

Can liver toxicity occur at repeated borderline supratherapeutic doses of paracetamol?

To the Editor—Kwok et al¹ recently presented a very illustrative case of paracetamol toxicity in the Journal. Although, in my opinion, it was a genuine case of paracetamol toxicity arising from borderline overdosing of paracetamol, some aspects of the case were confusing and need clarification.

Firstly, the 250-mg/kg dose of rectal paracetamol, which was divided into three doses per day for 3 days (each dose equivalent to 27 mg/kg) were overdoses, because the recommended dose is 10 to 15 mg/kg.² However, the authors failed to pinpoint this, and instead focused on the daily dose, which in fact was only at the upper limit of the recommended daily dose. The Pediatric Dosage Handbook recommends that 10 to 15 mg/kg be given every 4 to 6 hours, and not more than five doses per day.² Accordingly, the maximum dose allowed in a day is 75 mg/kg, which is about the same as the amount the patient was taking daily: roughly 80 mg/kg for 2 days and 70 mg/kg for 1 day.

Secondly, abundant evidence exists in the literature that slight overdosing in children can result in toxicity. Liver toxicity occurred in two patients: one at six doses of 25 mg/kg per day for 2 days and the other at six doses of 28 mg/kg per day for 2 days.³ Another case of liver toxicity occurred in a 12-year-old boy, who received a mean daily dose of 70 mg/kg for 6 days, although the maximum was 108 mg/kg on one particular day.⁴ These cases suggest that paracetamol has a rather narrow therapeutic index in some children. In a review article on paracetamol toxicity among children, the therapeutic index was 1.7.⁵ Instead of quoting the above examples which are more relevant, Kwok et al, however, quoted an example from the literature in which paracetamol toxicity occurred at normal dose of 20 mg/kg/day.⁶ Quoting this case fell short of illustrating that liver toxicity occurs at slight overdosing of paracetamol but actually led to another important controversial point: liver toxicity occurring at normal doses of paracetamol, which Kwok et al failed to elaborate further.

Finally, Kwok et al seemed ambivalent about whether N-acetylcysteine (NAC) is indicated in repeated supratherapeutic doses of paracetamol, and they did not administer

NAC. In my opinion, NAC was clearly indicated. In cases of single high-dose ingestion of paracetamol, the decision to administer NAC is usually determined by whether the serum paracetamol level has reached a toxic level, as defined by the graph of Rumack and Matthew.⁷ After repeated supratherapeutic doses, however, the standard recommendation in cases of toxicity is administration of NAC, regardless of the serum paracetamol level.⁸ The reason for initiating NAC therapy is that repeated supratherapeutic dosing of paracetamol could overwhelm the capacity of the liver to detoxify the metabolite N-acetyl-p-benzoquinone imine. The serum paracetamol level in this situation cannot serve as a guide to toxicity, because the half-life of the drug is 4 hours and supratherapeutic doses alternating with normal doses could nevertheless result in a non-toxic level in the graph of Rumack and Matthew.

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References

1. Kwok KL, Fu YM, Ng DK. Hepatotoxicity and persistent renal insufficiency after repeated supratherapeutic paracetamol ingestion in a Chinese boy. *Hong Kong Med J* 2004;10:61-4.
2. Taketomo CK, Hodding JH, Kraus DM, editors. *Pediatric dosage handbook*. 8th ed. Cleveland, US: Lexi-Comp Inc; 2002.
3. Rivera-Penera T, Gugig R, Davis J, et al. Outcome of acetaminophen overdose in pediatric patients and factors contributing to hepatotoxicity. *J Pediatr* 1997;130:300-4.
4. Hynson JL, South M. Childhood hepatotoxicity with paracetamol doses less than 150 mg/kg per day. *Med J Aust* 1999;171:497.
5. Heubi JE, Bien JP. Acetaminophen use in children: more is not better. *J Pediatr* 1997;130:175-7.
6. Miles FK, Kamath R, Dorney SF, Gaskin KJ, O' Loughlin EV. Accidental paracetamol overdosing and fulminant hepatic failure in children. *Med J Aust* 1999;171:472-5.
7. Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. *Pediatrics* 1975;55:871-6.
8. Sweetman SC. *Martindale: the complete drug reference*. 33rd ed. London: Pharmaceutical Press; 2002.

Unnecessary phobia of paracetamol

To the Editor—The case of paracetamol toxicity reported in the Journal by Kwok et al¹ was widely covered in the local press. Apart from the authors' goodwill to remind doc-

tors and to educate childcarers of the serious side-effects of paracetamol that can occur with even borderline overdosing, I am afraid that they might have unintention-