Take Home Messages

- Coxibs are preferable to non-selective NSAIDs with regard to adverse effects in the acute (and in the chronic) setting, and particularly post-operatively.
- Codeine is contraindicated in children under twelve years of age, in children younger than eighteen years of age who have undergone adeno-tonsillectomy for obstructive sleep apnoea, in breastfeeding mothers and in people of any age known to be ultrarapid metabolisers.
- Opioid-induced ventilatory impairment is the most feared complication of opioid use and requires assessment of sedation and dose reduction.
- The use of pethidine should be strongly discouraged because it has no true advantages, yet significant risks of neurotoxicity.
- Opioid prescribing for acute pain needs to be undertaken cautiously, and limited amounts only supplied.

Introduction

Acute Pain Management: Scientific Evidence, the Fourth Edition, combines ‘the best available evidence for acute pain management with current clinical and expert practice… to assist the practising clinician’. These documents have over the last sixteen years become the worldwide accepted references for acute pain management and the most recent addition has again been endorsed by many national and international organisations, including the International Association for the Study of Pain (IASP).

While a major focus of the most recent edition is on post-operative pain management, the principles presented may be applied to the management of acute pain after injuries, as well as many other acute pain conditions. The following article will summarise relevant and new findings regarding acute pain management, including the use of analgesics relating to this in General Practice (GP).
Multimodal Analgesia

One guiding principle that originates from post-operative pain management is the concept of multimodal, or ‘balanced’, analgesia. This concept is based on data that show that the better analgesia, the reduced the analgesic requirements (‘opioid-sparing’), and thereby a reduced number of adverse events. This may be achieved by combining analgesics that have a different mode or site of action.

A classic example in the GP setting is the combination of paracetamol with a non-steroidal anti-inflammatory drug (NSAID). The efficacy of this has been in particular well-demonstrated by the combination of ibuprofen with paracetamol. The combination of non-opioids with an opioid is another practical example. Efficacy has also been shown by combining non-opioids with weak opioids such as tramadol and codeine (although, as outlined below, there are significant concerns about the use of codeine).

More supportive data on components of multimodal analgesia are presented in ‘Acute Pain Management: Scientific Evidence, the Fourth Edition’. However, various combinations involving pregabalin or gabapentin, ketamine, intravenous lignocaine, clonidine and the use of regional anaesthesia are more relevant to the post-operative setting.

Paracetamol

With regard to the choice of analgesics, there is currently discussion about the effectiveness of paracetamol. This debate has been fuelled by meta-analyses showing little or no benefit in the setting of chronic low back pain and chronic osteoarthritic pain. Even in these settings, such data do not preclude benefits in individual patients. There is no doubt about the efficacy of paracetamol in the management of acute pain, as the number-needed-to-treat (NNT), a statistical concept estimating the number of patients that need to be treated in order to have an impact on one person compared to placebo, is 3.6 for 1,000mg of paracetamol in post-operative pain. This efficacy of paracetamol has been shown in a number of other acute pain conditions, including post-partum pain, migraine and tension-type headaches.

Therapeutic doses up to 4g/24h may slightly increase the serum aminotransferase activity, however do not result in hepatic failure or death, even in patients who consume moderate to large amounts of alcohol. However, paracetamol overdose remains a common cause of acute liver failure and needs urgent treatment with n-acetylcysteine. Retrospective epidemiological studies, sometimes contradictory, showing an association of paracetamol use with a number of conditions (reduced ovarian cancer, increased renal cancer, hypertension, increased asthma in children, use in pregnancy with resulting increase of asthma and attention-deficit hyperactivity disorder in children) need to be interpreted cautiously. They do not show a causal relationship and are subject to the effects of unknown or unmeasured confounding factors.

Non-steroidal Anti-inflammatory Drugs

Non-selective NSAIDs (nsNSAIDs) and Cox-2 selective NSAIDs (coxibs) are effective analgesics that are similarly effective in the management of acute pain. Their use is supported in post-operative pain, renal colic, primary dysmenorrhoea and acute ankle sprains.

However, with regard to adverse effects in the acute (and in the chronic) setting, and particularly post-operatively, coxibs are preferable to nsNSAIDs. nsNSAIDs increase the risk of minor and major bleeding compared to placebo and coxibs. Blood loss with post-operative coxib use is comparable to placebo, for example, after total knee replacement. In contrast to nsNSAIDs, coxibs do not cause bronchospasm in patients with known NSAID-exacerbated respiratory disease. Short-term use of coxibs results in similar rates of gastrointestinal ulceration to placebo, but rates with nsNSAIDs are much higher. The cardiovascular safety of nsNSAIDs and coxibs with short-term use is similar to placebo. The adverse effects on kidney function are similar for both nsNSAIDs and coxibs, although in one pharmaco-epidemiological study, increased COX-2 selectivity was associated with reduced
rates of acute kidney injury. The risk of adverse renal effects is increased when additional risk factors (such as pre-existing renal impairment, hypovolaemia, hypotension, or concomitant use of other nephrotoxic compounds, such as ACE inhibitors, diuretics or aminoglycoside antibiotics) are present. Careful consideration of these factors in addition to patient selection and monitoring will reduce these renal risks.

With regard to the commonly discussed impairment of bone healing by NSAIDs, there is limited data to show such a clinically relevant adverse effect for nNSAIDs (primarily with ketorolac in spinal fusion, and no effect with coxibs). A summarising review concludes that ‘there is not enough clinical evidence to deny patients with simple fractures the analgesic benefits of these compounds’. Topical NSAIDs (gels or creams containing diclofenac, ibuprofen, ketoprofen and piroxicam, but not indomethacin) are effective in the management of acute pain relating to strains, sprains and sports injuries (the NNT is 4.5). They cause systemic adverse effects comparable to placebo, and significantly lower adverse gastrointestinal effects than systemic nNSAIDs.

**Codeine**

There are increasing concerns about the efficacy, safety and risk of abuse of the weak opioid codeine. These concerns are focusing to some extent on pharmacogenomics, as codeine itself has nearly no effect as an opioid agonist and its analgesic action depends primarily on its metabolite morphine. The common assumption is that around 5-10% of the codeine administered is metabolised to morphine; thereby 60mg codeine has a similar clinical effect to 3-6mg morphine. However, this assumption does not consider that the metabolism of codeine depends on the cytochrome P450 isoenzyme CYP2D6, which is highly polymorphic. The range of phenotypes extend from poor metabolisers (approximately 8-10% of Caucasians), with no or minimal benefit from codeine for patients with normal enzyme activity, to ultra-rapid metabolisers (approximately 3-5% of patients) who obtain high morphine levels. This individual variability in analgesic response to codeine is further complicated by genetic differences relating to origin. Middle Eastern and North African populations may comprise up to 29% of ultra-rapid metabolisers, while in some Asian populations, the rate may be as low as 0.5%. These findings explain that in Australia, possibly around two million patients will have no benefit from codeine, while others are at an increased risk of opioid toxicity.

This is not only a theoretical concern. Severe opioid-induced ventilatory impairment (even leading to death), has been reported after codeine use in ultra-rapid metabolisers. In particular, this has been noted after intake by breastfeeding mothers and has led to the death of infants. In children, death has also occurred, especially after tonsillectomy or adenoidectomy for sleep-disordered breathing. In response, the World Health Organisation (WHO) has removed codeine from the list of analgesics suggested for use in children who have persistent pain. A number of regulatory authorities, including the US Food and Drug Administration (FDA) and the European Agency, have issued restrictions on the use of codeine. In Australia, the Advisory Committee on the Safety of Medicine (ACSoM) makes recommendations to the Therapeutic Goods Administration (TGA). It has advised that codeine be contraindicated for any indication in children under twelve years of age, in children younger than eighteen years of age who have undergone adeno-tonsillectomy for obstructive sleep apnoea, in breastfeeding mothers and in people of any age known to be ultrarapid metabolisers.

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The efficacy of codeine as an analgesic by itself is poor; 60mg codeine has the highest (i.e. worst) NNT of all analgesics studied in postoperative pain (the NNT is 12). However, taking into account the limitations of the data provided above, codeine increases the efficacy of either paracetamol or NSAIDs in combination. Combinations of 1000mg paracetamol or 400mg ibuprofen with 60mg codeine have NNTs of 2.2. The relative benefit of such combinations in comparison to the non-opioid alone is 1.3 (and only just significant for ibuprofen combinations). However, there are no supportive data in these meta-analyses on the analgesic efficacy of combinations with 12mg codeine or less, dosages that are currently listed as Schedule 3 (Pharmacist Only) in Australia. The assumption in the scientific literature is that at least 30mg codeine is required as part of a combination preparation to achieve efficacy.

Codeine use in general is problematic, in view of the high risks of misuse and abuse in Australia, in particular with the availability of over the counter (OTC) combinations. The rates of misuse and abuse continue to increase, as do the number of patients presenting to public Drug and Alcohol Clinics, the number entering opioid substitution therapy and even the incidence of codeine-related fatalities. In addition to this, there are serious complications of paracetamol and ibuprofen overdose, and too much of these may be taken in order to gain higher doses of codeine from combination preparations. This can result in further severe morbidity and mortality.

**Tramadol**

Tramadol is a weak opioid that is useful in the setting of acute pain. The dose-dependent NNTs are 7.1 for 50mg, 4.8 for 100mg and 2.4 for 150mg. The NNT for neuropathic pain is 4.7, making...
The efficacy is only partially affected by CYP2D6 polymorphism, and so there may be increased dose requirements and more non-responders if patients are poor metabolisers. Use of tramadol in combination with paracetamol increases efficacy and the NNT for tramadol 75mg/paracetamol 650mg combinations is 2.6.

The adverse event profile of tramadol is different to other opioids. Tramadol carries a reduced risk of opioid-induced ventilatory impairment in doses equivalent to other opioids, leading to only rare fatalities, even in overdose. Tramadol has also less of a constipating effect than other opioids. Finally, tramadol has a much lower risk of abuse, misuse and diversion compared to other opioids, something that has been recently reconfirmed in a review from the Expert Advisory Committee established by the German Federal Government. Disadvantages of this analgesic include an increased rate of nausea and vomiting. This was reported in some studies when compared to other opioids, however, there was a reduced rate of pruritus. Use of tramadol in combination with other serotonergic medications increases the risk of serotonin toxicity, although this has been possibly overestimated. The use of tramadol in elderly patients in the post-operative period increases the risk of delirium.

Opioid-induced Ventilatory Impairment

Opioid-induced ventilatory impairment, potentially causing death, is the most feared complication of opioid use; assessment of sedation and dose reduction, or opioid discontinuation in response to sedation are more reliable approaches to reduce this risk than is monitoring the respiratory rate. Specific risk factors for this complication include the use of morphine in patients with renal failure (because of retention of active metabolites), the use of morphine in patients who already have a reduced level of consciousness and the co-administration of sedating medications (especially benzodiazepines), and also drug and alcohol use. Other risk factors include sleep-disordered breathing (previously termed obstructive sleep apnoea), fatigue, obesity and chronic obstructive airways disease.

Tramadol and buprenorphine both carry a reduced risk of opioid-induced ventilatory impairment due to their ceiling effect for respiratory depression. Tapentadol, which has a low opioid receptor effect, is likely to be similar in reduced risk, as there have been only two fatal overdoses in over seven years of use reported in the USA and Europe.

Reducing Complications

Strong opioids are indicated and often needed during episodes of acute pain. No one opioid is necessarily superior to any of the others, but some opioids are better tolerated in certain patients. This may justify opioid rotation if there is poor efficacy and/or severe adverse effects. As many adverse effects of opioids (such as nausea, vomiting and constipation) are dose-related, opioid-sparing approaches (e.g. combinations with non-opioids in multimodal analgesia) and limiting doses as far as possible is recommended. Age is a better predictor of opioid requirement than weight, but the individual variability is extremely high.

In the treatment of chronic pain, combining opioids and antagonists with low oral bioavailability (e.g. the combination of oxycodone with naloxone) is a proven strategy to reduce the often difficult to manage complication of constipation. The benefits are not as obvious in the acute pain setting. Tapentadol, due to its low opioid receptor affinity, has a reduced rate of gastrointestinal adverse effects (such as nausea, vomiting and constipation) compared to other opioids. Data concerning the use of tapentadol...
in the management of acute pain are still limited,\(^6\) although an immediate release preparation has been recently released in Australia. This preparation was already widely available in Europe and the USA for a number of years, and there showed lower rates of abuse,\(^6\) doctor shopping for the medication and\(^7\) diversion,\(^7\) compared to conventional opioids such as oxycodone (the risks of these behaviours were similar to those reported for tramadol).

The use of pethidine should be strongly discouraged because it has no true advantages,\(^7\) yet significant risks of neurotoxicity due to its metabolite norpethidine.\(^8\) There are also significant rates of abuse and addiction with pethidine and an increased risk of delirium in the elderly.\(^4\)

Other issues with the use of opioids in acute pain management include an increased risk of falls, in particular in the first week following initiation of opioid therapy.\(^7\) Surprisingly, this is increased in younger patients (eighteen- to twenty-nine-year-olds).\(^6\) Furthermore, impairment of driving abilities needs to be considered; opioids diminish reaction times, reflexes, co-ordination and ability to concentrate;\(^6\) and there are reports of increased numbers of positive tests for opioids in fatalities related to traffic accidents in the USA.\(^7\) The risk of impairment when opioids are used in the short-term is increased with the recent initiation of opioid therapy,\(^9\) or associated with dosage increases.\(^7\) This situation is obviously different to chronic opioid use, where tolerance may develop. The risk of individuals taking stable opioid doses and no increased risk of motor vehicle accidents with stable doses has been reported.

Addiction

Last, but not least, the introduction of opioids for acute pain carries an increased risk of continuing on to long-term opioid use.\(^8\) Therefore, it is important to emphasise the short-term purpose of any such opioid prescription and to carefully consider any further prescriptions that could lead to potentially chronic use. Unused opioids prescribed for acute pain are a well-documented reservoir of medication that may feed misuse, abuse and be diverted to others.\(^9\) Patients tend to keep unused opioids and may be prepared to share them with friends or family members, thereby exposing others to adverse events or supporting their abuse.\(^8\) In Canada, opioids prescribed for acute pain were the source of fatal opioid overdoses in 6.6% of cases.\(^8\) Therefore, opioid prescribing for acute pain needs to be undertaken cautiously, and limited amounts only supplied. Patients should be advised to store them safely, to only disclose their opioid intake to others with good reason, and to dispose of unused opioids by returning them to a pharmacy.\(^8\)
Patients at risk of abuse (e.g. a history of alcohol or other drug use) should be identified, if necessary through using simple screening tools. The most commonly recommended screening tools are the ‘Opioid Risk Tool’ (ORT) and the ‘Screener and Opioid Assessment for Patients with Pain’ (SOAPP). ‘Universal precautions’ should always be followed when prescribing opioids. ‘Universal precautions’ include a risk assessment, appropriate dosing and limited prescribing, the monitoring of effect and compliance and also the initiation of a response plan, should misuse, abuse or diversion be suspected.

Clinical Resources

Since 1999, the Australian and New Zealand College of Anaesthetists (ANZCA), more recently, in co-operation with its Faculty of Pain Medicine (FPMANZCA), has provided an evidence-based document on acute pain management. This is kept up-to-date by revisions leading to a new edition every five years. The latest (fourth) edition was made available on the FPMANZCA website in December 2015.


Screener and Opioid Assessment for Patients with Pain (SOAPP). Inflexion; 2008.

References


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