Multimodal actions of gabapentin in anaesthesia

Thesis

Submitted for fulfillment the M.D degree in anaesthesia and intensive care unit

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2014))

AIM OF THE WORK

To evaluate the role of gabapentin in anaesthesia as it has multimodal actions, namely ; to decrease cardiovascular response to laryngescopy 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-valueis less than 0.05).

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

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. 5 23 40 43 64 73 92 93 129 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 Chemistry, pharmacokinetics, and adverse effects Gabapentin, 1-(aminomethyl)cyclohexane acetic acid, is a

structural analogue of the neurotransmitter g-aminobutyri

acid (GABA) (Fig. 1) with a molecular formula of $C_9H_{17}NO_2$ 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. 101 Thus, the oral bioavailability varies inversely with dose. After a single dose of 300 or 600 mg, bioavailabilitywas approximately 60% and 40%, respectively.120 125 Plasma concentrations are proportional with dose up to 1800 mg daily and then plateau at approximately 3600 mg
daily.109 Gabapentin is extensively distributed in human tissues and fluid after administration. It is not bound to plasma proteins124 and has a volume of distribution of 0.6–0.8 litre kg21.88 125 It is highly ionized at physiological pH; therefore, concentrations in adipose tissue are
low.124 After ingestion of a single 300 mg capsule, peak plasma concentrations (Cmax) of 2.7 mg ml21 are achieved within 2–3 h.120 126 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.8 9 77 In humans, gabapentin is not metabolized127 and does not induce hepatic microsomal enzymes.96 It is eliminated unchanged in the urine and any unabsorbed drug is excreted in the faeces.124 Elimination rate constant, plasma clearance, and renal clearance are linearly related to creatinine
clearance.17 88 127 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.91 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.
130 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,88 and antacids13 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 evaluated63 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.5 93
Anti-nociceptive mechanisms

A number of mechanisms may be involved in the actions of gabapentin.12 Possible pharmacologic targets of gabapentin are selective activation of the heterodimeric GABAB receptors which consist of GABAB1a and GABAB2 subunits;10 72 enhancement of the N-methyl-D-aspartate (NMDA) current at GABAergic interneurons;41 blocking a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor mediated transmission in the spinal cord;14 98 binding to the L-a-amino acid transporter;37 103 activating adenosine triphosphate sensitive K (KATP) channels;35 69 activating hyperpolarization-activated cation current (Ih) channels;104 105 and modulating Ca2 current by selectively binding to [3H]gabapentin (a radioligand), the a2d subunit of voltage-dependent Ca2 channels (VGCCs).33 36 61 99 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,15 aspartate,31 substance P, and calcitonin gene-related peptide (CGRP)30 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

in addition to a2d interaction.106 107

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 wellconducted, 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 GABAenhancing drugs such as GABAA agonists, GABAA 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 itsanalgesic effects result from an action at the $\alpha_2\delta_1$ subunits of the voltage-dependent Ca^2channel for which it has substantial affinityandwhich are upregulated in the dorsal root gangliaand spinal cord after peripheral nerve injuryas can be produced by surgical incision.Gabapentin may produce analgesia by binding to and inhibitingpresynaptic voltage-dependent Ca^2 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 Ca^{2+} channels) is the most likely anti-nociceptive target of gabapentin. The proposed consequence of gabapentinbinding to the α_{2^δ} 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 α_2 adrenergic receptors and an intact spino-bulbo-spinal circuit are crucial elements influencing the analgesic effects of gabapentin in addition to α_2 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

perioperative analgesic (6)

The perioperative administration of gabapentin produced significantly better postoperative analgesia. Postoperative analgesia as measured by pain scores and decreasedOpioid 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 settingits 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 kneesurgery (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 mostcommon 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 I b; 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 asses the effect of gabapentin in cardiovascular pressor response to laryngeoscopy and intubation and.its effect on postoperative nausea and vomiting after laparscopic cholycystectomy.

Data that will be assesed

- 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 star t 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 asses the effect of gabapentin; as preemptive analgesic in patients undergoing upper abdominal surgery under general anaesthesia.

Data that will be assesed

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 asses the effect of gabapentin as preemptive analgesic in patients undergoing lower limb surgery under spinal anaesthesia

Data that will be assesed

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 (SpaO $_2$).reagarding spinal anaesthesia patients will be preloaded with normal saline 10 ml/kg

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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 0.1mg/kg.

After tracheal intubation patients will be mechanically ventilated with the appropriate settings tailored for every one keeping end tidal CO_2 at 30-35 mmHg.

Anesthesia will be maintained by the administration of a volatile anesthetic (isoflurane) 1- 1.2 MAC in O_2. 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 adminsteration atropine 0.02mg atropine and 0.04mg 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

1 Su T., Lunney E., Campbell G., and et al (1995). Transport of gabapentin, a g-amino acid drug, by system L a-amino acid transporters: a comparative study in astrocytes, synaptosomes and CHO cells. J. Neurochem. 64, 2125–2131.

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

3 TunnicliffG, and Raess B.U(1991). GABA Mechanisms in Epilepsy. Wiley Liss, New York, p. 218.

4 , and55Olsen RW.(1994). GABAA Macdonald RL receptor channels. Annu Rev Neurosci.;17:569-602.

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5 Hurley RW, Cohen SP, Williams KA, and et al. (2006).The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. RegAnesth Pain Med; 31: 237–47.

6 Rorarius MGF, Mennander S, Suominen P, and et al. (2004). Gabapentin for the prevention of postoperative

pain after vaginal hysterectomy. Pain; 110: 175–81.

7 • Christophe M, Frederic A, Bruno G, and et al. (2005). Pre-operative Gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesthesia and analgesia, vol-100,no-S: 1394- 1399

8 - Fassoulaki A, Melemeni A, Paraskeva A, and et al. (2006). Gabapentin attenuates the pressor response to direct laryngoscopy and tracheal intubation. Br J Anaesth; 96: 769–73.

9 - Pandey CK, Priye S, Ambesh SP, and et al. (2006). Prophylactic gabapentin for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: a randomized, double-blind, placebo-controlled study. J Postgrad Med; 52: 97–100.

الملخص العربى

يسبب استعمال المنظار الحنجرى ووضع الانبوبة الحنجرية تغيرات بالقلب والأوعية الدموية مثل إرتفاع ضغط الدم، تزايد وعدم إنتظام دقات القلب ، نقص الأوكسجين بعضلة القلب وزيادة نسبة الكاتيكولامين بالدم .وقد أستخدم جابابنتين في تجارب عشوائية محكومة لعلاج القلق قبل الجراحة، للتخفيف من ارتفاع الضغط و النبض الناتج عن التنظير الحنجرى والتنبيب، للحد من الألم بعد العمليات الجراحية ومتطلبات ما بعد الجراحة من المسكنات، والغثيان والقيء ما بعد الجراحة، والهذيان.

هذه الدراسة تهدف لتقييم عقار الجابابنتين عن طريق الفم قبل الجراحة في التخفيف من إرتفاع ضغط الدم و النبض الناتج عن تنظير الحنجرة المباشر والتنبيب الرغامي .بالإضافة إلى ذلك، لرصد تأثيره فى تخفيف الألم بعد الجراحة، والغثيان والقيء ما بعد الجراحة.

في هذة الدراسة العشوائية، تم تقسيم المرضى عشوائيا إلى 3 مجموعات متساوية1)0.و2 و (3 كل مجموعة تنقسم الى مجموعتين متساويتين) أ , ب (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 جابابنتين كما فى مجموعة 1 او 1200 مج جابابنتين كما فى

مجموعة 2 و 3 عن طريق الفم 2 ساعة قبل الجراحة و لم يعط أي عقارات اخرى قبل التخدير .وشملت المراقبة جهاز قياس ضغط الدم و جهاز تخطيط كهربية القلب، وقياس نسبة الأوكسجين و ثانى اوكسيد الكربون . وتم قياس لكل مريض ضغط الدم الشرياني الإنقباضي ، ضغط الدم الشرياني الإنبساطي ، ضغط الدم الشرياني المتوسط ومعدل ضربات القلب في وقت ما قبل التخدير كقيم أساسية .وتم تكرار القياس قبل تنظير الحنجرة مباشرة ، وعلى فترات 10 , 5 , 1 دقيقة بعد التنبيب الحنجرى . تم تسجيل حالات عدم انتظام ضربات القلب بعد التنبيب ومقارنته بين المجموعتين .و بعد نقل المرضى إلى غرفة الإفاقة بعد التخدير، تم تسجيل الألم والغثيان والقيء ما بعد الجراحة.

وأظهرت هذه الدراسة أن إعطاء عقار الجابابنتين 900 مج ساعة واحدة قبل الجراحة يقلل بشكل ملحوظ تغييرات ضغط الدم الشرياني المتوسط لمدة 5 دقائق بعد التنبيب الحنجرى ويقلل تغييرات معدل ضربات القلب لمدة 3 دقائق بعد التنبيب الحنجرى ومع ذلك، ليس هناك فروق ذات دلالة إحصائية بين جابابنتين والدواء الوهمى في الألم بعد العمل الجراحي و والغثيان والقيء ما بعد الجراحة .

عقار الجابابنتين وتاثيراتة المتعددة فى التخدير

رسالة مقدمة توطئة للحصول على درجة الدكتوراه فى التخدير والعناية المركزة

من قبل الطبيب

رامى موسى صالح

ماجستير التخدير والعناية المركزة

كلية الطب،جامعة بنها

تحت اشراف

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