hours postoperatively.
2. **Group II:**

**Group II a:** control group, patients in this group will receive oral placebo 2 hours before induction of anaesthesia

**group IIb:** Patients in this group will receive 1200 mg oral **gabapentin** 2 hours before induction of anesthesia.

The patients in these groups will be investigated to assess the effect of gabapentin; as preemptive analgesic in patients undergoing upper abdominal surgery under general anaesthesia.

**Data that will be assessed**

1. Time elapsed from end of operation till patient asks for analgesia.

2. The total analgesic consumption over 24 hours after recovery.

3. Pain scoring: pain will be assessed by using visual analogue scale (0mm = no pain, 100 mm worst pain imaginable), at rest and during mobilization from supine to the sitting position. Will be checked every 6 hours for the first 24 hours.

3. **Group III**

**Group III a:** control group, patients in this group will receive oral placebo 2 hours before induction of anaesthesia

**Group III b:** Patients will receive 1200mg gabapentin orally 2 hours before induction of anesthesia.
the patients in these groups will be investigated to assess the effect of gabapentin as preemptive analgesic in patients undergoing lower limb surgery under spinal anaesthesia

**Data that will be assessed**

1- Time elapsed to start analgesia according to patient request.

2- The total analgesic consumption over 24 hours after recovery.

3-Pain scoring: pain will be assessed by using visual analogue scale (0mm = no pain, 100 mm worst pain imaginable), at rest and during mobilization of affected limb. Will be checked every 6 hours for the first 24 hours.
Anaesthetic management

All patients were evaluated initially by medical history and a complete physical examination. No premedication will be administered. Patients will be admitted to the operating room fasting for 6 h. A peripheral i.v. 18G catheter will be inserted preoperatively. Standard monitoring will be conducted before induction and throughout the surgery, including heart rate (HR), noninvasive arterial blood pressure (NIBP), electrocardiogram (ECG), and peripheral oxygen saturation (SpaO₂). Regarding spinal anaesthesia, patients will be preloaded with normal saline 10 ml/kg.

For general anaesthesia;

Anesthesia will be carried on using Fentanyl 1-2 µg/Kg intravenously, propofol 1-2 mg/kg, muscle relaxation will be achieved by atracurium 0.5 mg/kg and will be maintained using incremental doses of atracurium 0.1 mg/kg.

After tracheal intubation patients will be mechanically ventilated with the appropriate settings tailored for every one keeping end tidal CO₂ at 30-35 mmHg.

Anesthesia will be maintained by the administration of a volatile anesthetic (isoflurane) 1- 1.2 MAC in O₂. Crystalloids will be given 8 ml/kg/h plus the deficit estimated by 4-2-1 rule. Extubation will be smooth and awake and after administration atropine 0.02 mg atropine and 0.04 mg neostigmine.
For spinal anaesthesia

Patients will be injected by 3-4 ml of hyperbaric solution of 0.5% bupivacain into subarachnoid space. Crystalloids will be given 8 ml/kg/h plus the deficit estimated by 4-2-1 rule.

Postoperative management

All patients will receive 1 gm paracetamol i.v every 6 hours and ketorolac 30 mg every 12 hours and morphine
Data management and statistical analysis

Obtained data will be collected, tabulated and statistically analysed by suitable statistical test.
References


2. Welty D.F., Wang, Y., Busch,and et al. (1997). Pharmacokinetics and pharmacodynamics of CI-1008 (pregabalin) and gabapentin in rats usig maximal electroshock .Epilepsia 38(Suppl. 8), 35–36


الملخص العربي

يسبب استعمال المنظار الحنجرى ووضع الأنبوب الحنجرية تغيرات بالقلب والأوعية الدموية مثل ارتفاع ضغط الدم. تزايد وعدم إتلاح دقات القلب، نقص الأوكسجين بعضة القلب وزيدات نسبة الكاتيكولايين بالدم. وقد استخدم جابابتنين في تجارب عشوائية محكمة لعلاج القلق قبل الجراحة، للتخفيف من ارتفاع الضغط و النبض الناتج عن التنظير الحنجرى والتثبيب، للحد من الألم بعد العمليات الجراحية ومتطلبات ما بعد الجراحة من المسكنات، والغنيان والقيء ما بعد الجراحة، والهدىان.

هذه الدراسة تهدف لتقييم عقار الجابابتين عن طريق الفم قبل الجراحة في التخفيف من ارتفاع ضغط الدم و النبض الناتج عن تنظير الحنجرة المباشر والتثبيب الرغامي. بالإضافة إلى ذلك، لرصد تأثيره في تخفيف الألم بعد الجراحة، والغنيان والقيء ما بعد الجراحة.

في هذه الدراسة العشوائية، تم تقسيم المرضى عشوائيًا إلى 3 مجموعات متساوية(1)0 و (2) و (3) كل مجموعة تنقسم إلى مجموعتين متساويتين (ي حيث تحتوى كل مجموعة على عدد 25 مريض تلقيت مجموعة أ (من كل مجموعة الدواء الوهمي عن طريق الفم، ومجموعة ب(أخرى تلقت 900 مج جابابتين كما في مجموعة 1 أو 1200 مج جابابتين كما في
مجموعة 2 و 3 عن طريق الفم 2 ساعة قبل الجراحة. ولم يعثر
أي عقارب أخرى قبل التخدير. وشملت المراقبة جهاز قياس
ضغط الدم وجهاز تخطيط كهربية القلب، وقياس نسبة
الأوكسجين و ثاني اوكسيد الكربون. وتم قياس لكل مريض
ضغط الدم الشرياني الإنتقاضي، ضغط الدم الشرياني الانبساطي
، ضغط الدم الشرياني المتوسط ومعدل ضربات القلب في وقت ما
قبل التخدير كقيم أساسية. ثم تكرار القياس قبل تنظير الحنجرة
 مباشرة، وعلى فترات 10, 15, 1 دقيقة بعد التنبيب الحنجرى.
تم تسجيل حالات عدم انتظام ضربات القلب بعد التنبيب ومقارنته
بين المجموعتين. والبعد نقل المرضى إلى غرفة الإقامة بعد
التخدير، تم تسجيل الألم والغثيان والقيء ما بعد الجراحة.
وأظهرت هذه الدراسة أن إعطاء عقار الجابانتين 900 مغ
ساعة واحدة قبل الجراحة يقلل بشكل ملحوظ تغييرات ضغط الدم
الشرياني المتوسط لمدة 5 دقائق بعد التنبيب الحنجرى. ويلل
تغييرات معدل ضربات القلب لمدة 3 دقائق بعد التنبيب الحنجرى
مع ذلك، ليس هناك فروق ذات دلالة إحصائية بين جابانتين
والدواء الويمي في الألم بعد العمل الجراحي والغثيان والقيء
ما بعد الجراحة.
عقار الجابابنتين وتأثيراتها المتعددة في التخدير

رسالة مقدمة توطئة للحصول على درجة الدكتوراه في التخدير والرعاية المركزية

من قبل الطبيب

رامى موسى صالح

ماجستير التخدير والعناية المركزية

كلية الطب، جامعة بنها

تحت إشراف

الأستاذ الدكتور / إنعام فؤاد جاد الله

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الدكتور / إيهاب سعيد عبد العظيم

استاذ مساعد التخدير والعناية المركزية

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مدرس التخدير والرعاية المركزية

كلية الطب، جامعة بنها

(2014)