Theophylline Toxicokinetics in Premature Newborns

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Background: While cytochrome P4501A2 is the primary pathway for theophylline (aminophylline ethylenediamine) metabolism in adults, it is developmentally immature in the newborn.

Objective: To report the developmental differences in theophylline toxicokinetics of neonates.

Design: Case series. Three premature neonates received inadvertent intravenous overdoses of theophylline for apnea of prematurity while in newborn intensive care. Maximum serum concentrations ranged from 55 to 123 mg/L. Theophylline-derived caffeine levels plateaued at 8.4 to 13 mg/L and did not decline during the sampling period. All newborns experienced sinus tachycardia and agitation. Sequential theophylline and caffeine serum levels were obtained periodically for 62 to 100 hours. In contrast to older children and adults, in whom theophylline disposition follows zero-order kinetics at high concentrations, a monoexponential function best described theophylline elimination in the premature newborn, with half-lives ranging from 24.7 to 36.5 hours and estimated clearance from 0.02 to 0.05 L/kg per hour. These values are consistent with those previously reported in neonates. All patients were treated with supportive care without invasive procedures. No seizures or apparent sequelae occurred.

Conclusion: Developmental differences in the balance between nonrenal (ie, metabolic) and renal elimination pathways produce the unique toxicokinetics of theophylline in the neonate.


A PNEA OF prematurity may be associated with significant neonatal morbidity and mortality. Conventional therapy includes oxygen supplementation in conjunction with administration of theophylline or caffeine to increase respiratory drive.1 The pharmacodynamics and pharmacokinetics of theophylline in premature newborns are significantly different from those in older children and adults. For example, premature newborns have markedly diminished activity of many of the enzymes responsible for metabolism of the methylxanthines. Also, they exhibit accumulation of caffeine during long-term theophylline therapy consequent to the developmental immaturity of both renal and nonrenal pathways responsible for its elimination. In addition, the therapeutic index of theophylline is lower in newborns.2-7 Serum theophylline concentrations associated with reduced frequency and/or severity of central apnea (5-12 mg/L) are only slightly lower than those associated with early signs of toxicity (13-15 mg/L).8

The newborn and young infant are particularly vulnerable to medication errors leading to overdose because most commercially available formulations must be diluted to accurately deliver the small doses of theophylline required. This additional step not uncommonly has contributed to errors in medication administration in newborn intensive care nurseries.9-11

In adults and older children, elevated theophylline concentrations are associated with saturation of key drug metabolic pathways, resulting in a change in the kinetic characterization of elimination from first- to mixed-order (eg, Michaelis-Menton equation) or zero-order.12 In contrast, previous studies in newborns have reported that theophylline elimination kinetics remain at first order even at concentrations in excess of those regarded as “therapeutic.”13-16 We report 3 cases of theophylline intoxication in very low-birth-weight premature newborns in whom potentially toxic serum theophylline concentrations following large, acute overdoses declined in an apparent first-order fashion. Elimination half-life values were not markedly differ-
ent from those reported in association with “therapeutic” levels of the drug in this population. An explanation for this phenomenon based on known maturational characteristics of specific drug metabolic pathways responsible for theophylline metabolism and excretion is suggested.

**METHODS**

Each newborn was monitored clinically for signs and symptoms of theophylline intoxication, including hyperthermia, dehydration, seizures, agitation, tachycardia, blood pressure changes, emesis, and diuresis. Serum chemistry was repeatedly monitored to assess electrolyte and glucose balance. One newborn (case 3) received propanolol for control of sinus tachycardia and phenobarbital for seizure prophylaxis. No invasive techniques, such as gastrointestinal decontamination or extracorporeal methods, were used to accelerate theophylline elimination in any of the cases.

Theophylline and caffeine serum concentrations were measured at least every 24 hours by high-performance liquid chromatography until theophylline levels were less than 10 mg/L. Visual inspection of a semilog plot of progressive postoverdose serum theophylline concentrations demonstrated an apparent linear pattern of decline in each patient. Accordingly, the apparent terminal elimination rate constant \( k_e \), the extrapolated serum concentration at time zero \( C_0 \), and the area under the concentration-time curve (AUC) for each patient were estimated from a nonlinear least squares fit of the progressive theophylline concentrations. Best statistical fit of the data (Akaike criterion\(^*\)) was achieved using a simple 1-compartment open model (PkAnalyst software; MicroMath Scientific Software, Salt Lake City, Utah). Total body clearance (CI) was calculated from

\[
\text{CI} = \frac{V_d \times k_e}{D} = \frac{V_d \times (C_0 - C_{ss})}{D}
\]

where \( V_d \) is the average population volume of distribution (0.7 L/kg) for theophylline at steady state. The administered overdose was estimated from

\[
D = V_d \times (C_0 - C_{ss})
\]

where \( C_{ss} \) was the predicted average steady state serum concentration modeled from the patient-specific estimates of theophylline pharmacokinetic parameters and the prescribed dose prior to the overdose. A corrected dose was calculated to account for steady-state theophylline concentrations since the patients had received theophylline for at least 3 days prior to the overdose.

**CASE REPORTS**

**CASE 1**

A 670-g male newborn was delivered by vaginal breech extraction at an estimated gestational age of 24 weeks. Apgar scores were 2 and 4 at 1 and 5 minutes, respectively. His hospital course was complicated by respiratory distress syndrome, pulmonary interstitial emphysema, intraventricular hemorrhage, necrotizing enterocolitis, and bronchopulmonary dysplasia. By age 8 weeks, the infant weighed 880 g and was being gradually transitioned from receiving intermittent mandatory ventilation to continuous positive airway pressure. Intravenous aminophylline ethylenediamine (79% theophylline base) was administered at a prescribed dose of 1.7 mg (2 mg/kg) every 12 hours to facilitate discontinuation of mechanical ventilation and reduce recurrent central apnea.

On the 59th hospital day (32 weeks postconceptual age), the patient suddenly developed sinus tachycardia (>200 beats per minute), restlessness, and agitation associated with a serum theophylline concentration of 55.2 mg/L. Urine output increased from 2.1 to 4.3 mL/kg per hour without significant changes in fluid administration, accompanied by a reduction in serum potassium from 4.0 to 3.0 mEq/L. There were no significant changes in ventilatory requirements, arterial blood gases, or blood pressure, and no evidence of seizure activity was observed.

Following discontinuation of theophylline and treatment with supportive care, the patient had an uneventful recovery. His clinical symptoms dissipated during a 12- to 48-hour period, although serum theophylline concentrations did not fall below 10 mg/L for more than 60 hours. He was discharged from the hospital at 159 days of age with no sequela attributable to the theophylline overdose.

**CASE 2**

A 1220-g male newborn was delivered by emergency cesarean delivery for abruptio placenta at an estimated gestational age of 28 weeks. Apgar scores were 1 and 2 at 1 and 5 minutes, respectively. His hospital course included severe respiratory distress syndrome and persistent patent ductus arteriosus. By age 3 weeks, the patient weighed 1060 g and continued to require supplemental oxygen by hood. Intravenous aminophylline ethylenediamine (79% theophylline base), 2.7 mg (2.5 mg/kg), every 12 hours was prescribed for recurrent apneic episodes.

On the 28th hospital day (32 weeks postconceptual age), the patient suddenly developed sinus tachycardia to 220 beats per minute. The theophylline serum concentration at that time was 66.5 mg/L. Urine output increased from 2.1 to 3.2 mL/kg per hour and was associated with a reduction in serum potassium from 4.0 to 2.8 mEq/L. Serum glucose increased from 69 mg/dL prior to the previous aminophylline dose to 195 mg/dL at 6 hours and 179 mg/dL at 11 hours postoverdose with no significant increases in fluid or dextrose infusion rates. Arterial blood gases, blood pressure, respiratory rate, and oxygen requirement remained unchanged. No seizure activity was observed. Abdominal distention and bilious emesis were noted within an hour of the apparent aminophylline overdose. Plain abdominal films revealed multiple loops of dilated bowel but no evidence of pneumatosis intestinalis, obstruction, or free intraperitoneal air. The emesis and distention responded to open nasogastric drainage and temporary discontinuation of oral feedings.

The patient had an uneventful recovery following discontinuation of treatment with aminophylline and the pro-
Postoverdose in the absence of an associated change in fluid or dextrose infusion rates. Despite the tachypnea, the patient’s arterial blood gas, blood pressure, and oxygen requirement remained unchanged. Seizure activity was not clinically evident.

The patient continued to receive 5 mg/kg of phenobarbital per day for seizure prophylaxis for 48 hours postoverdose. Propranolol, 0.1 mg/kg, was given “as needed” for heart rate above 180 beats per minute and was discontinued 12 hours postoverdose. Despite the disappearance of symptoms during the 12 hours following the apparent overdose, the serum theophylline levels did not fall below 10 mg/L until 96 hours. The patient was discharged from the hospital at 39 days of age with no sequelae attributable to the theophylline overdose.

**RESULTS**

Patient demographics and patient symptoms are presented in Table 1. All patients exhibited sinus tachycardia, agitation, glucose and electrolyte abnormalities, and significant diuresis. One patient developed bilious emesis; the other 2 underwent gastric suction for suspected necrotizing enterocolitis. Symptoms of toxicity appeared shortly after the theophylline overdose in each patient but resolved well before theophylline concentrations returned to levels less than 20 mg/L. Sinus tachycardia was controlled in case 3 with short-term propranolol therapy. No patient developed seizures and all recovered without apparent permanent sequelae consequent to theophylline overdose.

Serum theophylline levels of 55.2 mg/L (case 1), 66.5 mg/L (case 2), and 123 mg/L (case 3), were measured in the initial blood samples obtained shortly after the onset of clinical symptoms. Monoexponential curve fits of progressive serum theophylline concentrations in each case provided support for elimination via first-order kinetics. Coefficients of determination for the curve fits were 0.997, 0.998, and 0.998 for cases 1, 2, and 3, respectively. Values for the pharmacokinetic parameters for each patient, presented in Table 2, were similar to those previously reported in premature newborns receiving therapeutic doses of theophylline.13,18

Although caffeine had not been administered to the patients, caffeine was identified in their serum samples at concentrations in the desired therapeutic range for the treatment of apnea and bradycardia of prematurity.19 Caffeine concentrations increased during the first 24 hours of intoxication before seeming to plateau in 2 of the pa-

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**Table 1. Demographics and Clinical Signs and Symptoms**

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, wk</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>0.67</td>
<td>1.22</td>
</tr>
<tr>
<td>Age when dose received, d</td>
<td>59</td>
<td>27</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Peak HR, bpm</td>
<td>224</td>
<td>220</td>
</tr>
<tr>
<td>Duration of HR &gt;180 bpm, h</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>Agitation</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Emesis</td>
<td>None</td>
<td>Bilious</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>41 (hypoglycemic)</td>
<td>195 (hyperglycemic)</td>
</tr>
<tr>
<td>∆ Urine output from baseline, mL/kg per hour</td>
<td>+2.2</td>
<td>+1.1</td>
</tr>
<tr>
<td>∆ K⁺ from baseline</td>
<td>−0.9</td>
<td>−1.9</td>
</tr>
<tr>
<td>Concurrent medications</td>
<td>Ampicillin</td>
<td>Ampicillin</td>
</tr>
<tr>
<td></td>
<td>sodium</td>
<td>Gentamicin</td>
</tr>
<tr>
<td></td>
<td>Gentamicin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>Calcium</td>
</tr>
<tr>
<td></td>
<td>Calcium</td>
<td>Calcium</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Phenytoin</td>
</tr>
</tbody>
</table>

**Table 2. Pharmacokinetic Results**

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated theophylline dose received, mg</td>
<td>33.4</td>
<td>46.3</td>
</tr>
<tr>
<td>Dose in mg/kg</td>
<td>38.0</td>
<td>43.7</td>
</tr>
<tr>
<td>Peak theophylline level, mg/L</td>
<td>55.2</td>
<td>66.5</td>
</tr>
<tr>
<td>Mean caffeine level, mg/L</td>
<td>8.4</td>
<td>11.5</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>25.1</td>
<td>36.5</td>
</tr>
<tr>
<td>Assumed volume of distribution, L/kg</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Clearance, L/h per kilogram</td>
<td>0.02</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*HR indicates heart rate; bpm, beats per minute; and K⁺, potassium.*
tients (Figure 1A and B) at levels ranging from 8 to 13 mg/L, suggesting attainment of a steady state.

**COMMENT**

The elimination of most drugs following therapeutic or nontoxic doses seems to proceed by a first-order process (ie, the rate of drug elimination is proportional to the amount of drug in the body). However, at high concentrations, drug elimination mechanisms (eg, routes of clearance or metabolism) may become saturated, resulting in concentration-dependent elimination; thus, the apparent decline of plasma drug concentration can be described by either the Michaelis-Menten equation (ie, mixed order) or zero-order kinetics.20

In older children and adults, theophylline elimination usually exhibits saturation kinetics at concentrations greater than 20 mg/L.20,21 Zero-order elimination kinetics have been reported in older children with toxic concentrations of theophylline.21 In contrast, theophylline elimination in our patients, with serum concentrations 5 to 12 times greater than the recommended therapeutic serum levels, seemed to be best described by a first-order process. Wells and Ferlauto22 previously described a premature newborn who had received an intravenous theophylline overdose from an improperly prepared parenteral nutrition solution resulting in a theophylline level of 330 mg/L—the highest theophylline level in a neonate documented in the literature. Although the authors did not describe the elimination kinetics in this case, independent modeling of the data revealed an apparent first-order elimination process. The persistence of first-order theophylline kinetics in premature newborns with overdose seems to be a consistent phenomenon in cases reported to date.13-16 We propose that this is because of immaturity of the rate-limiting metabolic pathway for theophylline.

Cytochrome P4501A2 (CYP1A2) is responsible for demethylation of theophylline to 1-methylxanthine and 3-methylxanthine3,4 (Figure 2). This pathway accounts for more than 80% of theophylline elimination at therapeutic doses. It also is partly responsible for the conversion to 1,3-dimethyluric acid, whereas CYP2E1 and CYP3A4 are responsible for C8 oxidation.23 In the neonate, these cytochrome P450 isozymes are not fully expressed and, as a consequence, their activity (ie, ability to biotransform a substrate) is markedly reduced.3-6,24-26

Cytochrome P4501A2 is not fully expressed until approximately 5 to 6 months of age.2,18,24 It is a high-affinity, low-capacity enzyme responsible for theophylline demethylation, and is saturable at supratherapeutic concentrations.9 In the absence of CYP1A2 activity, theophylline elimination is primarily dependent on renal elimination, which does not seem to be saturable. Accordingly, theophylline overdose in the neonate would
be expected to easily saturate the available CYP1A2, leaving renal excretion of the unchanged drug as the predominant pathway for drug clearance.

In contrast to CYP1A2, methyltransferase pathways are well developed in the newborn as reflected by the detection of caffeine (the 7N-methylated product of theophylline) in the serum of all 3 patients. Saturations of the theophylline 7N-methylation pathway would explain the relatively low apparent steady-state caffeine levels observed in the patients in this study despite very high concentrations of theophylline. The apparent plateauing of caffeine serum levels in the 2 patients in whom caffeine concentrations were repeatedly measured (Figure 1A and B) most likely represents a steady state between the ongoing formation from theophylline and the slow elimination of caffeine by renal clearance, previously documented by reports of long half-lives for caffeine in the neonate. It is speculated that this “therapeutic misadventure” occurred from dilutional errors, which are not uncommon in the administration of medication to newborns. The 3 newborns reported herein displayed clinical symptoms typically associated with methylxanthine toxicity. Tachycardia and hyperirritability are the most commonly reported symptoms while abdominal distention, emesis, diuresis, and hyperglycemia occur more sporadically. Hyperglycemia, hypoglycemia, diuresis, and reductions in serum potassium concentrations were transient and resolved within 24 hours of intoxication. Pharmacokinetic-based estimation revealed that the newborns actually received 10 to 25 times the prescribed dose. The acute theophylline overdoses were successfully treated with supportive care without the use of invasive procedures or methods to enhance drug clearance.

Limitations to this study exist. First, urine was not obtained from the 3 patients. Documentation of theophylline and its metabolites in the urine would have been particularly helpful in confirming the absence of CYP2A1 metabolites and excretion of unmetabolized theophylline. However, there is substantial support in the literature for our explanation of persistent first-order elimination at high concentrations in the newborns. Furthermore, this limitation does not detract from using the experience described in our study in the future treatment of neonatal theophylline intoxication. Second, lower serum theophylline concentrations were obtained for the third patient compared with the other 2. Although having more data points would optimize the pharmacokinetic calculations, the coefficient of determination (0.998) for this patient is such that a reasonable reliability of the estimate can be made.

In contrast to older children and adults, theophylline elimination remains a first-order process during acute intoxication in premature newborns, even at plasma concentrations 10 times those achieved with therapeutic doses. This can be attributed to normal developmental differences in activity of rate-limiting pathways required for theophylline clearance. The cases reported here document that large acute overdoses of theophylline in newborns, while inducing symptoms and signs of toxicity along with physiologic abnormalities, do not uniformly result in life-threatening cardiac dysrhythmias or seizures. Newborns may recover with no sequelae with supportive treatment without resorting to invasive treatments. Absence of life-threatening toxicity may obviate the use of extracorporeal (eg, hemodialysis, hemoperfusion) or enteral (eg, multiple dose activated charcoal) procedures designed to accelerate drug clearance, which in and of themselves may pose unacceptable risks to this population.

Accepted for publication March 27, 2001.
Supported in part by grant 3 U01 HD31313-07S1 from the Pediatric Pharmacology Research Unit Network, National Institute of Child Health and Human Development, Bethesda, Md.
Presented in part at the North American Congress of Clinical Toxicology, La Jolla, Calif, October 2, 1999.
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REFERENCES


Announcement

2001 Certifying Examinations of the American Board of Pediatrics

First-time applicants using fellowship training to qualify for subspecialty examinations may complete applications online during the registration periods for new applicants. The requirements for online applications (including eligibility requirements and registration dates, in addition to other information) may be found on the American Board of Pediatrics Web site: www.abp.org. Applications may be obtained by contacting the American Board of Pediatrics.

GENERAL PEDIATRICS EXAMINATION:
Examination Date: October 14-15, 2002

SUBSPECIALTY EXAMINATIONS:
Neurodevelopmental Disabilities Examination Date: April 9, 2002
Sports Medicine Examination Date: April 12, 2002
Pediatric Cardiology, Pediatric Critical Care Medicine and Pediatric Pulmonology Examination Date: August 19, 2002
Medical Toxicology Examination Date: October 26, 2002
Developmental-Behavioral Pediatrics, Pediatric Emergency Medicine, Pediatric Hematology-Oncology and Pediatric Rheumatology Examination Date: November 18, 2002