REVIEW ARTICLE

Intravenous paracetamol in pediatrics: A global perspective

Muzammil Irshad, MBBS; Mehjabeen Malik, MBBS; Aamir Furqan, MBBS

Correspondence: Dr. Muzammil Irshad, Chak # 119 TDA, Tehsil & District Layyah, Punjab (Pakistan);
Phone: 03326059617; E-mail: drmuzammilirshad@gmail.com

ABSTRACT

Intravenous (IV) Paracetamol is an excellent post operative analgesic and antipyretic in children. Efficacy and tolerability of IV Propacetamol have been established in pediatric practice. It is believed that paracetamol works by inhibiting cyclooxygenase-2 (COX-2) enzymes. Studies bring to light that therapeutic doses of IV acetaminophen are effective and tolerable in children with least chances of hepatotoxicity. However, overdose toxicity has been reported in children and drug induced hypotension in febrile critically ill patients. Therapeutic doses according to body weight of neonates and children can be administered in hospital settings. Special education of health care staff regarding precise dose and solution is necessary to assess the role of IV paracetamol preparation in pediatric practice.

Keywords: Acetaminophen; Paracetamol; Propacetamol; Cyclooxygenase-2 inhibitors

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INTRODUCTION

Paracetamol (acetaminophen) is one of the effective and well tolerated drugs by adults and children in therapeutic doses.[1] It is available in many countries as an over-the-counter drug. Paracetamol was discovered in Germany at the end of nineteenth century, and it was widely available until midway through the 20th century.[2] In 1951, acetaminophen was approved by Food and Drug Administration (FDA)[3] and was introduced in USA under the brand name *Tynelol®*. Since then it has been the cornerstone in the management of pain and fever for adults and children. Despite the broad usage of this drug, FDA approved marketing of first IV paracetamol formulation in USA in November 2010 under the brand name of *Ofirmev®*.[4] At present, IV Paracetamol has been approved and being used in more than 80 countries all over the world.

Prior to the approval of IV formulation of paracetamol by FDA, paracetamol pro-drug (propacetamol) had been approved and used in the Western world for a decade.[5] Intravenous propacetamol efficacy and safety has been established in pediatrics[1,6] and has shown to produce higher mean plasma concentrations that are more likely to be in the therapeutic range compared to rectal paracetamol in children undergoing major craniofacial surgery.[7] Consequently, IV paracetamol has been observed to be a more effective analgesic as compared to rectal formulation in this pediatric group of population.[7] However, rapid infusion of IV propacetamol has been found to be associated with increased pain at the injection site and a higher incidence of hypotension when compared to the injectable ketorolac.[8,9]

Although paracetamol has been used for the last century, its mechanism of action is still unknown. It is, however, generally considered to be a weak inhibitor of prostaglandins (PGs) synthesis.[10] In vivo, paracetamol effects are similar to selective COX-2 inhibitors. Although paracetamol decreases PGs, it does not reduce inflammation in rheumatoid arthritis as the other COX-2 inhibitors do. Moreover, studies bring to light that paracetamol works as a weak inhibitor of COX-1 and COX-2 where the concentration of arachidonic acid is low.[10]

Gastrointestinal tract (GIT) motility is decreased in the immediate post-operative period and it is the period when the patient needs immediate pain relief. As oral formulation cannot be given during this time period, IV paracetamol offers the advantage of providing rapid analgesia and reduced opioid requirement.[11] In short, IV paracetamol offers immediate and short term treatment of pain and fever. However, when administering paracetamol through IV route, one must be cautious in patients under 50kilogram of weight.

The introduction of IV paracetamol in the field of critical care medicine has broaden the utilization of paracetamol especially in patients who are unable to take oral medication due to impaired GIT motility contraindication to nasogastric tube use, or who require

faster onset of pain or fever reduction. However, paracetamol use may be a risk factor for the development of asthma, rhinoconjunctivitis and eczema in adolescent children.[12]

LITERATURE REVIEW

IV paracetamol use is becoming popular in neonates and children.[13-16] Population pharmacokinetics has been studied for IV prodrug (propacetamol) in neonates after administration of single or repeated doses.[17-19] Paracetamol is an effective and attractive analgesic for newborn babies and children especially in those who can not take oral preparation. It works as an alternative or as a supplement to opioid analgesic most importantly in those patients who are prone to opioid side effects. Moreover, IV paracetamol gives the same results as offered by the pro-drug propacetamol.

Palmer et al[20] studied IV paracetamol formulation, its clearance and effects on liver function tests in 50 neonates. In this study, neonates received a mean of 15 doses according to gestational age (28–32 weeks = 10 mg/kg, 32–36 weeks = 12.5 mg/kg and ≥36 weeks = 15 mg/kg) over a median 4 days along with daily serum paracetamol concentration measurement and liver function tests (LFTs). They found that IV paracetamol parameters resembled those of propacetamol. There was no reported significant hepatotoxicity in their patients except one patient whose alanine aminotransferase level got tripled. Investigators of this study recommended a lower dose of IV paracetamol in patients having unconjugated hyperbilirubinaemia. This study led to gestational age based dosing regimen and application of IV paracetamol in neonatal unit.

Similarly, Walson et al[21] carried out a randomized double blind placebo controlled trial on 41 children in order to know efficacy and tolerability of a single dose of IV propacetamol.. The patients with body temperatures 38.5°C to 41°C received 30 mg/kg of IV propacetamol (20 patients) or placebo (21 patients), administered as a 15 minutes infusion. Body temperature was measured at the start, after 15 minutes, one hour and thereafter for six hours. The primary efficacy was the reduction in body temperature at the time of evaluation at different periods. In IV propacetamol group, 10% needed rescue doses while in placebo group 52.4% children required the rescue medication. They observed that the efficacy of IV propacetamol was significantly greater than that of placebo. Moreover, both IV propacetamol and placebo were equally tolerable. This study, however, did not comment on comparison of IV propacetamol preparation with other antipyretic drugs.

At present, IV paracetamol is being used in children world-wide. Many trials have been carried out on the efficacy and tolerability in pediatrics. The following trials and studies can help to understand the efficacy of IV paracetamol in children.

USA: Murat and co-workers[14] studied the efficacy of IV paracetamol (15 mg/kg) and IV propacetamol (30 mg/kg) in183 children (below 12 years) after inguinal hernia repair. Effects of both the preparations were assessed after 25 minutes infusion for six hours. Both the preparations rapidly reduced the pain scores and offered pain relief for about 4 hours in most of the children. Moreover, 15% patients in IV paracetamol group and 33% patients in IV propacetamol complained of pain on injection. In another study by Hong and colleagues,[22,23] combination of parent anesthetic drug fentanyl and IV paracetamol reduced the total dose of fentanyl in patients undergoing uretroneocystostomy.

Saudi Arabia: In 2006, Alhashimi and Daghistani[24] carried out two randomized controlled trials, and compared IV paracetamol (30 mg/kg) and meperidine (1 mg/kg) in children. They found that both drugs were effective in 80 children who underwent tonsillectomy but the patients who were given IV paracetamol had shorter hospital stay. In 2007, both the researchers observed that IV paracetamol produced less initial pain relief as compared to meperidine in children undergoing dental surgery. [25]

Table 1: Some studies about efficacy of IV paracetamol and propacetamol

Study	Sample Size	Design	Results
Murat et al. (2005)[14]	183	R, DB, active comparator pain (hernia repair) single dose (SD) trial in 183 children (age 1 -12years)	IV paracetamol 15 mg/kg is efficacious and equivalent to IV Propacetamol (30 mg/kg). IV paracetamol produced a 50% reduction in PI by 30 min
Duhamel et al. (2007)	67	R, DB, active comparator fever (infectious origin) SD trial in 67 children (age 1 -12years)	IV paracetamol (15 mg/kg) is efficacious and equivalent to IV Propacetamol (30 mg/kg). IV paracetamol produced a mean of 0.6C/hour with 70% of patients below 38C.
Alhashemi et al. (2006)[24]	80	R, DB, active comparator pain (tonsillectomy) SD trial in 80 children (age 3 –15 years)	IV paracetamol 15 mg/kg is efficacious and equivalent to IM meperidine 1 mg/kg but with less sedation.
Capici et al. (2008)[15]	50	R, DB, active comparator pain (tonsillectomy) SD trial in 50 children (age 2 –5 years)	IV paracetamol 15 mg/kg is efficacious and equivalent to a PR paracetamol dose 2.7X larger (40 mg/kg). IV paracetamol group mean time to rescue = 7hours.

Table 2: MHRA recommended doses of Perfalgan® (IV paracetamol preparation)

	Term newborn, infants, toddlers and children (<10 kg)	Children (>10 kg and <33 kg)	Children, adolescents, adults (>33 kg and <50 kg)	Adolescents and adults (> 50 kg)
Dose per administration	One IV infusion of 7.5 mg/kg (0.75 ml solution/kg)	One IV infusion of 15 mg/kg (1.5 ml solution/kg)	One IV infusion of 15 mg/kg (1.5 ml solution/kg)	One IV infusion of 1 g (100 ml solution)
Maximum daily dose	30 mg/kg (3ml/kg)	60 mg/kg (6 ml/kg) without exceeding 2g (200 ml in total)	60 mg/kg (6 ml/kg) without exceeding 3g (300 ml in total)	Must not exceed 4 g (400 ml in total)

Alseify et al[26] conducted a study on the combination of IV paracetamol and parecoxib in 60 adult patients who underwent anterior cruciate ligament reconstruction. They concluded that the combination both these drugs offered better analgesia than that when used separately. Similarly, Maxwell also reviewed and reported the safety of IV paracetamol in children (Table 1).[27]

Israel: Hersch and co-workers[28] studied effects of IV propacetamol on blood pressure in 14 (aged 17-83) febrile critically ill patients. In this study, the patients were given intravenous infusion of propacetamol 2 grams over 15-20 minutes every 6 hours and blood pressure was measured after 15 minutes. They observed decrease in blood pressure in 33% patients requiring fluid resuscitation on six occasions and norepinephrine infusion on eighteen occasions. Hence, this study brought to light that antipyretic dose of IV propacetamol in critically ill patients leads to significant decrease in blood pressure after 15 minutes of the administration. Therefore, clinicians must be aware of this deleterious drug induced hypotension especially in febrile critically ill patients.

Pakistan: In Pakistan, IV paracetamol is frequently used as an analgesic and antipyretic agent in children. But, no study has been published from Pakistan regarding the efficacy and safety of IV paracetamol in children. However, recommended doses of paracetamol infusion are being used in children and adults with satisfactory pain relief and fever control in Pakistan. At Nishtar Hospital Multan, 15 mg/kg (1.5 ml/kg) of paracetamol infusion per administration is used in children weighing 10 kg to 33 kg.

Accidental overdoses of IV paracetamol have been reported with 10 mg/ml solution of paracetamol infusion.[29,30] These accidental overdoses happened to occur due to the confusion between milligrams of the drug and the solution (milliliters). Paracetamol is marketed in milligrams and administered in solution (infusion). Recommended dose of paracetamol depends on the weight of the infants, children or adults. Irrespective of dose, paracetamol is given four times a day with a minimum interval of four hours between the each administration. In order to avoid these accidental overdoses, Medicines and Healthcare products Regulatory Agency (MHRA) has issued a table guiding the doses and solution of Perfalgan® according to weight and age of the patients (Table 2).[29,30]

Dutch Pediatrics Society put forth evidence based guidelines regarding pain management in children and supported IV paracetamol (15 mg/kg, 6 hourly) administration to be used in babies.[31] Additionally, pediatricians considered the use of IV paracetamol preparation in order to reduce the dose of post operative opioids requirement. Serum levels of paracetamol and aspartate transaminase in children count for IV paracetamol safety.

Safety: IV paracetamol is believed to have excellent therapeutic index with least chances of hepatotoxicity. Though the toxicity is rare at therapeutic doses but it must be born in mind while treating the patients with IV preparation of paracetamol. Hepatic failures have been documented in the children who underwent chronic ingestion of paracetamol and in those patients who were apparently on therapeutic doses.[31-33] Hepatotoxicity occurs due to imbalance between reactive metabolite product (N-acetyl p-benzoquinone imine) and the supply of reduced glutathione.[31] In children (younger than 2 years), risk of hepatotxicity has been identified with sustained high doses of IV paracetamol given in the dose of more than 90 mg/kg/day. [34]

In order to avoid and to provide immediate management of IV paracetamol toxicity, it is administered in the hospital setting. Like other preparations IV paracetamol is contraindicated in some conditions like severe hepatocellular insufficiency (i.e. < 30mls/min), chronic alcoholism, chronic malnutrition and dehydration.[35] However, recent studies bring to light that IV paracetamol at its therapeutic doses does not harm the patients with liver disease. Additionally, there is no significant data about hepatotoxicity available in the patients with cirrhosis, possibly due to compromised liver function and low toxic metabolites.[36] In other words, IV paracetamol is not contraindicated in the patients with liver disease if therapeutic doses are not exceeded.

CONCLUSION

Intravenous paracetamol looks to be effective and safe for post-operative analgesia in children. Most importantly, IV Paracetamol preparation offers a means of administration in the patients who are not suitable for oral or rectal routes or in those who require instant relief. It reduces the doses of opioid analgesics following

surgical procedures and subsequently the post-operative sedation. Doses of IV paracetamol are different from those taken orally. It is safe in pediatrics but special care is required while calculating doses for neonates and critically ill patients. No hepatotoxicity has been reported with analgesic and antipyretic doses of IV paracetamol. However, it may lead to drug induced hypotension in critically ill patients. Therefore, health care providers must bear in mind the circulatory status of the patients before embarking on high doses of IV paracetamol.

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