Paracetamol: mechanisms and updates

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Key points

Paracetamol is an effective analgesic, especially when administered i.v., useful in a broad range of clinical conditions.

Its mechanism of action is yet to be fully determined, and is likely to involve a number of pain pathways.

Whilst its clinical significance may be equivocal, paracetamol may exert effects on virtually every organ system, warranting further research.

Toxicity may occur even within the recommended dose range in certain patient groups because of altered metabolism.

There have been a number of reports of paracetamol toxicity in children after the introduction of the i.v. formulation, prompting a recent update of the dosing guidelines by the Medicines and Healthcare products Regulatory Agency.

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Paracetamol was first synthesized in 1878 by Morse, and introduced for medical usage in 1883. However, due to misinterpretation of its safety profile, it enjoyed only limited use until the 1950s, when the chemically similar, and up until then preferred analgesic, phenacetin was withdrawn because of renal toxicity. Paracetamol is now probably the most commonly used drug worldwide, available over the counter, used in almost all ages, and forming Step 1 of the WHO analgesic ladder.

First-line treatment for pain and pyrexia, it plays an important role in multimodal analgesia,[1,2] and is considered to possess a generally excellent safety profile except in significant overdose, with few drug interactions. Oral and rectal administration can produce analgesia within 40 min, with maximal effect at 1 h, but large variations in bioavailability (ranging from 63 to 89% for oral, and 24 to 98% for rectally administered preparations) can make the onset and duration of action unpredictable. The introduction of its i.v. administered formulation within the last decade not only overcomes this issue of bioavailability that limits its speed of onset, but its ease of use when enteral administration is not possible has also cemented its position within virtually every anaesthetic/peroperative pain management plan. The onset of analgesia after i.v. paracetamol occurs within 5 min, peaking at 40–60 min, and lasting 4–6 h.[3]

Mechanisms of action

It is surprising that after more than 100 years, the exact mechanism of action of paracetamol remains to be determined. There is evidence for a number of central mechanisms, including effects on prostaglandin production, and on serotonergic, opioid, nitric oxide (NO), and cannabinoid pathways, and it is likely that a combination of interrelated pathways are in fact involved. A few of these are outlined below.[1, 4]

Prostaglandin inhibition

Paracetamol is termed a simple analgesic and an antipyretic. Despite enduring assertions that it acts by inhibition of cyclooxygenase (COX)-mediated production of prostaglandins, unlike non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol has been demonstrated not to reduce tissue inflammation. Two explanations have been put forward for this.

The enzyme responsible for the metabolism of arachidonic acid to the prostanoids (including prostaglandins and thromboxanes), commonly referred to as cyclooxygenase, is also more appropriately called prostaglandin H_2 synthetase (PGHS), and possesses two active sites: the COX and the peroxidase (POX) sites. The conversion from arachidonic acid to the prostanoids is in fact a two-stage process, requiring activity at the COX site to first produce the unstable intermediate hydroperoxide, prostaglandin G_2 (PGG_2), which is then converted to prostaglandin H_2 (PGH_2) via POX. The enzymatic activity of COX relies on its being in the oxidized form and it is suggested that paracetamol interferes indirectly with this by acting as a reducing co-substrate at the POX site. In intact cells, when levels of arachidonic acid are low, paracetamol is a potent inhibitor of PG synthesis, by blocking the physiological regeneration of POX. However, in broken cells, where the concentration of hydroperoxides is high, prostaglandin synthesis is only weakly inhibited. This peroxide-dependent COX inhibition explains the differential activity of paracetamol in the brain where peroxide concentrations are low, *vs* peripheral sites of inflammation with high peroxide levels (Fig. 1).

An alternative suggestion was that, unlike NSAIDS, which act on COX-1 and -2, paracetamol may act on a discrete COX-1 splice variant (initially thought to be a distinct isoenzyme, COX-3). This COX-1 variant was thought to be active in the central nervous system, rather than at the site of injured or inflamed tissue, such that inhibition by paracetamol here would explain its lack of anti-inflammatory and anti-platelet activity, whilst still affording it highly effective analgesic and antipyretic properties. However, the original work for this was performed on canine tissue, in which the COX-1 splice variant retains

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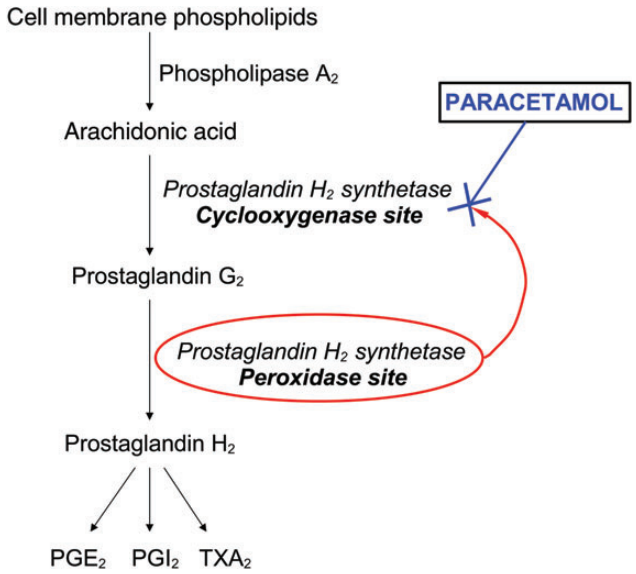

Fig 1 Role of paracetamol in inhibition of prostaglandin production.

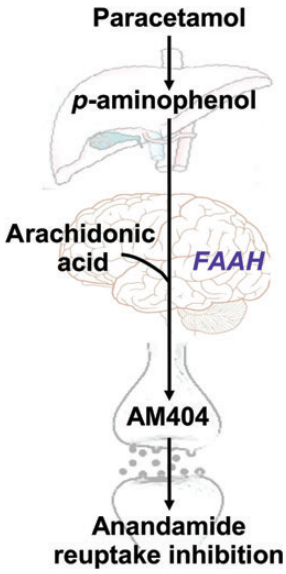

Fig 2 Conversion of paracetamol to AM404, an endocannabinoid reuptake inhibitor.

a COX-like action; in humans, however, the expressed protein has no role in the physiology of prostaglandins.[1, 4, 5]

Serotoninergic pathway activation

Serotonergic pathways are part of the descending pain system, originating in the brainstem nuclei, hypothalamus, and cortex, and interact with pain afferents in the dorsal horn. Serotonin receptors are present throughout the central nervous system, involved in a number of functions, including consciousness, mood, memory, and nausea and vomiting, the latter of which are mediated via the 5-HT_3-receptor subtype. It has become widely accepted that the activation of descending serotonergic pathways plays a key role in the action of paracetamol, and it has been demonstrated that the antinociceptive effects of paracetamol can be partially inhibited by co-administration of 5-HT_3-receptor antagonists, interestingly using anti-emetic drugs which are indeed frequently given together with paracetamol in the perioperative period.[5]

Endocannabinoid enhancement

In the presence of fatty acid amide hydrolase (FAAH), an enzyme found predominantly in the central nervous system, paracetamol (via an intermediary, *p*-aminophenol, formed in the liver) is conjugated with arachidonic acid to form the active metabolite, *N*-arachidonoylphenolamine (AM404). Analogous to the action of serotonin or norepinephrine reuptake inhibitors, AM404 inhibits the reuptake of the endocannabinoid, anandamide, from synaptic clefts, increasing cannabinoid receptor activation on the post-synaptic membrane. This would explain the experiences of relaxation, tranquility, and euphoria reported by many paracetamol users, apparently independent of analgesia.

AM404 appears to be a key player in a number of pain pathways. Apart from endocannabinoid reuptake inhibition, it has also been shown to activate transient receptor potential vanilloid type 1 (TRPV1) and inhibit cyclooxygenase, NO and tumour necrosis factor-alpha (TNF-α), all involved in acute and chronic pain states. The central production of AM404 would also account for the antipyretic effect of paracetamol, known to be related to inhibition of prostaglandin production in the brain, whilst still without peripheral actions (Fig. 2).

Efficacy

Paracetamol demonstrates efficacy comparable with that of standard equivalent doses of many NSAIDs (including ibuprofen, diclofenac, ketorolac, and parecoxib), tramadol, and 10 mg i.v. morphine, with fewer side-effects.[6] This applies across a variety of surgical procedures, as well as for other sources of acute and chronic pain such as musculoskeletal pain and headaches, including tension-type headache and migraine. As a component of a multimodal analgesic regime, it is generally considered to have useful opioid-sparing effects; a reduction in opioid consumption is mostly if not universally borne out with the statistical significance in clinical studies, but the addition of regular paracetamol invariably reduced pain scores and the incidence of nausea and vomiting, and improved patient satisfaction.[7]

It is a useful first-line drug, and works in synergy when combined with a number of other agents including ibuprofen, codeine, tramadol, and caffeine, improving analgesic efficacy whilst minimizing side-effects of the adjunct agent.

Although the onset of action of i.v. paracetamol is much faster compared with oral, a recent study showed no significant difference in overall efficacy between the two routes, as measured using pain

scores at 1 h after administration in patients having third molar extractions. This was, however in healthy, fasted individuals with presumed normal gastric emptying, undergoing daycase surgery, and results may not be readily extrapolated to other patient groups.[8]

Dose

The Medicines and Healthcare products Regulatory Agency (MHRA) licensed dose of paracetamol is the same for all routes of administration in adults over 50 kg (i.e. 1 g up to four times a day), with a minimum of 4 h between each administration (6 h for those with renal impairment, i.e. creatinine clearance $\leq$30 ml min^{-1}).

Despite its high lipid solubility and low protein binding, a weight-adjusted dosing regime has never been endorsed. However, in view of the pharmacokinetic data of paracetamol, a case has been made for a single loading dose of 2 g, followed by 4–6 hourly 1 g doses, and this has found its way into clinical practice over recent years. Studies comparing 2 g with 1 g loading doses for post-operative analgesia in otherwise healthy adult patients have demonstrated lower pain scores and greater duration of effective pain relief with no increase in side-effects or markers of toxicity.

Dosing in paediatrics

Up to 31 May 2010, 23 cases of accidental overdose with Perfalgan^{TM}, the most commonly used i.v. paracetamol formulation, had been reported worldwide in children under 1 yr old, one of which was fatal. In the UK, there have been seven reports of overdose in infants and neonates. In most of these cases, a 10-fold overdose was reported, most probably due to confusion between doses calculated in milligrams *vs* millilitres. Additionally, with administration of a 100% bioavailable drug, the differences in pharmacokinetics between the various stages of organ development, from neonate (particularly in those born prematurely) up to adolescence, affect plasma concentrations, and thus the risk of toxicity, far more than with enteral preparations.

To that end, in July 2010, the MHRA issued a Drug Safety Update and published new guidelines for dosing of i.v. paracetamol in neonates, infants, and children, echoed in the May 2013 guidelines published by the Royal College of Anaesthetists Safe Anaesthesia Liaison Group. In summary, the dose in children weighing $\leq$10 kg: 7.5 mg kg^{-1}; $>$10 kg: 15 mg kg^{-1} (Table 1).

Table 1 MHRA guidelines for i.v. paracetamol dosing in children

	Dose per administration	Max. daily dose
Term newborn infants, up to children $<$10 kg	7.5 mg kg^{-1}	30 mg kg^{-1}
Weight 10–33 kg	15 mg kg^{-1}	60 mg kg^{-1} up to max. 2 g
Weight 33–50 kg	15 mg kg^{-1}	60 mg kg^{-1} (max. 3 g)
Weight $>$50 kg	1 g	4 g

Pharmacokinetics

Oral paracetamol is absorbed, mainly from the small bowel, by passive transport, and has high, though variable, bioavailability. It is metabolized in the liver, predominantly by glucuronidation and sulphation to non-toxic conjugates, but a small amount is also oxidised via the cytochrome P450 enzyme system to form the highly toxic metabolite, *N*-acetyl-*p*-benzo-quinone imine (NAPQI). Under normal conditions, NAPQI is detoxified by conjugation with glutathione to form cysteine and mercapturatic acid conjugates, which are then renally excreted. However, when there is insufficient glutathione (e.g. in paracetamol overdose), or a glutathione deficiency, NAPQI reacts with cellular membrane molecules, causing acute hepatic necrosis.

Several forms of P450 in humans have been shown to catalyse the oxidation of paracetamol to NAPQI, at least one of which, CYP-2D6, is subject to genetic polymorphism and can contribute to significantly differing rates of production of NAPQI. Thus a CYP-2D6 ultra-rapid and extensive metabolizer is at higher risk of developing toxicity than a slow metabolizer.

Although the product information does not recommend any dose adjustment in the elderly, as pharmacokinetics of paracetamol are not specifically modified, glutathione stores may be low in certain patient groups and conditions, including the elderly, infants, and in starvation or malabsorption, etc., causing a predisposition to toxicity, and may warrant dose reduction.

In cases of severe renal impairment (creatinine clearance 10–30 ml min^{-1}), the elimination of paracetamol is slightly delayed; elimination of the glucuronide and sulphate conjugates is three times slower compared with healthy subjects. Whilst this does not preclude the use of paracetamol, the interval between doses should be a minimum of 6 h.

Peripartum drug handling

Paracetamol is safe for use in pregnancy and lactation, with only a negligible amount of the drug reaching breast milk. Interestingly, the total clearance of paracetamol has been demonstrated to be higher in women at delivery (including by Caesarean section) compared with 10–15 weeks postpartum, which itself was significantly lower than in the normal healthy volunteer population data. The increased total paracetamol clearance at delivery is attributed to a disproportionate increase in glucuronidation clearance and a proportional increase in both its oxidation clearance and of unchanged paracetamol.

Drug interactions

Interaction with a variety of other drugs may occur, and warrant caution in co-administration. For example, concomitant intake of enzyme-inducing substances, such as carbamazepine, phenytoin, or barbiturates, as well as chronic alcohol excess, may increase NAPQI production and the risk of paracetamol toxicity. Concurrent use with isoniazid also increases the risk of toxicity, though as an enzyme inhibitor, the mechanism is not entirely clear.

Concomitant use of paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations in INR values. Increased monitoring of INR should be conducted during the period

Table 2 Drug interactions with paracetamol

- Paracetamol absorption is increased by substances that increase gastric emptying (e.g. metoclopramide)
- Paracetamol absorption is decreased by substances that decrease gastric emptying (e.g. anticholinergic agents, and opioids)
- Cholestyramine (ion-exchange resin) reduces the absorption of paracetamol if given within 1 h of paracetamol
- Caution with concomitant intake of enzyme-inducing substances, such as carbamazepine, phenytoin, or barbiturates, or isoniazid, may increase the risk of paracetamol toxicity
- Probenecid causes an almost two-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the paracetamol dose should be considered for concomitant treatment with probenecid
- Salicylamide (analgesic and antipyretic) may prolong the elimination half life of paracetamol
- Concomitant use of paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values
- Paracetamol may also increase chloramphenicol concentrations

of concomitant use as well as for 1 week after paracetamol treatment has been discontinued (Table 2).

Toxicity

Although generally safe, potentially fatal kidney, brain, and liver damage may be caused by acute overdose of paracetamol, and in rare individuals, even after a therapeutic dose, attributable perhaps to the presence of subclinical risk factors such as 'fast-metabolizer' status, glutathione deficiency or both.

However, usage within the therapeutic range, particularly frequent regular use, can also impact on other organ systems, with effects that are less widely acknowledged.

Hepatic

Paracetamol toxicity is the foremost cause of acute liver failure and accounts for most drug overdoses in the UK, USA, Australia, and New Zealand. Paracetamol overdose is the most common and predictable cause, but, in certain individuals, hepatotoxicity may occur with doses within the therapeutic range. This may be secondary to deficiencies in glutathione, because of inadequate nutrition, P450 enzyme induction by chronic alcohol excess, or concomitant use of other drugs.

Paracetamol has, in fact, been shown to be well tolerated in hepatocellular insufficiency and even cirrhosis within the normal recommended dose range, albeit cautiously.

Renal

In general, paracetamol is thought to have only minor effects on renal function, of no clinical relevance in the vast majority of patients. Rare effects have included acute renal failure, acute tubular necrosis, and interstitial nephritis, but these are usually observed after either acute overdose, chronic abuse (often with multiple analgesics), or in association with paracetamol-related hepatotoxicity; that said, acute tubular necrosis has been observed as an isolated finding in rare cases.

There has been equivocal data regarding whether moderate to long-term use may increase the risk of end-stage renal disease. The mechanism of damage is thought, yet again, to involve the depletion of glutathione—a known anti-oxidant, rendering renal cells particularly sensitive to oxidative damage. Optimizing hydration and nutrition status is therefore of specific relevance in those receiving regular paracetamol.

GI effects

Paracetamol can be associated with non-specific gastrointestinal symptoms, such as nausea and vomiting, dyspepsia, abdominal pain, and bloating. In two large studies in patients with musculoskeletal pain, paracetamol was, in fact, associated with more 'digestive adverse effects' than ibuprofen after 6–14 days of regular oral use, though far less than with diclofenac. These effects, however, were mostly abdominal pain and some nausea, and led to no further complications.

Rarely, cases of acute pancreatitis have been reported, and one study has suggested that acetaminophen may precipitate acute biliary pain and cholestasis, possibly related to inhibition of prostaglandin and alterations in the regulation of the sphincter of Oddi.

Haemodynamic changes

Although also rare, hypotension is a recognized adverse effect, listed in the product information of paracetamol. The limited evidence on the subject would suggest that adults and neonates in a critical care setting, who are either febrile or have pre-existing low blood pressure, may have increased susceptibility to a period of hypotension after either enteral or i.v. paracetamol. Whilst often only modest and brief, a proportion of these hypotensive episodes did require supportive intervention, although no long-term sequelae were reported. In adult patients, the hypotension was associated with increased skin blood flow, consistent with its antipyretic action; these effects were not demonstrated in healthy afebrile volunteers, or in elective surgical patients when given paracetamol perioperatively.[9,10]

Conversely, regular use of oral paracetamol has been linked with a raised blood pressure. Whilst much of these data come from retrospective observational studies, results from two small randomized, placebo-controlled crossover trials conducted in patients with known coronary artery disease or treated hypertension suggest that after as little as 2 weeks of paracetamol at submaximal doses of 1 g three times a day, heart rate and blood pressure may show statistically, though perhaps not clinically, significant rises.

Respiratory effects

Although most certainly not an NSAID, paracetamol itself may be causally linked with the development of asthma. There has been mounting evidence since 2000 of an association between asthma and paracetamol usage, so strong that it is thought by some to have contributed to much of the dramatic increase in childhood asthma over the past 30 years. The product information for some commercial

preparations of paracetamol itself include in their list of possible adverse effects, difficulty breathing, and bronchospasm in patients having a tendency of analgesic asthma.

Aside from its role in detoxifiying paracetamol in the liver, glutathione is a pulmonary antioxidant, which may limit airway inflammation in asthma. Consistent with findings in animal and *in vitro* studies that paracetamol may deplete the lung of glutathione, a plethora of, largely epidemiological, data are strongly suggestive that frequent paracetamol usage may be a direct risk factor for wheezing, rhinitis, and asthma morbidity in adults and children.[11]

Cognitive effects

Paracetamol is almost universally acknowledged as the 'non-drowsy' painkiller, and there is no literature to support claims of associated alterations in consciousness in humans. However, there are many anecdotal reports of euphoria or sleepiness (particularly in children and the elderly—groups in which metabolism may be reduced), after paracetamol, even in the absence of pain or pyrexia.[5] As paracetamol is not a known member of any sedative drug group, these experiences are usually dismissed as because of either placebo effect, co-administration with another drug, or pain-relief allowing the user to relax. However, the mechanism of action of paracetamol remains to be determined; pathways gaining credence include the serotonergic and endocannabinoid systems, both of which are intrinsically involved in consciousness and cognitive function. With this in mind, and on the background of some animal studies that have demonstrated some memory impairment after high-dose paracetamol, this may be an avenue for further research.[12]

Haematological/oncological effects

Thrombocytopenia, leucopenia, and neutropenia are listed as very rare ($<$1/10 000) adverse-effects. Acute thrombocytopenia has also been reported as having been caused by sensitivity to acetaminophen glucuronide. Methaemoglobinemia with resulting cyanosis has been observed in the setting of acute overdose.

Looking at more long-term effects, one prospective cohort study of almost 64 000 men and women aged 50–76 yr showed an association between 'high use' of acetaminophen (defined as use on $\geq$4 days week^{-1} for $\geq$4 yr) and an almost two-fold increased risk of incident haematologic malignancies, that was not shared by NSAIDs. These included myeloid neoplasms, non-Hodgkin's lymphoma, and plasma cell disorders, but not chronic lymphocytic leukaemia or small lymphocytic lymphoma.

Somewhat in contrast to this, a protective effect of paracetamol in the development of ovarian cancer has been suggested. A meta-analysis of eight prospective observational studies to include data from over 746 000 patients showed that 'regular use' (definitions varying from use on 4 or more days each month for more than 6 months, to more than once a day for a year) was associated with a statistically significant 30% reduction in the risk of developing ovarian cancer compared with non-use.

The mechanisms of these proposed effects are unknown, and the role of any number of confounding factors cannot be excluded.

Dermatological effects

Pain or a burning sensation may be experienced at the injection site after i.v. administration and 100 ml volume should be infused over 15 min, but whilst uncomfortable, this is short-lived, and does not preclude further administration. The incidence of hypersensitivity is very rare ($<$1/10 000), reactions ranging from simple skin rash or urticaria to anaphylactic shock.

A range of other, extremely rare, dermatological effects have been reported, from the non-specific and transitory, such as erythema, flushing, peripheral oedema and pruritus, to severe, life-threatening conditions such as bullous erythema, purpura fulminans, toxic epidermal necrolysis (TEN), Stevens–Johnson syndrome (SJS), and acute generalized exanthematous pustulosis.

Headache

Paracetamol is effective in the management of tension-type headache and migraine, though not for cluster headaches. In a meta-analysis of six studies, paracetamol was equianalgesic to low-dose NSAIDs in the treatment of tension-type headache. A combination of paracetamol and caffeine has also been shown to be equivalent to sumatriptan in the acute treatment of migraine.[13]

However, although useful in the treatment of headaches, paracetamol may also contribute to the development of medication overuse headache attributed to excessive ingestion of analgesic agents for relief of other causes of chronic pain, including tension-type headache and migraine. Paracetamol is considered 'overused' when taken on more than 15 days of each month for more than 3 months.

Novel uses

Aside from its well-established analgesic and antipyretic effects, the i.v. preparation has found more novel uses as demonstrated in prospective, randomized, placebo-controlled studies in recent years.

When administered before induction of anaesthesia, 1 g i.v. paracetamol was found to be equally successful to ketamine (0.5 mg kg^{-1} bolus before induction, followed by 5 μg kg^{-1} min^{-1}) in preventing remifentanil-induced hyperalgesia, with the added advantage of reduced time to extubation and full anaesthetic recovery.[14]

During i.v. regional anaesthesia, adding paracetamol to the injected lidocaine was shown to improve the overall quality of the block. Onset of motor block was sooner, tourniquet pain was reduced, and recovery of motor and sensory block was delayed, resulting in lower intraoperative pain scores and total systemic analgesic requirements.[15] In view of the overall consensus that paracetamol's actions are centrally mediated, an analgesic benefit conferred from its addition to a peripherally sequestered pool of drug is a surprising finding.

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Please see multiple choice questions 5–8.