Paracetamol
Is it effective and safe for musculoskeletal pain?

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Paracetamol is widely recommended as the first choice for pain relief in common musculoskeletal conditions. However, recent research challenges its effectiveness and safety in patients with low back pain or osteoarthritis.

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Arthritis and other musculoskeletal conditions are leading causes of disease burden in Australia and around the globe.[1,2] These conditions affect people across the life span, with a higher prevalence in women than men.[1] The most common musculoskeletal conditions are back pain, neck pain and osteoarthritis. General practice surveys reveal that arthritis and musculoskeletal conditions are the most common health conditions managed in primary care.[3] In Australia, analgesic medicines are the most common treatment provided by GPs for patients with spinal pain or osteoarthritis.[4,5] Current treatment guidelines for musculoskeletal conditions advocate that the first choice for pain relief should be a simple analgesic such as paracetamol.[6-13]

Key points

- **A systematic review of trials of paracetamol as an analgesic has shown it is no more effective than placebo for low back pain and has a trivially small effect for osteoarthritis.**
- **There are no trials of paracetamol with long-term outcomes for either low back pain or osteoarthritis.**
- **Paracetamol toxicity is responsible for the hospitalisation of 150 patients per week in Australia; most cases of paracetamol toxicity are unintentional.**
- **Inadvertent paracetamol overdose is a particular risk among patients with chronic pain who may be taking modified-release formulations.**
- **GPs prescribing or recommending paracetamol should educate patients about paracetamol toxicity and the need to avoid taking two or more paracetamol formulations concomitantly (e.g. paracetamol-containing cold and flu remedies plus regular paracetamol for pain).**

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Paracetamol is one of the most readily accessible and commonly used nonprescription analgesic and antipyretic medicines. It is used as monotherapy or in combination with other analgesic medicines such as weak opioids (codeine) and NSAIDs for treating a range of pain conditions and has been proven effective in many situations. For example, a recent Cochrane review reported that it is effective for acute postoperative pain, with a number needed to treat of around four to achieve 50% pain reduction.[14] Paracetamol is also reported to be superior to placebo for the treatment of migraine.[15] It is widely considered to be safe when taken appropriately, and less likely to cause the gastrointestinal and renal adverse events that are commonly linked to NSAIDs.

However, recent evidence challenges the effectiveness of paracetamol as an analgesic for musculoskeletal conditions such as low back pain and osteoarthritis. Concerns have also been raised about the safety of paracetamol in long-term use and cases of inadvertent overdose, which can cause liver failure and death. This evidence and these concerns may lead to changed recommendations on pain relief in patients with low back pain and osteoarthritis as guidelines are revised.

Mechanism of action of paracetamol

The mechanism of action of paracetamol has been the topic of considerable interest and debate. Some reports support the inhibition of the enzyme cyclo-oxygenase-2 (COX-2) as the likely mechanism by which paracetamol exerts its analgesic effects, whereas others suggest the effects are mediated by inhibition of cyclo-oxygenase-3 (COX-3) in the brain.[16]

The general consensus is that the effects of paracetamol on the COX isoenzymes can explain, at least in part, some of its actions.[16] Inhibition of COX leads to inhibition of peripheral prostaglandin synthesis, resulting in analgesia. Many of the adverse effects of therapeutic doses of paracetamol (e.g. gastrointestinal upset and bleeding) are also linked to inhibition of COX isoenzymes. COX inhibition implies a potential anti-inflammatory effect of paracetamol, as NSAIDs similarly target this pathway. However, the anti-inflammatory effects of paracetamol are reported to be relatively weak at therapeutic doses.[16]

Efficacy of paracetamol for common musculoskeletal conditions

Low back pain

Since the first clinical practice guideline on low back pain was published in 1994, guidelines have uniformly endorsed paracetamol as the first-line analgesic for patients with acute or chronic low back pain.[6-10] However, these recommendations were not based on direct randomised controlled trial (RCT) evidence.[17] It was not until 2014 that the first placebo-controlled trial in this area was published, Paracetamol for Low Back Pain (PACE) .[18] This trial randomised 1650 patients with acute low back pain to paracetamol or placebo and surprisingly found no difference across a range of outcomes, such as pain, disability, quality of life and sleep quality.[18] The study also found that time-contingent dosing with the full dose of paracetamol (4 g daily) or dosing as needed (i.e. PRN) were similarly ineffective, their effects being no different to those of placebo. Our 2015 systematic review of trials of paracetamol in low back pain found two additional RCTs, but one of these yielded no usable data and the other was later retracted.[19-22] There are no paracetamol trials with long-term outcomes for either low back pain or osteoarthritis.

Hip and knee osteoarthritis

The American College of Rheumatology, Osteoarthritis Research Society International and the National Institute for Health and Care Excellence (NICE) guidelines for managing osteoarthritis all endorse paracetamol for pain relief in hip or knee osteoarthritis.[11-13] There was controversy when the NICE guidelines were recently revised because of concern that the effect of paracetamol might be too small to be worthwhile.[13] Our 2015 systematic review summarised the 10 placebo-controlled RCTs evaluating paracetamol in patients with hip and/or knee osteoarthritis and confirmed that the effect indeed was very small.[19] The immediate effect on pain was 3.3 points reduction on a 0 to 100 point pain scale and 1.7 points on a 0 to 100 disability scale. These effects would be too small to be discernible by an individual patient.

Neck pain and whiplash

The NHMRC guideline for whiplash-associated disorders recommends treatment with simple analgesics, whereas the Motor Accidents Authority guideline explicitly recommends paracetamol, although neither guideline substantiates its recommendation.[23,24] To our knowledge, there are no RCTs of paracetamol for whiplash or nonspecific neck pain.

Other musculoskeletal conditions

Other painful musculoskeletal conditions that are seen in primary care include acute sprains and strains from work and sports injuries, tendinopathies associated with overuse (e.g. Achilles tendinopathy), fractures caused by stress, insufficiency or trauma, inflammatory forms of arthritis such as rheumatoid arthritis and apophysitis in children (e.g. Sever's disease). Our systematic review was unable to find any placebo-controlled trials of paracetamol for these or any other musculoskeletal conditions. We did identify some comparative effectiveness trials of paracetamol, but in the absence of evidence that paracetamol is more effective than placebo these trials seem premature and the results difficult to interpret.

Safety of paracetamol

Paracetamol at therapeutic doses

Paracetamol is widely considered to be safe when taken appropriately. However, our recent systematic review provided high-quality evidence that patients with osteoarthritis taking paracetamol for pain relief are almost four times more likely to have abnormal results on liver function tests (typically aminotransferases) than patients taking placebo.[19] The clinical importance of these abnormal results is not clear. In most cases, liver function results return to normal when treatment with paracetamol is ceased. Given the widespread

use of paracetamol in the community (millions of doses ingested daily worldwide) the incidence of liver injury at therapeutic doses appears very low. Furthermore, studies investigating paracetamol-induced liver injury at therapeutic doses have often failed to exclude risk factors for hepatotoxicity, such as chronic alcohol intake, dehydration, hepatic or renal dysfunction or conditions that deplete glutathione stores (e.g. poor nutrition).

As a COX inhibitor, paracetamol has an adverse effect profile potentially similar to that of NSAIDs. Although paracetamol has not been traditionally associated with the gastrointestinal and renal adverse events commonly linked with NSAIDs, recent reports challenge this notion. A large clinical trial evaluating treatment with paracetamol, ibuprofen or a combination of the two over a 13-week period showed similar reductions in haemoglobin levels for paracetamol and ibuprofen, a possible consequence of occult gastrointestinal bleeding.[25] This is most likely the result of COX inhibition, which prevents the synthesis of gastroprotective prostaglandins. Furthermore, COX-2 inhibition in the endothelium by paracetamol raises concerns about cardiovascular risk with long-term use.[26]

Paracetamol overdose

A recent study showed that paracetamol toxicity is responsible for the hospitalisation of 150 patients per week in Australia.[27] Paracetamol overdose can result in liver failure and death.[28,29] Although one-fifth of all cases of paracetamol poisoning that result in emergency department admission are deliberate, most cases of paracetamol poisoning are unintentional.

Inadvertent paracetamol overdose is a growing cause for concern, particularly among patients with arthritis or other chronic pain conditions taking modified-release formulations of the drug.[27] Concomitant use of paracetamol (for example, taking cold and flu remedies containing paracetamol in addition to regular paracetamol for pain) is also on the rise and has been held responsible for unintentional hospitalisations both in Australia and overseas.[27]

Self-administration of opioid–paracetamol combination products for the opioid effect also appears to be growing and is likely to increase the risk of hepatotoxicity. A US study found that hepatic injury is greater when paracetamol is taken with an opioid, whereas in the absence of opioid-containing products, consumption of more than one paracetamol-containing product did not contribute to injury.[30]

Symptoms of paracetamol overdose include gastrointestinal upset, jaundice, convulsions and coma. Poisoning with modified release formulations of paracetamol can be problematic as toxic concentration of the drug may not be detected in the early stages and symptoms may manifest almost 12 hours or more after ingestion of the toxic dose.[31] The mechanism of paracetamol toxicity is largely related to acute liver injury and the subsequent build up of the toxic metabolite N-acetyl-p-benzoquinone imine. Depending on the form of paracetamol and the severity of symptoms, patients may be treated with medicines to relieve symptoms such as antiemetics or with laxatives, activated charcoal or N-acetylcysteine, an antidote to paracetamol.[32]

Strategies for GPs to reduce the risk of inadvertent paracetamol overdose

GPs who prescribe or recommend paracetamol to patients should routinely:

- enquire about patient use of any over-the-counter products
- counsel patients on the need to avoid concomitant use of two or more paracetamol products
- alert patients to the maximum recommended paracetamol dose of 4 g daily*

* Organisations such as the American Liver Foundation recommend a more stringent maximum paracetamol dose of 3 g daily, particularly if the drug is being used for an extended period.[35]

Safe use of paracetamol

Despite the above concerns, paracetamol is largely considered to be the appropriate choice of pain relief in patient populations in whom NSAIDs or opioid analgesics are contraindicated or best avoided. As a category A medicine, paracetamol is suitable for short-term use in women who are pregnant or breastfeeding. Given paracetamol's reasonable safety profile it is also the preferred analgesic for people being treated with warfarin or other anticoagulant therapy, people with asthma who may have sensitivity to aspirin or aspirin derivatives and frail older people.[33] It is also widely used as a pain relief medication for children, although the incidence of accidental overdose with paracetamol in this patient population has also sparked concern in recent years.[34]

Paracetamol should be avoided or used with caution in people with known liver impairment and alcoholism (alcohol may potentiate the hepatotoxic effects of paracetamol even at therapeutic doses).

Preventing paracetamol overdose

The frequency of hospitalisations caused by unintentional paracetamol overdose and the resulting health burden to society reinforce the need for healthcare professionals to educate consumers about safe paracetamol use. Strategies for GPs when prescribing or recommending paracetamol to patients to reduce the risk of paracetamol overdose are summarised in the Box.[35] Using these simple screening and counselling strategies could help prevent cases of inadvertent overdose.

Alternatives to paracetamol for musculoskeletal pain

Treatment options for low back pain

For GPs who choose not to prescribe paracetamol for patients with low back pain there are other effective nonpharmacological and pharmacological treatment options.

Nonpharmacological treatments

Nonpharmacological treatments recommended for patients with low back pain by the American Pain Society include:[8]

- advice to remain active
- evidence-based information on the expected course of low back pain
- books or handouts on effective self-care options.

For acute low back pain, other recommended treatments include:

- superficial heat (heating pads or heated blankets)
- spinal manipulation

For chronic low back pain, other recommended treatments include:

- spinal manipulation
- exercise therapy
- massage therapy
- acupuncture
- yoga
- cognitive behavioural therapy
- intensive interdisciplinary rehabilitation.

Pharmacological treatments

Pharmacological treatments apart from paracetamol recommended for patients with acute and chronic low back pain include:

- NSAIDs
- tricyclic antidepressants
- short-term cautious use of opioids such as tramadol, tapentadol or buprenorphine.[9,10]

Evidence supporting the long-term use of these medications in patients with low back pain is lacking, and patients taking these medications will require close monitoring. It is likely that in complex cases, patients will require a multidisciplinary approach to care, with treatment plans involving pharmacological and nonpharmacological interventions.

Treatment options for osteoarthritis

For GPs who choose not to prescribe paracetamol for patients with osteoarthritis, options for analgesic medicines include oral or topical NSAIDs and intra-articular corticosteroid injections. Effective nonpharmacological options that can be suggested by GPs include healthy lifestyle interventions such as weight loss, exercise, self-management and education, modifications to shoes or insoles and walking aids.

Conclusion

Recent research challenges the use of paracetamol as an analgesic medicine for musculoskeletal pain. There is level I evidence demonstrating that paracetamol is ineffective for back pain and has a trivially small effect for osteoarthritis. For other musculoskeletal conditions there is no evidence from clinical trials and so it is unclear whether paracetamol is beneficial, ineffective or potentially harmful for patients with these conditions. These findings suggest that GPs should reconsider the use of paracetamol to manage these conditions, particularly when there are other known effective treatments that they can provide for their patients. **PMT**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

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