Paracetamol in critical illness: a review

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ABSTRACT

Background: Paracetamol is one of the commonest medications used worldwide. This review was conceived as a consequence of evaluating the literature in the protocol development of two randomised, controlled clinical trials investigating the safety and efficacy of paracetamol in ICU patients (the HEAT [Permissive HyperthErmiA Through Avoidance of Paracetamol in Known or Suspected Infection in the Intensive Care Unit] study; the Paracetamol After traumatic Brain Injury [PARITY] Study).

Objective: To provide a historical perspective on the introduction of paracetamol into clinical practice, to present the pharmacology of paracetamol in critical illness, and evaluate the current evidence for its use as an antipyretic and analgesic in intensive care.

Design: Literature searches were performed using keywords: "paracetamol", "acetaminophen", "critical illness", "intensive care", "history", "pharmacology", "antipyre*", "analgesi*", "adverse effect*", "administration and dosage", "toxicity", "animals" and "humans".

Data sources: Embase, MEDLINE, PubMed (1947/1950 to July 2011).

Review methods: The authors examined each article's title and abstract, fully reviewing relevant articles, with searching of reference lists and additional hand-searching. The most recent and highest quality available evidence was included.

Results: Limited data are available on the pharmacology of paracetamol in the critically ill. Among patients with sepsis, paracetamol may inhibit the immunological response. Among patients with neurological injury paracetamol can reduce temperature but appears not to improve outcome. When administered with opioids after major surgery, paracetamol does not reduce the incidence of pain or opioid-related side-effects.

Conclusion: Despite the widespread use of paracetamol in critical illness, there is a paucity of data supporting its utility in this setting. Further research is required to determine how paracetamol should be used in the critically ill.

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Paracetamol is one of the most widely used medicines in the world, but there is a paucity of guidance on how to use it appropriately for antipyresis and analgesia in the critical care setting. In this review, we describe the history of paracetamol and its pharmacology, and review the available data to support its prescription for critically ill patients.

The history of paracetamol

The synthesis of paracetamol arose from major advances in chemistry occurring in the 19th century.[1,2] With the development of analytical chemistry came the ability to isolate and purify medicinal chemicals from natural sources, including morphine from opium and quinine from cinchona bark. However, chemists in continental Europe were hindered by wars, which increased demands and restrictions on the supply of foreign medicinal plants. Their attention moved to the development of synthetic alternatives from local resources, and the evolution of organic chemistry enabled the development of new compounds for testing against human disease. Quinine had been shown to reduce the fever and the disease course of malaria, and in the preantibiotic era, antipyretics were a major focus of medicinal chemistry.

The aniline derivatives (acetanilide, phenacetin and paracetamol) were identified as a class of antipyretic analgesics in the late 19th century. Paracetamol was first synthesised in 1878 by Harmon N Morse of Johns Hopkins University.[3] However, it was many decades before the clinical utility of paracetamol and its advantages over other drugs of the class were recognised.

The first report of the administration of an aniline derivative to a patient was published in 1886 when acetanilide was mistakenly dispensed at a clinic in Strasbourg.[4,5] Subsequently, acetanilide's antipyretic and analgesic effects were described and it was marketed for clinical use by Kalle and Company under the name antifebrin. The next year, chemists at the German dye manufacturer Friedrich Bayer and Company synthesised phenacetin (acetophenetidin).[5,6] Less toxic than antifebrin, phenacetin became a popular antipyretic analgesic and established Bayer as a leading pharmaceutical company.[5]

In 1893, Joseph von Mering, a prominent German physiologist, reported on his work with Bayer and Company evaluating a derivative of phenacetin, which was later named paracetamol.[5,7] von Mering found the drug to be an effective analgesic and antipyretic; however, possibly using contaminated preparations, he mistakenly attributed methaemoglobinaemia, a side effect of aniline derivatives, to this new drug. In 1894, Hinsberg and Treupel published work showing that paracetamol was comparable to acetanilide and phenacetin in antipyretic

effect, but in view of the report by von Mering, paracetamol was not widely used.[8] In 1899, Bayer produced aspirin, which commonly appeared in combination with phenacetin and caffeine in over-the-counter analgesic mixtures for decades to follow.[9]

It was not until the late 1940s that two teams of biochemists in the United States identified paracetamol as a major metabolite of acetanilide in human blood.[10-12] Paracetamol's role in causing methaemoglobinaemia was disputed,[13] and it was established as an efficacious analgesic.[11,14] In 1953, paracetamol was marketed in the US as a safer alternative to aspirin.[5] In the United Kingdom, paracetamol first entered the market in 1956 as 500 mg Panadol tablets available on prescription.[15]

Phenacetin was shown to be metabolised to paracetamol,[16] and, in the 1960s, the chronic use of phenacetin was associated with "analgesic nephropathy", which was characterised by renal papillary necrosis.[17-19] Phenacetin was eventually identified as a carcinogen[20] and subsequently withdrawn in many countries, including Australia in 1977.[21]

In the 1980s, paracetamol overtook aspirin as the most popular over-the-counter analgesic.[22] An intravenous formulation of paracetamol, which was developed in 2004 by Bristol–Myers Squibb, has further increased its use in the perioperative period.

Pharmacology of paracetamol in critical illness

Pharmacodynamics

Although paracetamol appears to act centrally, the details of its pharmacodynamics remain in question. Research to date has described two main mechanisms to account for paracetamol's antipyretic and analgesic effects: selective inhibition of cyclo-oxygenase (COX) in the central nervous system; and an indirect effect on cannabinoid and vanilloid tone.[23,24]

In the 1970s, paracetamol's antipyretic effect was shown to be associated with the inhibition of prostaglandin synthetase (since named COX) in the brain.[25] In contrast to non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit COX enzyme activity in central and peripheral tissues,[26] paracetamol has been found to exert a tissue-specific inhibitory effect on COX via a reduction reaction on the COX enzyme in the presence of a low peroxide environment, such as that of intact neuronal cells.[27] This peroxide-dependent specificity is thought to account for its comparatively poor anti-inflammatory and antiplatelet properties and better side-effect profile than NSAIDs.[28-30] Research has been conducted on various aspects of paracetamol's effect on COX, including isoform specific interactions;[31-33] however, a clinically significant role in paracetamol's mechanism of action remains to be proven.

More recently, research has suggested that paracetamol is a pro-drug of a fatty acid amide called *N*-arachidonoylphenolamine (AM404), which acts directly on vanilloid subtype 1 receptors and indirectly on cannabinoid type 1 (CB_1) receptors in central nervous system thermoregulatory and nociceptive pathways.[23] In the central nervous system, AM404 is formed from the conjugation of p-aminophenol (deacetylated paracetamol) with arachidonic acid in the presence of a catalyst, fatty acid amide hydrolase.[34] AM404 has been shown to inhibit in-vitro COX activity and prostaglandin E_2 formation,[34] and to increase the levels of an endogenous cannabinoid neurotransmitter, *N*-arachidonoylethanolamide (anandamide), via inhibition of the anandamide reuptake.[35] Cannabinoids act on cannabinoid receptors to lower temperature and modify nociceptive signals.[36,37] Ottani and colleagues demonstrated that blockade of CB_1 receptors in rats prevented the analgesic effect of paracetamol.[38] Furthermore, clinical effects, including euphoria and relaxation, are noted to be shared by cannabinoids and alanine derivatives.[23]

There is evidence that a relationship exists between paracetamol and endogenous opioid analgesic pathways. An animal study showed that paracetamol interacts at spinal and supraspinal levels to produce a synergistic analgesic effect.[39] Three subtype selective opioid receptor antagonists (μ, δ and κ) have been demonstrated to attenuate this synergy.[40] The clinical relevance of a potentiating effect of exogenous opioids on paracetamol analgesia in ICU patients is discussed later in this review.

Pharmacokinetics

The variability in pharmacokinetics as a result of different pathological processes among critically ill patients is well established.[41,42] In the case of paracetamol, both the peak and the area under the curve of serum paracetamol levels measured over 60 minutes after nasogastric administration are reduced among critically ill patients who are intolerant of nasogastric feeding.[43] However, postpyloric administration leads to rapid absorption,[44] and, based on a study of patients admitted to ICU following cardiac surgery, it appears that when paracetamol is administered nasogastrically, absorption is delayed rather than suppressed by critical illness.[45] Rectal absorption of paracetamol is probably poor.[46] Although there are very few data examining the pharmacokinetics of paracetamol among critically ill patients, it appears that the volume of distribution of paracetamol is increased in ICU patients compared with patients who are less unwell.[47] The clinical importance of these pharmacokinetic differences is unclear.

Paracetamol for antipyresis for critically ill patients

Antipyretic efficacy

Paracetamol is commonly used as an antipyretic in the ICU, although its effects on body temperature appear to be

modest. One retrospective study found that enteral paracetamol was associated with a greater temperature reduction (mean difference, 0.3°C) than no treatment in critically ill adults with fever occurring as part of systemic inflammatory response syndrome.[48] Schulman and colleagues studied non-neurologically injured, febrile trauma patients from enrolment to ICU discharge.[49] They found a statistically significant reduction in daily mean temperature (mean difference, 1.09°C; $P = 0.006$) in the group treated with paracetamol 650 mg 6-hourly for temperatures > 38.5°C, compared with those allocated no treatment until their temperature exceeded 40.0°C.[49]

Both of these studies had potential confounders including the concomitant use of other antipyretics. Randomised placebo-controlled studies in acute ischaemic stroke, although not specifically in febrile or ICU patients, have demonstrated that paracetamol 6 g, in a divided daily dose, reduces mean body temperature by 0.26°C (95% CI, 0.07–0.46°C) within 4 hours[50] and 0.26°C (95% CI, 0.18–0.31°C) at 24 hours.[51] The efficacy of intravenous paracetamol in reducing body temperature in patients with traumatic brain injury is currently under investigation in the Paracetamol After traumatic Brain Injury (PARITY) Study (Australian New Zealand Clinical Trials Registry no. ANZCTRN12609000444280).[52]

Paracetamol for neurological injury

There are compelling arguments for the prevention and treatment of fever among critically ill brain-injured patients. Fever promotes various undesirable pathophysiological reactions, both at local level (eg, increased proteolysis and free radical production) and systemic (eg, reduced cerebral perfusion pressure).[53-55] In a meta-analysis of observational clinical studies, the presence of elevated body temperature in patients with neurological injury (stroke and traumatic brain injury) was associated with adverse outcomes across multiple measures including mortality, stroke severity indexes and length of ICU and hospital stays.[56]

The medical treatment of fever in acute stroke is recommended in current guidelines,[57] however the only phase III trial to date, investigating high-dose paracetamol (6 g daily) in early stroke, failed to demonstrate improved functional outcomes.[50] There have been no randomised placebo-controlled trials demonstrating improved outcome with the administration of paracetamol to patients with traumatic brain injury.[58]

Paracetamol for sepsis

In contrast with the negative association with fever and neurological injury, there are beneficial associations with a febrile response to infection. At the cellular level, research has demonstrated direct inhibition of heat-sensitive microorganisms at febrile temperatures,[59,60] as well as the potentiation of protective cellular[61] and immune responses.[62] Some human observational studies have shown a positive correlation between febrile temperature during bacteraemia and survival.[63,64] Randomised controlled trials in non-ICU patients have demonstrated that paracetamol can prolong infection with varicella,[65] malaria[66] and rhinovirus[67] as well as impair immune responses.[67,68]

Recent data from Australia and New Zealand have found that paracetamol is administered to most ICU patients with known or suspected infection.[69] Only one randomised controlled trial has been published addressing the impact of different paracetamol-based antipyretic therapy strategies on the development of infectious complications.[49] This trial enrolled non-neurologically injured ICU patients who had been in a trauma ICU for longer than 72 hours who developed a temperature of >38.5°C. In the "aggressive treatment" arm, patients received paracetamol for temperatures > 38.5°C while the other arm received paracetamol only for temperatures > 40.0°C. The primary end point was the development of a culture-positive infection within the study period. The trial originally aimed to enrol 672 patients; however, it was stopped by the Data Safety Monitoring Board after enrolment of 82 patients due to a trend towards increased mortality in the aggressive treatment group. While all deaths were attributed to septic causes, conventional stopping rules were not used and differences between the study treatment arms could be due to chance. This study had other major limitations including a lack of blinding and placebo control, and potential confounding from the uncontrolled use of other antipyretic drugs and per-protocol use of external cooling.[49] On the basis of currently available data, the efficacy and safety of administering paracetamol and other antipyretics to critically ill patients with infection is unknown.[70] However, a randomised, placebo-controlled trial investigating the safety and efficacy of paracetamol in febrile ICU patients with known or suspected infection is currently underway (the HEAT [Permissive HyperthErmiA Through Avoidance of Paracetamol in Known or Suspected Infection in the Intensive Care Unit] study, Australian New Zealand Clinical Trials Registry no. ANZCTRN12611000981921).

Metabolic expense and physiological reserves

In critically ill patients, the metabolic cost of fever is another important consideration. The cardiovascular changes and metabolic demands associated with fever may be significant in patients with limited cardiopulmonary reserve.[71] In a study of febrile ICU patients, the energy expenditure index was found to significantly decrease from baseline within 4 hours of receiving intravenous propacetamol (a paraceta-

mol prodrug) for antipyresis, although significant concurrent metabolic changes, including serum pH and lactate levels, were not demonstrated.[72] This study had small numbers, examined a short time frame, had no placebo-control arm and was not primarily designed to compare the metabolic effects of fever and antipyretic medications. Placebo-controlled trials investigating the effects of paracetamol on markers of metabolic expense in the critically ill are currently lacking.

Paracetamol for analgesia among critically ill patients

Paracetamol is the most widely used analgesic in the world,[73] and evidence supporting its analgesic effect is strong.[74] However, the relevant question for many ICU patients is not whether paracetamol is an effective analgesic, but whether paracetamol offers an advantage over morphine alone. Many patients in ICU receive opioids for sedation, analgesic effects, or both.[75,76]

There is a significant body of data that provides some useful information in this regard. Three meta-analyses have convincingly demonstrated that addition of paracetamol to morphine administered via patient-controlled analgesia reduces morphine requirements by about 20%.[77-79] As a result, paracetamol is commonly administered alone with opioids as part of a strategy of multimodal analgesia.[73,77]

However, demonstration that the addition of paracetamol reduces morphine requirements does not mean that it is a clinically useful strategy. For paracetamol to have a practical advantage over morphine alone in this setting, it would need to reduce opioid-related side effects or pain severity. In fact, it appears that the observed reductions in opioid use are not associated with reduced opioid-related side effects. In the largest meta-analysis, the observed odds ratio for postoperative nausea and vomiting with addition of paracetamol to patient-controlled analgesia morphine was 1.00 (95% CI, 0.60–1.53).[78] In relation to sedation, the odds ratio was 1.62 (95% CI, 0.32–5.02) indicating a trend towards more sedation with paracetamol administration.[78]

The effect of paracetamol on pain scores was similarly disappointing. Meta-analyses show that addition of paracetamol to patient-controlled analgesia morphine has no significant effect on either a visual analogue scale assessment of pain[77] or overall satisfaction with pain control.[79]

The relevance of these studies to the ICU setting is unclear. Most of these studies included patients undergoing elective orthopaedic operations or gynaecological procedures. It is unlikely that many of the patients in these meta-analyses would have required intensive care. These studies used morphine via patient-controlled analgesia, which is often not practical for critically ill patients who are sedated and/or delirious. In these studies, there was considerable variation in the baseline morphine consumption. In the largest meta-analysis, morphine use ranged from 8.6 mg to 141.5 mg with a mean of 45.3 mg used over the first 24 hours after surgery.[78]

Oral paracetamol and intravenous morphine are both inexpensive and neither is likely to contribute significantly to health costs; however, increasingly, paracetamol is administered by the intravenous route, and intravenous paracetamol is not inexpensive. In New Zealand, 1 g of oral paracetamol costs 20 cents and 5 mg of intravenous morphine costs 30 cents, whereas 1 g of intravenous paracetamol costs NZD$4.[80] If paracetamol is administered intravenously, addition of paracetamol to morphine will increase costs.

Other than two studies performed in patients admitted to ICU following cardiac surgery,[81,82] there are no data specifically evaluating the analgesic efficacy of paracetamol for critically ill patients. These studies are consistent with other studies in patients receiving morphine after major surgery. The single placebo-controlled trial demonstrated that propacetamol reduces opioid requirements but does not demonstrate improved pain control or decreased opioid-related side effects.[81]

There is currently a marked discrepancy between the extent to which paracetamol is used for analgesia and the available evidence to support its usefulness for critically ill patients. However, evidence demonstrates that in other settings, paracetamol is an effective analgesic, and there is no convincing data that short-term administration of therapeutic doses of paracetamol administration is harmful.

Adverse effects of paracetamol among critically ill patients

Side effects are generally mild with the recommended doses of paracetamol, and the use of paracetamol has steadily increased due to its safety profile compared with NSAIDs. Paracetamol can cause transient abnormalities of liver function and may cause hypotension in critically ill patients.[47,83] Very rarely, blood disorders, including drug-induced immune thrombocytopenia, have been reported.[84] Pyroglutamic acidosis is a rare but possibly under-recognised adverse effect associated with therapeutic paracetamol use, most frequently identified in malnourished female patients who have renal insufficiency or failure.[85] Acute allergic reactions to paracetamol are very rarely described,[86] but there are recent reports of an association between the use of paracetamol in early childhood and the subsequent development of atopy.[87]

Progression from reversible abnormal liver function to acute liver failure is the most serious potential complication of the use of paracetamol. This may occur in the context of either deliberate overdose, doses above the usual recommended dose, or with recommended doses in conjunction

with certain predisposing conditions. Predisposing conditions include genetic susceptibility, certain drugs affecting the cytochrome P450 system, the metabolic effect of prolonged fasting or malnutrition, and chronic alcohol ingestion.[88] However, the clinical importance of these risk factors remains controversial,[89,90] and there are data that dispute the link between fasting, chronic alcohol use and their association with paracetamol-induced liver toxicity.[91-93] The conventional maximum daily dosage for paracetamol is 4 g. Although doses of 6 g a day have been used in clinical trials without evidence of increased risk of adverse effects, there is evidence that significant hepatotoxicity can occasionally occur even with conventional paracetamol dosing.[94] The key criteria for assessing potential hepatotoxicity with conventional doses of paracetamol may be low body weight and the presence of malnutrition. A pragmatic approach to dosing may be a total daily dose of less than 40 mg/kg for adults with body weight less than 50 kg.[94]

Conclusion

From its tentative introductions to clinical practice over a century ago, paracetamol has become one of the most ubiquitous drugs in medicine and a routine prescription in critical care. Yet many aspects of paracetamol's pharmacodynamics are not fully understood. The utility of paracetamol as an analgesic in the critically ill is not certain, and the impact of its antipyretic effects on outcomes in varying pathological processes is potentially significant. Further research is required to determine how we should be using paracetamol in the critically ill.

Competing interests

None declared.

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