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**Editorial II**

**Gabapentin: a new drug for postoperative pain?**

Consistent delivery of first-class postoperative pain control is still a major challenge. Opioids are inevitably associated with emesis and the risk of respiratory depression, local anaesthetic techniques are often short-lived or require interventional procedures, and the use of NSAIDs and COX-2 inhibitors is limited by well known complications and concerns. Consider the possibility of a drug which significantly improves the quality of opioid analgesia, reduces opioid requirement, possibly prevents or reduces opioid tolerance and relieves anxiety. Furthermore, what if this drug did not depress respiration and had no effect on the gastric mucosa, platelets and renal function? A paper published in this edition of the British Journal of Anaesthesia¹ and the work of others suggest that gabapentin may fit this profile.

Traditionally, the pathophysiology and treatment of postoperative pain and neuropathic pain have been considered as separate and distinct. Opioids, NSAIDs and local anaesthetics were the tools of those dealing with acute pain; anticonvulsants and tricyclic antidepressants were for the chronic pain specialist. However, there is considerable overlap in their pathophysiology. Allodynia and hyperalgesia are cardinal signs and symptoms of neuropathic pain but they are also often present after trauma and surgery. Sensitization of neurones in the dorsal horns, a mechanism in neuropathic pain, has been demonstrated in acute pain models.²³ The persistence of this mechanism may be responsible for the increasingly recognized problem of chronic pain after surgery.⁴⁵

Gabapentin was introduced for the treatment of epilepsy in the early 1990s. Several years later, anecdotal reports describing the efficacy of gabapentin for the treatment of neuropathic pain began to appear⁶⁻⁸ and off-label prescribing for this indication became widespread. Large
placebo-controlled, double-blind trials confirmed these reports\(^9\)\(^10\) and gabapentin became licensed in many countries for the treatment of neuropathic pain. Despite its name, gabapentin does not bind at the GABA\(_A\) or GABA\(_B\) receptor. However, it has a high binding affinity for the \(\alpha-6\) subunit of the presynaptic voltage-gated calcium channels\(^{11}\) which inhibits calcium influx and subsequent release of excitatory neurotransmitters in the pain pathways.

During the elucidation of the mechanism of action of gabapentin in animals, it became apparent that it was effective in some acute pain models. For example, in an acute postoperative pain model, efficacy in the prevention of mechanical hyperalgesia was superior to that of morphine.\(^{12}\) These and other findings were confirmed in some human investigations. For example, when a first degree burn was inflicted on volunteers who had been given gabapentin 1200 mg, there was no analgesic effect on normal skin but mechanical pain threshold was reduced significantly on the inflamed skin.\(^{13}\) Similar efficacy for gabapentin 600 mg was demonstrated in 12 volunteers using the cold pressor test\(^{14}\) and in 25 males subjected to the heat-capsaicin sensitization model (1200 mg).\(^{15}\) However, gabapentin 600 mg had no effect on hyperalgesia associated with an ultraviolet induced inflammation.\(^{16}\)

As well as a direct analgesic effect, gabapentin may prevent and/or reverse opioid tolerance. Using the rat paw-pressure and tail-flick model, Gilron and colleagues\(^{17}\) showed that gabapentin inhibited the development of antinociceptive tolerance to morphine. Further work by the same group confirmed this effect specifically in spinal opioid receptors.\(^{18}\)

In this issue of the British Journal of Anaesthesia, the effect of gabapentin on the quality of postoperative pain relief delivered by patient-controlled epidural analgesia in patients undergoing general anaesthesia is reported.\(^1\) The authors have described the efficacy of gabapentin in postoperative pain previously\(^{19-23}\) but this is the first investigation elucidating its effects on postoperative epidural analgesia. In a placebo-controlled, double-blind study, they demonstrated that gabapentin 1200 mg, administered before and for 2 days after surgery, was associated with a significant reduction in the requirement for patient-controlled epidural analgesia and escape analgesia. Furthermore, there was a statistical and clinically significant improvement in postoperative pain scores and patient satisfaction with less postoperative motor block. The study was well designed and involved 40 patients undergoing surgery to the lower extremities (scar revision and/or skin grafting). There was a significant increase in the incidence of dizziness (35% vs 5%) and a non-significant increase in somnolence (25% vs 10%). However, the occurrence of these recognized side-effects of gabapentin was not reflected in overall patient satisfaction with postoperative pain relief; this was significantly superior in the gabapentin group.

There is now considerable interest in the potential use of gabapentin for postoperative pain relief. In a recent review,\(^{22}\) seven studies of reasonable quality were identified. Significant reductions in postoperative analgesic requirements 24 h after surgery were found in six studies (abdominal hysterectomy, spinal surgery, vaginal hysterectomy, radical mastectomy and laparoscopic cholecystectomy);\(^{19,20,23-26}\) significant effects were found in the other study after 2 days (mastectomy).\(^{27}\) Since this review, more data confirming these findings have been published. For example, gabapentin 1200 mg, given 1 h before rhinoplasty or endoscopic sinus surgery under regional anaesthesia and propofol sedation, was associated with reduced postoperative pain scores and analgesic consumption.\(^{21}\) Again, the incidence of dizziness was significantly increased and the authors commented that this may be a problem in the context of day-case surgery. Further work has explored the effect of a gabapentin (1800 mg per day)-rofecoxib (50 mg) combination after abdominal hysterectomy.\(^{28}\) The data suggested that the combination was more effective than placebo and either single agent.

Patients are understandably anxious during the perioperative period and this can be a significant problem in some. Gabapentin has anxiolytic properties.\(^{29,30}\) In a recent study, gabapentin was given orally 2 h before surgery to patients undergoing arthroscopic cruciate ligament repair under general anaesthesia.\(^{31}\) Pre-induction VAS anxiety scores were impressively less in the gabapentin group (28 mm vs 68 mm; \(P < 0.0001\)); postoperative pain control and early knee mobility were also significantly better. Side-effects were not a problem in this study.

Pregabalin has recently obtained a license in many countries for the treatment of peripheral neuropathic pain.\(^{32,33}\) Its mechanism of action is probably the same as gabapentin but it has a superior pharmacokinetic profile.\(^{34}\) There is already some evidence that it may have efficacy in acute pain similar to that of gabapentin.\(^{35,36}\)

Available data suggest that gabapentin may indeed have a place in the management of postoperative pain. However, considerably more work is required before recommending that it is accepted for routine clinical use. The recommended starting dose of gabapentin for neuropathic pain is 300 mg on day 1, 300 mg twice daily on day 2 and then 300 mg three times daily thereafter. This dose is often insufficient and doses of up to 1800 mg may be required. The practice of administering a first dose of 1200 mg immediately before anaesthesia and surgery is clearly in contravention to this recommendation. The potential for dizziness and drowsiness has been discussed but, as yet, no serious side-effects have been reported in the acute pain studies. However, relatively few patients have been exposed to gabapentin in the perioperative period and there are no data on potential pharmacokinetic and pharmacodynamic interactions with other drugs administered at this time. Unfortunately, it may be that smaller doses are ineffective. For example, in a study investigating day-case laparoscopic procedures, gabapentin 300 mg had no significant effect on postoperative pain.\(^{27}\)
Despite all these uncertainties, the initial data indicate that gabapentin, and possibly pregabalin, may have a place in the treatment of postoperative pain. The challenge now is to assemble an evidence-base of sufficient size and quality to be sure of its efficacy and safety.

D. J. Rowbotham
Leicester, UK
E-mail: djr8@le.ac.uk

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