Cardiopulmonary bypass does not affect plasma concentration of preoperatively administered gabapentin

La circulation extracorporelle n'a pas d'effet sur la concentration plasmatique de gabapentine administrée avant l'opération

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Abstract

Purpose Drug effects can be unpredictable during cardiac surgery due to factors that may influence drug concentration, such as extracorporeal oxygenation and hemodilution. The primary aim of the current investigation was to determine whether plasma gabapentin concentration is altered by cardiopulmonary bypass (CPB).

Methods Following approval from the Research Ethics Board and written informed consent, we conducted this open-label prospective cohort investigation. A convenience sample of 16 patients, who were scheduled for coronary bypass surgery, received oral gabapentin 600 mg as follows: 90 min prior to induction of anesthesia, following tracheal extubation, and then every eight hours for a total of four doses. Plasma gabapentin concentration, as well as pain and sedation scores, were documented.

Results Plasma gabapentin concentrations were unaltered during CPB ($31.9 \pm 12.7 \mu\text{mol}\cdot\text{L}^{-1}$ prior to CPB, 35.6 ± 12.9 to $37.2 \pm 9.6 \mu\text{mol}\cdot\text{L}^{-1}$ during CPB). However, using the current protocol, drug accumulation (reflected by increased drug concentrations) was observed following the third ($58.2 \pm 19.5 \mu\text{mol}\cdot\text{L}^{-1}$) and the fourth ($71.9 \pm 34.3 \mu\text{mol}\cdot\text{L}^{-1}$) doses. Pain and sedation scores and opioid requirements were comparable with those found in other studies.

Conclusion Plasma gabapentin concentration is unaltered during CPB following preoperative administration.

Drug accumulation following third and fourth postoperative doses suggests the need for therapeutic drug monitoring in future trials. Gabapentin is well established as an effective adjunct analgesic in a number of surgical settings. Randomized controlled trials are necessary to evaluate analgesic efficacy, optimal dosing, and adverse effects in the setting of cardiac surgery. (ClinicalTrials.gov number, NCT01022736).

Résumé

Objectif Les effets des médicaments peuvent être imprévisibles pendant une chirurgie cardiaque en raison de facteurs pouvant influencer la concentration médicamenteuse, comme par exemple l'oxygénation extracorporelle et l'hémodilution. L'objectif principal de notre étude était de déterminer si la concentration plasmatique de la gabapentine changeait lors du recours à la circulation extracorporelle (CEC).

Méthode Après avoir obtenu l'autorisation du Comité d'éthique de la recherche et le consentement éclairé par écrit des patients, nous avons réalisé une étude de cohorte prospective ouverte. Un échantillon de commodité de 16 patients devant subir une chirurgie de pontage aorto-coronarien a reçu 600 mg de gabapentine orale selon le schéma posologique suivant : 90 min avant l'induction de l'anesthésie, après l'extubation trachéale, puis toutes les huit heures jusqu'à un total de quatre doses. La concentration plasmatique de gabapentine et les scores de douleur et de sédation ont été enregistrés et comparés en fonction du temps.

Résultats Les concentrations plasmatiques de la gabapentine n'ont pas changé pendant la CEC ($31,9 \pm 12,7 \mu\text{mol}\cdot\text{L}^{-1}$ avant la CEC, $35,6 \pm 12,9$ à $37,2 \pm 9,6 \mu\text{mol}\cdot\text{L}^{-1}$ pendant la CEC). Toutefois, selon le protocole utilisé dans cette étude, une accumulation médicamenteuse (réflétée par

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des concentrations médicamenteuses plus élevées) a été observée à la suite des troisième ($58,2 \pm 19,5 \mu\text{mol}\cdot\text{L}^{-1}$) et quatrième ($71,9 \pm 34,3 \mu\text{mol}\cdot\text{L}^{-1}$) doses. Les scores de douleur et de sédation et les besoins en opiacés étaient comparables à ceux d'autres études.

Conclusion La concentration plasmatique de gabapentine ne change pas durant la CEC après une administration préopératoire. En raison de l'accumulation médicamenteuse observée à la suite de l'administration des troisième et quatrième doses postopératoires, nous recommandons le monitoring des médicaments thérapeutiques dans les études futures. La gabapentine est reconnue comme un analgésique adjuvant efficace dans nombre de contextes chirurgicaux. Des études randomisées contrôlées sont nécessaires afin d'évaluer l'efficacité analgésique, le dosage optimal et les effets secondaires dans un contexte de chirurgie cardiaque. (Numéro de ClinicalTrials.gov, NCT01022736).

Drug pharmacokinetics during cardiac surgery can be affected by factors associated with the cardiopulmonary bypass (CPB) procedure. These include hemodilution, altered plasma protein binding, hypotension, hypothermia, separation of the lungs from circulation, and drug adsorption to the bypass circuit.^{1,2} Such effects have been observed with a number of drugs.¹⁻⁵ Due to the unpredictability of these effects, it is important to document possible consequences of CPB on drugs being introduced into the cardiac surgical setting.

Postoperative pain following cardiac surgery with sternotomy can be difficult to treat. While opioids are the treatment of choice, the high doses required may increase the risk of respiratory depression, sedation, and other side effects.⁶ A number of adjuvant analgesic drugs have been used in the setting of cardiac surgery, although their use may be limited by potential adverse effects. While shown to be effective analgesics, both non-selective and COX-2 selective nonsteroidal anti-inflammatory drugs (NSAIDs) have potentially serious risks in this surgical group.^{7,8} The alpha-2-delta ligand drugs, gabapentin and pregabalin, have been shown to reduce pain scores and opioid requirements and to improve postoperative pulmonary function in a number of surgical settings.^{9,10} To date, there have been no published reports on the use of these drugs in the setting of cardiac surgery.

The primary aim of the current investigation was to determine plasma concentrations of gabapentin during and after cardiac surgery with CPB, when administered 90 min prior to induction for anesthesia. Secondly, the feasibility of using repeated dosing of gabapentin as an adjuvant analgesic regimen in this setting was considered.

Methods

An open-label prospective cohort study design was followed. Following approval from the Institutional Ethics Review Board, a convenience sample of sixteen patients (15 male, one female), who were scheduled for coronary artery bypass graft involving median sternotomy and CPB, were recruited and provided informed consent. Exclusion criteria included: history of chronic pain, regular opioid, anticonvulsant, gabapentin or pregabalin use, recent congestive heart failure or ejection fraction < 35%, chronic pulmonary disease with anticipated prolonged ventilation, liver disease, renal insufficiency (preoperative serum creatinine > $140 \mu\text{mol}\cdot\text{L}^{-1}$), or history of adverse reaction to acetaminophen, morphine, gabapentin, or pregabalin.

Gabapentin 600 mg orally was administered 90 min prior to induction, one hour following tracheal extubation, then every eight hours to a total of four doses (mean total observation time = 23.8 ± 4.1 hr following the initial dose of gabapentin). All patients were anesthetized with sufentanil (maximum $2 \mu\text{g}\cdot\text{kg}^{-1}$), midazolam (maximum 3 mg), propofol, rocuronium, and isoflurane. During CPB, propofol was infused at $50 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ until weaning in the cardiovascular intensive care unit (CVICU). After induction, acetaminophen 1300 mg rectally was given; this was followed by 975 mg orally every six hours following tracheal extubation.

During CPB, body temperature was maintained within the slightly hypothermic to normothermic range ($35\text{--}38^\circ\text{C}$). The initial priming volume was typically 1,710 mL and consisted of Plasmalyte A® 1,000 mL (Baxter Healthcare Corporation, Deerfield, IL, USA), Voluven® 500 mL (Fresenius Kabi AG, Bad Homburg, Germany), 20% mannitol 200 mL, and heparin 10 mL (10,000 U). When the arterial-venous loop and the pre-bypass filter were removed prior to initiating bypass, 200-300 mL of this priming volume were discarded. Retrograde autologous priming (RAP) was used whenever possible, with the volume given back to the patients in accordance with individual fluid requirements. Approximately 300 mL were discarded when the arterial-venous loop and pre-bypass filter were cut and removed from the circuit. The bypass circuit consisted of uncoated tubing with an open system reservoir and a Quadrox VKMO 2031 hollow fibre membrane oxygenator (Maquet AG, Hirrlingen, Germany). Patients were weaned from ventilation with a target tracheal extubation time of one to six hours. Hemodynamic and coagulation drugs were used at the discretion of the attending physicians, as were blood products. Following tracheal extubation, intravenous or oral morphine was available upon patient request until time of discharge from CVICU.

Blood was drawn at induction, prior to CPB, ten minutes into CPB, ten minutes prior to separation from CPB,

30 min following CPB, and prior to and two hours following the next three doses of gabapentin. Plasma gabapentin concentrations were analyzed by the Department of Clinical Laboratories, St Joseph's Healthcare Centre, London, Ontario using high-performance liquid chromatography with ultraviolet detection.¹¹ Serum creatinine and liver enzymes were documented. Pain was assessed using a 0-10 visual analogue scale while supine at rest, while sitting up, during a forced expiratory maneuver with a peak flow meter, and while coughing. Pain scores were recorded before induction, two hours after tracheal extubation, and two hours following gabapentin administration on the first postoperative day. Opioid requirements were documented and reported as morphine equivalents. Sedation scores were obtained prior to drug administration, prior to induction, and at the times of the pain score assessments using a five-point scale: 1 = fully alert and oriented; 2 = drowsy; 3 = responds to commands only; 4 = rousable to mild physical stimulation; and 5 = not rousable to mild physical stimulation. Other side effects were documented as observed by research personnel.

Plasma gabapentin and serum creatinine levels were analyzed using one-way ANOVA for repeated measures, followed by Dunnett's post-hoc comparisons ($P < 0.05$). A Pearson correlation was conducted for plasma gabapentin vs creatinine concentrations on the day following surgery. Pain and sedation scores are reported as observational data only.

Results

The recruitment took place between May and September 2007. Intraoperative plasma gabapentin concentrations were determined for all 16 patients recruited, although two were withdrawn from the protocol postoperatively due to 1) excessive bleeding requiring re-operation, and 2) unsuitability for tracheal extubation within our target range of one to six hours. Table 1 shows demographic and surgical characteristics for all 16 subjects. Grafts included the left internal mammary artery in all patients, right internal mammary free graft in six patients, free radial artery in one patient, and saphenous vein harvesting. The mean time from arrival in CVICU to tracheal extubation was 172 ± 72 min. Mean heart rate and blood pressure measurements are shown in Table 2.

The mean time between the first dose of gabapentin and the onset of CPB was 206 ± 63 min, and mean CPB time was 85 ± 26 min. Plasma gabapentin concentrations (Figure 1) were similar to pre-induction levels for the duration of CPB. Significant increases in plasma gabapentin concentrations were observed following the third and fourth doses of gabapentin ($P < 0.05$) (Figure 1). There were no

Table 1 Patient & Surgical Characteristics ($n = 16$)

Age (yr)	65.3 ± 9.7	(46-76)
Weight (kg)	83.8 ± 12.9	(52-109)
Height (cm)	170 ± 10	(154-183)
Body mass index ($\text{kg}\cdot\text{m}^{-2}$)	28.2 ± 3.9	(20.3-36.8)
Surgery duration (min)	234 ± 55	(160-327)
CPB duration (min)	81 ± 27	(45-127)
Number of grafts*	4	(2-5)
Extubation time (min)†	172 ± 72	(15-305)

Data expressed as mean $\pm$ standard deviation (range), unless otherwise noted. CPB = cardiopulmonary bypass. * Median. † Time from arrival in recovery to extubation

Table 2 Hemodynamic parameters ($n = 16$)

	Systolic BP (mmHg)	Heart rate (beats·min ⁻¹)
Baseline	138 ± 28	66 ± 10
Post-induction lowest value	110 ± 31	58 ± 14
Post-induction highest value	135 ± 27	64 ± 9
CPB lowest value (mean BP)	54 ± 6	-
CPB highest value (mean BP)	68 ± 8	-

Data are given as mean $\pm$ standard deviation. BP = blood pressure; CPB = cardiopulmonary bypass

Fig. 1 Plasma gabapentin concentration ($\mu\text{mol}\cdot\text{L}^{-1}$, $n = 16$) over the 24 hr observation period (mean $\pm$ SD). The first dose of gabapentin (600 mg) was given 90 min prior to induction. CPB = cardiopulmonary bypass

* Indicates significant difference from induction ($P < 0.05$)

changes in serum creatinine levels throughout the observation period ($P = 0.413$), and no correlation was observed between plasma gabapentin and creatinine levels on postoperative day one ($P = 0.969$; $R^2 = 0.0002$).

Pain and sedation scores are shown in Figures 2 and 3, respectively. These summary data are presented as

Fig. 2 Resting vs evoked pain scores (visual analogue scale, VAS) on postoperative day one (mean $\pm$ SD). PEF = peak expiratory flow

Fig. 3 Sedation scores at baseline (preoperatively before gabapentin), before induction, following extubation, and on postoperative day one (mean $\pm$ SD)

observations only, since there was no comparison group. The range of pain scores was generally from 0 to 3 on the ten-point visual analogue scale: 0 = no pain and 10 = worst pain possible. The day after surgery, one patient reported a score of 6 while coughing, and on the day following surgery, two patients reported scores of 4 while sitting. Although some patients reported varying degrees of drowsiness on the day following surgery, all were rousable by verbal command (no scores > 3) at all time points. All other patients at all time points reported being completely alert and oriented (score = 1) or drowsy (score = 2). The mean total dose of morphine equivalents over the observation period was 22.7 ± 18.1 mg. Although two patients reported hallucinations following the second dose of gabapentin, these subjects had consumed more morphine (10.0 ± 1.4 mg vs 4.7 ± 3.5 mg) prior to the onset of the hallucinations.

Discussion

This observational, open-label investigation represents the first report of gabapentin administration for postoperative

pain in the setting of cardiac surgery. The study was designed primarily to examine the effects of CPB on gabapentin plasma concentration following a preoperative dose, as well as the variation in plasma concentration over the following 24 hr with subsequent gabapentin dosing. Secondly, we sought to determine the feasibility of using gabapentin as an adjuvant analgesic in the setting of cardiac surgery. Our results demonstrate that plasma gabapentin concentration remains stable throughout and following CPB, although, using the dosing protocol described, gabapentin concentration accumulated following the third and fourth doses.

The mean plasma concentration of gabapentin attained after a preoperative dose of 600 mg (31.9 ± 12.7 $\mu\text{mol}\cdot\text{L}^{-1}$) compares with that found in previous studies.¹² These levels remained constant throughout and after the period of CPB. Cardiac surgery may affect drug pharmacokinetics in a number of ways, including substantial fluid shifts and specific effects attributable to the CPB circuit and oxygenator. In particular, CPB entails acute hemodilution that reduces drug concentrations to a variable extent. In addition, some drugs are adsorbed to CPB components, particularly the oxygenator membrane.⁴ These effects have not been published previously for gabapentin and are essential to determining appropriate dosing of this drug.

The relative stability of gabapentin drug concentration during CPB observed in this study suggests that this drug is not subject to any substantial degree of adsorption to the bypass circuit or filtration by the membrane oxygenator. Similarly, hemodilution with priming solution did not lead to a clinically significant decrease in gabapentin plasma concentration. However, since the time to maximal gastrointestinal absorption of gabapentin is two to three hours, and since CPB was initiated over three hours following its administration, it is possible that tissue stores of drug were released when plasma concentration decreased during acute hemodilution.

In contrast, there was evidence of significant accumulation of gabapentin following the third and fourth doses on the first postoperative day. However, since the half-life of gabapentin is five to seven hours, and it takes approximately five half-lives to reach drug steady state, it is likely that reducing the dose or increasing the dosing interval of gabapentin would decrease the likelihood of accumulation. No correlation was seen between plasma gabapentin concentration and serum creatinine levels, suggesting that transient renal impairment and resulting reduction in drug clearance was not the cause of drug accumulation.

Although this study was not designed to assess analgesic efficacy of gabapentin in the setting of cardiac surgery, other cardiac surgery studies, not involving the use of gabapentin, reported average resting pain scores of 5.0 ± 2.0 on the VAS scale and sedation scores higher than 2 on the five-point

scale when measured on postoperative day one.¹³ In contrast, our scores were 1.1 ± 1.0 and 1.1 ± 0.32 , respectively. In addition, the total morphine equivalents administered in our investigation (22.7 ± 18.1 mg or 0.95 mg·hr⁻¹) were similar to those of Parlow *et al.*¹⁴ (0.78 mg·hr⁻¹ weighted average) but lower than those reported by Coventry *et al.*¹⁵ (1.27 mg·hr⁻¹). Despite the small numbers in this study, the pain and sedation scores we observed are similar to those reported elsewhere.

Adequate treatment of postoperative pain has both quality of life and clinical implications. Poorly controlled surgical pain has been related to postoperative pulmonary cardiac and thromboembolic complications.¹⁶ Given the pathogenic mechanisms of these complications, e.g., hypoventilation leading to atelectasis and decreased ambulation leading to venous stasis, it is imperative that pain evoked by coughing, breathing, and ambulation be managed more effectively. This is particularly important in the setting of cardiac surgery with CPB, where adequate lung expansion following tracheal extubation is essential to reducing postoperative atelectasis and hypoxemia. Recently, it has become apparent that evoked postoperative pain negatively influences pulmonary function during the recovery period after abdominal surgery.¹⁷ Conversely, effective pain management has been shown to improve indices of pulmonary function after abdominal surgery.⁹

Opioids remain a mainstay of treatment for pain following cardiac surgery. However, data suggest that opioids reduce spontaneous pain when given alone, but are relatively ineffective for pain evoked by movement.¹⁸ In cardiac surgical patients, opioid requirements are quite variable.¹⁴ When pain is severe, doses of opioids necessary to reduce evoked pain may lead to respiratory depression and side effects such as somnolence, nausea, and pruritis.

In addition to opioid analgesics, other pharmacological treatments commonly used to treat postoperative pain include NSAIDs.¹⁹ Adverse effects of gastropathy, impaired hemostasis, and nephrotoxicity may limit the utility of NSAIDs in the cardiac surgical population.^{7,20} NSAIDs with selective COX-2 inhibition have shown promise in reducing bleeding complications postoperatively.²¹ However, putative thrombotic complications have led to the withdrawal of some of these drugs from the market and, in effect, have eliminated their use in the setting of cardiac surgery.²²

Gabapentin is a 3-alkylated analogue of gamma-amino butyric acid (GABA) that has been shown to be effective in reducing pain scores and opioid consumption in a number of surgical settings.²³⁻²⁶ Also, when used in combination with a COX-2 inhibitor, gabapentin has been shown to have specific efficacy in reducing pain evoked by movement and respiration after surgery.⁹ Furthermore, gabapentin, both alone and in combination with a COX-2 inhibitor, led to improvement

in indices of pulmonary function during the recovery period after abdominal surgery.⁹ Such a benefit could be of particular importance in the cardiac surgical population where pulmonary disease is a common comorbid condition. Gabapentin has also been shown to attenuate the hemodynamic consequences of stressors such as laryngoscopy and tracheal intubation, which could be of benefit in patients at risk for myocardial ischemia.^{27,28}

Limitations of this study include its observational unblinded design; it was not intended to assess analgesic efficacy. However, it is noted that pain scores may be lower¹³ and opioid requirements appeared to be at least comparable with¹⁴ or lower¹⁵ than those reported in previous studies observing patients during CPB in the absence of gabapentin. In addition, a thorough pharmacokinetic analysis was not carried out, as the objective was to determine possible effects of CPB on gabapentin blood concentration. Finally, the documentation of side effects was a secondary consideration, as the study was not powered to confirm drug safety. A few patients experienced excessive sedation with this regimen; this appeared to be more common in those with higher gabapentin concentrations. However, all patients were responsive, and times to tracheal extubation and discharge from CVICU were not delayed. No other serious side effects were experienced in this small group of patients.

In summary, CPB does not alter drug concentration of gabapentin after a single preoperative dose. However, increasing gabapentin concentrations on the first postoperative day suggests that the optimal dosing regimen is yet to be determined, and therapeutic drug monitoring in future perioperative trials of gabapentin and pregabalin are advisable. This study indicates that a controlled randomized prospective trial is warranted to assess the analgesic efficacy and risk of adverse effects of gabapentin in the setting of cardiac surgery.

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Conflicts of interest Dr. Ian Gilron has received funding in the form of research support and/or consulting fees from Pfizer Inc., Novopharm, and Pharmascience all of which manufacture gabapentin. Dr. Gilron is also supported by an industry partnered mid-career investigator award supported by the Canadian Institutes of Health Research and Pfizer Canada Inc. No other author has any conflict of interest related to this article.

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