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A Case Report of Intravenous Paracetamol Overdose in a Paediatric Patient

Lisa Lee Pei Ling1, Run Jie Soo'[2]

[1,2] Department of Pharmacy, Hospital Wanita dan Kanak-kanak (Likas) Sabah, Malaysia
Sabah Women and Children Hospital, Malaysia

Summary

A two years old Kadazan girl was accidentally overdosed with 120mg/kg of IV paracetamol (PCM). The history, biochemical findings, clinical examination and discussions on paracetamol overdose management will be described in this case report.

Keywords: paracetamol overdose, paracetamol toxicity, medication error

Introduction

Paracetamol is also known as acetaminophen in the United States. It is available in oral, rectal and intravenous form. Paracetamol is categorised as the first line analgesic according to the WHO pain ladder.[1] Despite its well established safety and efficacy, unintentional intravenous paracetamol overdose among paediatric patients remain a concern since it is widely used for pain management. Most incidents are due to calculation error in which dosage is calculated in milligrams but administration is done in millilitres. The strength of paracetamol injection for all available brands around the world is 10mg/ml; hence, a 10-fold overdose.[2] 23 cases of unintentional overdose have been reported in children less than one

Corresponding author:
Run Jie Soo BPharm
Department of Pharmacy,
Hospital Wanita dan Kanak-kanak (Likas)
Sabah, Malaysia
incredible1_soo@yahoo.com

year old with Perfalgan (one brand of paracetamol injection) from 2002 to 2010, one of which was fatal.[2]

This is an example of case report of an iatrogenic intravenous paracetamol overdose in a paediatric patient.

Case Report

A two years old Kadazan girl was presented to the KPJ Sabah Specialist Hospital in October 2015 due to complaints of frequent falls in early September. She had three falls over five days prior to admission. She also experienced unsteady gait, hand tremor, loss of appetite and weight loss. During her hospital admission, patient was presented with ataxia gait and nystagmus; suggesting of space occupying lesion or infectious encephalitis. This prompted her referral to a pediatric neurologist in Hospital Wanita Dan Kanak-kanak Sabah (Likas) two days later for expert opinion and management. This is her second admission in which she was previously admitted to neonatal intensive care unit (NICU) in Hospital Likas for one week due to respiratory distress syndrome.

The result of her computed tomography scan (CT scan) showed a huge heterogeneous posterior fossa mass with associated hydrocephalus. The patient then underwent endoscopic third ventriculostomy to reduce the intracranial pressure. She was given one stat dose of IV cefuroxime as the perioperative antibiotic and IV paracetamol (PCM) for analgesia. A total of 1200mg of IV PCM was accidentally administered into the patient due to the incorrect doctor's assumption for the strength of PCM injection as 1mg/ml instead of 10mg/ml. The correct dose should be 153mg (15.3ml) of PCM injection based on 15mg/kg dosing and patient's weight of 10.2kg. The mistake was later discovered by another doctor when 120ml (1200mg) of IV PCM has been administered into the patient. The infusion was stopped and pharmacist's advice regarding management of PCM overdose was sought immediately. An urgent liver function test was suggested and IV N-Acetylcysteine (NAC) regimen as stated in Table 1 to be started as soon as possible. Therapeutic drug monitoring (TDM) of the PCM level in

the blood was recommended to be done four hours post PCM overdose.

Her liver function tests before and after the incident was compared. At post one hour after PCM overdose, her alanine transaminase (ALT) decreased from 6.8 to 4.7u/L, aspartate transaminase (AST) dropped from 43.9 to 33.9u/L and alkaline phosphatase (ALP) decreased from 247.2 to 228u/L. Subsequent liver function tests at 24 hour and 48 hour post PCM overdose also showed no signs of derangement. The measured PCM levels in the blood four hours and 22 hours post PCM overdose were 52mg/L and 3mg/L respectively. IV NAC regimen was completed for 21 hours and the girl did not show any sign of PCM toxicity.

Thereafter, the patient had five major operations for her medulloblastoma and was currently being ventilated in the paediatric surgical intensive care unit (PSICU). Her latest diagnosis was pseudomeningocelle due to the presence of residual tumour after five major surgeries. Her next treatment plan was either chemotherapy or further surgical intervention depending on parents' decision from the scheduled family conference with the oncology and surgical specialists.

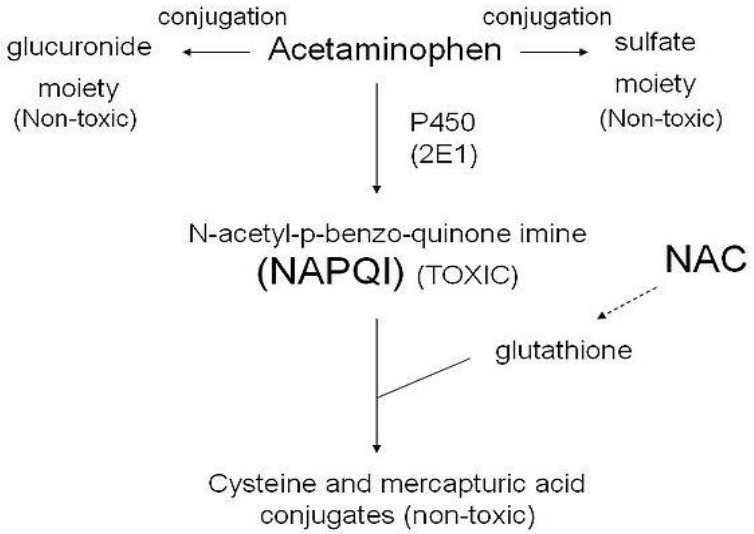

Figure 1. Metabolic pathway of acetaminophen a.k.a. paracetamol.

Discussion

In paediatric population, paracetamol is being metabolised in the liver by three pathways primarily sulfation, followed by glucuronidation and lastly oxidation by CYP2E1 into N-acetyl-p-benzoquinone imine (NAPQI), a toxic metabolite.[4] This metabolism pathway is illustrated in Figure 1. In a healthy individual, NAPQI is rapidly conjugated with glutathione into non-toxic cysteine and mercapturic acid conjugates that will be excreted renally. In case of acute PCM overdose, the glucuronidation and sulfation conjugation pathways become saturated, leading to an increased formation of oxidative NAPQI. Excessive NAPQI production results in depletion of glutathione stores to approximately 30% in which NAPQI starts to bind to hepatocellular proteins. NAPQI-protein adducts are formed, causing oxidative stress leading to cascade of inflammatory responses and subsequently, hepatocellular damage and death.[5] The severity of liver injury is correlated to the degree of elevation of alanine transaminase (ALT) and aspartate transaminase (AST). In this case report, monitoring of the liver function tests (LFT) over two days period did not show any elevation trend in ALT and AST, with all ALT and AST values within the normal range; suggesting no sign of liver injury.

The brand of paracetamol injection being used in this hospital setting is Ifimol with the standard strength of 10mg/ml. The usual dosing of oral and IV PCM for paediatric population is 15mg/kg per dose every four to six hours with a maximum of 60 mg/kg in 24 hours.[6] Administration of PCM exceeding 60mg/kg/day is considered as PCM overdose. An article by Dart and Rumack (2012) indicates that evaluation of PCM toxicity is necessary for cases with a single IV PCM dosing error over 150mg/kg.[2] In this case, the dosing error was only 120mg/kg suggesting that assessment for PCM toxicity is optional and there is no need for NAC intervention. However, the decision to initiate NAC intervention for this child was an ideal management. Two cases reported in United Kingdom in which one case of a five months old child who received 90mg/kg IV PCM with no NAC

intervention, developed hepatic impairment. Another case of six months old child was treated with NAC after administration of 75mg/kg IV PCM, remained well without hepatic impairment.[7] Beringer et. al (2011) suggests NAC regimen to be started regardless of any signs and symptoms of hepatic damage for any PCM dose of over 60mg/kg/day. On the other hand, Turkey National Poisons Information Service 2013, guided by Poisindex from Micromedex recommends NAC intervention for IV PCM overdose above 100mg/kg/day.[10] American Association of Poison Control Centers also urges the need to start NAC regimen of intake of PCM over 100mg/kg/day for children less than six years old.[11] Based on these findings, it is recommended to start NAC intervention for this child with IV PCM overdose of 120mg/kg/day.

In cases of suspected PCM toxicity, clinical practice guidelines propose that the serum level of PCM to be measured four hours post ingestion and to be plotted against Rumack-Matthew nomogram as shown in Figure 2 to justify the need for NAC regimen.[4] This was the main reason for the blood sample taken directly post PCM overdose was rejected since the measured PCM level cannot be plotted onto the Rumack-Matthew nomogram for less than four hours post PCM overdose. Rumack-Matthew nomogram is specifically designed for management of oral PCM overdose. Nonetheless, Dart and Rumack (2012) suggested that the same nomogram can be used for IV PCM overdose since there was no other similar standard protocol available.[2] Based on the measured TDM levels for PCM taken at four hours (52mg/L) and 22 hours (3mg/L) post PCM overdose and to be plotted onto the Rumack-Matthew nomogram, there will be no sign of hepatoxicity expected.

Table 1: NAC regimen for paracetamol overdose/toxicity for children less than 20kg.[9]

NAC Dose	Dilute in Dextrose 5%	Duration (Rate)
150mg/kg	3ml/kg (30ml)	1 hour (30ml/hr)
50mg/kg	7ml/kg (70ml)	4 hours (17.5ml/hr)
100mg/kg	14ml/kg (140ml)	16 hours (8.75ml/hr)

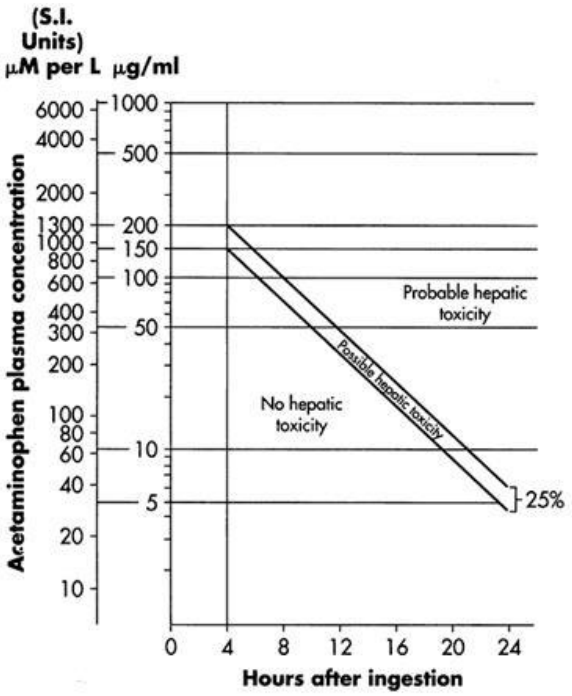

Figure 2: Rumack-Matthew Nomogram for paracetamol overdose cases.

However, NAC regimen was still being completed for 21 hours as a preventive step for possible hepatic damage.

N-Acetylcysteine (NAC) is the only antidote available for management of PCM overdose-induced hepatotoxicity cases. It is converted into glutathione pre-cursor L-cysteine to conserve and replenish glutathione concentration in the liver.[8] Perseverance of glutathione store in the liver shields any possible oxidative damages from NAPQI, indicating the need to administer NAC as soon as possible. Kerr et.al (2005) reported an increase risk of hepatoxicity by 3% if NAC regimen started after 10 hours post PCM overdose.[12] The American Association of Poison Control Centers' National Poison Data System also strongly recommend the urgency for NAC regimen within 8 to 10 hours post PCM overdose to minimise risk of PCM induced hepatotoxicity.[13] In this case report, IV NAC regimen was given to the child within one hour post PCM overdose and no sign and symptoms of hepatotoxicity was detected.

Conclusion

Despite being the safest analgesic, paracetamol overdose is still a common agenda in paediatric population, involving both intravenous and oral forms. Almost all IV PCM overdose cases happening around the world were iatrogenic and therefore, less likely to be reported in order to safeguard the professionalism and integrity of the personnel involved. This leads to an increase need to report such cases to the National Poison Centre in Malaysia to spread the awareness among the health professionals and also to promote the new formation of a standard management when it comes to unusual IV PCM overdoses cases.

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