Review Article บทฟื้นฟูวิชาการ

A Quick Dive into Perioperative Use of Paracetamol

Suraj Kafley, Sasikaan Nimmaanrat, Arpawan Thepsuwan
Department of Anesthesiology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand

Abstract

Paracetamol (acetaminophen) is commonly used worldwide for the management of fever and pain. It has also been administered via multiple routes in the perioperative period. Paracetamol is an effective component of multimodal analgesia. In addition to patient-specific considerations when using paracetamol, both economic and environmental factors should also be taken into account when selecting the most appropriate route of administration in perioperative care. This approach can enhance cost-efficiency and support environmental sustainability, while maintaining optimal patient care and effective pain management.

Key words: acetaminophen, paracetamol, perioperative

Paracetamol (Acetaminophen), an aniline derivative, was first synthesized by Morse in 1878. Its initial clinical application was documented in 1887 by von Mering. However, its use remained limited due to the preference for phenacetin. In the 1950s, phenacetin was discontinued due to its nephrotoxic, hematotoxic, and psychotropic effects. Consequently, paracetamol reemerged as a widely used analgesic, with its prevalence increasing significantly by the 1970s.[1]

Pharmacokinetics

The pharmacokinetics of paracetamol are as follows. Paracetamol is absorbed primarily in the proximal small intestine through passive diffusion. First-pass hepatic metabolism is relatively minor, with a hepatic extraction ratio ranging from 0.11-0.37 in adults, and an oral bioavailability of 60-89%.[2] Several factors can influence its absorption. Absorption is reduced by coadministration with food[3,4], decreased gastric emptying such as that observed during pregnancy[5], and the use of morphine.[6] Conversely, factors that enhance absorption include caffeine intake[7] and drugs that promote gastric emptying.[8] Notably, preoperative pain, stress, and age do not significantly impact paracetamol absorption.[9] Rectal absorption of paracetamol is highly variable, with bioavailability ranging from 24-98%.[10] This variability is influenced by factors such as the formulation, size, and number of suppositories, differences among

Correspondence to: Sasikaan Nimmaanrat, E-mail: snimmaanrat@yahoo.com.au
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manufacturers, and rectal pH.[11]

The volume of distribution of paracetamol ranges from 1-2 L/kg in adults and 0.7-1 L/kg in children. Paracetamol is non-ionized at physiological pH and can freely cross the placenta and the blood-brain barrier. At equilibrium, plasma and tissue concentrations are equal across all tissues except for fat and cerebrospinal fluid (CSF), with a CSF-to-plasma partition coefficient of approximately 1.18.[1]

Protein binding is minimal, typically less than 5%, and ranges from approximately 8-43% when plasma concentrations are below 60 mcg/mL, below 90 mcg/mL, and at toxic plasma concentrations of 250 mcg/mL, respectively.[12] The minimal plasma concentration required for analgesic and antipyretic effects is 10 mcg/mL, with a therapeutic range of 10-20 mcg/mL. A plasma concentration of 150 mcg/mL is considered the threshold for hepatotoxicity.[13] The onset of analgesic activity occurs within 30 minutes following oral administration in fasted subjects. The duration of analgesic effect is approximately 4 h.[14] The time to peak plasma concentration is approximately 30, 45-60, and 60-120 min after oral administration in liquid form, regular oral form, and extended-release oral form, respectively.[3] The time to peak plasma concentration for rectal doses ranges from 107-288 min.[17] To achieve a therapeutic plasma concentration, the recommended dosage for rectal administration in children is 40 mg/kg.[18] However, a dosage of 45 mg/kg may result in a mean peak plasma concentration of 13 mcg/mL.[19]

In adults, approximately 25% of paracetamol undergoes first-pass hepatic metabolism. Paracetamol is extensively metabolized in the liver through glucuronide conjugation (60-67%), sulfate conjugation (20-46%), and cysteine conjugation (3%) into non-toxic metabolites, facilitated by the enzymes UDP-glucuronosyl-transferase and sulfotransferase.[20] Sulfate conjugation is the predominant form of conjugation in newborns and infants.[1] The conjugation process into inactive metabolites is saturable, primarily due to co-substrate depletion.[21] Approximately 5-15% of paracetamol undergoes oxidation via the cytochrome P450 system (CYP2E1, CYP1A2, CYP3A4, and CYP2A6), resulting in the formation of a highly reactive metabolite, N-acetyl-p-benzoquinoneimine (NAPQI).[1] NAPQI is conjugated with glutathione, facilitated by the enzyme glutathione-S-transferase, forming non-toxic cysteine or mercaptate conjugates, which are subsequently eliminated in the urine.[1,20]

In rat models, paracetamol undergoes deacetylation in the liver to form p-aminophenol. P-aminophenol is conjugated with arachidonic acid to form N-arachidonoyl-phenolamine (AM404) with the help of enzyme fatty acid amide hydrolase (FAAH). This conjugation takes place in brain, spinal cord and dorsal root ganglia. AM404 action is one of the hypothesized mechanisms of analgesia and antipyresis of paracetamol.[1]

The kidney plays a primary role in the elimination process. However, a complex transport of substrates occurs between the kidney, liver, and intestine before final excretion in the urine, with a urinary clearance of 13.5 L/h.[20] Only 1-4% of paracetamol is excreted unchanged in the urine.[1] The elimination

half-life is 2-4 hours in adults, 4-5 h in newborns, and 11 h in premature infants.[1] The half-life is reduced by 40-50% in patients undergoing hemodialysis, but not in those undergoing peritoneal dialysis.[22]

Mechanism of action

The exact mechanism of action of paracetamol is still unknown, although multiple theories have been proposed. Various mechanisms could be involved in the action of paracetamol, including its effects on TRP channels, the endocannabinoid system, the serotonergic system, Kv7 potassium channels, CaV3.2 calcium channels, or a protein variant of COX-1.[23]

Transient receptor potential (TRP) channels: Paracetamol is metabolized in the liver to p-aminophenol, which is further converted into N-acetylphenolamine (AM404) by fatty acid amide hydrolase in the brain. AM404 acts on the transient receptor potential vanilloid-1 (TRPV1) channel at supraspinal levels to produce an analgesic effect. Mice in which TRPV1 has been abolished by the injection of capsazepine, a TRPV1 antagonist, show an absence of analgesic effects following the administration of AM404. The analgesic and antipyretic effects of paracetamol are also mediated through the activation of transient receptor potential ankyrin 1 (TRPA1) channel in nociceptive sensory neurons. TRPA1 channels are activated by N-acetyl-p-benzoquinoneimine (NAPQI) and p-benzoquinone (p-BQ), both metabolites of paracetamol. The antipyretic effect of NAPQI was absent in mice treated with TRPA1 antagonists.[23]

Cav3.2 calcium channels: Cav3.2 T-type calcium channels play a role in pain perception within the central nervous system (CNS). AM404, due to its lipoamino acid structure, can interact with these channels in the brain but not in the spinal cord, contributing to the analgesic effects of paracetamol.[23]

Nitric oxide pathway: Paracetamol is believed to inhibit the activation of spinal N-methyl-D-aspartate receptors (NMDARs) by painful stimuli and release of neurotransmitter nitric oxide (NO) leading to analgesic effect.[23]

Kv7 potassium channels: Paracetamol metabolite, NAPQI, enhances Kv7.2 and Kv7.3 potassium channel activity in dorsal root ganglion and spinal dorsal horn neurons, leading to analgesic and anticonvulsant effects. Additionally, NAPQI reduces arterial tone, resulting in a decrease in arterial blood pressure. This mechanism may explain the transient drop in blood pressure observed during intravenous administration of paracetamol.[23]

Inhibition of cyclooxygenase activity: Paracetamol primarily inhibits the peroxidase activity of cyclooxygenase (COX) isoenzymes, mainly COX-2, but with limited clinical effect. Another COX isoenzyme, COX-3, discovered in canines, is highly sensitive to inhibition by paracetamol. However, no significant clinical effects have been observed from paracetamol's inhibition of COX-3 isoenzymes in humans. Therefore, COX isoenzyme inhibition is not considered the primary mechanism behind the analgesic effects of paracetamol.[23]

Activation of cannabinoid 1 receptors: Paracetamol metabolite, AM404, increases the

concentration of the endocannabinoids N-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG) in the brain by inhibiting anandamide reuptake into brain cells. These endocannabinoids activate cannabinoid type 1 (CB1) receptors, primarily in the rostral ventromedial medulla (RVM), leading to the inhibition of GABA release in the brain. This, in turn, suppresses the activity of descending serotonergic fibers from the RVM to the spinal cord, resulting in analgesia. The role of CB1 receptors in this mechanism is supported by the loss of analgesic effects in mice lacking these receptors.[23]

Unwanted events

Drug interactions: Several studies have reported pharmacokinetic interactions between paracetamol and warfarin. Paracetamol competes with the metabolism of R-warfarin via CYP1A2 and CYP3A4, leading to the inhibition of CYP2C9, the enzyme responsible for metabolizing S-warfarin. This results in increased S-warfarin levels, causing a slight increase in INR.[24,25] Additionally, hepatotoxicity has been reported with drugs that induce cytochrome P450, such as rifampicin and carbamazepine. However, a review has not demonstrated a significantly increased risk when paracetamol is used alongside these enzyme inducers.[26]

Adverse effects: Paracetamol is well tolerated, and adverse reactions are rare.[13] Reports of adverse effects include gastrointestinal complaints and hypersensitivity reactions. However, systematic reviews have found no significant difference in the rates of adverse events when compared to placebo.[27,29]

Toxicity: Hepatotoxicity is rare within therapeutic dosing, even in individuals with chronic liver disease or conditions associated with reduced glutathione stores, such as malnutrition, hepatitis C, cirrhosis, or HIV. There is no evidence of hepatotoxicity when paracetamol is used at therapeutic doses alongside alcohol consumption.[13] Hepatotoxicity can occur at doses exceeding 150 mg/kg. Under normal therapeutic conditions, glutathione supply is sufficient to detoxify NAPQI. However, in cases of overdose, the rate and quantity of NAPQI formation can surpass available glutathione stores. Excess NAPQI leads to cell death through oxidation of enzymes, DNA fragmentation, and mitochondrial injury.[1]

Paracetamol toxicity progresses through four stages:

Stage I (≤ 24 h post-ingestion): Nonspecific symptoms such as anorexia, nausea, vomiting, and malaise.

Stage II (24-48 h post-ingestion): Onset of liver injury, marked by a rise in AST levels.

Stage III (3-4 days post-ingestion): Peak hepatotoxicity, characterized by jaundice, fulminant hepatitis, multi-organ failure, or even death.

Stage IV (4-11 days post-ingestion): Recovery phase for individuals who survive Stage III.

The antidote for paracetamol toxicity is N-acetylcysteine (NAC). When administered early (within 8-10 h of overdose), NAC increases available glutathione, allowing it to bind with NAPQI by acting as both a glutathione precursor and substitute.[1]

Dosage

The therapeutic dosage for analgesia in adults is 10-15 mg/kg. For rectal administration, a loading dose of 30-40 mg/kg followed by 15-20 mg/kg every 4-6 h is recommended. The maximum daily dosage should not exceed 4 g/day.[1] In cases of severe liver disease, the dosage should be reduced, as the elimination half-life may be prolonged.[13]

Efficacy of perioperative paracetamol

The efficacy of paracetamol in postoperative pain management has been extensively evaluated in clinical studies. Its effectiveness is demonstrated through several key outcomes, including pain reduction, time to first rescue analgesic, decreased opioid consumption, and a reduction in opioid-related adverse effects. The use of paracetamol as part of a multimodal analgesic regimen has been shown to enhance pain control while minimizing the need for stronger analgesics, thereby improving overall patient recovery and safety.

Comparison of oral, intravenous, and rectal routes of paracetamol administration versus placebo

Oral paracetamol

A systematic review from the Cochrane Database, analyzing 51 studies with a total of 5,762 patients, evaluated the efficacy of a single dose of oral paracetamol for postoperative pain management in adults. The findings indicated that 500 mg of oral paracetamol was approximately twice as effective as placebo in achieving at least 50% pain relief over a period of 4-6 h, with a risk ratio (RR) of 1.91 (95% CI: 1.57-2.32; $P < 0.001$). A higher single dose of oral paracetamol (975-1000 mg) demonstrated an even greater effect compared to placebo, with a risk ratio of 2.67 (95% CI: 2.36-3.02; $P < 0.001$). However, the number needed to treat (NNT) for achieving at least 50% pain relief remained similar between the two doses, with an NNT of 3.5 (95% CI: 2.7-4.8) for 500 mg and 3.6 (95% CI: 3.2-4.1) for 975-1000 mg, suggesting no clear dose-response relationship for a single dose of oral paracetamol.[27]

Comparative analyses indicate that nonsteroidal anti-inflammatory drugs (NSAIDs) provide superior pain relief compared to oral paracetamol. The NNT for achieving 50% pain relief was lower for NSAIDs, with values of 1.6 for etoricoxib 120 mg, 1.8 for diclofenac 100 mg, 2.5 for ibuprofen 400 mg, 2.6 for ketorolac 10 mg, and 2.7 for naproxen 400 mg, in contrast to an NNT of 3.8 for 1000 mg of oral paracetamol.[28]

Patients who received oral paracetamol required less rescue analgesic within 4-6 hours postoperatively compared to those receiving placebo. The RR for the need for rescue analgesic was 0.56 (95% CI: 0.45-0.69; $P < 0.001$) for 500 mg and 0.76 (95% CI: 0.68-0.77; $P < 0.001$) for 975-1000 mg of oral paracetamol. Similar to the outcome of achieving at least 50% pain relief, no clear dose-response relationship was observed between the different doses of paracetamol regarding the need for rescue analgesic. This was evidenced

by the overlapping 95% confidence intervals for the NNT, which were 3.6 (95% CI: 3.0-6.0) for 500 mg and 5.2 (95% CI: 4.3-6.7) for 975-1000 mg. Additionally, the weighted mean time to first rescue analgesic was longer for oral paracetamol (3.8 h) compared to placebo (2.9 h), suggesting prolonged analgesic efficacy with paracetamol administration.[27]

In terms of safety, the incidence of adverse events did not differ significantly between patients receiving oral paracetamol and those given placebo. The risk ratio for adverse events was 1.12 (95% CI: 0.97-1.29; $P = 0.12$), indicating no statistically significant increase in side effects associated with oral paracetamol use.[27]

Intravenous paracetamol

A Cochrane systematic review analyzing 72 studies with 7,200 patients evaluated the efficacy of a single dose of intravenous (IV) paracetamol for postoperative pain management in adults. The findings demonstrated that IV paracetamol provided superior pain relief compared to placebo, achieving at least 50% pain relief over both 4 h (RR: 4.8; 95% CI: 2.3-10.0; $P < 0.001$) and 6 h (RR: 3.7; 95% CI: 2.2-6.2; $P < 0.001$) postoperatively.[29]

Patients who received IV paracetamol required fewer rescue analgesics compared to those given placebo, with a risk ratio of 0.75 (95% CI: 0.7-0.8; $P < 0.001$). Additionally, the time to first rescue analgesic was significantly prolonged in the IV paracetamol group, with a mean difference of 5.78 h (95% CI: 3.9-7.7; $P < 0.001$) compared to placebo. IV paracetamol also demonstrated opioid-sparing effects, reducing opioid consumption by 26% at 4 h and 16% at 6 h postoperatively. The mean difference in opioid consumption was -1.33 (95% CI: -1.8 to -0.9; $P < 0.001$) at 4 h and -1.83 (95% CI: -2.4 to -1.3; $P < 0.001$) at 6 h, indicating a significant reduction in opioid requirements. These findings suggest that IV paracetamol not only improves postoperative pain control but also decreases opioid use, potentially minimizing opioid-related adverse effects.[29]

Similar to oral paracetamol, IV paracetamol did not show a significant difference in the incidence of adverse events compared to placebo. The risk ratio for adverse events was 1.06 (95% CI: 0.9-1.2; $P = 0.39$), indicating that IV paracetamol is well-tolerated and does not increase the risk of adverse effects in postoperative patients.[29] These findings support the safety of IV paracetamol as an effective analgesic option with a favorable side effect profile.

Rectal paracetamol

There is limited literature directly comparing the efficacy of rectal paracetamol with the oral and intravenous routes. A systematic review of 24 randomized controlled trials (RCTs) involving 2,023 patients, including 7 RCTs that evaluated rectal paracetamol, found that its use led to a reduction in postoperative pain scores for up to 8 h and decreased opioid consumption compared to placebo.[30] However, the review did not include direct comparisons of time to rescue analgesic or adverse effects between rectal paracetamol and placebo, leaving gaps in understanding its full clinical impact.

Comparison of oral, intravenous, and rectal routes of paracetamol

A meta-analysis of 14 RCTs involving 1,695 patients compared the perioperative efficacy of oral versus intravenous paracetamol. The analysis showed no significant differences in postoperative pain scores between the two routes at various time intervals postoperatively. The standardized mean differences (SMD) were as follows:

• 0-2 h: SMD = -0.17 (95% CI: -0.45 to 0.10; *P* = 0.22)

• 2-6 h: SMD = -0.09 (95% CI: -0.24 to 0.06; *P* = 0.25)

• 6-24 h: SMD = 0.06 (95% CI: -0.12 to 0.23; *P* = 0.52)

• 24 h: SMD = 0.03 (95% CI: -0.22 to 0.28; *P* = 0.83)

This meta-analysis also found that postoperative opioid consumption and time to rescue analgesic were not significantly different between the oral and intravenous paracetamol groups. The mean differences were:

• Opioid consumption: -0.13 (95% CI: -1.75 to 1.49; *P* = 0.87)

• Time to rescue analgesic: -0.19 (95% CI: -4.20 to 3.82; *P* = 0.93)

Furthermore, the incidence of postoperative nausea and vomiting did not significantly differ between the two groups, with an odds ratio of 0.98 (95% CI: 0.72-1.33; *P* = 0.87), indicating a similar safety profile.[31]

Another meta-analysis that included RCTs and retrospective studies involving 1,573 patients found no significant differences in postoperative pain scores between oral and IV paracetamol at equivalent doses. The mean differences in pain scores were as follows:

• At 2 h: -0.14 (95% CI: -0.58 to 0.29; *P* = 0.51)

• At 24 h: 0.09 (95% CI: -0.02 to 0.21; *P* = 0.12)

• At 48 h: 0.04 (95% CI: -0.08 to 0.16; *P* = 0.52) The time to rescue analgesic was also not significantly different between the two groups, with a mean difference of -0.58 (95% CI: -5.51 to 2.35; *P* = 0.43). However, opioid consumption and side effects were not analyzed in this study, leaving those outcomes unexamined in this comparison.[32]

Direct comparisons of oral, IV, and rectal routes of paracetamol are limited, particularly in adult populations, as the rectal route is more commonly used in pediatric surgeries. A systematic review of 14 RCTs involving 829 pediatric patients compared the efficacy of the three paracetamol routes for postoperative analgesia.

• At 0-2 h, there were significant differences in pain scores between the routes:

- Oral vs. IV: Mean difference of -0.60 (95% CI: -1.20 to 0.01; *P* = 0.99)

- Rectal vs. IV: Mean difference of -0.28 (95% CI: -0.62 to 0.06; *P* = 0.49)

- Oral vs. Rectal: Oral paracetamol provided better pain scores than rectal, with a mean difference of -0.88 (95% CI: -1.44 to -0.31; *P* = 0.03).

• At 0-6 hours, no significant differences were found between the three routes:

- Oral vs. IV: Mean difference of -0.54 (95% CI: -1.20 to 0.01; *P* = 0.99)

- Oral vs. Rectal: Mean difference of -0.53

(95% CI: -1.26 to 0.19; *P* = 0.29)

- IV vs. Rectal: Mean difference of 0 (95% CI: -0.48 to 0.48; *P* = 0.30)

However, the confidence rating of the evidence was assessed as very low to low[33], indicating that the conclusions should be taken with caution due to the variability and quality of the included studies.

Financial impact of paracetamol

In a systematic review by Mallama et al., it was estimated that switching from IV to oral paracetamol for just half of the patients would save the hospital approximately £38,711 (or €43,960, US$47,498) annually, highlighting the substantial financial savings that could be realized by favoring more cost-effective routes of administration, such as oral paracetamol.[31]

Environmental Impact of paracetamol

A multicenter international life cycle analysis compared the carbon footprint of different forms of perioperative paracetamol. The results showed that the carbon emissions associated with each form of paracetamol varied significantly:

• Oral tablet paracetamol: 38 gm of carbon dioxide equivalent (CO_2e) for a 1 gm dose

• Oral liquid paracetamol: 151 gm CO_2e for a 1 gm dose

• IV paracetamol: 310-628 gm CO_2e for a 1 gm dose

The analysis revealed that IV paracetamol has a 12-fold greater life cycle carbon emission compared to oral tablet paracetamol, making it a considerably less environmentally sustainable option.[34] This finding highlights the potential for reducing the environmental impact of healthcare practices by considering more eco-friendly alternatives such as oral paracetamol when possible.

Conclusion

Paracetamol proves to be effective when used as part of multimodal analgesia in the postoperative period. Additionally, both financial and environmental considerations should be factored in when determining the most appropriate route of paracetamol administration for perioperative use. By choosing the right form of paracetamol, healthcare settings can optimize both cost-effectiveness and environmental sustainability, while maintaining high standards of patient care and pain management.

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