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

To the Editor—Kwok et al[1] 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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Unnecessary phobia of paracetamol

To the Editor—The case of paracetamol toxicity reported in the Journal by Kwok et al[1] was widely covered in the local press. Apart from the authors' goodwill to remind doctors 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-

ally created a sense of phobia of paracetamol among prescribing clinicians, particularly because of the inclusion of some ambiguous literature reviews.

The authors quoted a report in which dosages as low as 20 $mg \cdot kg^{-1} \cdot d^{-1}$ for 7 days resulted in toxicity.[2] According to that report, we would be confronted with a new situation—namely, that paracetamol is an unsafe drug that is capable of causing serious toxicity in children at normal doses. This finding is contrary to the general assumption that paracetamol is a safe drug when appropriately used. In my search of the literature, liver toxicity due to therapeutic doses of paracetamol has never been proven beyond doubt, because of the poor quality of the existing paediatric data. There were cases of alleged hepatotoxicity arising from ingestion of reportedly normal dosages: 20 $mg \cdot kg^{-1} \cdot d^{-1}$ for 7 days in 129-month-old child,[2] which was quoted by Kwok et al in the 'discussion' part of their article, 71 $mg \cdot kg^{-1} \cdot d^{-1}$ for 4 days in a 31-month-old child,[2] 78 $mg \cdot kg^{-1} \cdot d^{-1}$ for 1 day in a 4-year-old boy,[3] and 45 $mg \cdot kg^{-1} \cdot d^{-1}$ in a 7-week-old female infant for 6 to 8 days.[4] The corresponding drug levels were 27 μg/mL (180 μmol/L) 1 day after admission, 24.2 μg/mL (160 μmol/L) 1 day after admission, 250 μg/mL on admission, and 10.7 μg/mL 54 hours after the last dose, respectively. These are toxic levels according to the Rumack-Matthew normogram,[5] which would imply that much larger doses might have been ingested. The authors of the reports cautioned that because the consumed drug amounts were inevitably derived from the prescription history only, they might not reflect the true doses given. Attempted confirmation from childcarers sometimes has to be taken with a grain of salt. Hence, measurement of the blood drug level is the only reliable guide to dosing.

Because liver toxicity may result from supratherapeutic doses of paracetamol, the frequency of such occurrence is crucial to the safety margin of the drug and hence the safety of the prescription and the prescribing doctor. According to a recent report of Children's Mercy Hospital at Kansa City reviewing 10 years' experience of paracetamol toxicity,[6] they identified two types of toxicity: repeated unintentional overdosing of paracetamol and ingestion of single high-dose paracetamol as a result of suicidal attempts. Only one case of hepatocellular toxicity occurred in a total of 172 cases in the former group whereas 25 cases of hepatocellular toxicity occurred in 140 cases in the latter group. Hence, the tragedy that some children are unpredictably susceptible to liver toxicity at even borderline supratherapeutic doses is fortunately uncommon. Factors increasing susceptibility are malnutrition: causing increased P-450 mixed-function oxidase activity and depletion of the glutathione necessary to detoxify the metabolite N-acetyl-p-benzoquinone imine; previous liver injury from, say, prematurity or necrotising enterocolitis; concomitant chronic dosing of P-450–inducing agents, such as isoniazid and phenobarbitone; and genetic predisposition.

I agree that overenthusiastic prescription of paracetamol as a precaution to fever development is not necessary. Frequent, large doses given for a prolonged duration are prone to creating overdosing. However, I would assert that on the basis on current scientific knowledge, phobia of paracetamol given in the usual dose to treat pyrexia is unnecessary.

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Authors' reply

To the Editor—We would like to thank Drs Lee and Ng for their comments on our article.[1]

We agree with Dr Lee that the recommended dose for paracetamol is 10 to 15 mg/kg every 4 to 6 hours. However, we would like to stress the importance of including a daily maximum dosing frequency, which is four times per day, as quoted by British National Formulary.[2] Hence, provided that paracetamol is given according to this recommendation, we concur with Dr KW Ng that phobia of paracetamol is unnecessary.

However, we disagree with Dr Lee that the toxicity should be attributed solely to rectal paracetamol. Firstly, the pharmacokinetics of rectal paracetamol have been extensively studied,[3-6] and it has been suggested that even a rectal regimen of 25 mg/kg every 6 hours for a mean of 2 to 3 days did not result in supratherapeutic concentration.[3] Secondly, because oral and rectal paracetamol are metabolised through the same mechanism, we do not agree that toxicity from rectal paracetamol would contribute differently to the hepatotoxicity of the patient described in our report. Nevertheless, this scenario highlights the risk of concomitant use of both oral and rectal paracetamol resulting in overdose of the drug.

In our report,[1] we wanted to illustrate the possibility of hepatotoxicity resulting from doses as low as 20 $mg \cdot kg^{-1} \cdot d^{-1}$ given for 7 days. However, we do not want to imply that paracetamol is an unsafe drug. The discordance between drug history and serum drug level, as mentioned by Dr KW Ng, illustrates two points. On one hand, the discrepancy might reflect the possibility of inaccurate drug history, as pointed out by Dr Ng. On the other hand, a high serum paracetamol level might reflect the failure to metabolise and excrete the paracetamol. Hence, we would like to remind readers to look out for risk factors associated with impaired metabolism of paracetamol as listed in our article.[1]

We are grateful that Dr Lee reiterate the importance that N-acetylcysteine (NAC) should be considered in cases suspected to have hepatotoxicity secondary to chronic paracetamol poisoning, irrespective of the serum level. The reason NAC was not given in our case was because paracetamol overdose was not suspected in the first few days because of difficulty in obtaining a full drug history. The serum paracetamol assay was performed only after exhaustive inquiry on the patient's drug history, which raised the suspicion of paracetamol overdose. A blood sample that was taken at the time of admission was used to confirm our suspicion. Thus, we would like to alert health care workers about the possibility of chronic paracetamol overdose when faced with patients with unexplained liver derangement, because—unlike acute paracetamol overdose, which often bears a simple, straightforward history—chronic paracetamol overdose is an entity that is often missed because of the difficulty in obtaining an accurate drug history.

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Minimally invasive parathyroidectomy for regional hospitals

To the Editor—As one with a lifetime passion for perfecting surgical techniques, I was particularly thrilled to read a recent article in the Journal extolling the virtues of focused dissection of a preoperatively localised parathyroid adenoma through a small direct wound[1]—a technique I have come to realise, after almost a decade's search, as the optimal minimalist approach to parathyroidectomy in the setting of a general hospital. With the advent of videoscopic technology, the past decade has witnessed dramatic and revolutionary changes in parathyroid surgery.[2] No sooner had I reported the first series of totally endoscopic parathyroid adenectomy than it dawned on me that the technique was unnecessarily cumbersome.[3,4] I went on to try the simpler—but still cumbersome—endoscopy-assisted technique, until I settled recently for the most expedient, non-endoscopic technique, as described by the authors.[5] Notably, a local university hospital has also just reported the outcome of endoscopy-assisted parathyroidectomy for 66 adenomas.[6] Compared with the authors' open-dissection technique, the endoscopy-assisted technique was associated, understandably, with a longer operating time (77 versus 63 minutes) and a higher incidence of recurrent laryngeal nerve injury (3% versus 0%)—even in expert hands.[6] These findings reinforce my aforementioned conviction; however, some more controversies still exist.

I take issue with the authors' call for larger-scale randomised controlled trials comparing the focused approach with conventional bilateral exploration. Firstly, a plethora