

## Recent advances in postoperative pain therapy

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*Br J Anaesth* 2005; **95**: 43–51

**Keywords:** analgesic techniques, i.v.; analgesics non-opioid, acetaminophen; analgesics non-opioid, nitroxyparacetamol; analgesics opioid, peripheral; enzymes, cyclooxygenase 2, inhibitors; pain, acute, postoperative; pain, neuropathic; therapy, non-pharmacological

Despite many advances in the provision of pain services, acute pain after surgery remains a serious cause of severe suffering that is often undermanaged despite our best efforts.<sup>6,34,37</sup> Acute pain teams have been introduced in many hospitals, but recent evidence from a UK national postal questionnaire suggests that they are struggling with the problem of alleviating acute pain successfully.<sup>90</sup> In a review of published data of pooled pain scores from nearly 20 000 surgical patients having intramuscular, patient controlled analgesia (PCA) or extradural analgesia, the overall mean (95% confidence interval) incidence of moderate to severe and severe pain was 29.7 (26.4–33.0)% and 10.9 (8.4–13.4)%, respectively.<sup>37</sup> Often the provision of effective postoperative analgesia is limited by side-effects, and these have been quantified in contemporary anaesthetic practice by Cashman and Dolin with special attention to respiratory depression and hypotension after intramuscular, PCA and extradural analgesia,<sup>28</sup> in a companion paper to their study of analgesic efficacy.<sup>37</sup> Cashman and Dolin concluded that assuming an acute pain service uses a mixture of the three analgesic techniques studied (intramuscular, PCA, and extradural analgesia), then the expected incidence of respiratory depression (defined by a low ventilatory frequency) should be less than 1%, and the expected incidence of hypotension related to analgesic technique should be less than 5%. Interestingly, while the incidence of respiratory depression decreased over the period 1980–99, the incidence of hypotension did not.<sup>28</sup> The risk of side-effects from other analgesics in use for acute postoperative pain therapy is well defined. NSAIDs, for example, are effective analgesics, but have potential adverse effects that may render them contraindicated in many patients having surgery.<sup>47,76</sup>

Acute pain can be persistent, the tissue damage of surgery setting up pathophysiological processes in the peripheral and central nervous systems that may produce chronicity.<sup>32</sup> The association between surgery, acute postoperative pain and ongoing severe chronic pain is well defined,<sup>72,85</sup> one paper noting that the severity of acute pain was a predictive factor

for chronic ongoing pain.<sup>85</sup> The significance of this association has been reinforced by recent studies demonstrating that it is a problem even in previously healthy young women having Caesarian section,<sup>82</sup> and is a source of long-term pain and disability after the relatively minor procedure of inguinal hernia repair.<sup>14</sup>

There is therefore a pressing need for advances in the agents and techniques we can use to improve analgesia efficacy, and perhaps reduce the incidence of chronic suffering after surgery. The methods that have been at our disposal for some years for acute pain relief have been assessed critically<sup>81</sup> and are summarized in Table 1.

In this review of postoperative pain relief, consideration will be given to advances in our understanding of the role of non-pharmacological techniques, peripheral opioid analgesia, selective cyclooxygenase 2 inhibitors, i.v. paracetamol and nitroxyparacetamol, and the diagnosis and management of acute postsurgical neuropathic pain.

### Non-pharmacological methods of postoperative pain relief

Although the accepted definition of pain emphasizes the cognitive, emotional response to tissue damage, the role of psychological techniques in the relief of acute pain has been minimized. An example of the importance of this is that such factors affect recovery after acute sports injury. After anterior cruciate ligament repair, ‘catastrophizing’ is displayed and is associated with higher pain scores.<sup>106</sup> Perhaps surprisingly, catastrophizing was a particularly strong factor in postoperative pain differences between adolescents and adults, being more pronounced in the younger patients.<sup>106</sup> Over 10 yr ago a meta-analysis of 191 studies of surgical patients demonstrated that ‘psychoeducational care’ has beneficial effects on recovery, postoperative pain and psychological distress after surgery.<sup>36</sup> Psychoeducational care was classed as health-care information (information in preparation for surgery, timing of procedures, functions

**Table 1** Methods of acute pain relief assessed for by the NHMRC and ANZCA Acute Pain Management: Scientific Evidence working party<sup>81</sup>

Non-pharmacological
Cognitive-behavioural approaches
Physical therapy
Pharmacological
Opioids
NSAIDs
Local anaesthetics
Paracetamol
Ketamine
Adjuvants

and roles of health-care providers, self-care actions, and pain and discomfort information); skills teaching (coughing, breathing and bed exercises, relaxation, hypnosis, cognitive reappraisal); and psychosocial support (identifying and alleviating concerns, reassurance, problem-solving, encouraging questions, and increasing the frequency of support). Unfortunately, such non-pharmacological therapy is seldom used for acute postoperative pain relief, although it is beneficial and devoid of any significant adverse effects.

Well-designed clinical studies are required to investigate the role of non-pharmacological techniques in relieving postsurgical pain. An example of this is acupuncture, which has been examined recently after shoulder surgery in a randomized study and found to reduce pain, improve movement and increase patient satisfaction.<sup>46</sup> Moreover, in another well-designed study acupuncture has been shown to reduce somatosensory evoked potentials to noxious stimuli in anaesthetized volunteers.<sup>75</sup>

### Peripheral opioid analgesia

Traditionally, opioids are viewed as basic components of postoperative analgesia given into the systemic circulation by injection, but even their use is changing considerably. The use of oral opioid immediate- and sustained-release opioid preparations provides quick and effective analgesia and can be used to bridge the analgesic gap that is often apparent after patient-controlled or extradural analgesia has been stopped and when the patient eventually attains comfort on simple analgesics.<sup>99</sup> Indeed, prescriber confidence in using effective doses of oral opioids may allow the delivery of good analgesia without recourse to parental injections or invasive procedures. In a similar manner, the development of opioid nasal sprays may facilitate the delivery of effective analgesia.<sup>60 84</sup>

Whilst opioids are the mainstay for relief of severe pain, they are far from perfect analgesics as they have many significant adverse effects.<sup>104</sup> The common opioid side-effects of respiratory depression, sedation, depression of gastrointestinal motility, nausea and vomiting, and the potential risk of abuse reflect the striking and generalized role endogenous opioids play in general human physiology.<sup>19</sup> The majority of opioid-related side-effects are associated with their central nervous system actions, so much recent work has concentrated instead

upon the presence and function of opioid receptors on peripheral sensory nerves,<sup>101 112</sup> endogenous opioid agonist production by inflammatory leucocytes,<sup>24 27 79</sup> reports of effective peripheral opioid analgesia,<sup>56 66 87 92 100</sup> and work on the development of novel selectively peripherally acting opioid agonists with more favourable safety and efficacy profiles.<sup>40 70 103</sup> One group has paraphrased this new and exciting focus on the peripheral effects of opioids at the site of tissue damage as 'attacking pain at its source'.<sup>103</sup> The hope is that drugs can be developed that activate peripheral opioids only, thus avoiding centrally mediated actions and many adverse effects.

The  $\mu$ ,  $\delta$  and  $\kappa$  opioid receptors (MOR, DOR, and KOR) are found throughout the nervous system and produce analgesia (KOR may have anti-analgesic effects in some circumstances). The cell bodies of sensory nerves in the dorsal root ganglion produce MOR, DOR and KOR,<sup>102</sup> and the receptors are then transported peripherally in the nerve axons.<sup>101 103</sup> When activated, opioid receptors in peripheral nerves modulate nerve activity by inhibition of high-voltage calcium channels<sup>102</sup> and suppression of tetrodotoxin-resistant selective sodium channels and non-selective cation currents stimulated by inflammatory PGE<sub>2</sub>.<sup>103</sup> In summary, when activated, opioid receptors reduce the excitability of nociceptors, afferent action potential propagation and inflammatory peptide release from sensory nerve endings.

Inflammatory cells play a central role in peripheral opioid analgesia by migrating to and delivering opioid peptides to the receptors expressed by the sensory nerve terminals at the very site of tissue damage. In injured tissue endorphin, enkephalin and dynorphin production is increased in lymphocytes, monocytes, macrophages and granulocytes, and these peptides bind to all three opioid receptors. Various stimuli, including cytokines, endotoxins, corticotropin releasing hormone (CRH) and catecholamines, increase the expression of opioids by inflammatory cells.<sup>17 71 79</sup> White cells are attracted to injured tissue by selectins (L selectin on leucocytes, and P and E selectin on endothelial cells), adhere to endothelia via the action of intracellular adhesion molecules, and migrate through the vessel wall under the direction of platelet-endothelial cell adhesion molecules.<sup>68 69 80 103</sup> Having been attracted to injured, inflamed tissue, the extravasated inflammatory cells' production of opioids is governed by CRH, interleukin-1 $\beta$  and catecholamines.<sup>17 79</sup> Interestingly, effective central afferent nerve blockade modulates the recruitment of opioid-producing inflammatory cells to damaged tissue.<sup>97</sup>

In conjunction with such advances in the understanding of endogenous peripheral opioid analgesia, the development of clinically useful peripherally acting opioid drugs has been stimulated. The aim is to produce substances that activate peripheral opioid receptors, but which do not cross the blood-brain barrier,<sup>9 55</sup> thus producing analgesia with less central adverse effects.<sup>25</sup> Asimadoline is a peripherally active  $\kappa$  opioid agonist that initially produces analgesia then, unfortunately, delayed proinflammatory effects in

animal models of chronic inflammation.<sup>8,70</sup> Encouragingly, new tetrapeptide  $\kappa$  agonists with high peripheral selectivity due to their poor central nervous system penetration have been found to have potent analgesic and anti-inflammatory actions.<sup>16</sup> From preclinical studies it appears that peripheral opioids are effective in various animal models of inflammatory, visceral, bone and neuropathic pain.<sup>103</sup>

Clinical studies have demonstrated that small doses of morphine applied peripherally to the site of tissue damage can produce significant analgesia with minimal side-effects. Intra-articular morphine gives analgesia after knee surgery in a dose-dependent fashion,<sup>65</sup> and 5 mg is effective for up to 24 h.<sup>56</sup> Morphine injected at the site of iliac bone harvesting for spinal grafting produced intense prolonged analgesia and a reduction in persisting pain.<sup>92</sup> Importantly, a number of clinical studies have demonstrated that the analgesic effect of peripheral morphine is only apparent in the presence of inflammation. For example, in patients with a unilateral corneal abrasion, topically applied morphine produces effective analgesia in the injured eye only,<sup>87</sup> and after dental surgery 1 mg morphine injected locally into the submucosa is an effective analgesic<sup>67</sup> only when inflammation is present around the tooth.<sup>66</sup> The negative results found in some studies of peripheral opioids<sup>88</sup> may in part be due to the opioid application to normal peripheral nerves in the absence of any inflammation, when the opioid may not have access to intraneuronal opioid receptors in transit to the periphery.

Early clinical trials with peripherally acting  $\kappa$  opioid receptor agonists gave disappointing results.<sup>15</sup> Indeed, systemic administration of asimadoline to patients after knee surgery had a hyperalgesic effect, possibly because the drug has a  $\kappa$  agonist antinociceptive effect followed by a non-opioid hyperalgesic and proinflammatory effect in experimental animals.<sup>70</sup> However, a recent clinical study using a peripherally selective  $\kappa$  opioid agonist given to patients with chronic pancreatitis and pain demonstrated a significant analgesic effect, supporting the hypothesis that human visceral afferents express KOR, and that peripherally restricted KOR agonists produce analgesia in patients with chronic visceral pain.<sup>40</sup>

### **Cyclooxygenase-2-selective inhibitors (COX-2 inhibitors)**

New drugs have been developed that selectively inhibit the inducible cyclooxygenase enzyme COX-2 and spare constitutive COX-1. The COX-2 inhibitors available at present include meloxicam, nimesulide, celecoxib, etoricoxib, lumiracoxib, valdecoxib and parecoxib, the injectable precursor of valdecoxib (rofecoxib having been withdrawn recently).<sup>5</sup> By sparing physiological tissue prostaglandin production whilst inhibiting inflammatory prostaglandin release, COX-2 inhibitors offered the potential of effective analgesia with fewer side effects than the NSAID, but this desired outcome has been achieved only partially.

The COX enzyme was first isolated in 1976, but more recently isoenzymes have been isolated. The two isolated COX isoenzymes have 75% amino acid homology with complete preservation of the catalytic sites for cyclooxygenase and peroxidase activity, with almost identical enzyme kinetics. COX-1 is a membrane-bound haemoglycoprotein with a molecular weight of 71 kDa, found in the endoplasmic reticulum of prostaglandin (PG)-producing cells. The enzyme cyclizes arachidonic acid and then adds a 15-hydroperoxy group to form the endoperoxide PGG<sub>2</sub>, which is then reduced to the hydroxy form of PGH<sub>2</sub> by a peroxidase in the same COX enzyme protein. The COX-1 isoenzyme integrates into only a single leaflet of the lipid bilayer, and this is described as a 'monotopic' arrangement. The enzyme has three independent folding units: an epidermal growth factor-like domain, a membrane-binding domain and an enzymatic domain. The  $\alpha$ -helices of the membrane-binding domains form a channel entrance to the active site, are inserted into the membrane, and thereby allow arachidonic acid to gain access into the interior of the lipid bilayer. The sites for COX and peroxidase activity are spatially distinct but are adjacent to each other. The COX active site is a long hydrophobic channel with tyrosine 385 and serine 530 at the apex. NSAIDs block COX-1 halfway down the channel by hydrogen bonding to the polar arginine at position 120 (reversible). Aspirin acetylates serine 530, irreversibly preventing access for arachidonic acid.

COX-2 has a molecular weight of 70 kDa, with similar sites to COX-1 for the attachment of arachidonic acid and a similar three-dimensional structure to COX-1. However, its active site has a greater volume, because it has a larger central channel with a wider entrance and a secondary internal pocket. Therefore, COX-2 can accommodate larger drugs than COX-1. A single amino acid difference at position 523 is critical for the COX-1 and COX-2 selectivity of the NSAID. In COX-2 a valine molecule replaces the isoleucine molecule present at position 523 in COX-1. This valine molecule in COX-2 is smaller (by one methyl group) and produces a gap in the wall of the channel, giving access to a side pocket, which is the binding site of the COX-2-selective inhibitors. The larger isoleucine at position 523 in COX-1 blocks access of drug molecules to the side pocket.

The genes for the two isoenzymes are found on different chromosomes: chromosome 9 for COX-1 and chromosome 1 for COX-2. Under physiological conditions COX-1 activity predominates to produce prostaglandins that regulate rapid physiological responses, such as vascular homeostasis, gastric function, platelet activity and renal function. The concentration of the COX-1 isoenzyme is low but this may increase two- to four-fold in response to stimulation by hormones or growth factors. Low concentrations of COX-2 can normally be detected in the brain, kidney and gravid uterus. COX-2 mRNA expression by monocytes, synovial cells and fibroblasts may be increased 10- to 80-fold when stimulated by growth factors, cytokines, bacterial

lipopolysaccharides or phorbol esters. These factors increase COX-2 production and tissue PGE<sub>2</sub> concentrations, resulting in pain and inflammation.

### *Prostaglandin inhibition*

Prostaglandins have many physiological functions, including gastric mucosal protection, renal tubular function and vasodilation, bronchodilation, endothelial prostacyclin, which produces vasodilation and prevents platelet adhesion, and platelet thromboxane, which produces aggregation and vessel spasm. Such physiological roles are mainly regulated by COX-1 and are the basis for many of the adverse effects associated with NSAID use. Tissue damage induces COX-2 production with the production of prostaglandins that produce pain and inflammation. COX-2 may be constitutive in some tissues, including the kidney. NSAIDs, like aspirin, are 'non-selective' cyclooxygenase inhibitors that inhibit both COX-1 and COX-2. Aspirin acetylates and inhibits cyclooxygenase irreversibly, but NSAIDs are reversible inhibitors of the enzymes. The COX-2 inhibitors have been developed to inhibit selectively the inducible form.<sup>57</sup>

### *The analgesic efficacy of COX-2 inhibitors*

Clinical studies have confirmed that COX-2 inhibitors can produce analgesia similar to NSAIDs for moderate to severe acute pain,<sup>10 11 13 29 39</sup> and the number needed to treat (NNTs) from such studies are comparable to those for conventional NSAIDs: celecoxib 200 mg, 4.5; parecoxib 20 mg i.v., 3.0; parecoxib 40 mg i.v., 2.2; valdecoxib 20 mg, 1.7.

### *Adverse effects*

#### *Gastrointestinal*

Large outcome studies have demonstrated that COX-2 inhibitors produce less clinically significant peptic ulceration than NSAIDs.<sup>51</sup> Both rofecoxib and celecoxib have been associated with a substantial reduction in endoscopic ulcers compared with NSAID comparators.<sup>20 98</sup> In the VIGOR study,<sup>21</sup> all upper gastrointestinal events were reduced from 4.5 per 100 patient years to 2.1 per 100 patient years with doses of rofecoxib compared with naproxen. In the CLASS study,<sup>98</sup> over a period of 3 days to 6 months, the incidence of ulcer complications was 0.76% with celecoxib and 1.45% for ibuprofen or diclofenac. The less substantial reduction in events in the CLASS study compared with VIGOR may be because a fifth of the patients were also on low-dose aspirin. There is continuing debate on the role of COX-2 inhibitors in patients who have other risk factors for ulcer disease: the elderly; patients on aspirin or corticosteroids; patients who have a previous ulcer; or patients who have *Helicobacter pylori* infection. It has been estimated that the number of patients needed to treat with COX-2 inhibitors in preference to NSAIDs to avert one gastrointestinal clinical event in one

year is 40–100.<sup>64</sup> In summary, peptic ulceration remains a reduced but significant adverse effect of the COX-2 inhibitors.

#### *Platelet function and thrombotic sequelae*

Platelets produce only COX-1, not COX-2, and as a corollary COX-2-selective inhibitors do not impair platelet function. Clinical studies have confirmed the lack of an antiplatelet effect of COX-2 inhibitors and a reduction in surgical blood loss in comparison to NSAIDs.<sup>52</sup> Whilst reviews have concluded that NSAIDs need not increase surgical blood loss,<sup>77</sup> the lack of antiplatelet effects of COX-2 inhibitors may be an advantage for the patient with a bleeding diathesis, when anticoagulants are given, where central neuraxial blockade is performed, or where surgical blood loss is expected to be considerable.

The question has been raised of whether COX-2 inhibitors can produce a tendency to thrombosis, because they inhibit endothelial prostacyclin production whilst sparing platelet thromboxane synthesis and aggregation. The VIGOR study, in which patients on low-dose aspirin were excluded, found an increased risk of myocardial infarction for patients given rofecoxib compared with naproxen.<sup>20 21</sup> After coronary artery bypass graft surgery, one acute pain study demonstrated a concerning increase in cerebrovascular accidents (and renal dysfunction and sternal wound problems) when parecoxib then valdecoxib was used in patients for up to 2 weeks.<sup>83</sup> A recent review found that whilst the pharmacological evidence for a prothrombotic effect of COX-2 inhibitors is plausible, the published data give a conflicting body of evidence on the clinical risk, and that more clinical trials are needed to address this concern.<sup>31</sup> The authors suggested that 'In view of the evidence reviewed, it is recommended that selective COX-2 inhibitors should be prescribed with caution, only in patients with conditions for which these drugs have proven efficacy and with careful monitoring of outcomes and adverse events. This is particularly important in the elderly, in patients with cardiovascular/renal disease and in patients with other risk factors that might predispose them to adverse events'.<sup>31</sup> Rofecoxib has recently been withdrawn by the manufacturer for precisely such a reason.<sup>5</sup> 'APPROVe' was a randomized controlled study of the effects of rofecoxib on recurrence of neoplastic bowel polyps in 2600 patients who had a history of colonic adenoma. The study was stopped prematurely at 18 months when it was realized that the group given rofecoxib had twice the risk of myocardial infarction compared with placebo treatment.<sup>5</sup> Rofecoxib has been withdrawn by the manufacturer in each of the 80 countries it was marketed in.

#### *Renal function*

COX-2 is constitutively expressed in the kidney, is highly regulated in response to alterations in intravascular volume, and is important for normal renal development. COX-2 metabolites have been implicated in the maintenance of

renal blood flow, the mediation of renin release and the regulation of sodium excretion. In essence, COX-2 inhibitors have similar adverse effects on renal function to conventional NSAIDs.<sup>30 33 62</sup>

#### *Aspirin-induced asthma*

Investigations of patients with aspirin induced asthma has provided encouraging evidence that COX-2-selective inhibitors, when administered at analgesic doses, may not produce bronchospasm in such individuals.<sup>74 105</sup>

#### *Bone healing*

At present, the effect of COX-2 inhibitors on bone healing remains one that has been demonstrated under laboratory conditions, but with little evidence as yet of clinical importance.<sup>45 50</sup>

COX-2-selective inhibitors are effective analgesics. Active peptic ulceration and significant renal impairment remain contraindications to COX-2-selective inhibitor administration. The potential prothrombotic effect may be a concern for the class of drugs, and has led to the withdrawal of rofecoxib.

#### *Intravenous paracetamol and nitroxyparacetamol*

The efficacy of single-dose paracetamol as a postoperative analgesic has been confirmed by various studies, with the following estimated NNTs: 325 mg, 3.8 (2.2–13.3); 500 mg, 3.5 (2.7–4.8); 600/650 mg, 4.6 (3.9–5.5); 975/1000 mg, 3.8 (3.4–4.4); and 1500 mg, 3.7 (2.3–9.5).<sup>12</sup> The mechanism of action remains unclear as, unlike opioids and NSAIDs respectively, paracetamol has no known endogenous binding sites and does not inhibit peripheral cyclooxygenase activity significantly. There is increasing evidence of a central antinociceptive effect, and potential mechanisms for this include inhibition of a central nervous system COX-2, inhibition of a putative central cyclooxygenase ‘COX-3’ that is selectively susceptible to paracetamol, and modulation of inhibitory descending serotonergic pathways.<sup>22 23 61 109</sup> Paracetamol has also been shown to prevent prostaglandin production at the cellular transcriptional level, independent of cyclooxygenase activity.<sup>73</sup> Paracetamol is therefore an effective postoperative analgesic, with potency slightly less than a standard dose of morphine or the NSAIDs.<sup>12 59</sup> The introduction of an i.v. preparation and reports of the analgesic and anti-inflammatory properties and safety advantages of a nitric oxide (NO)-releasing form may represent significant advances in the use of this drug.

#### *Intravenous paracetamol*

The availability of i.v. paracetamol will enhance and extend the use of this drug as a fundamental component of multimodal analgesia after surgery.<sup>26 59 91</sup> The injectable prodrug propacetamol has been available in various countries for some time, but has the disadvantage that it must be reconstituted before use (2 g propacetamol is equivalent to 1 g

paracetamol). Now a more convenient ready for use solution (Perfalgan; Bristol Myers-Squibb) is available, and 1 g of Perfalgan is equivalent in pharmacokinetic studies to 2 g of propacetamol, with better injection site tolerance.<sup>42</sup> The increased cost implications of using new preparations of old drugs are considerable, and efforts should be made to ensure the use of oral rather than i.v. paracetamol when appropriate.<sup>93</sup> However, the i.v. formulation may have a safety advantage over the oral by producing more predictable plasma paracetamol concentrations in the immediate post-operative period. One clinical study found oral administration of paracetamol given as part of multimodal pain management immediately after surgery resulted in a huge and unpredictable variation in plasma concentration compared with i.v. administration.<sup>86</sup> The availability of i.v. paracetamol preparations may aid accurate administration of paracetamol to patients at higher risk of dose-related hepatic toxicity, including neonates,<sup>3 4</sup> although overdosage has already been reported in this group of patients.<sup>35</sup> The efficacy of i.v. paracetamol appears to be convincing. In volunteers i.v. paracetamol has been shown to reduce central hyperalgesia, further evidence of a central action.<sup>61</sup> In one recent study performed after surgery for removal of impacted third molar teeth, propacetamol administered i.v. in repeated doses (2 g followed by 1 g) had a significant analgesic effect indistinguishable from that of i.m. morphine (10 mg followed by 5 mg), but with improved tolerability.<sup>107</sup> Propacetamol reduces PCA morphine requirements after spinal surgery<sup>53</sup> and is effective after tonsillectomy.<sup>54</sup> More research is required as other studies have found either less impressive opioid sparing with i.v. paracetamol<sup>7 63</sup> or evidence of a ceiling to the analgesia at lower doses than expected.<sup>49</sup>

#### *Nitroxyparacetamol*

Nitroxyparacetamol (or nitroacetaminophen) is a new, potent NO-releasing version of paracetamol that has both analgesic and also anti-inflammatory properties.<sup>58 78</sup> The described mechanism of action in the spinal cord may differ from that of paracetamol,<sup>2 78 94</sup> and there is evidence that nitroxyparacetamol may be less hepatotoxic.<sup>43</sup>

In an animal model of tissue damage, nitroxyparacetamol had a more potent antinociceptive effect than paracetamol, and, unlike the parent drug, was also anti-inflammatory over a similar dose range.<sup>2</sup> It is estimated that nitroxyparacetamol is 3–20 times more potent than paracetamol.<sup>78</sup> Like NSAIDs, nitroxyparacetamol has been shown, in an animal model, to enhance opioid analgesia.<sup>44</sup> In animal models of arthritic pain, nitroxyparacetamol has been found to be an effective antinociceptive drug in arthritic animals, reduces wind-up, and has a mechanism of action located in the spinal cord, perhaps different from that of paracetamol.<sup>94 95</sup> In models of liver damage nitroxyparacetamol does not produce the damage associated with equimolar doses of paracetamol, suggesting that nitroxyparacetamol represents a safer alternative to paracetamol.<sup>43 78</sup> NO appears to produce these beneficial actions through several mechanisms,

including the suppression of synthesis of several proinflammatory cytokines, and may be *per se* a useful therapy for paracetamol-induced liver damage.<sup>108</sup>

### Acute neuropathic pain in the postoperative period

It is recognized that chronic pain after surgery is common and can be severe.<sup>14 32 48 72 82 85 89</sup> Recently emphasis has been given to the development of neuropathic pain acutely after surgery or trauma.<sup>41</sup> Interestingly, much research is still required even to determine how common acute neuropathic pain is after different surgical procedures. Nevertheless, it is accepted that neuropathic pain can develop after surgery, be persistent, and be the basis for ongoing suffering for the patient.<sup>81</sup> Therefore, it is now accepted that neuropathic pain must be diagnosed promptly and managed correctly after surgery to ensure the best outcome for the patient.<sup>85</sup> The diagnosis of neuropathic pain can be obtained from the presenting features of burning, stinging or shooting pain, increasing despite apparent tissue healing, with a relative lack of response to doses of opioids used in the postoperative period (this does not imply that neuropathic pain is unresponsive to opioids), and some or all of the features of allodynia, hyperaesthesia and dysaesthesia.<sup>81</sup>

Treatment of neuropathic pain can be guided by high-level evidence from large studies, reviews and meta-analyses, although these studies are mostly of chronic neuropathic pain states.<sup>38 81 96 110</sup> In general, therapy should be commenced with either an anticonvulsant or a tricyclic antidepressant, but in the early postoperative period this may not be possible if the patient cannot take oral medications. In such a situation the antineuropathic effects of systemic low-dose lidocaine or ketamine can be employed to help control severe neuropathic pain quickly. A reasonable approach to the control of postoperative neuropathic pain would be to use initially a continuous subcutaneous infusion of either lidocaine 1–1.5 mg<sup>-1</sup> kg<sup>-1</sup> h<sup>-1</sup> or ketamine 5–15 mg<sup>-1</sup> h<sup>-1</sup>, followed by oral anticonvulsant or tricyclic antidepressant maintenance therapy when this is possible.<sup>111</sup> Of course, surgical reasons for postoperative neuropathic pain should be considered.<sup>18</sup> Before they are discharged from hospital, patients who have developed postoperative neuropathic pain and require ongoing therapy should be advised of the potential adverse effects of the drugs prescribed, and arrangements should be made for their ongoing review.

### Conclusion

Acute postoperative pain remains difficult to treat and chronicity is a common problem after surgery. The advances described here in the pharmacological and non-pharmacological therapy of acute postoperative pain may improve patient care significantly.

### References

- 1 Ahuja N, Singh A, Singh B. Rofecoxib: an update on physicochemical, ISSN pharmaceutical, pharmacodynamic and pharmacokinetic aspects. *J Pharm Pharmacol* 2003; **55**: 859–94
- 2 al-Swayeh OA, Futter LE, Clifford RH, Moore PK. Nitroparacetamol exhibits anti-inflammatory and anti-nociceptive activity. *Br J Pharmacol* 2000; **130**: 1453–6
- 3 Allegaert K, Anderson BJ, Naulaers G, et al. Intravenous paracetamol (propacetamol) pharmacokinetics in term and preterm neonates. *Eur J Clin Pharmacol* 2004; **60**: 191–7
- 4 Allegaert K, Verbesselt R, Devlieger H, de Hoon J, Tibboel D. Cerebrospinal fluid pharmacokinetics of paracetamol after intravenous propacetamol in a former preterm infant. *Br J Clin Pharmacol* 2004; **57**: 224–5
- 5 Anon. Vioxx: an unequal partnership between safety and efficacy. *Lancet* 2004; **364**: 1287–8
- 6 Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg* 2003; **97**: 534–40
- 7 Aubrun F, Kalfon F, Mottet P, et al. Adjunctive analgesia with intravenous propacetamol does not reduce morphine-related adverse effects. *Br J Anaesth* 2003; **90**: 314–9
- 8 Barber A, Bartoszyk GD, Bender HM, et al. A pharmacological profile of the novel, peripherally-selective kappa-opioid receptor agonist, Emd-61753. *Br J Pharmacol* 1994; **113**: 1317–27
- 9 Barber A, Bartoszyk GD, Greiner HE, et al. Central and peripheral actions of the novel kappa-opioid receptor agonist, Emd-60400. *Br J Pharmacol* 1994; **111**: 843–51
- 10 Barden J, Edwards J, McQuay H, Moore RA. Oral valdecoxib and injected parecoxib for acute postoperative pain: a quantitative systematic review. *BMC Anesthesiol* 2003; **3**: 1
- 11 Barden J, Edwards J, McQuay HJ, Moore RA. Single dose oral celecoxib for postoperative pain (Cochrane Review). *The Cochrane Library*. Chichester: John Wiley & Sons, 2004
- 12 Barden J, Edwards J, Moore A, McQuay H. Single dose oral paracetamol (acetaminophen) for postoperative pain (Cochrane Review). *The Cochrane Library*. Chichester: John Wiley & Sons, 2004
- 13 Barden J, Edwards J, Moore RA, McQuay HJ. Single dose oral rofecoxib for postoperative pain (Cochrane Review). *The Cochrane Library*. Chichester: John Wiley & Sons, 2004
- 14 Bay-Nielsen M, Perkins FM, Kehlet H. Pain and functional impairment 1 year after inguinal herniorrhaphy: A nationwide questionnaire study. *Ann Surg* 2001; **233**: 1–7
- 15 Bickel A, Dorfs S, Schmelz M, Forster C, Uhl W, Handwerker HO. Effects of antihyperalgesic drugs on experimentally induced hyperalgesia in man. *Pain* 1998; **76**: 317–25
- 16 Binder W, Machelska H, Mousa S, et al. Analgesic and anti-inflammatory effects of two novel kappa-opioid peptides. *Anesthesiology* 2001; **94**: 1034–44
- 17 Binder W, Mousa SA, Sitte N, Kaiser M, Stein C, Schafer M. Sympathetic activation triggers endogenous opioid release and analgesia within peripheral inflamed tissue. *Eur J Neurosci* 2004; **20**: 92–100
- 18 Blunt C, Schmiedel A. Some cases of severe post-mastectomy pain syndrome may be caused by an axillary haematoma. *Pain* 2004; **108**: 294–6
- 19 Bodnar RJ, Hadjimarkou MM. Endogenous opiates and behavior: 2002. *Peptides* 2003; **24**: 1241–302
- 20 Bombardier C. An evidence-based evaluation of the gastrointestinal safety of coxibs. *Am J Cardiol* 2002; **89** (6A): 3D–9D
- 21 Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in

- patients with rheumatoid arthritis. *N Engl J Med* 2000; **343**: 1520–8
- 22 Bonnefont J, Courade JP, Alloui A, Eschaliere A. Mechanism of the antinociceptive effect of paracetamol. *Drugs* 2003; **63**: 1–4
  - 23 Botting R. COX-1 and COX-3 inhibitors. *Thrombosis Research* 2003; **110**: 269–72
  - 24 Brack A, Rittner HL, Machelska H, et al. Mobilization of opioid-containing polymorphonuclear cells by hematopoietic growth factors and influence on inflammatory pain. *Anesthesiology* 2004; **100**: 149–57
  - 25 Brower V. New paths to pain relief. *Nat Biotechnol* 2000; **18**: 387–91
  - 26 Burkle H, Gogarten W, Van Aken H. Intravenous non-opioid analgesics in anaesthesia—the role of paracetamol, metamizol, tenoxicam and parecoxib in the perioperative treatment of acute pain. *Anesthesiol Intensivmed* 2003; **44**: 311–20
  - 27 Cabot PJ, Carter L, Schafer M, Stein C. Methionine-enkephalin- and dynorphin A-release from immune cells and control of inflammatory pain. *Pain* 2001; **93**: 207–12
  - 28 Cashman JN, Dolin SJ. Respiratory and haemodynamic effects of acute postoperative pain management: evidence from published data. *Br J Anaesth* 2004; **93**: 212–23
  - 29 Chavez ML, DeKorte CJ. Valdecoxib: A review. *Clin Ther* 2003; **25**: 817–51
  - 30 Cheng HF, Harris RC. Cyclooxygenases, the kidney, and hypertension. *Hypertension* 2004; **43**: 525–30
  - 31 Clark DWJ, Layton D, Shakir SAW. Do some inhibitors of COX-2 increase the risk of thromboembolic events? Linking pharmacology with pharmacoepidemiology. *Drug Saf* 2004; **27**: 427–56
  - 32 Cousins MJ, Power I, Smith G. Pain—a persistent problem. *Reg Analg Pain Med* 2000 **25**: 6–21
  - 33 Curtis SP, Ng J, Yu QF, et al. Renal effects of etoricoxib and comparator nonsteroidal anti-inflammatory drugs in controlled clinical trials. *Clin Ther* 2004; **26**: 70–83
  - 34 Dahl JL, Gordon D, Ward S, Skemp M, Wochos S, Schurr M. Institutionalizing pain management: The post-operative pain management quality improvement project. *J Pain* 2003; **4**: 361–71
  - 35 de la Pintiere A, Beuchee A, Betremieux PE. Intravenous propacetamol overdose in a term newborn. *Arch Dis Child* 2003; **88**: 351–2
  - 36 Devine EC. Effects of psychoeducational care for adult surgical patients—a metaanalysis of 191 studies. *Patient Educ Couns* 1992; **19**: 129–42
  - 37 Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute postoperative pain management: I. Evidence from published data. *Br J Anaesth* 2002; **89**: 409–23
  - 38 Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol* 2003; **60**: 1524–34
  - 39 Edwards J, Moore RA, McQuay H. Individual patient meta-analysis of single-dose rofecoxib in postoperative pain. *BMC Anesthesiol* 2004; **4**: 3
  - 40 Eisenach JC, Carpenter R, Curry R. Analgesia from a peripherally active kappa-opioid receptor agonist in patients with chronic pancreatitis. *Pain* 2003; **101**: 89–95
  - 41 Eisenberg E. Post-surgical neuralgia. *Pain* 2004; **111**: 3–7
  - 42 Flouvat B, Leneveu A, Fitoussi S, Delhotal-Landes B, Gendron A. Bioequivalence study comparing a new paracetamol solution for injection and propacetamol after single intravenous infusion in healthy subjects. *Int J Clin Pharmacol Ther* 2004; **42**: 50–7
  - 43 Futter LE, al-Swayeh OA, Moore PK. A comparison of the effect of nitroparacetamol and paracetamol on liver injury. *Br J Pharmacol* 2001; **132**: 10–12
  - 44 Gaitan G, Del Soldato P, Herrero JF. Low doses of nitroparacetamol or dexketoprofen trometamol enhance fentanyl antinociceptive activity. *Eur J Pharmacol* 2003; **481**: 181–8
  - 45 Gerstenfeld LC, Thiede M, Seibert K, et al. Differential inhibition of fracture healing by non-selective and cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs. *J Orthop Res* 2003; **21**: 670–5
  - 46 Gilbertson B, Wenner K, Russell LC. Acupuncture and arthroscopic acromioplasty. *J Orthop Res* 2003; **21**: 752–8
  - 47 Gillis JC, Brogden RN. Ketorolac. A reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. *Drugs* 1997; **53**: 139–88
  - 48 Greiner A, Rantner B, Greiner K, et al. Neuropathic pain after femoropopliteal bypass surgery. *J Vasc Surg* 2004; **39**: 1284–7
  - 49 Hahn TW, Mogensen T, Lund C, et al. Analgesic effect of i.v. paracetamol: possible ceiling effect of paracetamol in postoperative pain. *Acta Anaesthesiol Scand* 2003; **47**: 138–45
  - 50 Harder AT, An YHH. The mechanisms of the inhibitory effects of nonsteroidal anti-inflammatory drugs on bone healing: a concise review. *J Clin Pharmacol* 2003; **43**: 807–15
  - 51 Hawkey CJ, Skelly MM. Gastrointestinal safety of selective COX-2 inhibitors. *Curr Pharm Des* 2002; **8**: 1077–89
  - 52 Hegi TR, Bombeli T, Seifert B, et al. Effect of rofecoxib on platelet aggregation and blood loss in gynaecological and breast surgery compared with diclofenac. *Br J Anaesth* 2004; **92**: 523–31
  - 53 Hernandez-Palazon J, Tortosa JA, Martinez-Lage JF, Perez-Flores D. Intravenous administration of propacetamol reduces morphine consumption after spinal fusion surgery. *Anesth Analg* 2001; **92**: 1473–6
  - 54 Hiller A, Silvanto M, Savolainen S, Tarkkila P. Propacetamol and diclofenac alone and in combination for analgesia after elective tonsillectomy. *Acta Anaesthesiol Scand* 2004; **48**: 1185–9
  - 55 Jonker JW, Wagenaar E, van Deemter L, et al. Role of blood-brain barrier P-glycoprotein in limiting brain accumulation and sedative side-effects of asimadoline, a peripherally acting analgesic drug. *Br J Pharmacol* 1999; **127**: 43–50
  - 56 Kalso E, Smith L, McQuay HJ, Moore RA. No pain, no gain: clinical excellence and scientific rigour—lessons learned from IA morphine. *Pain* 2002; **98**: 269–75
  - 57 Kam PCA, Power I. New selective Cox-2 inhibitors. *Pain Rev* 2000; **7**: 3–13
  - 58 Keeble JE, Moore PK. Pharmacology and potential therapeutic applications of nitric oxide-releasing non-steroidal anti-inflammatory and related nitric oxide-donating drugs. *Br J Pharmacol* 2002; **137**: 295–310
  - 59 Kehlet H, Werner MU. Role of paracetamol in acute pain management. *Drugs* 2003; **63**: 15–22
  - 60 Kendall JM, Latter VS. Intranasal diamorphine as an alternative to intramuscular morphine—pharmacokinetic and pharmacodynamic aspects. *Clin Pharmacokinet* 2003; **42**: 501–13
  - 61 Koppert W, Wehrfritz A, Korber N, et al. The cyclooxygenase isozyme inhibitors parecoxib and paracetamol reduce central hyperalgesia in humans. *Pain* 2004; **108**: 148–53
  - 62 Kramer BK, Kammerl MC, Komhoff M. Renal cyclooxygenase-2 (Cox-2)—physiological, pathophysiological, and clinical implications. *Kidney Blood Press Res* 2004; **27**: 43–62
  - 63 Lahtinen P, Kokki H, Hendolin H, Hakala T, Hynynen M. Propacetamol as adjunctive treatment for postoperative pain after cardiac surgery. *Anesth Analg* 2002; **95**: 813–19
  - 64 Laine L. Gastrointestinal effects of NSAIDs and coxibs. *J Pain Symptom Manage* 2003; **25**: S32–40

- 65 Likar R, Kapral S, Steinkellner H, Stein C, Schafer M. Dose-dependency of intra-articular morphine analgesia. *Br J Anaesth* 1999; **83**: 241–4
- 66 Likar R, Koppert W, Blatnig H, et al. Efficacy of peripheral morphine analgesia in inflamed, non-inflamed and perineural tissue of dental surgery patients. *J Pain Symptom Manage* 2001; **21**: 330–7
- 67 Likar R, Sittl R, Gragger K, et al. Peripheral morphine analgesia in dental surgery. *Pain* 1998; **76**: 145–50
- 68 Machelska H, Cabot PJ, Mousa SA, Zhang Q, Stein C. Pain control in inflammation governed by selectins. *Nat Med* 1998; **4**: 1425–8
- 69 Machelska H, Mousa SA, Brack A, et al. Opioid control of inflammatory pain regulated by intercellular adhesion molecule-1. *J Neurosci* 2002; **22**: 5588–96
- 70 Machelska H, Pfluger M, Weber W, et al. Peripheral effects of the kappa-opioid agonist EMD 61753 on pain and inflammation in rats and humans. *J Pharmacol Exp Ther* 1999; **290**: 354–61
- 71 Machelska H, Schopohl JK, Mousa SA, Labuz D, Schafer M, Stein C. Different mechanisms of intrinsic pain inhibition in early and late inflammation. *J Neuroimmunol* 2003; **141**: 30–9
- 72 Macrae WA. Chronic pain after surgery. *Br J Anaesth* 2001; **87**: 88–98
- 73 Mancini F, Landolfi C, Muzio M, et al. Acetaminophen down-regulates interleukin-1 beta-induced nuclear factor-kappa B nuclear translocation in a human astrocytic cell line. *Neurosci Lett* 2003; **353**: 79–82
- 74 Martin-Garcia C, Hinojosa M, Berges P, Camacho E, Garcia-Rodriguez R, Alfaya T. Celecoxib, a highly selective COX 2 inhibitor, is safe in aspirin-induced asthma patients. *J Investig Allergol Clin Immunol* 2003; **13**: 20–5
- 75 Meissner W, Weiss T, Trippel RH, Hecht H, Krapp C, Miltner WH. Acupuncture decreases somatosensory evoked potential amplitudes to noxious stimuli in anesthetized volunteers. *Anesth Analg* 2004; **98**: 141–7
- 76 Merry A, Power I. Perioperative NSAIDs: towards greater safety. *Pain Rev* 1995; **2**: 268–91
- 77 Moiniche S, Romsing J, Dahl JB, Tramer MR. Nonsteroidal anti-inflammatory drugs and the risk of operative site bleeding after tonsillectomy: a quantitative systematic review. *Anesth Analg* 2003; **96**: 68–77
- 78 Moore PK, Marshall M. Nitric oxide releasing acetaminophen (nitroacetaminophen). *Dig Liver Dis* 2003; **35**: S49–60
- 79 Mousa SA, Bopaiah CP, Stein C, Schafer M. Involvement of corticotropin-releasing hormone receptor subtypes 1 and 2 in peripheral opioid-mediated inhibition of inflammatory pain. *Pain* 2003; **106**: 297–307
- 80 Mousa SA, Machelska H, Schafer M, Stein C. Co-expression of beta-endorphin with adhesion molecules in a model of inflammatory pain. *J Neuroimmunol* 2000; **108**: 160–70
- 81 NHMRC. Acute pain management: scientific evidence. Canberra: National Health and Medical Research Council, 1999
- 82 Nikolajsen L, Sorensen HC, Jensen TS, Kehlet H. Chronic pain following Caesarean section. *Acta Anaesthesiol Scand* 2004; **48**: 111–6
- 83 Ott E, Nussmeier NA, Duke PC, et al. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 2003; **125**: 1481–92
- 84 Paech MJ, Lim CB, Banks SL, Rucklidge MWM, Doherty DA. A new formulation of nasal fentanyl spray for postoperative analgesia: a pilot study. *Anaesthesia* 2003; **58**: 740–4
- 85 Perkins FM, Kehlet H. Chronic pain as an outcome of surgery—a review of predictive factors. *Anesthesiology* 2000; **93**: 1123–33
- 86 Pettersson PH, Owall A, Jakobsson J. Early bioavailability of paracetamol after oral or intravenous administration. *Acta Anaesthesiol Scand* 2004; **48**: 867–70
- 87 Peyman GA, Rahimy MH, Fernandes ML. Effects of morphine on corneal sensitivity and epithelial wound-healing—implications for topical ophthalmic analgesia. *Br J Ophthalmol* 1994; **78**: 138–41
- 88 Picard PR, Tramer MR, McQuay HJ, Moore RA. Analgesic efficacy of peripheral opioids (all except intra-articular): a qualitative systematic review of randomised controlled trials. *Pain* 1997; **72**: 309–18
- 89 Poobalan AS, Bruce J, Smith WC, King PM, Krukowski ZH, Chambers WA. A review of chronic pain after inguinal herniorrhaphy. *Clin J Pain* 2003; **19**: 48–54
- 90 Powell AE, Davies HTO, Bannister J, Macrae WA. Rhetoric and reality on acute pain services in the UK: a national postal questionnaire survey. *Br J Anaesth* 2004; **92**: 689–93
- 91 Prescott LF. Future perspectives with paracetamol. *Drugs* 2003; **63**: 51–6
- 92 Reuben SS, Vieira P, Faruqi S, Verghis A, Kilaru PA, Maciolek H. Local administration of morphine for analgesia after iliac bone graft harvest. *Anesthesiology* 2001; **95**: 390–4
- 93 Ripouteau C, Conort O, Lamas JP, Auleley GR, Hazebroucq G, Durieux P. Quality improvement report—effect of multifaceted intervention promoting early switch from intravenous to oral acetaminophen for postoperative pain: controlled, prospective, before and after study. *Br Med J* 2000; **321**: 1460–3
- 94 Romero-Sandoval EA, Del Soldato P, Herrero JF. The effects of sham and full spinalization on the antinociceptive effects of NCX-701 (nitroparacetamol) in monoarthritic rats. *Neuropharmacology* 2003; **45**: 412–9
- 95 Romero-Sandoval EA, Mazario J, Howat D, Herrero JF. NCX-701 (nitroparacetamol) is an effective antinociceptive agent in rat withdrawal reflexes and wind-up. *Br J Pharmacol* 2002; **135**: 1556–62
- 96 Scadding JW. Treatment of neuropathic pain: Historical aspects. *Pain Med* 2004; **5**: S3–S8
- 97 Schmitt TK, Mousa SA, Brack A, et al. Modulation of peripheral endogenous opioid analgesia by central afferent blockade. *Anesthesiology* 2003; **98**: 195–202
- 98 Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis—the CLASS study: A randomized controlled trial. *J Am Med Assoc* 2000; **284**: 1247–55
- 99 Smith G, Power I. Audit and bridging the 'analgesic gap'. *Anaesthesia* 1998; **53**: 521–2
- 100 Stein A, Yassouridis A, Szopko C, Helmke K, Stein C. Intra-articular morphine versus dexamethasone in chronic arthritis. *Pain* 1999; **83**: 525–32
- 101 Stein C. Opioid receptors on peripheral sensory neurons. *Adv Exp Med Biol* 2003; **521**: 69–76
- 102 Stein C, Machelska H, Schafer M. Peripheral analgesic and anti-inflammatory effects of opioids. *Z Rheumatol* 2001; **60**: 416–24
- 103 Stein C, Schafer M, Machelska H. Attacking pain at its source: new perspectives on opioids. *Nat Med* 2003; **9**: 1003–8
- 104 Stein C, Schafer M, Machelska H. Why is morphine not the ultimate analgesic and what can be done to improve it? *J Pain* 2000; **1**: 51–6
- 105 Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol* 2003; **111**: 913–21
- 106 Tripp DA, Stanish WD, Reardon G, Coady C, Sullivan MJL. Comparing postoperative pain experiences of the adolescent and adult

- athlete after anterior cruciate ligament surgery. *J Athl Train* 2003; **38**: 154–7
- 107** Van Aken H, Thys L, Veekman L, Buerkle H. Assessing analgesia in single and repeated administrations of propacetamol for post-operative pain: comparison with morphine after dental surgery. *Anesth Analg* 2004; **98**: 159–65
- 108** Wallace JL. Acetaminophen hepatotoxicity: NO to the rescue. *Br J Pharmacol* 2004; **143**: 1–2
- 109** Warner TD, Mitchell JA. Cyclooxygenase-3 (COX-3): filling in the gaps toward a COX continuum? *Proc Natl Acad Sci USA* 2002; **99**: 13371–3
- 110** Wiffen P CS, McQuay H, Carroll D, Jadad A, Moore A. Anticonvulsant drugs for acute and chronic pain (Cochrane Review). *The Cochrane Library*. Chichester: John Wiley & Sons, 2004
- 111** Wilson JA, Colvin LA, Power I. Audit and the evidence base of anaesthesia: acute neuropathic pain after surgery. *Bull R Coll Anaesth* 2002; **15**: 739–42
- 112** Zhou L, Zhang Q, Stein C, Schafer M. Contribution of opioid receptors on primary afferent versus sympathetic neurons to peripheral opioid analgesia. *J Pharmacol Exp Ther* 1998; **286**: 1000–6