Predicting concentrations in children presenting with acetaminophen overdose

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Objective: To predict serum concentrations to evaluate and improve guidelines for the treatment of children (1 to 5 years) with accidental ingestion of acetaminophen elixir.

Methods: Acetaminophen concentrations for 1000 children were simulated with pharmacokinetic parameters and their expected variability. The distribution of concentrations arising from a 300 mg/kg dose at different age groups was predicted. These predictions were validated by comparison with concentrations obtained at 4 hours from 121 children with accidental ingestion of acetaminophen elixir.

Results: No child who presented with overdose had a concentration in the probable risk area of the Rumack-Matthew toxicity nomogram. Enteral charcoal administered 98 minutes (SD 44) after ingestion had no effect on serum concentrations. The simulation predicted that an acetaminophen dose of 300 mg/kg would result in concentrations of 32 to 208 mg/L (95% CI) at 4 hours after ingestion. The maximum concentration occurred before 2 hours in 95% of simulated children.

Conclusion: Children (1 to 5 years) with reported ingestion of >250 mg/kg acetaminophen elixir should have serum concentrations measured at 2 hours after ingestion rather than at the 4-hour time point recommended in adults. This can be expected to speed discharge and reduce anxiety. The use of enteral charcoal is unlikely to enhance acetaminophen elimination, unless it is given within an hour of acetaminophen ingestion. (J Pediatr 1999;135:290-5)

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Severe liver toxicity caused by a single dose of acetaminophen (paracetamol) elixir is rare in children 1 to 5 years.[1] Based on U.S. emergency department data, the estimated cost to evaluate a child who accidentally ingested acetaminophen was $272.[1] The diagnosis of potential acetaminophen toxicity is usually delayed until the serum concentration is measured 4 hours after ingestion. The diagnostic delay, blood sample requirement, and consequent anxiety may be an unnecessary inconvenience for many patients and their families when the children could be safely treated at home.

See editorial, p. 269.

Children between the ages of 1 and 5 years are thought to be less susceptible to toxicity than older children and adults.[2] The population pharmacokinetic model used in this study partly explains the relative protection that young children have against acetaminophen toxicity. Clearance of drugs is a nonlinear function of weight that decreases with increasing weight, whereas doses are commonly expressed as a linear function of weight. As a consequence, to achieve similar concentrations younger children require larger doses on a weight basis than older children and adults.

We have used simulation as a technique to explore the range of likely concentrations expected in children after an acetaminophen elixir overdose and have compared these concentrations with a

set of measured values. Simulation allows investigation of sensitivity to various assumptions about relationships between clearance and body weight. The pharmacokinetic model used allowed variability in the various model parameters and in the measured concentration. It also allowed incorporation of reasonable sources of study execution error such as variability in sampling time and times of reported ingestion.

METHODS

A retrospective review of children (1 to 5 years) who presented to a children's emergency department with accidental acetaminophen elixir ingestion from January 1995 to June 1997 was performed. The records of patients who had reported ingestions >50 mg/kg and who had serum acetaminophen concentrations >1.5 mg/L (minimum quantifiable concentration) at 4 hours were identified. These concentrations were compared with concentrations predicted by a 1-compartment, first order input, first order elimination model. Simulation was performed with a pharmacokinetic-pharmacodynamic simulation program (PharSight Trial Designer[3]). Parameter estimates and their variability from a standard reference text[4] and those reported from our institution[5] (Table I) were used to simulate time-concentration curves in 1000 subjects in each of 3 groups; age 1 year (weight 8 to 12 kg), 5 years (weight 16 to 22 kg), and adults (weight 55 to 85 kg). Pharmacokinetic parameter variability was assumed to have a log-normal distribution and used the coefficients of variation listed in Table I. The assay technique for analyzing high concentrations in our laboratory requires dilution of the sample and has a proportional measurement error of 10% and a minimal quantifiable concentration of 1.5 mg/L. This error was incorporated into the model. Error in the reported time of acetaminophen ingestion was given an SD of 10 minutes. No error was assumed in the time of blood sampling (4 hours). The simulation dose was 300 mg/kg. The weight for each child was sampled from a uniform distribution in the range associated with each group.

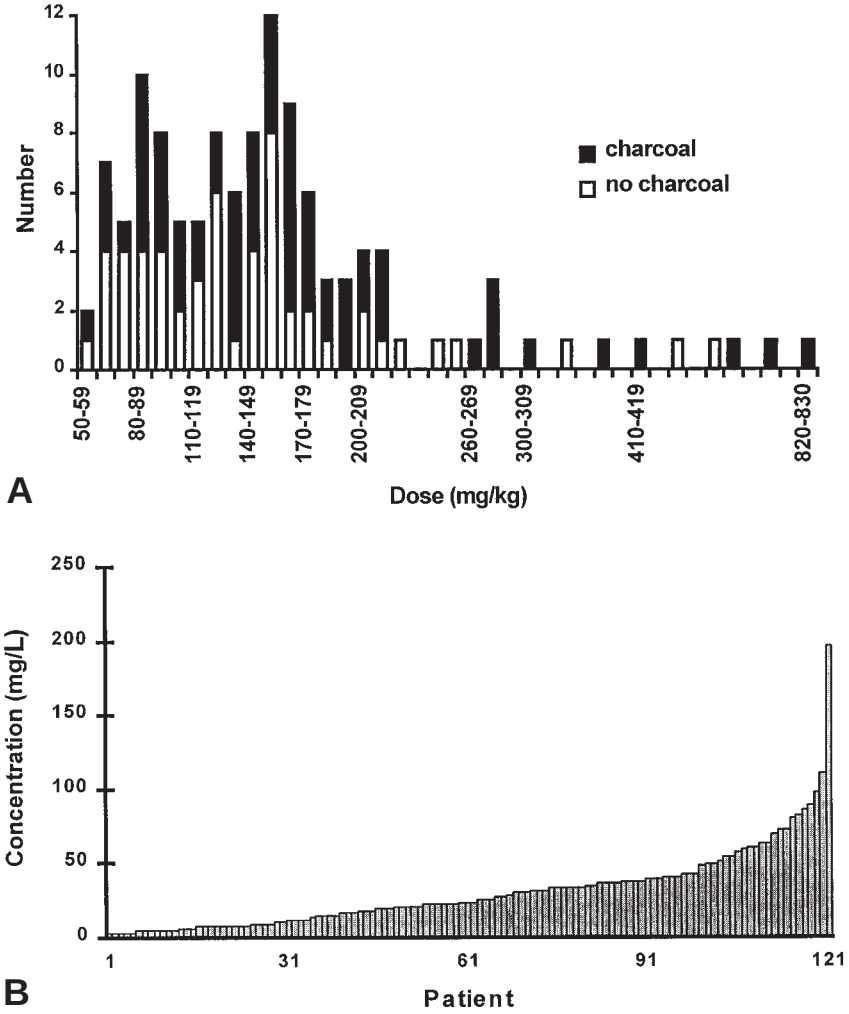

Fig 1. **A,** Reported dose ingested in children presenting with accidental acetaminophen ingestion. Proportion of children given charcoal in each dose range is shown as filled bar and those not given charcoal as open bar. **B,** Distribution of measured concentrations in children presenting with accidental acetaminophen ingestion.

Table I. Pharmacokinetic parameter estimates

	Per kilogram[4]		Allometric[5]	
Parameter	Value	CV%	Value	CV%
Clearance	0.3 L/h/kg	28	13.5 L/h/70kg	46
Volume of distribution	0.9 L/kg	23	60 L/70kg	21
Absorption half-time	10.3 min†	50	4.5 min*	63

*Elixir.
†Tablets and capsules.

Clearance and volume of distribution were expressed in the standard reference text as a linear function of weight (the per kilogram model), whereas our institution has reported parameter values derived with an allometric power model[6]:

$$P_i = P_{std} * (W_i / W_{std})^{PWR}$$

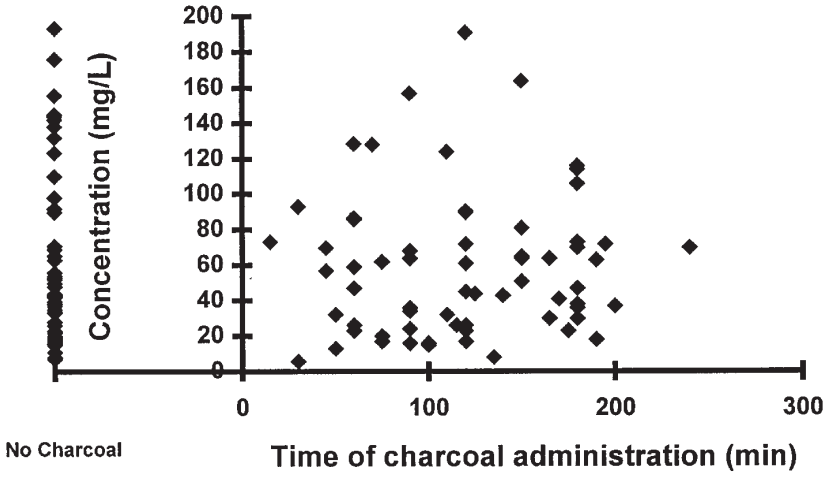

Fig 2. Lack of effect of charcoal on serum concentration in children presenting with overdose. Concentrations are normalized to dose of 300 mg/kg.

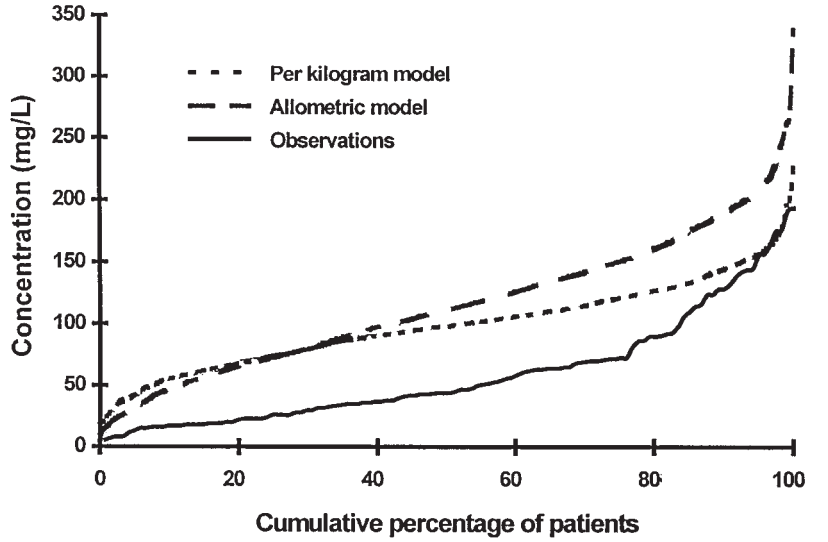

Fig 3. Distribution of simulated concentration estimates at 4 hours for 1000 children (8 to 22 kg) generated with per kilogram and allometric size models. These are compared with measured concentrations in children presenting with overdose. Observations are normalized to dose of 300 mg/kg.

Table II. Demographic data of children presenting with accidental acetaminophen ingestion (n = 121)

Mean age (SD)	33 (9) months
Mean weight (SD)	14.6 (2.8) kg
Median dose (range)	165 (50-822) mg/kg
Median concentration (range)	30 (5.5-181) mg/L at 4 h

where P_i is the parameter in the ith individual, W_i is the weight in the ith individual, and P_{std} is the parameter in an individual with a weight W_{std}. The standard person was assigned a weight of 70 kg. The *PWR* parameter was 0.75 for clearance and 1 for distribution volume.[7,8] The absorption half-life was not standardized for size, because this parameter is formulation-determined. It was assumed that acetaminophen elixir is prescribed for children (absorption half-life 4.5 minutes)[5] and tablets or capsules for adults (absorption half-life 10.3 minutes)[4].

RESULTS

A total of 218 children presented with accidental acetaminophen elixir ingestion, and of these 121 children (Table II) met the study criteria. The accuracy of the 4-hour sampling time is limited by the interpretation of retrospective chart reviews. The dose distribution and measured 4-hour concentrations are shown in Fig 1. No child had a serum acetaminophen concentration >200 mg/L.

Of the 121 children, 24 were given syrup of ipecac, 18 within the first hour after ingestion. Activated charcoal was given to 66 of the 121 children at a mean time of 98 minutes (SD 44) after ingestion. Children given charcoal ingested a mean (SD) acetaminophen dose of 180.9 mg/kg (134.2), whereas the dose in those not given charcoal was 146.9 mg/kg (90.9) ($P = .11$). Measured concentrations were normalized to a 300 mg/kg dose to compensate for the range of doses ingested. The mean (SD) concentration (normalized to a 300 mg/kg dose) without charcoal was 58 mg/L (47) and with charcoal 61 mg/L (42) (*t* test, $P = .7$). Neither the use nor the timing of charcoal administration had any apparent effect on concentration (Fig 2).

Population predictions at 4 hours with the per kilogram model had a bias[9] of 35.9% (CI 6.3% to 65.6%) when compared with the observed concentrations measured at 4 hours, whereas the bias for the allometric model was 18.1% (CI –6.2% to 65.7%). Fig 3 shows the distribution of 4-hour concentration predictions in 1- to 5-year-old (8 to 22 kg) children given 300 mg/kg with either the per kilogram or the allometric size model. They are compared with the distribution of the 4-hour concentrations observed in children with overdose after normalization to a 300 mg/kg dose. The Kolmogorov-

Smirnov 1-sample goodness-of-fit test showed the observed distribution was from the same distributions of populations specified by either the allometric model (D = 0.164, $P < .01$) or the per kilogram model (D = 0.246, $P < .01$).

The concentration range generated by simulation studies with the allometric model was lowest in the youngest patients (Table III). Simulated time-concentration profiles (95% CI) for children and adults after 300 mg/kg acetaminophen with the allometric model are shown in Fig 4. As expected, there was no age- (ie, weight) related trend with the per kilogram parameters (Table III). The population of patients in whom the maximum concentration was predicted to occur before 2 hours by the allometric model decreased with increasing body size (Table IV).

Acetaminophen doses that resulted in a serum concentration <200 mg/L (95% CI) are shown in Table V. The allometric model predicted lower doses than the per kilogram model. A dose of 250 mg/kg gave concentrations <200 mg/L in 99% of children 1 to 5 years. The percent of individuals with half-lives ≥4 hours in each of the age groups is shown in Table VI. Elimination half-lives increase with size, and adults have more than 4 times as many individuals with half-lives 4 hours and over when compared with 1-year-old children. Individuals with prolonged half-lives of ≥4 hours were disproportionately represented in the subpopulation, with concentrations >200 mg/L at 4 hours (Table VII).

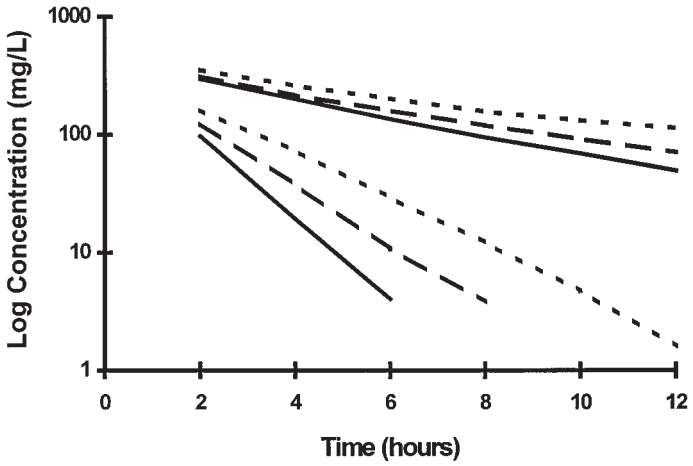

Fig 4. Confidence intervals (CI, 5% to 95%) of simulated concentration-time profiles for children and adults given 300 mg/kg acetaminophen (*solid line* = 1 year; *dashed line* = 5 years; *dotted line* = adults). Rumack-Matthew action line is same as 95% CI concentration-time profile for 1-year-old child.

Table III. Predicted concentrations (95% CI) after acetaminophen (300 mg/kg)

Age group	2 hours	4 hours	12 hours
Allometric model			
1 year (8-12 kg)	97-294 mg/L	19.5-199 mg/L	<MQC-50 mg/L
5 year (16-22 kg)	124-311 mg/L	38-214 mg/L	<MQC-71 mg/L
Adult (55-85 kg)	161-352 mg/L	73-259 mg/L	1.6-115 mg/L
Per kilogram model			
1 year (8-12 kg)	129-264 mg/L	45-159 mg/L	1.5-33 mg/L
5 year (16-22 kg)	127-265 mg/L	42-161 mg/L	1.5-32 mg/L
Adult (55-85 kg)	127-270 mg/L	48-161 mg/L	<MQC-35 mg/L

MQC, Minimal quantifiable concentration (1.5 mg/L).

Table IV. Percent of subjects with a maximum concentration achieved before 2 hours

Age group	Per kilogram (%)	Allometric (%)
1 year (8-12 kg)	97.1	96.3
5 year (16-22 kg)	97.1	93.5
Adult (55-85 kg)	97.6	91.2

DISCUSSION

The Rumack-Matthew[2] nomogram, widely used to guide management of acetaminophen overdose in adults and children, was derived from a study of 30 adult patients who ingested an overdose of acetaminophen.[10] The half-life was <4 hours in all patients without liver damage. The Rumack-Matthew nomogram is simply a line drawn on a time-log concentration plot from 200 mg/L at 4 hours with a half-life of 4 hours. An ad hoc "possible toxicity" line 25% below the standard nomogram (150 mg/L at 4 hours and 5 mg/L at 24 hours) has been proposed to allow for possible errors in plasma assays and ingestion times.[11] The risk of severe liver damage (as assessed by a plasma alanine aminotransferase activity exceeding 1000 U/L) increases with acetaminophen concentration.[12] Concentrations at 4 hours >150 mg/L, 250 mg/L, and 300 mg/L are said to be associated with a 25%, 40%, and 100% risk of severe liver damage, respectively, in adults.[12]

Toxicity and half-life are typically viewed as if there were a cause and effect relationship between them.[10,12] This implies that a long half-life seen after ingestion is due to impairment of liver function coinciding with the first passage of acetaminophen through the liver. This is unlikely because hepatic

Table V. Acetaminophen dose (upper 95% of CI) with peak concentration less than 200 mg/L at 4 hours

Age group	Dose mg/kg
1 year (8-12 kg)	300
5 year (16-22 kg)	280
Adult (55-85 kg)	230
Per kilogram (all ages >1 year)	375

Table VI. Age-related elimination half-lives (T1/2)

Age group	5%-95% CI for half-life (h)	% with T1/2 >4 hours
Allometric model		
1 year (8-12 kg)	0.3-10.6	7.9
5 year (16-22 kg)	0.5-11.6	14.4
Adult (55-85 kg)	0.7-14	37.5
Per kilogram model		
All ages >1 year	1.2-3.9	3.9

Table VII. Prolonged elimination half-lives in those individuals with concentrations greater than 200 mg/L at 4 hours after acetaminophen (300 mg/kg)

Age group	% Population with concentration >200 mg/L	% Population with half-life ≥4 hours
Allometric model		
1 year (8-12 kg)	4.4	40
5 year (16-22 kg)	8.2	66
Adult (55-85 kg)	23.8	76
Per kilogram model		
All ages >1 year	0.6	30

damage is not instantaneous and occurs progressively as hepatotoxic metabolites are formed. Half-life increases progressively with time in patients with liver failure.[12] This change coincides with liver function tests becoming abnormal 12 to 24 hours after ingestion of a hepatotoxic dose, but maximum derangement does not occur until day 3.[12] It seems more likely that hepatotoxicity occurs more commonly in those individuals who have low acetaminophen clearance and that these individuals have a longer half-life a priori. Furthermore the clearance of acetaminophen in 13 children with chronic liver disease is reported as no different from values reported in healthy children of a similar age.[13]

With the use of acetaminophen parameter estimates determined in children and based on an allometric size model, 37.5% of the adult population is predicted to have a half-life of 4 hours or more. This group of "slow metabolizers" occur more frequently (76%) in those adults with simulated concentrations >200 mg/L at 4 hours. Children (1 to 5 years) are estimated to have 7.9% to 14.4% of individuals in this age group with half-lives ≥4 hours. The allometric model is potentially a more accurate predictor of size than the per kilogram model for metabolic processes.[6,8] Age-related changes are not seen when the per kilogram model is used, and this model predicts only 0.6% of subjects in all age groups will have concentrations >200 mg/L at 4 hours; a percentage not born out clinically in adults in whom concentrations >200 mg/L at 4 hours are predicted to occur in 37% of individuals given 200 mg/kg.[14]

Children under the age of 6 years are thought to be less susceptible to toxicity than older children and adults.[2] It is estimated that <5% of children under 6 years with acetaminophen concentrations above the nomogram treatment line will have transient hepatic abnormalities.[15] This may be partly attributable to the shorter half-lives seen in children. Adults may be more susceptible to hepatic damage because of its complex interaction with ethanol.[16] Under-reporting of dosage during suicide attempts[17] and absorption variability resulting from other drugs (eg, dextopropoxyphene[18]) or acetaminophen formulation may also contribute to the increased toxicity seen in adults.

The distribution of observed concentrations was not significantly different from the distributions of predictions specified by either the allometric model or the per kilogram model. These distributions were similar to those reported by Prescott[14] in a study of 43 convalescent adult patients who had concentrations measured 1 hour after three 500 mg tablets. Simulation with both models overpredicted the concentrations compared with observed concentrations normalized to a 300 mg/kg dose. The doses reported in the clinical records are usually the maximum possible ingested,[1] and this overestimation is a contributor to bias.

No child in our study showed any sign of acetaminophen toxicity. Morbidity and mortality after accidental acetaminophen ingestion in young children are extremely low.[19,20] Bond et al[1] reviewed 866 children aged 1 to 6 years in whom a timed serum acetaminophen concentration was reported from the database of the American Association of Poison Control Centers. Only 3 patients had concentrations in the probable risk area of the toxicity nomogram. These children were treated with N-acetylcys-

teine and had no hepatic damage. This low morbidity rate is also partly due to the commonly available preparations (120 mg/5 mL, 2.4 g maximum or 250 mg/5 mL, 5 g maximum), safety-enclosed containers, and aggressive management with N-acetylcysteine.

Few children in our series were given an emetic agent. Vomiting may reduce absorption in children if it occurs in the first 30 minutes after ingestion, but it is useless when delayed for >1.5 hours.[21,22] Although the extent of absorption of acetaminophen was significantly reduced in healthy adult volunteers given activated charcoal up to 2 hours after ingestion of tablets,[23] activated charcoal is unlikely to have much effect unless given early in children who have accidentally ingested the elixir formulation, because there is no dissolution phase compared with capsules or tablets. Gastric emptying and duodenal absorption are rapid. Peak concentrations of 39 minutes (SD 20)[24] and absorption half times as low as 2.7 minutes (SEM 1.2)[25] have been reported in febrile children given elixir. Little acetaminophen is likely to be available for charcoal to bind to when administered after 5 absorption half-lives. A recent position statement by the American Academy of Clinical Toxicology and the European Association of Poisons Centers and Clinical Toxicologists suggests there are insufficient data to support or exclude charcoal use after 1 hour of ingestion.[26]

Serum concentrations are measured at 4 hours in adults because of long absorption half-lives resulting from formulation properties and other self-administered medications that delay gastric emptying. In contrast, young children ingesting elixir have short absorption half-lives and an earlier peak time because of shorter elimination half-lives. The maximum concentration was reached before 2 hours in 95% of children who underwent simulation. Early concentration measurements at 2 hours may potentially shorten the length of time children spend in an emergency department, decrease delays in diagnosing toxicity, and reduce consequent parental anxiety. We recommend a serum concentration measurement be taken in children who have ingested >250 mg/kg of elixir. The upper 99% CI for the 4-hour concentration predicted for this dose in children 1 to 5 years was 200 mg/L. A concentration of 225 mg/L (25% below the 2-hour nomogram concentration of 300 mg/L) could be used to indicate possible toxicity.

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