ORAL SURGERY

Oral Surgery ISSN 1752-2471

ORIGINAL ARTICLE

Paracetamol (acetaminophen) for pain after oral surgery

P. Coulthard, E. Bailey & N. Patel

School of Dentistry, The University of Manchester, Manchester, UK

Key words:
oral, pain, surgery

Correspondence to:
Mr E Bailey
School of Dentistry
The University of Manchester
Coupland 3 Building
Coupland Street
Manchester, M13 9PL
UK
Tel.: 0161 306 0220
Fax: 0161 306 0220
email: edmund.bailey@manchester.ac.uk

Accepted: 3 November 2013

doi:10.1111/ors.12079

Abstract

Aim: To describe the role of paracetamol (acetaminophen) in the management of pain after oral surgery.

Materials and methods: A review of the literature describing the pharmacokinetics, benefits and harms of paracetamol in terms of systematic review evidence, interactions, use in children, pregnancy and breastfeeding.

Results: Paracetamol inhibits cyclooxygenase (COX)-3 isoenzyme and reduces prostanoid release in the central nervous system. The analgesic effectiveness of paracetamol in the control of pain after oral surgery has been shown in a number of clinical trials with a number needed to treat for 1 g paracetamol of 1.87. There are few adverse events, but at toxic doses, harm to the liver may arise and paracetamol poisoning remains the commonest cause of acute liver injury in Europe and North America.

Conclusions: Paracetamol is an effective analgesic for mild to moderate pain and has an excellent safety record in adults and children. It is also one of the safest analgesics to use if needed during pregnancy and breastfeeding.

Clinical relevance

Scientific rationale

This article provides an update for Oral Surgeons on the use of paracetamol (acetaminophen) for pain after oral surgery.

Principal findings

Paracetamol is widely available without prescription, possesses antipyretic activity in addition to its analgesic property and has an excellent safety record.

Practical implications

Paracetamol should be used for the management of mild to moderate pain after oral surgery. Many compound medicines contain paracetamol so patients should be advised to take care not to exceed the therapeutic dose of 4 g/24 h.

Introduction

This second article in the series discusses the use of paracetamol in the management of pain in patients undergoing oral surgery procedures in primary and secondary care. Other articles in this series describe pain pathways and the use of Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids in the management of pain following oral surgery and pain measurement[1–4].

Patient-reported outcome measures (PROMS)

Patients are commonly concerned about the post-operative pain that they may experience when scheduled for oral surgery. Pain management is important to patients. PROMs are gaining global recognition as important measures of healthcare quality and are important to clinicians and researchers wishing to develop patient-centred care[5].

The collection and reporting of PROMs is a key priority in Britain as set out in the Government's 2010 White Paper, 'Equity and excellence: Liberating the NHS'[6] where the commitment was made to 'extend PROMs across the NHS wherever practicable'. In 2013 'Securing Excellence in commissioning NHS Dental Services' was published by the NHS Commissioning

Board[7] setting out it's vision for a patient-centred service that delivers best outcomes and proposes a care pathway approach for all dental services with the entire dental pathway as a single, consistent, integrated model of service delivery. The oral surgery guidance for commissioners of services recommends that all patients be contacted by telephone 24 h after their surgery to enquire about unmanaged pain, haemorrhage and nerve injury. This is a major step forward in advancing post-operative pain and other clinical outcomes as priorities in patient care.

Background

Paracetamol (acetaminophen) was introduced in the 1950s and is one of the most commonly used non-opioid analgesics around the world[8]. It is widely available without prescription. Paracetamol possesses antipyretic activity in addition to its analgesic property and has an excellent safety record[9–11]. It is not restricted to 'prescription only' in most countries of the world. It does not cause euphoria or alter mood. The US Approved Name is acetaminophen and paracetamol is the International Non-proprietary Name and the British Approved Name.

Acetaminophen first went on sale in the USA in 1955 under the brand name *Tylenol*. In 1956, 500 mg tablets of paracetamol went on sale in the UK under the brand name *Panadol*. Originally, these were only available by prescription. In 1958, a children's formulation, *Panadol Elixer*, was released. Subsequent formulations included suppositories, melt tablets, rapid release preparations and injectable forms. There are over 900 individual branded products of paracetamol around the world.

Pharmacokinetics

The mechanism of analgesic action of paracetamol is understood to be by inhibition of cyclooxygenase (COX)-3 isoenzyme, a COX-1 variant and subsequent reduced prostanoid release in the central nervous system[12,13]. This central inhibition also represents a primary mechanism by which paracetamol reduces fever[13]. Paracetamol is rapidly absorbed in the small intestine when given orally as either a tablet or liquid with peak plasma concentrations reached at 30–60 min. A variable proportion is bound to plasma proteins, and the drug is inactivated by the liver as conjugated to give glucuronide or suphate and excreted via the kidneys. The plasma half-life of paracetamol is relatively short at 2–4 h, and at toxic doses, this may be extended to 4–8 h[14].

Benefit

The efficacy of analgesics is reported in a number of ways in randomised clinical trials. There has been an increasing trend to report a 50% reduction in total pain relief but probably a more helpful measure is the number needed to treat (NNT), that is, number of patients that achieve at least a 50% pain relief as compared with placebo. The NNT for 1 g paracetamol is 1.87 for patients after oral surgery. This indicates that for every two (1.87) patients who receive 1 g dose of paracetamol, one will get greater than 50% pain relief who would not have done so if they had received a placebo. The NNT for 1 g paracetamol is 3.77 for patients undergoing orthopaedic surgery and is therefore less effective after this type of surgery[15].

Paracetamol is used for the management of mild to moderate pain and fever. The analgesic effectiveness of paracetamol in the control of pain after oral surgery has been shown in a number of clinical trials[16–19] and a recent Cochrane systematic review[20]. This review included 21 trials of 2048 patients and showed significant benefit when compared with placebo for pain relief and pain intensity at both 4 and 6 h. There was no statistically significant difference between the number of patients who reported adverse events, overall this being 19% in the paracetamol group and 16% in the placebo group.

Paracetamol has been described as a weak analgesic as it is effective for mild to moderate pain rather than severe pain and because it does display a ceiling effect such that increasing the dose above that recommended will not increase the analgesic efficacy[21]. However, in severe pain, paracetamol used in combination with other analgesics will provide superior pain relief and permit a reduction in opioid drug doses[22,23].

The indications for paracetamol include headache, feverish conditions, period pain, toothache and other dental pain, back pain, muscular and joint pains, neuralgia, pains associated with colds and flu and as an antipyretic. Paracetamol is the analgesic of choice for children as it is not associated with Reye's syndrome. It is also preferred in the elderly as it lacks gastric erosive properties.

Harm

Some analgesics have adverse affects in therapeutic doses, and all analgesics are toxic in overdose. Paracetamol is considered safe because it does not have side effects such as gastrointestinal ulceration and haemorrhage, cardio-renal adverse effects or show impairment of platelet aggregation[24]. Also, any effects on bone are clinically insignificant[25].

The principal harm from paracetamol is to the liver, and paracetamol poisoning remains the commonest cause of acute liver injury in Europe and North America. Because the drug is widely available, overdose with paracetamol, which is deliberate in the overwhelming majority of cases, is among the single largest causes of acute liver failure. Accidental overdose needs to be guarded against by advising patients to follow the dosing regime on the label and to avoid prolonged or excessive doses. Patients and their escorts should always be informed if paracetamol has been used intra-operatively or post-operatively before discharge. They should also be warned that many combination analgesics may contain paracetamol and so they should take only the analgesics recommended or prescribed by their surgeon. Recent evidence suggests that at high-dose levels, paracetamol may be associated with the same gastrointestinal and cardiovascular adverse events as the non-selective NSAIDs[26].

A dose of more than 150 mg/kg (or 12 g, whichever is smaller) paracetamol is recognised as potentially hepatoxic (or less if patients are in a high-risk group)[27]. Adolescents with eating disorders or others with glutathione depletion may be at increased risk, as may patients who are taking enzyme-inducing drugs such as phenytoin or rifampicin, but this has not been definitely shown[28]. Chronic alcohol ingestion is reported to reduce the ceiling of toxicity[29].

Many individuals may have no symptoms in the first 24 h after overdose, while others develop vague abdominal pain and nausea. Signs of liver failure then start with encephalopathy, hypoglycaemia and coagulopathy.

The aim of treatment is to prevent or minimise liver injury following paracetamol overdose. An attempt should be made to establish the exact timing and amount of paracetamol ingested. If a hepatotoxic dose has been ingested within the past hour, then gastric decontamination with activated charcoal would generally be considered. The decision to start treatment with N-acetylcysteine will depend on the clinical scenario (e.g. time of presentation after the overdose) and, in many cases, the serum levels of paracetamol and/or liver enzymes[30].

Drug interactions

Prolonged regular use of paracetamol may enhance the anticoagulant effect of coumarins, but short-term use for post-operative pain is unlikely to have any effect. The metabolism of paracetamol may possibly be accelerated by antiepileptic drugs such as carbamazepine, phenobarbital and phenytoin and so reduce its analgesic efficacy a little. The metabolism of the cytotoxic drug busulfan is inhibited by paracetamol and so caution is advised within 72 h of paracetamol use[31].

Therapeutics

Analgesics should be administered at high enough dose and frequency appropriate to their half-life to ensure optimal therapeutic plasma levels. However, persuading adult patients to take 1 g paracetamol four times a day may not be straightforward.

Paracetamol has a relatively short half-life and at a dose of 1 g provides analgesia for 4 h but cannot be taken every 4 h over a 24 h period as this would exceed the maximum dose for safety of 4 g. Controlled release is reported to improve compliance and provide uninterrupted night-time sleep that might be important for some patients[32]. Controlled release formulations should be taken regularly and not 'as required' as they may take as long as 4 h to reach peak analgesic effect. Modified release paracetamol preparations such as *Panadol Extend* available in Australia and New Zealand consist of a bilayer tablet containing paracetamol 665 mg, one layer containing immediate release paracetmol (31%) and the second layer containing sustained release paracetamol (69%). The recommended dosage is two 665 mg tablets (1.33 g) three times a day with a maximum daily dose of six tablets (3.99 g). These proportions result in a dissolution profile that releases paracetamol to give plasma levels adequate for analgesic relief for up to 8 h. *Tylenol Extended Release* formulation is available in the USA and Canada and similarly consists of a bilayer tablet that provides up to 8 h pain relief. A similar formulation is not available in the UK.

While the oral route with tablets for drug administration is usually preferable, consideration should be given as to whether the oral route with liquid or rectal or intravenous routes might be more appropriate according to the age of the patient and the nature of the surgery[33].

Intravenous paracetamol may be administered intra-operatively followed by oral administration after discharge home. Parenteral paracetamol has a more predictable onset and duration of action and 1 g of intravenous paracetamol has a similar analgesic efficacy to 2 g of the prodrug of paracetamol, propacetamol[32].

Children

The use of aspirin has almost disappeared because of the risk of Reyes syndrome and ibuprofen has taken second place for treatment of pain and fever in

children. Paracetamol is first-choice over-the-counter treatment of analgesia and antipyresis in children[34].

Children should not be treated as small adults as there can be fundamental differences in drug pharmacokinetics. Fortunately, the therapeutic window (safety margin) is very wide for paracetamol, and children seem to be less susceptible to acute toxicity when compared with adults. Also, while there is limited evidence from trials, the efficacy, safety and tolerability of paracetamol appears to be similar in children and adults[35].

Globally the paediatric dose varies between 10 and 15 mg/kg. In the UK, 10 mg/kg is given every 4–6 h up to a maximum of 4 doses/day. In the US recommended dosage is 10–15 mg/kg up to five times/day to a total dose of 50–75 mg/kg. In Australia, 15 mg/kg is administered every 4 h up to a total dose of 60 mg/kg/day (see Table 1).

Rectal dosing of paracetamol is popular in children in many parts of the world. Oral elixirs are very poorly absorbed rectally and should not be used as a substitute for the purpose-made suppositories. The overall bioavailability is between 30% and 40% but serum levels vary considerably between doses even within the one child[36]. Similarly, the time to peak serum concentration varies considerably between 1 and 4 h. Despite these disadvantages, rectal dosing is regularly used in the post-operative setting[37].

Parents who use paracetamol over the counter should be advised to follow the dosing regime on the label and to avoid prolonged or excessive doses. They should be informed if paracetamol has been used intra-operatively or post-operatively before discharge.

Table 1 Table describing paracetamol (acetaminophen) doses used by route and patient group in the UK

By mouth
Adult
1 g every 4–6 h to a maximum of 4 g/24 h
Child
2–4 years
180 mg
4–6 years
240 mg
6–8 years
240–250 mg
8–10 years
360–375 mg
10–12 years
480–500 mg
12–16 years
480–750 mg
By intravenous infusion over 15 min
Child 10–50 kg weight
15 mg/kg every 4–6 h max 60 mg/kg/24 h
Adult and child over 50 kg
1 g every 4–6 h max 4 g/24 h
By rectum
Adult and child over 12 years
1 g every 4–6 h to max 4 g/24 h
Child
1–5 years
125–250 mg
5–12 years
250–500 mg to max 4 g/24 h

Pregnancy and lactation

Paracetamol is considered the analgesic of choice in pregnancy, although some manufacturers provide labelling advising medical-seeking advice. Two case control studies with over 7500 pregnant women from Boston, USA, showed that up to 65% used paracetamol[38]. A UK study has also demonstrated that women have used paracetamol without adverse effect at all stages of pregnancy[39].

Paracetamol is excreted in breast milk but not in clinically significant amounts, and so the use of paracetamol is not contraindicated when breastfeeding[31].

Compound analgesics

Many compound medicines contain paracetamol, but probably one of the most common and most useful is when combined with codeine. Codeine alone is a poor analgesic for acute pain[40], but when combined with paracetamol, it adds to the analgesia of the codeine and paracetamol synergistically. The NNT for paracetamol 600/650 mg in combination with codeine 60 mg is 3.6[41], and when paracetamol 1 g is combined with codeine 60 mg, the NNT is 2.2[42]. However, this large dose of codeine is associated with significant reporting of constipation, and at smaller more commonly used doses of 16 mg codeine with 1 g paracetamol, the analgesic effectiveness is not so beneficial.

Paracetamol 325 mg combined with dextroproxyphene 32.5 mg (co-proximol) was withdrawn from the UK market by the UK Medicine and Healthcare product Regulatory Agency in 2005 but is still available in many other counties including the USA. This combination has not been shown to be more effective than paracetamol 1 g alone in acute pain[43] and withdrawn in the UK because of the fatal toxicity with often as little as 15–20 tablets particularly when taken with alcohol.

A popular combination analgesic in the USA is paracetamol with oxydone, and this does seem to offer an improved NNT over paracetamol alone[44].

Combinations of paracetamol with NSAIDs have been less popular, and the evidence for superiority of analgesic efficacy has been sparse for combination with ketoprofen or diclofenac[45]. More recently, a Cochrane systematic review has shown superiority of paracetamol and ibuprofen combination formulations compared with taking the individual drugs separately[46].

Summary

More oral surgery is undertaken on an outpatient or day-surgery basis, and there is a continuing trend away from the greater cost of inpatient care. These patients require effective analgesia, without side effects, that are safe and easy to use at home. The choice of analgesic will depend on the anticipated severity of post-operative pain and take into account the patients age and general health. Paracetamol is an effective analgesic for mild to moderate pain and has an excellent safety record. It is one of the safest analgesics to use if needed during pregnancy and breastfeeding. Paracetamol has growing popularity as an intravenous preparation for use during day-case general anaesthesia for oral surgery. Moderate to severe pain not managed by paracetamol or NSAIDs alone should be treated with a combination of paracetamol with opioid or NSAID.

References

1. Coulthard P, Bailey E, Patel N, Coulthard MB. Pain pathways, preemptive and protective analgesia for oral surgery. Oral Surg 2014;7:74–80.
2. Bailey E, Patel N, Coulthard P. NSAIDs for pain after oral surgery. Oral Surg DOI: 10.1111/ors.12073. Epub ahead of print.
3. Patel N, Bailey E, Coulthard P. Opiods for pain after oral surgery. Oral Surg DOI: 10.1111/ors.12076. Epub ahead of print.
4. Coulthard P, Patel N, Bailey E, Coulthard MB. Measuring for pain after oral surgery. Oral Surg DOI: 10.1111/ors.12075. Epub ahead of print.
5. Coulthard P, Patel N, Bailey E, Armstrong D. Barriers to the use of morphine for the management of severe postoperative pain – a before and after study. Int J Surg in press.
6. Equity and excellence: liberating the NHS. July 2010. Department of Health. London.
7. Securing Excellence in commissioning NHS Dental Services. The NHS Commissioning Board. February 2013. Department of Health. London.
8. Day RO, Graham GG, Whelton A. The position of paracetamol in the world of analgesics. Am J Ther 2000;7:51–4.
9. Barden J, Edwards J, Moore A, McQuay H. Single dose oral paracetamol (acetaminophen) for postoperative pain. Cochrane Database Syst Rev 2004;(1) CD004602.
10. Moore RA, Collins S, Carroll D, McQuay H, Edwards J. Single dose paracetamol (acetaminophen), with and without codeine, for postoperative pain. Cochrane Database Syst Rev 1998;(4)CD001547.
11. Day RO, Graham GG, Whelton A. The position of paracetamol in the world of analgesics. Am J Ther 2000;7:51–4.
12. Botting RM. Mechanism of action of acetaminophen: is there cyclooxygenase. Clin Infect Dis 2000;5:202–10.
13. Chandrasekharan NV, Dai H, Roos KL, Evanson NK, Elton TS. COX-3 a cyclooxgenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning structure and expression. Proc Natl Acad Sci U S A 2002;99:13926–31.
14. Rang Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. Rang and Dale's Pharmacology, 7th edition. Edinburgh: Elsevier Churchill Livingstone, 2012.
15. Gray A, Kehlet H, Bonnet F, Rawel N. Predicting postoperative analgesia outcomes: NNT league tables or procedure-specific evidence? Br J Anaesth 2005;94: 710–14.
16. Mehlisch DR, Sollecito WA, Helfrick JF, Leibold DG, Markowitz R, Schow CE Jr. Multicenter clinical trial of ibuprofen and acetaminophen in the treatment of postoperative dental pain. J Am Dent Assoc 1990;121: 257–63.
17. Kiersch TA, Halladay SC, Hormel PC. A single-dose, double-blind comparison of naproxen sodium, acetaminophen, and placebo in postoperative dental pain. Clin Ther 1994;16:394–404.
18. Skoglund LA, Skjelbred P, Fyllingen G. Analgesic efficacy of acetaminophen 1000 mg, acetaminophen 2000 mg, and the combination of acetaminophen 1000 mg and codeine phosphate 60 mg versus placebo in acute postoperative pain. Pharmacotherapy 1991;11: 364–9.
19. Seymour RA, Hawkesford JE, Sykes J, Stillings M, Hill CM. An investigation into the comparative efficacy of soluble aspirin and solid paracetamol in postoperative pain after third molar surgery. Br Dent J 2003;194: 153–7.
20. Weil K, Hooper L, Afzal Z, Esposito M, Worthington HV, van Wijk A *et al*. Paracetamol for pain relief after surgical removal of wisdom teeth. Cochrane Database Syst Rev 2007;(3)CD004487.
21. Hahn TW, Mogensen T, Lund C. Analgesic effect of iv paracetamol: possible ceiling effect of paracetamol in postoperative pain. Acta Anaesth Scand 2003;47:138–45.

22. Miranda HF, Puig MM, Prieto JC, Pinardi G. Synergism between paracetamol and nonsteroidal anti-inflammatory drugs in experimental acute pain. Pain 2006;121:22–8.
23. Toms L, Derry S, Moore RA, McQuay HJ. Single does paracetamol (acetaminophen) with codeine for post-operative pain in adults. Cochrane Database Syst Rev 2009;(1)CD001547.
24. Kehlet H, Werner MU. Role of paracetamol in the acute pain management. Drugs 2003;63:15–22.
25. Joshi GP. Multimodal analgesia techniques for ambulatory surgery. Int Anesthes Clin 2005;43:215–18.
26. Chan AT, Manson JE, Albert CM. Nonsteroidal antiinflammatroy drugs, acetaminophen and risk of cardiovascular events. Circulation 2006;113:1578–87.
27. Larson AM, Polson J, Fontana RJ. Acetaminophen-induced acute liver failure: results of a United States multicentre prospective study. Hepatology 2005;42: 1364–72.
28. Dargan PJ, Wallace C, Jones AL. A flowchart for management of paracetamol poisoning. J Emerg Med 2002;19(3):202–5.
29. Prescott LF. Paracetamol, alcohol and the liver. Br J Clin Pharmacol 2000;49:291–301.
30. Thanacoody HK, Gray A, Dear JW, Coyle J, Sandilands EA, Webb DJ *et al*. Scottish and Newcastle Antiemetic Pre-treatment for paracetamol poisoning study (SNAP). BMC Pharmacol Toxicol 2013;14:20.
31. Joint Formulary Committee. British National Formulary, 65th edition. London: Brit Med Journal Group and Pharmaceutical Press of the Royal Pharmaceutical Society, 2013.
32. Coulthard P, Hill M, Frame JW, Barry H, Ridge D, Bacon TH. Pain control with paracetamol from a sustained release formulation and a standard release formulation after third molar surgery: a randomised control trial. Br Dent J 2001;191:319–24.
33. Coulthard P. Postoperative oral surgery pain: a review. Oral Surg 2009;1:167–77.
34. Cranswick N, Coghlan D. Paracetamol efficacy and safety in children: the first 40 years. Am J Ther 2000;7:135–41.
35. Temple AR. Pediatric dosing of acetaminophen. Pediatr Pharmacol 1983;3:321–7.
36. Anderson BJ. What we don't know about paracetamol in children. Paediatr Anaesth 1998;5:451–8.
37. Anderson BJ, Woolard GA, Holford NGH. Pharmacokinetics of rectal paracetamol after major surgery in children. Paediatr Anaesth 1995;5:237–42.
38. Werler M, Mitchel A, Hernandez-Diaz S, Honein M. Use of over-the-counter medications during pregnancy. Am J Obstet Gynecol 2005;193:771–7.
39. Headley J, Northstone K, Simmons H. Medication use during pregnancy: data from the Avon longitudinal study of parents and children. Eur J Clin Pharmacol 2004;60:355–61.
40. Moore RA, McQuay HJ. Single-patient data meta-analysis of 3453 postoperative patients: oral tramadol versus placebo, codeine, and combination analgesics. Pain 1997;69:287–94.
41. Moore RA, Collins S, Carroll D, McQuay H. Paracetamol with and without codeine in acute pain: a quantitative systematic review. Pain 1997;70:193–201.
42. Smith LA, Moore RA, McQay H, Gavaghan D. Using evidence from different sources: an example using paracetamol 1000mg plus codeine 60mg. BMC Med Res Methodol 2001;1:1.
43. Collins SL, Edwards JE, Moore RA, McQuay HJ. Single dose dextopropoxyphene, alone and with paracetamol (acetaminophen) for postoperative pain. Cochrane Database Syst Rev 2000;(2)CD001440.
44. Edwards JE, Moore RA, McQuay HJ. Single dose oxycodone and oxycodone plus paracetamol (acetaminophen) for acute postoperative pain. Cochrane Database Syst Rev 2000;(3)CD002763.
45. Hyllested M, Jones S, Pedersen JL, Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. Br J Anaesth 2002;88:199–214.
46. Bailey E, Worthington HV, van Wijk A, Yates JM, Coulthard P, Afzal Z. Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth. Cochrane Database Syst Rev 2004;(1)CD004624.