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Approaches Toward Repeated Supratherapeutic Doses of Paracetamol in Children

A Survey of Medical Directors of Poison Centres in North America and Europe

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Abstract

Background: During the last few years there has been an increase in the number of reports of liver failure associated with prolonged paracetamol (acetaminophen) administration in children for therapeutic reasons.
Objective: To describe the approach taken by medical directors of poison centres regarding the treatment of repeated supratherapeutic doses of paracetamol in children.
Methods: Questionnaires mailed to the medical directors of 76 poison centres in North America and 48 poison centres in Europe asked respondents to comment on the management of a hypothetical case of a child who had received repeated doses of paracetamol at a daily dose of 90 mg/kg during a febrile illness and who presented to the emergency department with mildly elevated serum transaminase levels.
Results: The response rate was 62% for North American centres and 44% for European centres. There was a wide range of answers regarding the maximal safe daily dose of paracetamol. For the case described, 71% of the respondents suggested measuring paracetamol serum concentration. Fifty-four percent suggested treating the patient with acetylcysteine and 35% suggested not treating the patient.
Conclusions: Our study showed that there is little agreement among medical directors of poison centres on the toxic threshold for chronic exposure to paracetamol in children and on how these cases should be managed.

Background

Paracetamol (acetaminophen) is the most frequently used over-the-counter medication for children in the US.[1] When given in the recommended doses (10 to 15 mg/kg/dose every 4 to 6 hours),[2,3] paracetamol is a well tolerated medication. During the last few years, however, there has been an increase in the number of reports[4-11] of liver failure associated with prolonged paracetamol use for therapeutic reasons. Heubi et al.[8] described 47 children who received repeated doses of parace-

tamol that exceeded the recommended dose. Twenty-five (53%) of these children died and three (6%) needed liver transplantation. The paracetamol dose in the children who died ranged from 61 to 625 mg/kg/day. Five of the affected children in this series received only 50 to 75 mg/kg/day of paracetamol by history.

Nomograms[12,13] based on paracetamol serum concentrations and time after ingestion, predict the possibility of liver injury in cases of acute paracetamol ingestion, but do not predict toxicity in cases of chronic or recurrent exposures. Currently there is no consensus or accepted guidelines on how to treat such exposures. In the absence of such guidelines it is important to know the current practice regarding these cases and to highlight areas of disagreement. The objective of the current study was to describe the approaches taken by medical directors of poison centres regarding the treatment of repeated supratherapeutic paracetamol exposure of children.

Materials and Methods

In November 2000 we mailed questionnaires to 124 medical directors of poison centres in the US, Canada, and Europe. We identified 76 poison centres in North America from the 1999-2000 American Association of Poison Control Centers directory and the membership list of the Canadian Association of Poison Centres. We also identified 48 poison centres in Europe from the 1999 European Association of Poison Centres and Clinical Toxicologists Directory of Members. When the e-mail address was available, we sent an e-mail 2 weeks after the questionnaire. If we still received no response, we mailed a second letter and a second e-mail.

The questionnaire asked several questions about how the medical directors would manage a hypothetical case of a 2-year-old boy who had a runny nose, mild cough, had vomited three times and had a fever for 4 days. He had been treated with amoxicillin and with paracetamol 15 mg/kg every 4 hours (including during the night). When seen in an emergency department, the child was slightly dehydrated but otherwise well. The respondents were asked whether they would recommend checking the serum concentration of paracetamol and whether they would treat the patient with acetylcysteine. The respondents were asked to give the rationale for their decision. They were also asked what they consider to be the safe maximal daily dose of paracetamol and at what daily dose of paracetamol they would recommend checking liver enzymes. The hypothetical case and the questionnaire are presented in table I.

The Research Ethics Board of the Hospital for Sick Children, Toronto approved the study.

Data Analysis

We looked at the frequency of responses about the safe daily dose of paracetamol for children. We used the chi-square test to compare the answers given by toxicologists from the North America

Table I. Clinical scenario and survey questions

Clinical scenario	Questions
A 2-year-old boy was brought to an emergency department for fever. He had fever in the last 4 days. He also had a runny nose and mild cough. He has been drinking less than usual and refusing to eat. He vomited three times in the last 2 days. He was treated with amoxicillin for ear infection (50 mg/kg/day) and with paracetamol (acetaminophen) syrup 15 mg/kg every 4 hours (including during the night). In the emergency department the child is mildly dehydrated but looks otherwise well. His AST level is 95IU, ALT level is 75IU and his bilirubin is normal.	What do you consider to be the safe maximal daily dose of paracetamol for adults? What do you consider to be the safe maximal daily dose of paracetamol for children? At what daily dose of paracetamol will you recommend to check liver enzymes? What are your recommendations to the treating physician: Would you decide to recommend checking paracetamol serum concentration in the blood? Y/N Would you decide to recommend treating this child with acetylcysteine? Y/N What is the rationale for your decision?

with those of toxicologists from Europe. We considered a $p < 0.05$ as significant.

Results

We received 68 responses to 124 questionnaires, for an overall response rate of 55%. We received 47 responses from 76 North American centres for a response rate of 62% and 21 responses from centres in Europe for a response rate of 44%.

Sixty-five (96%) of the 68 respondents answered the question about the safe daily dose of paracetamol for children. Seven gave doses based on age groups rather than those based on bodyweight and were not included in the analysis. Fifty-eight (86%) of the 65 respondents answered in terms of milligram per kilogram. The median maximal daily dose considered safe for children was 75 mg/kg (range 50 mg/kg/day to 200 mg/kg/day). The distribution is presented in figure 1.

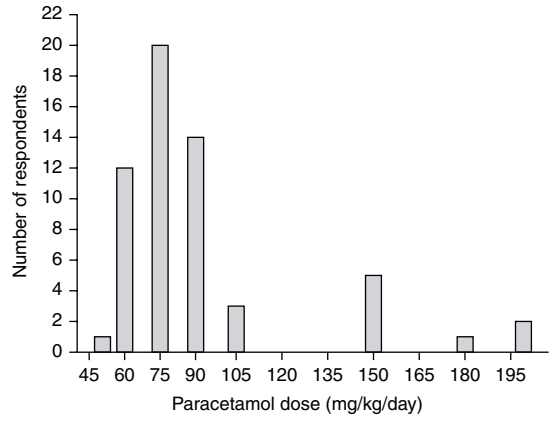

Fig. 1. Maximal daily dose of paracetamol (acetaminophen) considered by medical directors of poison centres to be safe for a child.

There was a wide range of answers regarding the daily dose of paracetamol at which liver function should be tested, with a median value of 90 mg/kg/day (range 60 mg/kg/day to as high as 200 mg/kg/day).

For the case presented, 48 (71%) of 68 respondents suggested measuring paracetamol concentrations in the serum, whereas 18 (26%) did not recommend measuring paracetamol serum concentration and 2 (3%) did not answer the question. Significantly more toxicologists from North America, 40 of 47 (85%), suggested measuring paracetamol serum concentration, whereas 10 of 20 (50%) respondents from Europe suggested doing so ($p = 0.007$).

Sixty-five respondents answered the question about treating the patient with acetylcysteine. Thirty-five (54%) of these suggested treating with acetylcysteine, 23 (35%) suggested not treating the patient, 4 (6%) suggested treating the patient if paracetamol serum concentration were high (although the definition of 'high' serum concentration was not given), and 3 (5%) could not reach a decision based on the information we provided. Of those who responded, 25 (68%) of the 37 medical directors from North America and 10 (48%) of 21 from Europe suggested treating the patient with acetylcysteine. This difference was not statistically significant ($p = 0.23$).

Discussion

Our survey found variability among the respondents on the management of repeated exposure to supratherapeutic doses of paracetamol of children. There was a wide range of responses as to the safe daily dose.

The differences we found are probably because of conflicting evidence and recommendations found in the published research on this drug. The toxic threshold for acute paracetamol ingestion is relatively well established, but the toxic threshold for chronic ingestion in children is not known. In a review article, Cranswick and Coghlan[14] suggested that the minimum toxic threshold is 175 mg/kg/day over 2 to 4 days. However, there have been cases[5,11] in which the chronic ingestion of more than 140 mg/kg/day for 2 to 3 days was associated with hepatotoxicity in infants and children. Heubi et al.[8] described some cases in which lower daily doses of 50 to 75 mg/kg had been associated with liver failure. Based on these cases, it has been

argued[15-17] that for young, febrile children, the therapeutic index of paracetamol may be lower than expected – between 75mg/kg/day and 90 mg/kg/day – if paracetamol is given for more than 24 hours.

The interpretation of paracetamol serum concentration in patients who have been exposed to repeated doses of the drug may be difficult. About two-thirds of the respondents in our survey suggested measuring paracetamol serum concentration in case of a child who received repeated doses of paracetamol in a cumulative dose of 90 mg/kg/day. It has been suggested that a serum concentration above the nomogram line might help in predicting the prognosis in these cases.[8] Although knowing the paracetamol serum concentration of children who have been exposed to repeated doses of the drug would help to establish the diagnosis of an paracetamol overdose; the finding of a low, or even undetectable, serum concentration cannot exclude such a diagnosis.[15,18] The decision whether or not to treat such patients with acetylcysteine should not rely solely on the values of the paracetamol serum concentration.[16] It is interesting that five respondents would have based their decision to treat with acetylcysteine on patients' paracetamol serum concentration. Our finding that North American toxicologists were more likely to recommend measurement of paracetamol serum concentration in these cases may indicate a higher awareness of liver toxicity after repeated supratherapeutic doses of paracetamol or a more risk-averse approach to treatment.

The approach taken by two-thirds of the toxicologists to treat the hypothetical patient with acetylcysteine is based on reported cases[4-9] describing therapeutic misadventures with paracetamol. Some of the children in reported overdose cases[6-9] received paracetamol in doses just slightly above the recommended 60 to 75 mg/kg/day. However, it is possible that the dose given in these cases was underreported.

Heubi and Bien[19] suggested that the reported cases of paracetamol intoxication after supratherapeutic doses are the tip of the iceberg, but the evidence is conflicting. An Australian study[9] reported that for 11 out of 18 children referred to a liver transplantation unit, the cause of liver failure was chronic exposure to paracetamol, whereas an American study[20] found that therapeutic misadventure with paracetamol was relatively uncommon, as was hepatocellular injury. It is important to note that all these studies are case reports or case series. It is possible that in some of these cases the infectious disease itself caused the liver disease, not the exposure to paracetamol.

The true incidence of paracetamol intoxication from repeated supratherapeutic doses is not known. Many parents are worried when their child has fever which they often treat with antipyretic drugs.[21-23] In a recently published study,[23] 14% of parents reported giving paracetamol at 3-hour intervals when their children had a fever. Another study[24] found that 15% of parents gave more than the recommended dose of paracetamol to their children. Therefore, patients similar to the hypothetical case presented by us may occur.

The study has several limitations. Because of the relatively low response rate from the European centres, the results may not reflect current practice in Europe. The low response rate also decreased the statistical power to detect differences between North American and European centres. It is also possible that the differences found in management, especially regarding the dose considered safe for a child, simply reflect different dosing guidelines in North America and Europe.

Clearly, among the medical directors of poison centres included in this survey there were differences in the response on how to treat children who have been exposed to repeated supratherapeutic doses of paracetamol. Since paracetamol is widely used for children and many parents may give supratherapeutic doses, it is important to have treatment strategies for such cases. Further studies are needed to establish such treatment strategies for children exposed to repeated supratherapeutic doses of paracetamol.

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