KL Kwok 郭嘉莉
YM Fu 符儒明
DKK Ng 吳國強

Hepatotoxicity and persistent renal insufficiency after repeated supratherapeutic paracetamol ingestion in a Chinese boy

一名華裔男童重覆服用過量對乙酰氨基酚後出現肝中毒及持續腎功能不全

Paracetamol has always been regarded as a useful and safe drug. The risk of toxicity with repeated supratherapeutic paracetamol is an underrecognised condition. We report on a 12-month-old boy who presented with hepatotoxicity, disseminated intravascular coagulation and persistent renal insufficiency 4 days after repeated ingestion of a supratherapeutic dosage of paracetamol. To the best of our knowledge, this is the first reported case of paediatric chronic paracetamol poisoning among the Chinese population. In addition, persistent renal insufficiency has not been a previously reported feature of chronic paracetamol poisoning. We propose that renal damage is the result of the synergistic effect of hypoperfusion and paracetamol overdose.

對乙酰氨基酚一向被視為有用及安全的藥物；但重覆服用過量對乙酰氨基酚引致中毒的可能性，並未得到重視。本文報告一名12個月大男童，重覆服用過量對乙酰氨基酚4天後，出現肝中毒、分散的血管凝固，以及持續的腎功能不全。就作者所知，這是對乙酰氨基酚慢性中毒的首宗華裔兒童個案。而持續腎功能不全亦非有紀錄的慢性對乙酰氨基酚中毒徵狀。我們認為，腎臟受損是灌注不足及過量對乙酰氨基酚，兩者互相作用而引致的。

Introduction

Paracetamol is the antipyretic and analgesic of choice for children because its safety and efficacy are well recognised. However, the perceived safety of paracetamol may contribute to a failure to identify children who are at increased risk, as well as a delay in diagnosis and treatment of paracetamol intoxication.

Case report

A 12-month-old boy with good past health presented to the Department of Paediatrics of the Kwong Wah Hospital in August 2003 because he had had a fever and cough for 3 days. Upper respiratory tract infection was diagnosed, for which oral and suppository paracetamol were given, together with cefaclor, chlorpheniramine, promethazine, and vitamin supplements. He developed vomiting, diarrhoea, and mucus in the stool subsequently 2 days later, for which paracetamol, dimenhydrinate, and kaolin were given. The diarrhoea persisted, and paracetamol, ceftibuten, domperidone, kaolin, and *Saccharomyces boulardii* (as a 'probiotic') were prescribed later on the same day. The Table summarises the treatments administered during the three consultations.

Four days after the initial consultation, the boy's parents noticed that he was less active and they brought him back to the hospital. Drug history taken by contacting all the doctors that patient visited before admission revealed that a supratherapeutic dose of paracetamol had been taken by the patient: 80 $mg \cdot kg^{-1} \cdot d^{-1}$ on the first 2 days and 70 $mg \cdot kg^{-1} \cdot d^{-1}$ on the third day of presentation; the total

Key words:
Acetaminophen;
Drug toxicity;
Infant;
Overdose

關鍵詞：
對乙酰氨基酚；
藥物中毒；
嬰兒；
過量

Hong Kong Med J 2004;10:61-4

Department of Paediatrics, Kwong Wah Hospital, 25 Waterloo Road, Kowloon, Hong Kong
KL Kwok, FHKAM (Paediatrics)
YM Fu, MRCPCH
DKK Ng, FRCP, FHKAM (Paediatrics)

Correspondence to: Dr KL Kwok (e-mail: cklkwok@yahoo.com)

Table. Treatments given in three medical consultations

Date	Treatment given	Dosing schedule	Actual amount taken
Day 1 12:00	Paracetamol suppository	250 mg/d as needed	3 doses from day 1-3
	Paracetamol oral	125 mg every 6 hours	4 doses on day 1 and 4 doses on day 2
	Cefaclor	62.5 mg every 8 hours	6 doses from day 1-2
	Promethazine	5 mg	Not taken
	Kiddi Pharmaton*	5 mL/d	2 doses
	Chlorpheniramine	1.5 mg every 6 hours	4 doses on day 1 and 4 doses on day 2
Day 3 02:00	Kaolin/pectin	5 mL	2 doses
	Dimenhydrinate	7.5 mg	2 doses
	Paracetamol	120 mg	2 doses
Day 3 16:30	Paracetamol	125 mg	1 dose
	Domperidone	5 mg	1 dose
	Kaolin/pectin/dimethicone/dicyclomine	0.625 g/1.875 mg/12.5 mg/1.25 mg	1 dose
	Ceftibuten	125 mg	1 dose
	Saccharomyces boulardii	250 mg/d	1 dose

* Kiddi Pharmaton (per 15 mL): lysine 300 mg, calcium 130 mg, phosphorus 200 mg, vitamin B_1 3 mg, vitamin B_2 3.5 mg, vitamin B_6 6 mg, vitamin D_3 600 IU, vitamin E 15 mg, nicotinamide 20 mg, D-panthenol 10 mg

amount of paracetamol consumed had been 2115 mg (232 mg/kg) within the past 3 days prior to this admission. On admission, the patient's body weight was 9.2 kg and he was febrile and lethargic. His heart rate was 225 beats per minute (reference range for 1-year-olds, 105-170 beats per minute) and blood pressure was 90/79 mm Hg (mean for 1-year-olds, 90/55 mm Hg). The initial diagnosis was shock secondary to dehydration as a result of gastro-enteritis and sepsis. Ampicillin and cefotaxime were given.

The patient was transferred to the intensive care unit (ICU) where he had an episode of hypotension. Echocardiography revealed impaired left ventricular contractility and an ejection fraction of 45% (reference level, ≥63%). Dopamine (10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was required for 1 day to maintain stable haemodynamic status. Creatine kinase (CK) was elevated, at 53 600 U/L; tests for CK isoenzymes were not available, but repeated assays of troponin I gave normal results. The abnormally high CK level might have been due to rhabdomyolysis secondary to paracetamol overdose,[1] although neither hyperkalaemia nor myoglobinuria could be documented. The CK level returned to normal after 5 days. Ampicillin was stopped 1 day after admission and cefotaxime was continued, for a total of 11 days. Bacterial cultures of blood, urine, cerebrospinal fluid, and stool were negative. Viral culture of stool and paired viral titres of blood were also negative. Signs of hepatotoxicity were evidenced by raised levels of aspartate aminotransferase (7450 U/L; reference level, <48 U/L) and alanine aminotransferase (2720 U/L; reference level, <33 U/L). The patient had coffee-ground aspirate and haematuria. Clotting profile was deranged (prothrombin time, 28 s [reference range, 9-13 s]; activated partial thromboplastin time, >120 s [24-41 s]; international normalised ratio, 2.6; D-dimer, 2.0-8.0 μg/mL [<0.5 μg/mL]). In addition, he had thrombocytopenia (platelet count, 62 $x10^9$ /L). These findings were compatible with the diagnosis of disseminated intravascular coagulopathy, which was corrected by multiple transfusions of fresh frozen plasma and platelet concentrates over the first 2 days of admission. The bilirubin level, however, was normal (3 μmol/L) on admission. Levels of liver enzymes returned to normal after 18 days. The serum paracetamol level, 4 hours after the last paracetamol ingestion, was 0.06 mmol/L (9.06 μg/mL). According to POISINDEX,[2] N-acetylcysteine (NAC) is warranted when the paracetamol level exceeds 10 μg/mL on presentation. In addition, the condition of the patient had improved already, NAC was not given.

The patient had severe metabolic acidosis (pH 6.93; base excess, -24.2 mmol/L) and transient hypoglycaemia (1.2 mmol/L) on day 1 at ICU. Urinalysis for metabolic and toxicology screening gave negative results, but the ammonia level was slightly above normal (55 μmol/L [reference range, 21-50 μmol/L]). Lactate and pyruvate levels were increased to three times the normal level on admission, but were completely normalised after 2 weeks.

The boy had persistent diarrhoea and abdominal distension after admission, with sluggish bowel sounds and bile-stained vomitus. *Clostridium difficile* cytotoxin and rotavirus were absent from the stool. An abdominal X-ray showed bowel distension and multiple fluid levels, which were compatible with the diagnosis of paralytic ileus. The serum amylase level was elevated, at 1143 U/L (reference range, 25-85 U/L), but it normalised after 5 days. Computed tomography of the abdomen was unremarkable. The abdominal distension improved subsequently with conservative management. Diarrhoea persisted, however, despite the administration of elemental formula. Oesophagoduodenoscopy with biopsy did not show any significant disease. Parenteral nutrition was given for 17 days; elemental formula was reintroduced with success and normal formula was resumed and tolerated 1 month later.

The patient maintained normal urine output (5 $mL \cdot kg^{-1} \cdot h^{-1}$) in spite of shock. However there was severe proteinuria in the nephrotic range. Tubular dysfunction was shown by an increased fractional excretion of sodium (10%) and raised β_2-microglobulin in the urine (8.49 μg/mL). The glomerular filtration rate (GFR) was low (34 mL/min/1.73 m^2). Anti-

nuclear antibody and rheumatoid factor were negative. Sonography of the kidneys was normal. The proteinuria and tubular dysfunction recovered 2 weeks later. There was one episode of urinary tract infection caused by *Pseudomonas* spp, which cleared up after 1 week of ceftazidime. Septrin was given as prophylaxis. The micturiting cystourethrogram was normal. The dimercaptosuccinic acid scan (a contrast study of the renal excretory function) showed bilateral renal scars and mildly right atrophic kidney. Proteinuria subsided gradually and GFR improved from 34 to 44 mL/min/1.73 m^2 (lower limit of normal GFR for 1-year-olds, 63 mL/min /1.73 m^2). Review of previous computed tomograms did not show any calcification diagnostic of 'analgesic nephropathy'.[3] At the time of writing, the patient has been followed up for 10 months, and the GFR has remained low (54 mL/min/1.73 m^2).

Discussion

Paracetamol is generally perceived as a safe drug. The recommended paediatric dose is 10-15 mg/kg four times a day, or up to 60 $mg \cdot kg^{-1} \cdot d^{-1}$.[4] A minimum toxic threshold of total paracetamol ingestion of 175 mg/kg over 2 to 4 days has been suggested.[5] In a paediatric population, chronic or repeated supratherapeutic paracetamol ingestion has been defined as the repetitive ingestion of greater than 90 mg/kg over a 24-hour period.[2] There is evidence that hepatotoxicity might result from doses of as low as 20 $mg \cdot kg^{-1} \cdot d^{-1}$ given for 7 days.[6] Although the risk of developing severe toxicity after a single, high dose of paracetamol ingestion appears to be lower in children than in adults,[5] which may be because of the age-related difference in metabolism,[6] there have been reports of severe hepatotoxicity[7] and even death[8] resulting from prolonged repeated therapeutic and supratherapeutic dosing.

Paracetamol itself is a nontoxic substance. It is metabolised mainly in the liver by conjugation with glucuronic acid and sulphuric acid into nontoxic metabolites. A small proportion is metabolised through cytochrome P-450, leading to the production of the hepatotoxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). Normally, NAPQI is detoxified by glutathione conjugation in the liver. But when the NAPQI level exceeds the capacity of glutathione stores, hepatotoxicity will result from the binding of NAPQI to hepatocytes, thereby causing hepatic necrosis.

Proposed risk factors for toxicity with chronic use of paracetamol are shown in the Box.[5] This patient fitted into the risk profile proposed by Kearns et al[10]: he was a febrile infant who was younger than 2 years with poor feeding and was given a supratherapeutic dose of paracetamol for a period of time. He had typical features of paracetamol overdose—namely, normal bilirubin level despite liver derangement, which was consistent with previous reported findings.[2] A high amylase level without clinical signs of pancreatitis has also been reported.[2]

A few points need to be highlighted. Firstly, doctors should always be alert for the possibility of paracetamol overdose. Failure to recognise the risk factors and in cautious prescription of an appropriate dose according to body weight led to hepatotoxicity in the patient in our case.

Risk factors for hepatotoxicity caused by paracetamol
- Younger age
- Total dose, frequency of dose, duration
- Prolonged fasting or chronic malnutrition
- Febrile illness or viral infection
- Family history of hepatotoxic reaction or genetic predisposition
- Concomitant usage of drug that induced enzyme cytochrome p-450

Secondly, we should correct the behaviour of 'fever phobia'. Russell et al[11] illustrated how one should view fever as a symptom, not as a disease. The American Academy of Pediatrics reminds parents that the complete normalisation of a child's temperature is neither necessary nor possible.[12] The current recommendation by the World Health Organization for management of fever in children includes the use of paracetamol when the body temperature is 39°C or higher.[13] Adjuvant therapy such as tepid sponging can be employed in refractory fever. There is no evidence that rectal paracetamol is superior or that a higher dose of rectal paracetamol should be used in children.[14] In contrast, peak drug levels after rectal administration are unpredictable and often do not achieve therapeutic levels after recommended dosing.[15] Instructions should also be given to parents not to administer oral and rectal paracetamol concomitantly.

Thirdly, failure to recognise paracetamol overdose and administer NAC timely might prolong the course of recovery. It has been proposed that NAC be given to all patients who show measurable serum paracetamol irrespective of clinical status, and that treatment be continued until 36 hours after the last dose.[5] There is no consensus on the cut-off level of serum paracetamol. Some authors have suggested that 40 μmol/L (10 μg/mL) or greater at 24 hours after ingestion of a dose could predict the likely development of liver failure,[16,17] as portrayed in the normogram adapted from Rumack and Mathews. Using this normogram to predict hepatotoxicity might be inappropriate, however, because it is derived from adult patients who have taken a single suicidal overdose—not from children with repeated oral doses of paracetamol. Furthermore, the serum concentration varies widely after multiple doses of paracetamol.[18]

Fourthly, persistent renal impairment secondary to chronic paracetamol toxicity has not been reported. Isosthenuria (loss of urinary concentration capacity—that is, high normal urine output despite shock) was present in this patient and could have been secondary to renal hypoperfusion or analgesic-related toxic injury.[19] There is currently insufficient evidence in the literature to conclude that chronic use of acetaminophen is associated with an increased

risk of chronic renal disease.[20] In addition, the fact that there was absence of papillary calcification, which is a sensitive test for analgesic nephropathy,[3] did not support this causal relationship. However, renal hypoperfusion alone seems insufficient to explain the persistence of renal impairment and the heavy proteinuria (to the extent of inducing nephrosis). Hence, we propose that the combination of both the presence of shock and paracetamol overdose led to the observed renal problem in the patient in our case.

Finally, special precaution should be taken when making prescriptions to small children. This patient in our case was initially diagnosed to have gastro-enteritis, for which kaolin and pectin, as well as dimenhydrinate were prescribed. In fact, kaolin and pectin are not recommended for acute diarrhoea in the presence of high fever in infants and children younger than 3 years.[21]

Conclusion

Paracetamol is the antipyretic of choice for many doctors. However, we should not have a false sense of security towards commonly used drugs. Meticulous calculation is always essential in prescribing to paediatric patients. Education is important to eliminate 'fever phobia' and to increase the awareness of the serious adverse effects of paracetamol, so that this drug is used with due care and respect.

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