Life-Threatening Events After Theophylline Overdose

A 10-Year Prospective Analysis

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**Background:** Despite the declining use of theophylline, episodes of intoxication continue to occur, producing seizures, arrhythmias, and death.

**Objectives:** To further characterize major toxic effects and to examine the efficacy of existing interventions.

**Methods:** We conducted a longitudinal cohort study of patients with theophylline overdose. For a 125-month period, all patients referred to the Massachusetts Poison Control System in Boston with a serum theophylline concentration of 167 µmol/L (≥30 µg/mL) or more were followed up prospectively. Recommended management by the poison center was uniform and protocol based.

**Results:** Three hundred fifty-six patients were enrolled. Mean age was 34.5 years (range, 3 days to 98 years). Mean peak serum theophylline concentration was 336 µmol/L (60 µg/mL) (range, 167-1360 µmol/L [30-245 µg/mL]). One hundred sixty-two patients (45.5%) had acute, 144 (40.4%) had chronic, and 50 (14.0%) had acute-on-therapeutic poisoning. Seventy-four patients (20.8%) developed cardiac arrhythmias, and 29 (8.2%) developed seizures. Fifteen patients (4.2%) died, 11 (73%) of whom had chronic overmedication. Arrhythmias were significantly more common after chronic overmedication than after acute intoxication (35% vs 10%; odds ratio, 4.97; 95% confidence interval, 2.68-9.23; *P* < .001). Eight percent of patients with chronic overmedication died compared with 2.5% of those with acute intoxication (odds ratio, 3.20; 95% confidence interval, 1.01-10.39; *P* = .04). There was no significant difference in the rate of major toxic effects (25.9% vs 30.0%) or death (4.6% vs 3.7%) among patients referred from 1986 to 1991 and from 1992 to 1996.

**Conclusions:** Theophylline intoxication results in substantial morbidity and mortality, particularly in those with chronic overmedication. Treatment strategies fail to improve clinical outcome. With safer alternative options available, the current indications for theophylline should be rigorously evaluated with a goal toward minimal use of this agent.

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PATIENTS AND METHODS

This investigation was initiated in July 1986 at the Massachusetts Poison Control System (MPCS) in Boston, a certified, regional poison control center serving the state of Massachusetts. The MPCS provides consultation to 120 health care facilities and receives approximately 38,000 poisoning-related calls annually for a total call volume of approximately 78,000. Initial information is received and recorded by poison information specialists, and there is 24-hour availability to a consulting medical toxicologist. For a 125-month period ending November 1996, all cases of theophylline intoxication (peak serum theophylline concentration, >167 µmol/L [≥30 µg/mL]) referred to the MPCS were prospectively studied.

For each patient with theophylline intoxication referred, data, including time of ingestion, coingestants, current medications, previous serum theophylline concentrations, and medical history, were obtained. At presentation, patients were categorized as having acute intoxication, chronic overmedication, or acute-on-therapeutic intoxication. Acute intoxication was defined as the single ingestion or intravenous administration of theophylline, more than 10 mg/kg. Chronic overmedication was toxic effects developing after the repeated administration of theophylline. Acute-on-therapeutic intoxication was acute overdose in a patient who was taking or receiving theophylline in appropriate doses. History of theophylline use was obtained where possible through a review of the patient's medical history and discussion with family members.

Initial recommendations were protocol-directed and included the provision of supportive care, a 12-lead electrocardiogram, measurement of serum electrolyte and glucose levels, serum and/or urine analyses for coingestants, treatment of seizures or cardiac arrhythmias, gastrointestinal decontamination, administration of multiple-dose activated charcoal, and, if necessary, hemodialysis or hemoperfusion. Under MPCS protocol, criteria for hemodialysis or hemoperfusion included the following: (1) theophylline concentration of more than 444 to 555 µmol/L [≥80-100 µg/mL] after acute intoxication, (2) theophylline concentration of more than 222 to 278 µmol/L [≥40-50 µg/mL] after chronic overmedication, and (3) recurrent seizures or cardiac arrhythmias, regardless of theophylline concentration. A toxicologist would make immediate telephone contact whenever urgent consultation was requested by the poison specialist or referring physician.

All cases were reviewed by a toxicologist within 8 hours of referral.

During the 10-year investigation, there were 4 significant changes in treatment protocol based on newly published recommendations: (1) the criterion for hemodialysis or hemoperfusion after chronic overmedication was changed to chronicologic age older than 60 to 65 years, regardless of serum theophylline concentration; (2) hemodialysis was recommended as an equivalent option to hemoperfusion; (3) the agent of choice for treatment of seizures became a benzodiazepine rather than phenytoin; and (4) adenosine became the recommended treatment for supraventricular tachycardia. Patients were monitored through telephone communication with the treating facility 3 to 8 times daily. During these contacts with the managing nurse or physician, the most recent vital signs, results of toxic screens and serum drug concentrations, and important clinical events were recorded. Outcome measures under investigation were the alterations in serum potassium, glucose, or bicarbonate levels (obtained when peak serum theophylline concentration was measured) and the development of minor or major toxic effects. Minor toxic effects were vomiting, tremor, or cardiac disturbances without hemodynamic compromise. Major toxic effects were defined as the development of seizures or cardiac arrhythmias associated with hemodynamic instability.

The 2-tailed Student t test or 1-way analysis of variance, followed by the Scheffé multiple comparisons procedure, was used for intergroup comparison of normally distributed continuous variables. The χ² test was performed for comparison of categorical variables; Pearson product-moment test was used to calculate bivariate correlations. Relative risks and crude odds ratios (ORs) with 95% confidence intervals (CIs) were calculated according to the Mantel-Haenszel test. A multiple logistic regression model was constructed to identify clinical factors associated with the development of major toxic effects. Independent variables entered into the model were age, peak theophylline concentration, and coingestants. Drug coingestants were placed in 4 dichotomously coded categories: cardiac agents, proconvulsant drugs, diuretics, and β-agonists. Statistical analyses were performed using SPSS for Windows, release 7.0 (SPSS Inc, Chicago, Ill), or SAS, version 6.11 (SAS Institute Inc, Cary, NC). Data are expressed as mean ± SD. Statistical significance was established at P < .05. Because this was an observational study of existing clinical practice, investigational review board approval was exempted.
Seizures were typically brief and generalized, although status epilepticus occurred in 7 patients and focal seizures occurred in 3. A broad range of cardiac arrhythmias were found on electrocardiogram (Table 2). Peak theophylline concentration was higher in those who developed major toxic effects than in those without (386 vs 317 µmol/L [70 vs 57 µg/mL], P = .01). For 71 patients (73%), major toxic effects were the presenting clinical feature of theophylline intoxication, which occurred before any intervention had been instituted.

In addition to general supportive and decontamination measures, 59 patients (17%) underwent an extracorporeal drug removal procedure. This included 41 (11.5%) who received hemodialysis, 17 (4.8%) who received hemoperfusion, and 1 infant who underwent an exchange transfusion. Fifteen patients died (mortality rate, 4.2%; 95% CI, 2.1-6.4), 11 (73%) of whom had chronic overmedication. All deaths resulted from intractable cardiac arrhythmias (Table 3). Mean age of patients who died was 71 ± 18 years. Among all patients older than 65 years with theophylline intoxication, 11 (15%) died.

There was no difference in incidence of major toxic effects from 1986 to 1991 and from 1992 to 1996 (25.9% and 30.0%, respectively), or in mortality rate (4.6 vs 3.7%, respectively).

ACUTE INTOXICATION

Acute theophylline intoxication resulted from a suicide attempt in 150 patients, a drug administration error in 6, and ingestion by a child in 6. Mean age was 22.8 years. Mean peak theophylline concentration was 391 ± 209 µmol/L (70 ± 38 µg/mL). Mean potassium concentration was 3.03 ± 0.45 mmol/L; 83% were hypokalemic. There was a significant correlation between theophylline and potassium concentrations (r = 0.40, P = .01). Major toxic effects occurred in 22 patients (14%), 16 of whom sustained a life-threatening arrhythmia (Table 2), 8 of whom developed seizures. Mean peak theophylline concentration in patients who developed major toxic effects was significantly higher than in those without (690 vs 342 µmol/L [124 vs 62 µg/mL]; P = .001). Four patients with acute intoxication died, having peak theophylline concentrations of 435, 916, 999, and 1171 µmol/L (78, 165, 180, and 211 µg/mL). The highest theophylline concentration associated with survival was 1360 µmol/L (245 µg/mL).

CHRONIC OVERMEDICATION

Among the 144 patients with chronic overmedication, identified causes are listed below.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Patients, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician dosing error</td>
<td>21</td>
</tr>
<tr>
<td>Patient dosing error</td>
<td>17</td>
</tr>
<tr>
<td>Cardiac or hepatic disease</td>
<td>14</td>
</tr>
<tr>
<td>New prescription of medication</td>
<td>8</td>
</tr>
<tr>
<td>that decreased theophylline clearance</td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>3</td>
</tr>
</tbody>
</table>

The most common cause was increased or erratic dosing by the patient. However, physician error—either excessive dosing or concomitant prescription of a drug that inhibits theophylline clearance—was responsible in
Incidence of major toxic effects was significantly greater in patients with chronic overmedication than in those with acute intoxication (45% vs 14%; crude OR, 4.99; 95% CI, 2.85-8.74; P = .009). There was no significant difference in peak theophylline concentration between the 64 patients who developed major toxic effects and the 80 who did not (257 vs 279 µmol/L [46 vs 50 µg/mL]). Eleven patients (8%) died; this compared with 4 deaths (2.5%) among those with acute intoxication (relative risk, 1.6; crude OR, 3.2; 95% CI, 1.01-10.39; P = .04). Peak theophylline concentration among fatalities did not differ significantly from that among survivors (306 vs 262 µmol/L [55 vs 47 µg/mL]) in this subgroup.

Compared with patients aged 6 months to 30 years, those who were 30 to 65 years old had a significantly greater risk of major toxic effects (adjusted OR, 3.2; 95% CI, 1.03-10.1), and those older than 65 years had an even greater risk (OR, 7.8; 95% CI, 2.9-21.1).

**ACUTE-ON-THERAPEUTIC INTOXICATION**

Among the 50 patients with acute-on-therapeutic intoxication, 6 developed intoxication as a result of a 10-fold error in drug administration. The remaining episodes occurred in patients who were taking theophylline then ingested an overdose in a suicide attempt. Mean peak theophylline concentration was 360 ± 183 µmol/L (65 ± 33 µg/mL). Mean potassium concentration was 3.23 ± 0.47 mmol/L; 58% developed hypokalemia. There was a significant correlation between theophylline and potassium concentrations (r = -0.41, P = .01) but not glucose or bicarbonate concentrations. Major toxic effects developed in 10 patients (20%), including seizures in 4 (8%) and cardiac arrhythmias in 7 (14%). There were no deaths in this group. Peak theophylline concentration among

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**Table 1.** Clinical Characteristics of Patients With Theophylline Overdose

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute</th>
<th>Chronic</th>
<th>Acute-on-Therapeutic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>162</td>
<td>144</td>
<td>50</td>
<td>356</td>
</tr>
<tr>
<td>Age, y</td>
<td>22.8 (13.2)</td>
<td>51.5 (29.5)</td>
<td>26.0 (18.9)</td>
<td>34.5 (25.6)</td>
</tr>
<tr>
<td>Female, %</td>
<td>60</td>
<td>59</td>
<td>71</td>
<td>65</td>
</tr>
<tr>
<td>Peak serum theophylline, µmol/L [µg/mL]</td>
<td>391 (209) [70 (38)]</td>
<td>268 (95) [49 (17)]</td>
<td>360 (183) [65 (33)]</td>
<td>336 (176) [60 (32)]</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>3.03 (0.45)</td>
<td>3.83 (1.03)</td>
<td>3.23 (0.47)</td>
<td>3.35 (0.81)</td>
</tr>
<tr>
<td>Glucose, mmol/L [mg/dL]</td>
<td>11.2 (3.7) [202 (67)]</td>
<td>8.0 (2.5) [144 (45)]</td>
<td>10.9 (4.8) [196 (86)]</td>
<td>10.0 (4.0) [180 (72)]</td>
</tr>
<tr>
<td>Bicarbonate, mmol/L</td>
<td>18.7 (4.2)</td>
<td>24.7 (6.7)</td>
<td>18.4 (4.5)</td>
<td>21.0 (6.1)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD).*
patients who developed major toxic effects was significantly higher than in those who did not (390 vs 350 µmol/L [70 vs 63 µg/mL]; *P* = .02). However, in the logistic model—compared with patients having a peak theophylline concentration of 167 to 276 µmol/L (30-50 µg/mL)—the adjusted OR for those with peak concentrations of more than 440 µmol/L (79 µg/mL) was 0.67 (95% CI, −0.05 to 8.7).

**COMMENT**

This longitudinal study of theophylline intoxication was designed to clarify the short-term complications of this poisoning. The use of a single poison center was designed to enroll a large series and provide consistency in recommended management. Investigation of long-term sequelae, such as permanent neurologic injury, was not a part of our study design, although it is the most disabling outcome in survivors of theophylline intoxication.22-26

The main findings of this investigation confirm many previous observations. For example, it is clear that patients experiencing chronic theophylline overmedication—particularly the elderly—are at greater risk of seizures, arrhythmias, and death than those with acute intoxication.23 While such heightened morbidity and mortality may result from a deteriorating cardiorespiratory status in older patients, the same pattern occurring in younger, healthier patients suggests that theophylline overdose is a primary cause of major toxic effects.22-24 That theophylline concentrations are not predictive of toxic effects in patients with chronic overmedication has been recognized for many years.22,24 This unusual feature of chronic overmedication, which is also seen after chronic aspirin and lithium overdose,27-30 can be explained by alterations in theophylline pharmacokinetics. For example, the volume of distribution of theophylline is 0.4 to 0.7 L/kg.23,31 Chronic overexposure to the drug would increase tissue concentrations, resulting in a greater body burden of drug relative to serum concentration. The lack of association between theophylline concentration and adverse clinical effects in patients with chronic overmedication complicates the identification of high-risk ones who might benefit from early hemodialysis or hemoperfusion.25 Increasingly, chronologic age has been shown to have greater predictive value in identifying the patients at high risk, with those older than 60 to 65 years most likely to develop major toxic effects.22

The cardiotoxicity of theophylline is evidenced by the appearance of cardiac arrhythmias more often than seizures and the high incidence of associated myocardial infarction.32,33 In a canine model of theophylline intoxication, Curry et al34,35 found that theophylline toxicity produces marked cardiovascular disturbances, including a decrease in mean arterial pressure and systemic vascular resistance in conjunction with tachycardia and an increase in cardiac index. These physiologic changes collectively result in increased myocardial oxygen demand. For patients with compromised coronary blood flow, greater myocardial demands could result in ischemia or infarction. Theophylline's potent antagonism of cardiac adenosine receptors also contributes to its cardiotoxicity.36-38

The metabolic complications of theophylline intoxication have been well characterized. Interestingly, despite the higher incidence of major toxic effects in those with chronic theophylline overmedication, these patients had a lower incidence of hypokalemia and metabolic acidosis. In a previous study,39 we demonstrated that plasma epinephrine concentrations are higher in patients who develop metabolic disturbances; in contrast, plasma norepinephrine predominates after chronic overmedication. Disturbances in glucose, potassium, and bicarbonate levels have no apparent physiologic consequences.

With acute intoxication, the most notable finding was the tolerance of extremely high serum theophylline concentrations without development of major toxic effects. This likely results from the relatively younger age of these patients. Analysis of our data also revealed a significant correlation between peak serum theophylline concentration and major toxic effects, which others have also found.40,41 This supports the recommendation that hemodialysis or hemoperfusion should be preserved for patients with acute intoxication who have theophylline concentrations greater than 44 to 555 µmol/L (≥80-100 µg/mL).40,41

Acute-on-therapeutic theophylline intoxication was relatively uncommon, occurring in only 14% of patients. In this subgroup, neither chronologic age nor peak theophylline concentration was clearly associated with major toxic effects. Therefore, the subset of these patients who might benefit from early hemodialysis or hemoperfusion could not be identified by our data. Future studies investigating this group will be necessary to develop clearer treatment guidelines.

An unexpected result was that, despite a marked diminution in the number of episodes of theophylline intoxication referred to our poison center, there was no change in the rate of major toxic effects or mortality during 10 years of observation. It may be that, despite advances in diagnosis and management, the clinical toxicity of theophylline is such that current treatment protocols—which include more liberal use of hemodialysis—cannot effect further improvements in outcome. Alternatively, there may have been so few patients who presented before major toxic effects had occurred that the number in whom a preventive intervention could be instituted was small; the lack of a significant reduction may represent a type II error (erroneous acceptance of the null hypothesis). The high rate of major toxic effects as the presenting feature underscores the suddenness with which life-threatening events can appear after theophylline intoxication and illustrates the greatest danger of this overdose.

Data from this cohort study indicate that theophylline is an extremely toxic drug that, in overdose, may cause harm or death. Three distinct patterns of intoxication exist, namely, acute intoxication, chronic overmedication, and acute-on-therapeutic intoxication. Within each category, the risk factors associated with major toxic effects vary. The elderly are at high risk for a fatal outcome after chronic overmedication. Management strat-
egies have been thwarted by the high frequency of seizures and arrhythmias as presenting events. Therefore, while potential roles for this drug remain, the availability of alternative agents that are at least as effective argues for a redefinition of theophylline's place in pharmacotherapy.

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REFERENCES