Editorial

Paracetamol (Acetaminophen) toxicity in children

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As a result of the possible role of aspirin in pathogenesis of Reye syndrome, paracetamol has become the most widely used medication for relief of pain and fever in infants and children. In the June 2003 issue of the Sri Lanka Journal of Child Health, an insert by the sponsors, advertising 'Panadol for children', claimed lack of hepatic injury after acute paracetamol doses of up to 200 mg/kg in children. This insert is highly misleading as it implies that acute use of paracetamol in doses of up to 200 mg/kg is free of hepatotoxicity. This is certainly not the case. The insert quotes an observational study by Mohler et al published in the Annals of Emergency Medicine in support of their stance. Mohler et al studied 1019children (average age 2.3 years) who had accidentally ingested paracetamol in a single dose of 20-200 mg/kg[1]. Children were monitored at home without receiving any specific treatment and at 72 hour follow-up had no signs or symptoms of paracetamol toxicity. The insert further states that Mohler et al had reviewed available worldwide literature and failed to identify a fatal outcome after a confirmed acute single ingestion of paracetamol in a child younger than 7 years of age. The results of this study are not in dispute. In fact, in a prospective study of acute childhood poisoning in Sri Lanka there were no cases of paracetamol toxicity[2]. The concern today, however, and the 'adverse publicity' referred to in the insert are regarding case reports of hepatotoxicity associated with multiple supra-therapeutic doses of paracetamol. These concerns have not been addressed in the above study. The Editors have to take responsibility for allowing this misleading insert to be published in our esteemed journal and apologise to the readers for same ('mea culpa'). Our trust in the sponsors has been misplaced. In fact, the Editorial Board has decided that, in future, all inserts by sponsors should be strictly scrutinized by the Editors before publication in the Journal. Anyhow, 'every cloud has a silver lining'. This insert has created an opportunity to update our readers on paracetamol toxicity.

Paracetamol is absorbed rapidly after an oral therapeutic dose and produces a peak plasma level between 30 to 60 minutes after ingestion. This absorption may be delayed in overdose so that peak plasma levels may not occur until as long as 4 hours postingestion[3]. The drug is then metabolized in the liver with about 2% being excreted unchanged in urine. About 94% is metabolized to glucuronide or sulphate conjugate. The remaining 4% is metabolized through cytochrome P-450 mixed function oxidase system to form the highly reactive N-acetyl-p-benzoquinonemine (NAPQI) which is then immediately conjugated with glutathione and subsequently excreted as cysteine and mercapturate conjugates[3].

When single toxic doses of paracetamol are ingested, glucuronidation and sulphation pathways become saturated and P-450 pathway assumes importance for drug biotransformation leading to production of greater amounts of NAPQI. Initially, NAPQI is conjugated with glutathione and excreted as nontoxic cysteine and mercapturate conjugates; however, when glutathione stores are depleted by excess NAPQI, hepatotoxicity results from covalent binding of NAPQI to hepatocyte proteins[4]. It was believed that toxicity is not observed until hepatic glutathione stores are depleted to about 70% of normal; however, recent evidence suggests that lesser glutathione reductions may lead to cellular injury[4]. It appears that immature animals have a higher turnover of glutathione which indicates that more may be available for detoxification[5]. Additionally, experiments in young animals indicate a higher mean lethal dose (LD_{50}) indicating a requirement for more drug to provide toxicity[6].

With repeated overdoses of paracetamol, changes in metabolic pathways may affect the development of hepatic injury. In most multiple accidental overdoses, infants and children are febrile and acutely malnourished. Reductions in caloric or protein intake combined with multiple doses of paracetamol may have profound effects on sulphation, glucuronidation and glutathione production. Increased sulphation and glutathione production have been cited as explanations for lower hepatotoxicity caused by paracetamol observed in children[7]. However, hepatic sulphation substrates may become depleted with multiple therapeutic doses of paracetamol[8]. In animals, fasting and increasing doses of paracetamol

lead to reduced amounts of sulphated and glucuronate metabolites[9] and reduced glutathione stores[5]. Paracetamol administration also leads to reduced hepatic glutathione, increased turnover and reduced synthesis[9]. The combination of fasting and repeated paracetamol administration may lead to even greater reductions in hepatic glutathione, increases in turnover and reduced synthesis. There is a trend toward increased paracetamol levels in children with repeated dosing which may be inversely related to age[10]. Polymorphism in expression of the cytochrome P450 enzyme such as CYP2E1 may make certain children more prone to hepatic injury[11]. Cumulatively, these alterations may singly, or in combination, potentiate paracetamol toxicity after multiple overdoses.

Several cases of presumed chronic paracetamol toxicity have been described in the literature. Greene et al. reported 2 infants < 8 weeks of age who developed hepatic dysfunction and hypoglycaemia after paracetamol therapy for 2-8 days[12]. In the first patient, serum paracetamol level was 10.7 mg/L 54 hours after last dose. The second patient had a level of 119 mg/L at 12 hours after last dose. Agran et al. reported a 15 month old child who developed fulminant hepatitis and encephalopathy after treatment with paracetamol at an estimated dosage of 150 mg/kg/day for 4 days[13]. A thorough evaluation for viral, toxic and metabolic cause was unrevealing. Liver biopsy demonstrated centrilobular hepatocellular necrosis consistent with paracetamol toxicity. Swetnam and Florman's patient was an 18 month old who developed hepatic dysfunction after 2 days of paracetamol therapy at a dose of 12.3 mg/kg/dose 2 hourly or 148 mg/kg/day[14]. Tests for hepatitis A and B were negative. Paracetamol level, 36 hours after last reported dose, was 14 mg/L. Nogen and Bremner reported a 3.5 year-old girl who died of hepatic and renal failure after 24 hours of excessive paracetamol therapy[15]. She received 720 mg 3 hourly for a total of 5g. At time of hospital admission, 14 hours after her last dose, serum paracetamol level was 53 mg/L. A liver biopsy demonstrated centrilobular necrosis typical of massive acute paracetamol overdose. Blake et al. reported the death of a 6 year old who received 500 mg paracetamol more often than 4 hourly for fever associated with measles[16]. The child had a serum paracetamol level of 163 mg/L 11 hours after last dose and developed hepatic and renal failure followed by seizures. Smith et al. described a 7 month old boy with fulminant hepatic failure after taking 12 doses of 325 mg paracetamol suppositories 6 hourly for 3 days (38 mg/kg/dose or 152 mg/kg/day)[17]. This infant had levels of paracetamol of 72 mg/L at 4 hours and 22 mg/L at 16 hours after last known dose. Henretig et al. reported 2 children aged 11 and 22 months respectively with well substantiated hepatotoxicity due to repeated paracetamol overdosing[18]. They had paracetamol levels on hospital admission of 240 mg/L and 32 mg/L respectively, 11 and 24 hours after last reported doses and extensive evaluations were negative for infectious, metabolic or toxic causes of hepatic failure. In Sri Lanka De Silva et al. reported 5 cases of acute liver cell damage following repeated doses of paracetamol exceeding maximum therapeutic dose (90 mg/kg/24 hr)[19].

Paracetamol is currently the paediatric analgesic and antipyretic of choice. Although children appear to tolerate single, high-dose ingestions well, the literature is replete with reports of significant morbidity and mortality after repeated supra-therapeutic dosing. Risk factors for injury with chronic use include age, total dose, duration, presence of intercurrent febrile illness, starvation, co-administration of cytochrome P450-inducing drugs, underlying hepatic disease and unique genetic makeup[20]. Clinicians should be aware that merely doubling recommended therapeutic dosage of paracetamol for several days would put children at risk for severe hepatotoxicity. As so many parents are unaware of the potential risk of inappropriate dosing, education is the key to prevention.

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