# Is there a role for intravenous paracetamol in postoperative pain relief?

The management plan for relief of anticipated postoperative pain is based upon the surgical procedure and expected pain severity, often beginning intra-operatively. Joanne Harding reviews the types of pain regimens commonly used, including the use of intravenous paracetamol, emphasising that a multimodal and stepwise approach is often taken to maximise analgesic efficacy and tolerability.

## Introduction

Current best practice for the management of pain is based on the World Health Organisation's (WHO) or the World Federation of Societies of Anesthesiologists' (WFSA) analgesic pain ladders.[1,2]

The WHO pain relief ladder is divided into three rungs and was originally developed for the treatment of pain in cancer patients. The principle behind the ladder is that when pain occurs there should be prompt oral administration of medicines adopting a 'step up' approach until the patient is free of pain. The three steps are:

- Step 1: non opioids (e.g. paracetamol and aspirin) +/- adjuvants (e.g. non-steroidal anti-inflammatory drugs — NSAIDs)
- Step 2: mild opioids (e.g. codeine) +/- adjuvants
- Step 3: strong opioids (e.g. morphine) +/- adjuvants.

The WHO pain management system also encourages regular 'by the clock' administration of analgesic medicines as opposed to 'on demand' administration to maintain freedom from pain.[1]

Because postoperative pain is often severe from the outset analgesia can be started at rung two or three of the WHO pain relief ladder and a 'step down' approach adopted according to patients needs.[1]

The World Federation of Societies of Anesthesiologists in association with the International Association for the Study of Pain analgesic ladder adopts a similar 'step-down' approach to the management of acute pain as shown in Figure 1.[3]

## Pharmacists' role in acute pain management

Pharmacists have an important role to play in the management of acute pain. The foremost responsibility is to ensure that acute pain is adequately managed because the under-treatment of pain is both a humanitarian issue as well as being associated with a number of adverse clinical outcomes. The pharmacist can ensure the adoption of an optimal and evidence-based treatment strategy for acute pain and can offer advice about the subsequent selection of the most appropriate agents.

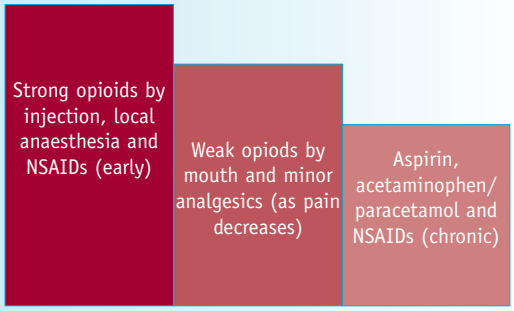
In recommending individual analgesic agents pharmacists must consider a number of factors including: the appropriateness of the agent (for example its licensed indications, cautions, contraindications), the adverse event profile, safety (particularly with the use of injectable and/or sedating agents), the optimal route of administration, the mechanism and duration of action, availability of the agent (including possible administration delays with the use of class two controlled drugs) and the cost.

## Minimising postoperative pain

It is important to undertake a detailed pre-operative evaluation to assess and prepare a patient's pain management plan. A number of factors can influence the severity of postoperative pain. The site and nature of surgery is an important factor — with procedures on the upper abdomen or thorax being the most painful, followed by lower abdominal procedures and then procedures on the peripheral limbs. Any procedure involving deep tissues, large joint surfaces or a body cavity should be regarded as painful, however.[2]

Many patient-specific factors will also influence the degree of postoperative pain experienced by a patient. Anxiety plays a very important role and this can be strongly influenced by the intention of the proposed operation. For example, if the operation is curative (such as a hernia repair) then the patient will have positive expectations associated with the procedure. However,

**Figure 1. The WFSA acute pain treatment ladder[2]**



if the intended operation is unknown or exploratory (such as for cancer procedures) then the patient may have a negative perception of the surgery with associated high levels of fear and anxiety. Patients that are generally fearful of anaesthesia or surgery may also be more prone to experiencing difficult to treat postoperative pain.[2]

Therefore, along with good patient counselling to inform patients and allay their fears, it is important that a planned and structured approached to the management of acute postoperative pain is taken. Of utmost importance is that the administration of postoperative analgesia should begin in the immediate postoperative period before the end of anaesthesia.[4] In this circumstance it might be appropriate to administer a one-off dose of intravenous (IV) paracetamol to achieve baseline analgesia in the sedated patient.

## Use of analgesics for postoperative pain relief

Particularly for deep surgery, initial postoperative pain may be expected to be severe and, basing pain management on the WFSA pain ladder, it may necessary to control this pain with strong analgesics in combination with local anaesthetic blocks and peripherally-acting drugs.[2] The oral route of administration may not be appropriate at this stage because of the nature of the surgery and/or factors such as uncontrolled postoperative nausea and vomiting or sedation/lack of consciousness so medicines may need to be administered by alternative routes.[5]

Table 1 shows the advantages and disadvantages of commonly used analgesics in the postoperative setting. Strong opiates, such as morphine, are efficacious in the treatment of severe pain, but, their usefulness is often limited by adverse events including respiratory depression, nausea, vomiting, pruritis, urinary retention and prolongation of postoperative ileus.[4,6] Furthermore, their use is often not acceptable to patients because of adverse events such as somnolence, vivid dreams and feelings of euphoria.[4,6] Hence the single-agent management of postoperative pain with strong opioid medicines is not recommended.[4]

There are obvious benefits in using mild, non-sedating analgesics such as paracetamol and NSAIDs to manage postoperative pain. They are cheap, efficacious, easy to administer and generally well tolerated. They are particularly useful in providing mild or mild-to-moderate pain relief, but, their efficacy is often too limited to be the sole analgesic in more severe pain states.

## Multimodal analgesia

To maximise both efficacy and tolerability of analgesics a multimodal approach to analgesia is preferred. A multimodal approach to analgesia uses a combination of different classes of analgesics as well as different sites of administration to improve pain relief. Secondarily, because the individual

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doses of each agent are often lower than they would have been if they were given as monotherapy this approach improves tolerability because the adverse event profile of the different analgesics vary.[7] A true multimodal approach to postoperative pain management also needs to incorporate non-pharmacological methods of pain control such as acupuncture, physiotherapy, massage, aromatherapy and reflexology. Trans-electrical nerve stimulators (TENS machines) may also be used as an adjunct to pharmacological analgesia.[8]

In line with the WHO analgesic pain ladder, the combination of NSAIDs with paracetamol is widely used clinically although evidence for improved analgesia with such a combination is weak. A review of the effectiveness of paracetamol in combination with a NSAID showed that concurrent use of rectal or intravenous/intramuscular (IV/IM) paracetamol with a NSAID was superior to treatment with paracetamol alone, but the combination was not shown to be superior to treatment with an NSAID alone.[7,9] The combination of NSAIDs with morphine given through a patient controlled administration device (PCA) significantly reduces the incidence of sedation, nausea, and vomiting.[4] Hynes and colleagues compared the safety and effectiveness of two infusions of 2g IV propacetamol (equivalent to 1g paracetamol) taken five hours apart (n = 40) compared with a single dose of 75mg IM diclofenac (n = 40) compared with placebo (n = 40) in 120 patients with moderate to severe pain undergoing total hip arthroplasty. Although both IV propacetamol and IM diclofenac were significantly better than placebo there was no significant difference between the active treatments in safety or efficacy.[10] However, the lack of robust, large, well-controlled studies makes drawing firm conclusions about the comparative efficacy of NSAIDs and paracetamol difficult. On the basis of the evidence available paracetamol given by any route is an important, well tolerated analgesic when used for the acute management of mild or mild-to-moderate postoperative pain.[9]

## Routes of administration

Oral administration is the route of choice for most postoperative pain relief, particularly for non-severe pain in people who have no swallowing difficulties or other preclusions to oral administration. Previous concerns that the administration of oral medications immediately before or after general anaesthesia may complicate surgery or would not be efficacious are no longer thought to be true in the majority of cases.[11] Oral administration avoids the risks associated with injections (e.g. infection, local pain or inflammation), takes up significantly less nursing time, and prepares the patient for discharge. For NSAIDs in particular the oral route is considered to be as fast and as effective as using rectal or injectable routes. However, for oral analgesia to be effective the patient needs to have normal motility of stomach and

**Table 1. Analgesics commonly used in the treatment of postoperative pain**

| Drug | Routes of Administration | Pharmacokinetics | Advantages | Disadvantages |
|---|---|---|---|---|
| **Aspirin**[2] | PO, PR | Rapidly metabolised to salicylic acid. Elimination half-life is approximately 4 hours at therapeutic doses (dose-dependent excretion). | Readily available, effective and cheap. | Not recommended for use postoperatively due to gastrointestinal (GI) side-effects, such as nausea, vomiting and GI bleeding. |
| **Paracetamol**[2,11] | PO, PR, IV | Unclear mechanism of action — analgesic activity may be due to prostaglandin synthesis inhibition. Good oral bioavailability, variable rectal bioavailability, extensively hepatically metabolised. | Non-narcotic with analgesic and antipyretic actions. Well tolerated at normal dosages. Drug of choice for baseline analgesia either alone or in combination with NSAIDs and opioids. | No anti-inflammatory effect. |
| **NSAIDs**[2,6,19] | PO, PR, IV, IM | Mechanism of action is predominantly via inhibition of prostaglandin synthesis by cyclo-oxygenase including in the gastric mucosa, which may lead to bleeding. | Has both analgesic and anti-inflammatory effects. When the oral route is available ibuprofen is the drug of choice because it is better tolerated than other NSAIDs. Diclofenac, ibuprofen, ketoprofen, ketorolac, parecoxib and flurbiprofen are licensed for postoperative use. | Wide individual variation in response to these agents so recommending the best NSAID is impossible. Increased risk of bleeding due to the anti-platelet effect may restrict their use in the postoperative setting. There is a high incidence of side-effects with longer-term (> 1 week) use. Need to use caution in patients with asthma or renal impairment (such as the elderly). High risk patients may experience adverse events even with short term use (eg, patients with hypovolaemia, renal impairment, active or recent gastroduodenal ulcer, bleeding disorders). |
| **Codeine**[2,6] | PO | An opium alkaloid derivative with markedly less activity than morphine (1/12 as potent). Approximately 10% is demethylated to morphine. | Codeine is effective in the treatment of mild to moderate pain and has a well documented adverse event profile when given orally. May be combined with paracetamol and NSAIDs. | Constipation can be an issue particularly with longer term use. Not as effective as stronger opioids (e.g. morphine). Metabolic capacity varies considerably, which can lead to marked inter-patient variation of response and tolerability. |
| **Tramadol**[6,8] | PO, IM, IV | A centrally acting synthetic opioid with 1/10 the potency of oral morphine. Two pronged analgesic effect; an opioid effect and one by enhancing serotinergic and adrenergic pathways. | Tramadol has fewer opioid adverse effects such as respiratory depression, less constipation and less potential for addiction. | Has been associated with hallucinations and seizures (hence it is contraindicated in patients with a history of epilepsy). |
| **Morphine**[6,8] | PO, IM, IV, SC, PR | An opioid receptor agonist acting mainly at mu receptors. Morphine undergoes glucuronidation to form one active (morphine-6-glucoronide) and one antagonistic (morphine-3-glucoronide) metabolite. | Morphine is the standard against which the potency of other opioid analgesics are measured. Relieves moderate to severe pain and also causes a state of mental detachment and euphoria. | When given orally morphine has poor bioavailability as it undergoes extensive first pass metabolism. Frequently associated with nausea and vomiting. Repeated administration may lead to tolerance and dependence. |
| **Fentanyl**[6,8] | IV, buccal, transdermal | Synthetic, highly potent opioid, with a higher lipid solubility and a shorter duration of action compared with morphine. Acts within 1–2 minutes when given by injection. | Good for a rapid but short duration of action. Often administered intra-operatively to reduce the requirements of other anaesthetic drugs | Can accumulate to cause respiratory depression that can persist or manifest postoperatively when repeated intravenous injections are used intra-operatively. Causes muscle rigidity, particularly of the chest wall. |
| **Pethidine**[6,8] | PO, SC, IV, IM | Synthetic opioid with shorter duration of action and less potency than morphine even in high doses. | Pethidine has a fast onset of action but a short duration of action. | Norpethidine (metabolite) can accumulate, particularly in renal impairment, to cause stimulation of the central nervous system including hallucinations and convulsions. |

To minimise adverse events and to maximise efficacy a multimodal approach to pain management should be used. Mild to moderate pain is best managed using paracetamol adding in an NSAID or a weak opioid if necessary.

small intestine. After abdominal or gastric surgery normal stomach motility may not be restored for 15 hours or more and hence an alternative administration route would need to be considered. There are many other situations in the postoperative setting, as mentioned previously, where the oral route may not be appropriate, such as for children, sedated or unconscious patients, sites of surgery around the throat or mouth, or in the management of severe pain where a rapid onset of analgesic action is required.[11]

Alternative methods of analgesic administration include IM, subcutaneous (SC), IV, rectal and sublingual (SL). The transdermal route is generally not appropriate in the acute setting because doses cannot be titrated and analgesia delivered by this route has a slow onset of action.

The IM administration of opioids, such as morphine, is commonplace, inexpensive and is associated with a gradual onset of pain relief that permits easy assessment of possible overdose. The disadvantages of this administration route are that dose titration is not easy to achieve often resulting in administration of doses that cause side-effects (too large) or they are ineffective (too small). Delayed onset of activity and pain at the injection site are also limitations of this route.[2]

The rectal route of administration offers a good alternative to oral or IM administration particularly for opioid analgesics (that are subject to extensive first pass metabolism when given orally) or when the oral route is otherwise not appropriate or available. However, the slow and often erratic absorption of opioids and paracetamol via this route mean that the rectal route is not recommended for the administration of analgesics for the immediate relief of acute postoperative pain. The rectal route can provide a useful alternative for the administration of maintenance analgesia but this is subject to patient acceptability.[2,12]

The IV route may be preferred when a patient is experiencing severe pain that needs rapid relief or when the oral route is not appropriate or available. Potential disadvantages of this route include the significant risks of IV administration (including phlebitis, infiltration, extravasation, haematoma, haemorrhage, pneumothorax, air embolism, fluid overload, septicaemia and thrombosis), increased nursing time and potential fluctuation of plasma levels of analgesics after repeated IV bolus doses. Furthermore between June 2005 and June 2006 the NPSA received approximately 800 reports each month of errors pertaining to injectable medicines (of which approximately 70% were administration errors) representing approximately 24% of total medication incidents.[13] Hence the increased risk of medication errors, particularly administration errors must always be balanced against the clinical needs of the patient.

Generally, strong opioids are not safe to give in bolus IV doses except in an anaesthetic or high-dependency setting, and hence IV opioids are most commonly given via a PCA device, sometimes in combination with a background infusion.[2]

## Role of intravenous paracetamol in managing postoperative pain

### *Mild or mild-to-moderate pain*

For the management of mild or mild-to-moderate postoperative pain where alternative routes are inappropriate or unavailable IV paracetamol may provide useful analgesia while negating the need for analgesics with increased side-effects such as NSAIDs or opioids. Intravenous paracetamol has distinct advantages over rectal paracetamol in that it has improved bioavailability and a faster onset of action.[12] When compared with oral paracetamol in 35 patients undergoing day surgery, 2g of IV propacetamol (bioequivalent to 1g of IV paracetamol[14]) gave a median plasma paracetamol concentration of 85 micromol/L (range 65–161) after 40 minutes whereas 40% of patients administered oral paracetamol showed undetectable plasma paracetamol levels. After 80 minutes patients receiving oral paracetamol (1 gram dose) demonstrated a median plasma concentration of 36 micromol/L.[15] There is also considerable variability in the time to peak plasma concentration and median plasma paracetamol levels after oral administration of paracetamol.[15] Intravenous paracetamol requires a dedicated line for intravenous administration[16] and it is considerably more expensive than oral paracetamol, however, it is often cheaper than similar doses of rectal paracetamol (approximate price of a 1g dose of paracetamol: 2 x 500mg tablets is £0.02, 1 x 1gram vial is £1.98 and 2 x 500mg suppositories is £2.00).[6]

### *Severe pain*

A meta-analysis of randomised controlled trials investigating the effects of paracetamol combined with PCA morphine compared with PCA morphine alone in patients who had undergone major surgery found that the administration of paracetamol, given either via the oral or IV route (data were combined in the analysis) was associated with a 20% reduction of morphine consumption (95% CI, -15 to -3mg; P=<0.005 ). However, improved tolerability was not demonstrated.[17] In another study 36 women undergoing mammoplasty were randomised to receive IV propacetamol 2g or placebo one hour before the end of surgery. The propacetamol group consumed significantly less morphine in the recovery room compared with placebo (p=0.01), however, the incidence of morphine-associated adverse events did not differ between treatment groups.[18] Therefore, IV paracetamol may also be used in combination with strong opioids to achieve an opiate-sparing effect and predictable plasma paracetamol levels. Thus, in patients with severe pain for whom the oral route is not available or

appropriate, IV paracetamol has a role to play as part of a multimodal treatment strategy in reducing opioid consumption and effectively managing pain.

## Benefits of optimising acute severe postoperative pain management

It is essential that a patient's journey from pre- to post-operative care is optimised to ensure positive outcomes and a reduction in stress and anxiety for the patient. Optimal postoperative pain management is integral to this because it not only decreases pain intensity but improves the patient experience and postoperative outcomes. It is also essential that although effective analgesia must be prescribed and administered, the potential side-effects, which may in themselves cause poor patient outcomes and a prolonged length of stay, are avoided. A balance between effective pain control and tolerability needs to be reached and, particularly for severe pain, optimum postoperative pain control may be best achieved with a multimodal approach to analgesia using a combination of paracetamol and/or NSAIDs with strong opioids given via the appropriate route. A multimodal approach will ensure effective analgesia is attained while minimizing opioid doses and promoting faster recovery times.

Inadequately controlled pain whatever the severity can cause increased patient morbidity. Pain often causes reduced patient mobility, thus increasing the risk of deep venous thrombosis, pulmonary atelectasis, muscle wasting and urinary retention.[5] Uncontrolled moderate to severe postoperative pain may be associated with an increased risk of patients going on to develop chronic pain syndromes. Treatment of acute pain by pre-emptive analgesia may prove to be beneficial in avoiding this complication.[5]

Adequate pain control as described above will help to reduce complications of postoperative pain such as platelet aggregation and immune system suppression, which can both be caused by the cellular response to pain and tissue damage. Furthermore, uncontrolled pain can increase the risk of myocardial infarction or ischaemia secondary to tachycardia and hypertension caused by the release of catecholamines in response to pain. However, it is equally important to minimise the adverse effects of analgesic medicines, particularly opioid medications. By decreasing opioid demand through combination with non-opioid agents such as paracetamol and/or NSAIDs it is possible to avoid unnecessary prolongation of hospital admission. IV paracetamol has a key role to play here because it can be administered with guaranteed bioavailability for the rapid management of severe postoperative pain in this patient group where the oral route may not be available or appropriate.

## Summary

By maximising pain relief and minimising complications enhanced patient recovery and improved patient outcomes can be achieved. This is best achieved by a thorough assessment of both procedural and patient factors in planning an appropriate postoperative analgesic regimen. It is essential that, where a patient is identified as being at risk of experiencing severe postoperative pain, a pre-emptive approach is taken, ensuring that effective analgesia is administered both intra-operatively and immediately postoperatively before the anaesthetic effect has worn off.

To minimise adverse events and to maximise efficacy a multimodal approach to pain management should be used. Mild to moderate pain is best managed using paracetamol adding in an NSAID or a weak opioid if necessary. Administration via the oral route is preferred; however, injectable analgesia may be considered where other routes are unavailable or inappropriate. For severe pain the combination of a strong opioid with paracetamol and/or NSAIDs can achieve effective analgesia while minimising any opioid-associated adverse events. It is essential that the best route of administration is chosen to ensure good bioavailability and a rapid onset of action. It may be advisable to consider intravenous analgesics such as paracetamol with a strong opioid particularly for the immediate postoperative treatment of severe pain and when the oral route is unavailable or not appropriate. ✣

## Declarations of interest

The author has no interests to declare.

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