PARACETAMOL - A REVIEW OF THREE ROUTES OF ADMINISTRATION

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Paracetamol is used extensively in the treatment of both acute and chronic pain. Previously only manufactured for oral and rectal use, an IV formulation is now available. This article provides a short review of paracetamol as an analgesic and discusses the benefits of each route in the perioperative period.

Mechanism of Action

Although paracetamol was found to be an effective analgesic more than a century ago, its mechanism of action remains unclear and is the subject of continuing research. Unlike non-steroidal anti-inflammatory drugs (NSAIDs), whose analgesic and anti-inflammatory effects are thought to relate to their inhibition of the cyclooxygenase enzymes (COX-1 and COX-2), paracetamol is a weak anti-inflammatory agent with an abscence of COX-related adverse effects. Experimental studies show that paracetamol can inhibit both COX-1 and COX-2 in an environment where the ambient concentrations of arachidonic acid and peroxides are kept low. However, where extracellular concentrations of these two chemicals are high, in inflammatory conditions such as rheumatoid arthritis, paracetamol shows limited in vivo suppression of inflammation and platelet activity.[1]

It has been demonstrated that paracetamol may exert its analgesic effect via molecular targets distinct from COX. In the brain and spinal cord paracetamol is conjugated with arachidonic acid to form N-arachidonoylphenolamine (AM404).[2] AM404 is a known activator of the capsaicin receptor (TRPV1) and the cannabinoid CB1 receptor system both of which confer analgesia in the central nervous system. This pathway may also account for the antipyretic effect of paracetamol, known to be related to inhibition of prostaglandin production in the brain.[3] Cerebrospinal fluid levels of prostaglandin are shown to be high in rats during pyrogen induced fever, and these levels are reduced, along with the fever after paracetamol administration.[4] At this time, however, such a link remains speculative.

Analgesic Efficacy

There is good evidence to show paracetamol as an analgesic is effective and safe. A Cochrane systematic review of oral paracetamol use in acute postoperative pain analysing 47 studies, including 4186 patients, found the *number-needed-to-treat* (NNT) - see box - for at least 50% pain relief, over 4-6 hours was 3.8 (*95% confidence intervals:* 3.4-4.4).[5] There was no significant difference in the frequency of reported adverse effects between paracetamol and *placebo*. Side-effects after paracetamol use are rare, and usually mild and transient. At therapeutic doses paracetamol use is associated with an extremely low rate of liver dysfunction (less than 1 in 500000)[6] and there are only two contra-indications; paracetamol hypersensitivity and severe hepatocellular insufficiency. There are few known drug interactions and breast-feeding women may use paracetamol. Paracetamol has been shown to have a comparable benefit to ibuprofen and diclofenac in general and orthopaedic surgery[7] and can significantly reduce the opiate requirement postoperatively – it has an **opioid-sparing effect**.[8]

Number-needed-to-treat (NNT) – This gives the clinician an indication of the size of the treatment effect described by a clinical trial of a treatment. It tells the reader the number of patients that they would need to treat in order to see an effect in one patient.

95% confidence intervals – These give the reader of a study an indication of the reliability of the result of the study. If you repeated the study 100 times, 95 of the studies would give a result within these two confidence intervals. Larger studies tend to give narrower confidence intervals (i.e. results that more accurately represent reality). 95% (rather than a higher or lower figure) is a generally agreed acceptable level of certainty that a study result reflects a true treatment effect.

A **placebo** is a pharmacologically inert substance that may have a medical effect based solely on the power of suggestion. This is known as the placebo effect. By comparing drugs to a placebo, the pharmacological effects of the study drug are identified.

Route of Administration

Plasma concentrations of paracetamol between 10-20 mcg/ml are known to produce an antipyretic effect, but the concentrations required to provide analgesia are not well defined.[9] One study, in which 120 children were given oral or rectal paracetamol post tonsillectomy, concluded an effect site concentration of 10mcg/ml was needed to achieve pain scores of less than 4/10.[10] However, both higher and lower values than this have been suggested.[11,12] There are significant differences in the absorption of paracetamol, and therefore in the time to reach peak plasma levels, when it is given orally, rectally or intravenously. All three routes are able to achieve adequate plasma concentrations, but intravenous (IV) administration can achieve these levels in a shorter time.

Oral administration

Paracetamol is well absorbed from the gastrointestinal tract with low *first pass metabolism (see box)* in the liver, and *oral bioavailability* is estimated at 63-89%. Two recent trials have compared the administration of oral and intravenous paracetamol. In a study of 35 patients undergoing day-surgery, intravenous propacetamol (the IV *prodrug* of paracetamol) reached therapeutic plasma concentrations more quickly and predictably than oral paracetamol.[11]

Paracetamol plasma concentrations were observed for the first 80 minutes after administration of either 1g or 2g oral paracetamol or 2g intravenous propacetamol. Intravenous paracetamol provided an average concentration within the therapeutic range after 20 minutes. There was a large and unpredictable variability with oral administration; some patients who received 1g orally did not achieve detectable plasma levels within the 80 minute study period, and the average plasma concentration after receiving this dose was subtherapeutic throughout. 2g oral paracetamol achieved a median plasma concentration within the therapeutic range after 40 minutes, suggesting that when paracetamol is given orally, a loading dose can reduce the time needed to achieve therapeutic levels.

Clinically, this difference has been shown to lead to a faster onset of analgesia when paracetamol is given intravenously. Propacetamol infusion provided a significantly faster onset of analgesia than oral paracetomol, after 3rd molar surgery.[13] Intravenous propacetamol had a greatly reduced time until meaningful pain relief (8 minutes for propacetamol compared to 37 minutes for oral paracetamol) and maximal pain relief (15 minutes for propacetamol compared to 1 hour for oral paracetamol).

Rectal administration

Rectal absorption of paracetamol is more unpredictable, with a bioavailability between 24-98%. The variability in the rate and extent of absorption of suppositories is thought to be due to several factors. Regarding the formulation of the suppositories, lipophilic bases provide greater bioavailability than hydrophilic bases, and absorption is affected by the volume of the suppository, the number of suppositories used, and the particle size of the paracetamol.[14] Rectal pH may also influence the absorption of paracetamol, altering the degree of dissociation and therefore the ability of the drug to pass through biological membranes. In children, rectal pH can vary from 7.8-11.4, and in this range the degree of dissociation of paracetamol will vary from 2-99%.[15]

Several studies have shown that the time needed to achieve therapeutic plasma levels with rectal administration is significantly greater than with the oral or intravenous routes. In healthy adult volunteers given doses of 15 mg/kg, 25 mg/kg, 35 mg/kg and 45 mg/kg, only doses of 35 mg/kg and 45 mg/kg provided concentrations above the minimum therapeutic level of 10mcg/ml for a significant period of time (median 5.5 and 6 hours respectively).[16] A minimum duration of 1-2 hours was needed before this level was achieved. 15mg/kg failed to achieve a median plasma concentration above 10 mcg/ml at any time, while 25mg/kg achieved plasma concentrations at the lower end of the therapeutic range. A higher loading dose (45mg/kg) was not associated with a significantly greater risk of overdose, as the highest plasma concentration measured in the study was 25 mcg/ml, substantially less than the accepted toxic concentration of 120mcg/ml.

A study of the pharmacokinetics of paracetamol, after repeated rectal administration of 25mg/kg, 6 hourly, in 23 children following major surgery showed large variations in the absorption and resulting steady state concentrations.[15] The mean time to reach 90% of the steady state concentration was 11.4 hours.

In a randomised study of 48 patients admitted to ICU after cardiac surgery,[17] half received paracetamol as suppositories and half received intravenous injections. Mean plasma concentration peaked at 14.4mcg/ml within 20 minutes after intravenous administration of 1g, while after a 1g suppository, the mean plasma concentration at 80 minutes was 1.2mcg/ml. Stable plasma concentrations within the therapeutic range were not reached until after the 3rd rectal dose. Similarly, a study of oral and rectal paracetamol in 24 women following minor gynaecological laparoscopic surgery found that after the administration of 2g rectally, the mean plasma concentration at 4 hours was below the minimum analgesic level (8.4mcg/ml, range 4.2-16.3).[18]

There is some evidence to show that the delay in reaching therapeutic plasma levels may limit the usefulness of rectal paracetamol as analgesia in the immediate postoperative period. Hein et al performed

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First Pass Metabolism – A drug taken orally is absorbed through the intestine wall into the portal vein system and then delivered to the liver. It may therefore be partially metabolised in the liver before reaching its target site. Drugs given sublingually, intramuscularly or intravenously avoid first pass metabolism.

Oral Bioavailability – The fraction of an oral dose of a drug that reaches the systemic circulation, compared to the same dose given intravenously. Drugs given intravenously have 100% bioavailability.

A **prodrug** is the inactive form of a drug that is broken down by a body enzyme into its active form. This can provide a way of administering drugs that would otherwise be toxic if given systemically in the active form.

a randomised controlled, double-blinded trial involving 140 women undergoing elective termination of pregnancy.[19] Following surgery, patients were randomly allocated to receive either 1g paracetamol rectally, or a placebo suppository. There was no difference in postoperative pain scores between the 2 groups, and no difference in the need for additional analgesia or for time to discharge.

Intravenous administration

As well as being available for oral and rectal administration, paracetamol has previously been available for intravenous use in the form of its pro-drug, propacetamol. Used in France since 1985, propacetamol, provided as a powder for reconstitution, is water soluble and rapidly hydrolysed by plasma esterases to form paracetamol and diethylglycine; a dose of 1g propacetamol provides 0.5g paracetamol after hydrolysis.

The analgesic benefit of propacetamol is well recognised. In a double-blinded study of analgesia following gynaecological surgery, 200 women were randomised to receive either 2 intravenous doses of propacetamol 2g, or ketorolac 30mg, alongside morphine via a *patient-controlled analgesia (PCA)* system.[20] Patients were monitored for 12 hours and propacetamol was found to be comparable to ketorolac in terms of pain scores and reduction in morphine consumption. In a study of patients undergoing dental extraction, propacetamol was significantly better than placebo for all measured parameters; pain relief, pain intensity, patient's global evaluation and duration of analgesia.[13] Similarly propacetamol and diclofenac were found to be similarly effective and superior to placebo following total hip arthroplasty.[21] Although an effective analgesic, propacetamol has a relatively high incidence of adverse effects (up to 49% of patients will develop local pain at the injection site)[22] and there have been reports of contact dermatitis in health-care workers administering the drug.

Intravenous paracetamol (Perfalgan, Bristol-Myers Squibb) is formulated as a 10 mg/ml aqueous solution in 50ml and 100ml glass vials, for infusion over 15 minutes. Solubility is achieved through addition of the hydrophillic ingredients mannitol and disodium phosphate, while hydrolysis to 4-aminophenol, a toxic nitrogenous compound, is avoided by the addition of buffers to sustain neutral pH. Containment in glass vials prevents oxidation. Advantages of intravenous paracetamol over propacetamol are that it is available in a preformed solution, and it is not associated with pain on injection or contact dermatitis. Paracetamol is bioequivalent to propacetamol.[23]

A number of trials have shown comparable efficacy between intravenous paracetamol and propacetamol. Recently, two randomised, double-blinded placebo controlled trials of paracetamol analgesia, after major orthopaedic surgery and dental surgery, found no difference between intravenous paracetamol and propacetamol.[6,22] Both interventions were significantly superior to placebo for pain relief, time to morphine rescue, and overall morphine sparing. Both studies showed intravenous paracetamol to have a rate of adverse effects almost identical to that of placebo, and no cases of injection site reaction were reported.

> **Patient Controlled Analgesia** – An infusion pump filled with an opiate is connected to the patient via an intravenous drip. The pump can deliver a pre-set dose of analgesic (e.g. 1mg) on demand when the patient presses the PCA button. A lockout time (usually 5 minutes) is set when the pump is started, and during this period no further doses are given. This prevents the patient inadvertently overdosing.
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> **Bioequivalence** describes pharmaceutical compounds that are equal to each other in bioavailability and potency.

Cost[24]

Route of administration	Cost per 1g dose
Oral	£0.02
Intravenous	£1.50
Rectal	£1.98

Summary

The disproportionate cost, slow onset time and wide variation in bioavailability make rectal paracetamol less attractive in the presence of the intravenous formulation. Given the similar cost, intravenous paracetamol should be considered as a more effective alternative to suppositories, when oral dosing is not possible. It may also have a role to play when prompt analgesia is required and oral administration is not appropriate. Oral paracetamol is a simple well-tolerated analgesic; however a more generous loading dose is needed if meaningful early plasma concentrations are to be achieved. Intravenous paracetamol provides a method of achieving rapid therapeutic concentrations of paracetamol that can subsequently be maintained by oral absorption.

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BOOK REVIEW - OXFORD SPECIALIST HANDBOOKS IN ANAESTHESIA: PAEDIATRIC ANAESTHESIA

Edited by Edward Doyle

This small book is surprisingly comprehensive. It covers paediatric physiology, pharmacology and anatomy, the nuts and bolts of paediatric anaesthesia, including a thorough section on equipment, practical procedures and pain management, specific operations and problems. The section on specific procedures is well set out, with practical information on preoperative assessment, highlighting likely problems encountered in each patient population, advice on anaesthetic technique, including likelihood of pain and the postoperative course, with advice on analgesia and oral intake. The chapter on syndromes and conditions gives succinct advice on what is relevant to the anaesthetist, and includes both the common (such as cerebral palsy and diabetes) and the rare. It has useful advice on stabilising a child for transfer, with a handy checklist, and has the latest resuscitation guidelines. The book offers advice on paediatric fluids, but does not include the recent National Patient Safety Agency guidelines (see below), probably due to the lag time between writing and publication. The format of the book means that there is some repetition of information between chapters. However, overall I found this book useful and easy to read. It is relevant to the anaesthetist in district hospitals doing routine paediatric surgery, but also covers specialist surgery confined to specialist centres. It will therefore be useful to trainees undertaking a paediatric anaesthesia module. I suspect I shall end up carrying it around with me.

Further reading
The NPSA alert 22 on paediatric fluid management is available at: http://www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/intravenous-infusions/

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