ACUTE PAIN MANAGEMENT – AN UPDATE

Dr Jim Olson

North Shore Hospital,
Auckland

Declaration

Within the last five years I have accepted hospitality from the pharmaceutical industry, received honoraria from Mundipharma NZ and attended meetings sponsored by Eisai Europe Ltd.

Introduction

I have been asked to give a practical guide to acute pain problems and a refresher on current practice of this. Since the publication of the ANZCA Acute Pain Management: Scientific Evidence 3rd edition[1] there have been a number of studies published which seem relevant.

First Remember the WHO Ladder...

But there are many things that can be done to reduce pain – remove the cause (surgery, splinting), regional anaesthesia (neuraxial or nerve block), drugs (paracetamol, NSAIDs, opioids, adjuncts), physical (physiotherapy, manipulation, TENS), psychological (relaxation, reassurance, hypnosis, environment). Always think, how many different approaches can I utilise?

Paracetamol

Oral

Perioperative use was well reviewed in an article in 2009.[2] The exact site and mechanism of action of paracetamol remains poorly defined, though it likely involves central COX inhibition and cannabinoidergic effects, along with indirect analgesic serotoninergic effects. The easiest and cheapest method of administration is oral but that is not an option in all patients at all times.

Rectal

Evidence suggests that the rectal form has poor bioavailability (30-54% of oral), delayed uptake (103-140 min vs 45-60 min for oral) and that sub-therapeutic plasma levels occur frequently.[3,4,5]

IV

As with most drugs, intravenous administration is more reliable and reaches peak concentrations faster compared with oral routes.[6] The IV preparation is available in 80 countries although not currently in the United States (US).

Single dose propacetamol or IV paracetamol for postoperative pain is the subject of a Cochrane review at present. Meanwhile there have been two separate meta-analyses published this year on the subject.[7,8] The first reviewed 16 studies, 11 of which enrolled less than 40 patients. IV paracetamol had similar pain outcomes when compared with oral ibuprofen (NNT 2.6) and IV parecoxib. They included a wide range of surgeries, with follow up

from between one and three days. Two of the 14 placebo-controlled studies found no pain improvement or reduced opioid use with IV paracetamol.

The second meta-analysis had wider inclusion criteria, incorporated 36 studies, and looked at a primary measure of efficacy of 50% pain relief over 4-6 hours. They found an NNT of 4.0 (95% CI 3.5–4.8). They concluded that propacetamol and paracetamol were superior to placebo over both 4 and 6 hours. Pre-emptive dosing to time the peak pharmacodynamic effect of IV paracetamol to optimise analgesic effectiveness has been studied clinically. In a study in 90 patients undergoing total abdominal hysterectomy,[9] IV paracetamol 1g administered 30 minutes prior to surgical incision (ie prior to induction) appeared to result in a greater reduction in total morphine consumption in the first 24 hours compared with administering the same dose at the end of surgery just prior to skin closure.

IV or Oral Paracetamol?

Intravenous paracetamol costs $4 per dose compared to four cents per dose for oral. You decide!

Liver Effects

Since it is metabolised in the liver, liver impairment may necessitate cautious administration. Two case reports in 2009 highlight the need to beware in patients at risk for hepatotoxicity.[10] Patients on enzyme-inducing agents like phenytoin, alcohol or rifampicin may produce more toxic metabolites via the cytochrome p 450 route. Obesity and liver steatosis may be associated with depletion of glutathione (GSH) stores due to impaired hepatocellular function. In addition, patients with chronic malnutrition and also some alcohol abusers may have low reserves of glutathione to counteract the N-acetyl-p-benzoquinone-imine produced. Advisory committees to the US Food and Drug Administration (FDA) endorse relabeling of paracetamol-containing products to better inform the consumer of the potential for liver injury with supratherapeutic doses when combined with consuming thre or more alcoholic drinks per day. In addition, the advisory committees support lowering the maximal dosage of paracetamol to 2,600 mg/d. These recommendations have not yet been instituted.

However, patients with hepatitis C treated with interferon, or those with liver cirrhosis, seem to tolerate paracetamol well, if normal doses are adhered to.[11] Studies from the Mayo clinic[12] concur, and also suggest that for short-term use or one-time dosing in cirrhotic patients, 3 to 4g appears safe; however, with the new FDA guidelines in mind, a maximum dosage of 2 to 3g/d is recommended. Although a systematic review suggested that therapeutic dosing of paracetamol in patients with chronic alcoholism is safe, no studies of longer-term therapy have been performed.[13] General consensus from the hepatologists seems to recommend limiting the dose to 2g per day.

NSAIDs

Cardiovascular Risk

Further evidence for the dangers of NSAIDs is outlined in a population-based, case-control study in northern Denmark,[14] which examined 32,602 cases. They found that the use of non-aspirin NSAIDs was associated with an increased risk of atrial fibrillation or flutter. Compared with non-users, the association was strongest for new users, with a 40-70% increase in relative risk (lowest for non-selective NSAIDs and highest for COX 2 inhibitors). This suggests that atrial fibrillation or flutter needs to be added to the cardiovascular risks to be considered when prescribing NSAIDs.

Another recent meta-analysis by Trelle et al[15] reviewed 31 trials involving 116,429 patients with more than 115,000 patient years of follow-up. Patients were allocated to naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib, lumiracoxib, or placebo. Compared with placebo, rofecoxib was associated with the highest risk of myocardial infarction (rate ratio 2.12, 95% CI 1.26 to 3.56), followed by lumiracoxib (2.00, 0.71 to 6.21). Ibuprofen was associated with the highest risk of stroke (3.36, 1.00 to 11.6), followed by diclofenac (2.86, 1.09 to 8.36). Etoricoxib (4.07, 1.23 to 15.7) and diclofenac (3.98, 1.48 to 12.7) were associated with the highest risk of cardiovascular death. Although uncertainty remains, little evidence exists to suggest that any of the investigated

drugs are safe in cardiovascular terms. Naproxen seemed least harmful. Cardiovascular risk needs to be taken into account when prescribing any non-steroidal anti-inflammatory drug.

Anastomotic Leak Risk

Two recent European studies have also suggested that NSAIDs may be a risk factor for colorectal anastomotic leaks.[16,17] The first showed an increased risk after diclofenac with laparoscopic colorectal surgery. The second showed increased risk with COX 2 inhibitors after fast-track colonic surgery. A recent Canadian retrospective case control study examined perioperative NSAID use in elective colorectal patients and their association with anastomotic leaks. They identified 48 cases and 130 controls and failed to identify a significant relationship between perioperative NSAID exposure and anastomotic leaks in elective colorectal surgery. There was however a non-significant dose response curve, raising the possibility of an association given adequate power.

Bone Healing

Little new. Evidence for an effect on bone healing remains conflicting. In one study of 88 patients, 30 of whom were given ketorolac after spinal fusion, the incidence of incomplete union or non-union was higher in those given ketorolac.[18] In another study of 405 patients, 228 of whom were given ketorolac after similar surgery, there was no significant difference in the non-union rates between the two groups.[19] Apart from ketorolac, and possibly indomethacin, there is not much evidence that NSAIDs or coxibs make any difference to bone healing after surgery or trauma, unless perhaps continued for months. Smoking appears to have major effects on bone function, on risk of fracture, and on bone healing. The size of the effect would be a major confounding factor in investigations looking at coxibs or NSAIDs.

Bleeding

Again, little new. After a variety of different operations, the use of non-selective NSAIDs was associated with a significant increase in the risk of severe bleeding (increased from 0 to 1.7%), compared with placebo (NNH 59).[20]

Six efficacy studies have been performed in surgical patients looking at the effect of COX 2 inhibitors on platelet function, with a further three studies in adult volunteers. The latter studies compared supratherapeutic doses of selective COX 2 inhibitors with standard doses of non-selective NSAIDs. All three studies reported that COX 2 inhibitors had no effect on platelet function, but that non-selective NSAIDs were associated with significantly increased bleeding time and reduced platelet function. One study in surgical patients reported that rofecoxib was associated with less platelet disturbance and intra-operative blood loss than diclofenac. Five efficacy studies that evaluated surgical blood loss reported no difference in blood loss with COX-2 inhibitors compared with opioid or placebo.[21]

NSAIDS and Alzheimers

Perhaps on a positive note a we should remember a 2003 study appeared to show that NSAIDs offer some protection against the development of Alzheimer's disease.[22] The authors acknowledged that the appropriate dosage and duration of drug use and the ratios of risk to benefit are still unclear.

Pregabalin

Efficacy

A recent systematic review examined the effect of pregabalin on post-operative analgesia in surgical patients.[23] Pregabalin improved analgesia in three of 12 study arms after ambulatory surgery, and in eight of 11 after major surgery. Pregabalin did not reduce postoperative nausea / vomiting, pruritus and headache, but increased the frequency of visual disturbance, drowsiness, severe sedation and dizziness during the first postoperative hours, without severe clinical consequence. Severe sedation was clearly dose dependant, while drowsiness, dizziness or

visual disturbance was not. The authors conclude that a favourable benefit risk-ratio is demonstrated only for major surgery.

Another recent meta-analysis of perioperative pregabalin and postoperative analgesia identified 11 studies.[24] Pregabalin produced a dose-related reduction in postoperative opioid use. Pregabalin reduced postoperative nausea and vomiting, but the incidence of visual disturbance was increased.

Perioperative Oral Pregabalin

An RCT by Buvanendran (2010)[25] involved 240 patients undergoing total knee arthroplasty (TKA). Patients were randomised to placebo or 300mg pregabalin preoperatively, then for 14 days of 50-150mg mg/day. Leeds assessment of neuropathic symptoms & signs scores (LANSS) were performed at 3 and 6 months. At both 3 and 6 months postoperatively, the incidence of neuropathic pain was less frequent in the pregabalin group (0%) compared with the placebo group (8.7% and 5.2% at 3 and 6 months, respectively; P=0.001 and P=0.014). However, only 5.2% had demonstrable neuropathic pain in the placebo group at 6 months. Other studies estimate the incidence of persistent post-surgical pain to occur in 27-44% of TJR patients, with neuropathic pain occurring much less commonly.[26] Thus the Buvanendran study may look overly optimistic due to the selective screening for neuropathic pain only, not the nociceptive pain that most are complaining of.

Currently pregabalin remains non-funded in NZ.

Gabapentin

What did we know? “A number of meta-analyses have shown that perioperative gabapentinoids improved analgesia (at rest and with movement) and reduced postoperative opioid consumption, but increased the incidence of sedation compared with placebo. Three of these meta-analyses also reported a decrease in vomiting and pruritus; the NNT was 25 for nausea, 6 for vomiting. The effects of gabapentin were not dose-dependent in the range of 300 to 1200mg.”[1]

What’s new? A Cochrane review published in 2010[27] looked at single-dose oral gabapentin for acute postoperative pain. It described four unpublished clinical trials with 370 participants who received either gabapentin or placebo. Gabapentin 250mg provided some relief in acute postoperative pain, NNT of 11 (6.4 to 35).

Another systematic review examined gabapentin and pregabalin for acute post-operative pain.[28] Twenty two gabapentin (1,640 patients), eight pregabalin (707 patients) RCTs and seven meta-analyses were included in this review. The authors conclude that gabapentin and pregabalin reduce pain and opioid consumption after surgery in comparison with placebo.

Gabapentin and pregabalin seem not to have any influence on the prevention of PONV.

So in conclusion… “Trials analysed in these meta-analyses used a wide variety of gabapentin dosing regimens. It is therefore not possible to recommend a particular regimen and furthermore, conclusions cannot be drawn regarding optimal treatment duration or potential long-term benefits”[1]

Oxycodone

Mode of Action

“Oxycodone is a potent opioid agonist derived from the opium alkaloid thebaine. It is metabolised in the liver primarily to noroxycodone and oxymorphone, but these metabolites have clinically negligible analgesic effects. Oxymorphone, the production of which relies on CYP2D6, is more potent than oxycodone, but plasma concentrations are low; noroxycodone, the major metabolite and the production of which relies on CYP3A4, is only weakly active. Unlike codeine, inhibition of CYP2D6 with quinine does not reduce the analgesic effect of oxycodone.”[1] Oxycodone is also thought to act as a kappa-receptor agonist[29] and these receptors may play an important role in the mediation of visceral pain.[30]

Oxycodone with Naloxone

One recent development is the presentation of oral oxycodone with naloxone. The naloxone is metabolised in the liver so that it only antagonises the opioid effects locally in the gut. This is designed to decrease opioid induced constipation. Various studies have demonstrated that this does work, with little effect on analgesia at least in chronic pain patients.[31,32]

IV Oxycodone

Equipotent with morphine when administered IV, but roughly double the oral bioavailability. A comparison of IV oxycodone with IV morphine in 91 patients post laparoscopic surgery showed that those on oxycodone consumed less drug and had better pain scores for the first hour post operatively and had less sedation for 24 hours.[33]

Ketamine

Ketamine is an NMDA antagonist known to be opioid sparing although there is not much evidence to support its widespread use for postoperative pain alone. A recent review of trials adding ketamine to morphine PCA, identified six studies showing significantly improved postoperative analgesia and five studies which showed no significant clinical improvement.[34] Ketamine is probably more useful in a select population, and has been advocated as an adjuvant in the management of patients receiving long-term opioid therapy. Evidence for post-operative use in opioid tolerant patients was published in 2008.[35] A new study last year[36] showed that intraoperative ketamine also reduced perioperative opiate consumption in opiate dependent, chronic back pain patients who were undergoing back surgery.

A very recent review of the beneficial effects of ketamine[37] included anti-nociception, potentiation of opioid analgesia and prevention of opioid tolerance as well as anti-inflammatory effects, prevention of awareness and recall during general anaesthesia, anti-tumour effects and a neuroprotective effect in cerebral & spinal ischaemia.

Methadone

The three seminal papers on intraoperative use were by Gourlay et al[38,39,40] nearly 30 years ago. A study published earlier this year showed that giving intraoperative methadone improved post-operative pain for patients undergoing complex spinal surgery.[41] It used a single intraoperative bolus dose of methadone (0.2 mg/kg) or a sufentanil infusion and then post-operative PCA morphine, fentanyl, or hydromorphone. The authors found improved post operative pain control in the methadone group. Their results are probably related to the slow rate of methadone elimination, and potentially to NMDA receptor antagonism by methadone.

Intraoperative use seems limited by three common misconceptions. Firstly that it is of slow onset, secondly that the duration of methadone analgesia is shorter than its elimination half-life and thirdly, that methadone is considered to have a highly variable clearance and significant susceptibility to metabolic drug interactions. All of these have been largely debunked in the last 30 years.[42]

References

1. Acute Pain Management: Scientific Evidence (3rd Edition 2010) edited by Macintyre PE, Scott DA, Schug SS, Visser EJ, Walker SM
2. Oscier C, Milner Q. Peri-operative use of paracetamol. Anaesthesia 2009; 64: 65–72
3. Hansen TG, O'Brien K, Morton NS, Rasmussen SN. Plasma paracetamol concentrations and pharmacokinetics following rectal administration in neonates and young infants. Acta Anaesthes Scand 1999; 43: 855-9
4. Anderson BJ, Holford NH. Rectal paracetamol dosing regimens: determination by computer simulation. Ped Anesth 1997; 7: 451-5
5. Beck DH, Schenk MR, Hagemann K, Doepfmer UR, Kox WJ. The pharmacokinetics and analgesic efficacy of larger dose rectal acetaminophen (40 mg/kg) in adults: a double-blinded, randomized study. Anesth Analg 2000; 90: 431-6

6. Holmer Pettersson P, Owall A, Jakobsson J. Early bioavailablity of paracetamol after oral or intravenous administration. Acta Anaesthesiol Scand 2004; 48(7): 867-70
7. Macario A, Royal MA. A literature review of randomized clinical trials of intravenous acetaminophen (paracetamol) for acute postoperative pain. Pain Pract. 2011; 11(3): 290-6
8. McNicol ED et al. Single-dose intravenous paracetamol or propacetamol for prevention or treatment of postoperative pain: a systematic review and meta-analysis. British Journal of Anaesthesia 2011; 106(6): 764–75
9. Arici S, Gurbet A, Türker G, Yavascaoglu B, Sahin S. Preemptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy. Agri 2009; 21: 54–61
10. Forget P, Wittebole X, Laterre PF. Therapeutic dose of acetaminophen may induce fulminant hepatitis in the presence of risk factors: a report of two cases. Br J Anaesth. 2009; 103: 899–900
11. McIntyre N. The General management of liver disease. In: Bircher J, Benhamou, JP, McIntyre, N, et al, editors. Oxford Textbook of Clinical Hepatology. Oxford: Oxford University Press 1999: 1917-23
12. Chandok N, Watt KD. Pain management in the cirrhotic patient: the clinical challenge. Mayo Clin Proc. 2010 May; 85(5): 451-8
13. Dart R, Bailey E: Does therapeutic use of acetaminophen cause acute liver failure? Pharmacotherapy. 2007; 27(9): 1219-1230
14. Schmidt M. Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: population based case-control study. BMJ. 2011; 4; 343-50
15. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: Network meta-analysis. BMJ 2011; 342: c7086
16. Klein M, Andersen LP, Harvald T, Rosenberg J, Gogenur I. Increased risk of anastomotic leakage with diclofenac treatment after laparoscopic colorectal surgery. Dig Surg. 2009; 26(1): 27-30
17. Holte K, Andersen J, Jakobsen DH, Kehlet H. Cyclo-oxygenase 2 inhibitors and the risk of anastomotic leakage after fast-track colonic surgery. Br J Surg. 2009; 96(6): 650-4
18. Park SY, Moon SH, Park MS et al. The effects of ketorolac injected via patient controlled analgesia postoperatively on spinal fusion. Yonsei Med J. 2005; 46(2): 245–51
19. Pradhan BB, Tatsumi RL, Gallina J et al. Ketorolac and spinal fusion: does the perioperative use of ketorolac really inhibit spinal fusion? Spine 2008; 33(19): 2079-82
20. Elia N, Lysakowski C, Tramer M. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. Anesthesiology 2005; 103(6): 1296–304
21. Zemmel M H. The role of COX-2 inhibitors in the perioperative setting: efficacy and safety. A systematic review. AANA Journal 2006; 74(1): 49-60
22. Mahyar E., Sudeep G., Ali S. Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies. BMJ 2003; 327: 128
23. Remérand F, Couvret C, Baud A, Laffon M, Fusciardi J: Benefits and safety of perioperative pregabalin: A systematic review. Ann Fr Anesth Reanim. 2011; 30(7-8): 569-77
24. Zhang J, Ho KY, Wang Y. Efficacy of pregabalin in acute postoperative pain: a meta-analysis. Br. J. Anaesth. 2011; 106 (4): 454-462
25. Buvanendran A, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ: Perioperative Oral Pregabalin Reduces Chronic Pain After Total Knee Arthroplasty: A Prospective, Randomized, Controlled Trial. Anaesth Anal 2010; 110 (1): 199-207
26. Wylde V et al. Persistent pain after joint replacement: Prevalence, sensory qualities, and postoperative determinants. Pain 2011; 152: 566–572
27. Straube S, Derry S, Moore RA, Wiffen PJ, McQuay HJ. Single dose oral gabapentin for established acute postoperative pain in adults. Cochrane Database Syst Rev. 2010; 12(5): CD008183
28. Dauri M, Faria S, Gatti A, Celidonio L, Carpenedo R, Sabato AF. Gabapentin and pregabalin for the acute post-operative pain management. A systematic-narrative review of the recent clinical evidences. Curr Drug Targets. 2009; 10(8): 716-33
29. Nielsen CK, Ross FB, Lotfipour S et al. Oxycodone and morphine have distinctly different pharmacological profiles: radioligand binding and behavioural studies in two rat models of neuropathic pain. Pain; 2007; 132(3): 289–300
30. Staahl C, Christrup LL, Andersen SD et al. A comparative study of oxycodone and morphine in a multi-modal, tissue-differentiated experimental pain model. Pain; 2006; 123(1-2): 28–36
31. Meissner W, Leyendecker P, Mueller-Lissner S, et al. A randomized controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation. Eur J Pain 2009; 13: 56–64

32. Vondrackova D, Leyendecker P, Meissner W, et al. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. J Pain 2008; 9: 1144–54
33. Lenz H, Sandvik L, Qvigstad E, Bjerkelund CE, Raeder J: A comparison of intravenous oxycodone and intravenous morphine in patient-controlled postoperative analgesia after laparoscopic hysterectomy. Anesth Analg. 2009; 109(4): 1279-83
34. Carstensen M, Møller AM. Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomized trials. Br J Anaesth. 2010 Apr; 104(4): 401-6
35. Urban MK, Ya Deau JT, Wukovits B et al. Ketamine as an adjunct to postoperative pain management in opioid tolerant patients after spinal fusions: a prospective randomized trial. HSS J 2008; 4; 1: 62–5
36. Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, Sengupta DK, Beach ML. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing surgery. Anesthesiology 2010; 113: 639-46
37. Hirota K, Lambert DG. Ketamine: new uses for an old drug? Br. J. Anaesth. 2011; 107(2): 123-126
38. Gourlay GK, Wilson PR, Glynn CJ. Pharmacodynamics and pharmacokinetics of methadone during the perioperative period. Anesthesiology 1982; 57: 458–67
39. Gourlay GK, Willis RJ, Wilson PR. Postoperative pain control with methadone: Influence of supplementary methadone doses and blood concentration–response relationships. Anesthesiology 1984; 61: 19–26
40. Gourlay GK, Willis RJ, Lamberty J. A double-blind comparison of the efficacy of methadone and morphine in postoperative pain control. Anesthesiology 1986; 64: 322–7
41. Gottschalk A, Durieux ME, Nemergut EC. Intraoperative methadone improves postoperative pain control in patients undergoing complex spine surgery. Anesth Analg 2011; 112: 218-23
42. Kharasch ED. Intraoperative Methadone: Rediscovery, Reappraisal, and Reinvigoration? Anesth Analg 2011; 112: 13-6