Predictors of Major Toxicity after Theophylline Overdose

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■ *Objective:* To identify patients at high risk for major toxicity after theophylline intoxication who might benefit from early charcoal hemoperfusion.
■ *Design:* A 67-month prospective study.
■ *Setting:* Massachusetts Poison Control System.
■ *Patients:* 249 consecutive patients referred after theophylline intoxication (defined by a peak serum theophylline concentration ≥167 μmol/L [30 mg/L]).
■ *Interventions:* Uniform, protocol-directed management recommendations.
■ *Main Outcome Measures:* Identification of risk factors for major toxicity.
■ *Results:* 119 patients (48%) not receiving theophylline therapy had acute intoxication; among those receiving such therapy, 92 (37%) had theophylline intoxication because of chronic overmedication and 38 (15%) had acute intoxication. Major toxicity developed in 62 patients (25%); 13 patients (5%) died. Major toxicity was more common in patients with intoxication due to chronic overmedication than in those with acute intoxication who were not receiving theophylline therapy (49% compared with 10%, risk ratio, 4.85; 95% CI, 2.96 to 7.94), even though the former group had lower peak serum theophylline concentrations (283 μmol/L compared with 777 μmol/L, $P = 0.001$). Logistic regression analysis identified two major factors associated with the development of major toxicity: 1) peak serum theophylline concentrations in cases of acute intoxication and 2) patient age in cases of chronic overmedication. Receiver-operating characteristic curve analysis indicated that major toxicity occurred in patients with a peak serum theophylline concentration of greater than 555 μmol/L (100 mg/L) after acute intoxication and in patients older than 60 years (regardless of peak serum theophylline concentration) after chronic overmedication.
■ *Conclusions:* Predictors for major toxicity after theophylline intoxication differ by type of overdose.

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Used medicinally for more than five centuries, theophylline and related compounds have retained their therapeutic importance (1). Theophylline continues to be widely prescribed for asthma and other syndromes of reversible bronchospasm, although its use has declined over recent years as beta-adrenergic agonists and corticosteroids have assumed greater roles in these illnesses (2–4).

The continued popularity of theophylline, coupled with its narrow therapeutic index, makes occurrences of unintentional, chronic theophylline overmedication common. In addition, the drug's wide availability in the home also makes the occurrence of acute overdose frequent. The incidence of theophylline intoxication is difficult to assess; however, reported estimates range from a hospitalization rate of 7.8/10 000 person-years to an overall rate of 21% in patients taking theophylline regularly (5–8). In 1991, the American Association of Poison Control Centers reported 9259 cases of theophylline intoxication, with 32 fatalities (9).

The spectrum of clinical toxicity after theophylline poisoning varies widely (10, 11). Mild toxicity includes nausea, vomiting, abdominal pain, tachycardia, and muscle tremor (12–15). Clinical manifestations of severe toxicity include hypotension, cardiac arrhythmias, seizures, and death (16–22).

Treatment of theophylline intoxication involves cardiorespiratory support, correction of electrolyte disturbances, and administration of multiple-dose activated charcoal (19, 23–26). However, charcoal hemoperfusion appears to be the most efficacious therapy for the prevention of severe toxicity (19, 22, 27–29). In contrast, therapeutic hemoperfusion done after the onset of major toxicity may not prevent the continued occurrence of seizures or cardiac arrhythmias (12, 20, 23, 27, 30).

Recognizing the role of hemoperfusion as a prophylactic intervention reinforces the need to identify predictors of major toxicity in patients with theophylline intoxication. Although many studies have suggested that the peak serum theophylline concentration is an accurate predictor of major toxicity (2, 8, 16), others have not found such a correlation (16–18, 31, 32). Also, data suggest that patients who are chronically overmedicated have a greater risk for life-threatening manifestations, with major toxicity occurring when serum theophylline concentrations are in what is considered the range for mild toxicity. Finally, there is clinical evidence that in cases of intoxication due to chronic overmedication, patient age may be a more sensitive predictor of major toxicity than the peak serum theophylline concentration (8, 31).

This study was done to identify predictors of major toxicity that might be useful for clinical decision making in cases of theophylline intoxication.

Methods

For a 67-month period ending May 1992, we conducted a prospective evaluation of all patients 12 years or older who were referred to the Massachusetts Poison Control System because of theophylline intoxication (defined as a peak serum theophylline concentration of 167 μmol/L [30 mg/L] or greater). The Massachusetts Poison Control System is a certified regional poison center for the state of Massachusetts that receives more than 60 000 calls annually. The Massachusetts Poison Control System offers 24-hour availability to a consulting medical toxicologist.

For each patient referred, an expanded data set was collected that included time of ingestion, other drugs being taken at the time of theophylline ingestion, previous theophylline dosing, and past medical history. Based on their history of recent theophylline use, patients were categorized at referral as having acute intoxication in the absence of theophylline therapy, intoxication due to chronic overmedication, or acute intoxication while receiving therapy. Acute intoxication in the absence of theophylline therapy was defined as the ingestion or intravenous administration of a toxic dose of theophylline in a patient not currently receiving the medication. Intoxication due to chronic overmedication was defined as repeated administration of theophylline without the ingestion of a single, toxic dose (greater than 10 mg/kg body weight). Acute intoxication while receiving therapy was defined as the ingestion or administration of a toxic quantity of theophylline in a patient who was receiving theophylline in appropriate doses. Confirmation of theophylline dosing and documentation of previous serum theophylline concentrations were obtained through review of the patient's medical record and discussion with family members.

Uniform treatment recommendations included supportive care, treatment of seizures or arrhythmias, assessment of serum electrolyte and blood glucose levels, electrocardiographic evaluation, determination of serum drug levels, toxic screens (for suspected ingestion of other drugs), gastrointestinal decontamination, correction of metabolic disturbances, administration of multiple-dose activated charcoal (1 g/kg [maximum 60 g] every 4 hours or 20 g every 2 hours) and, if needed, hemoperfusion (or, if unavailable, hemodialysis). Under the Massachusetts Poison Control System protocol, the criteria for hemoperfusion included 1) a serum theophylline concentration greater than 444 μmol/L (80 mg/L) in cases of acute intoxication; 2) a serum theophylline concentration greater than 222 to 278 μmol/L (40 to 50 mg/L) in cases of chronic intoxication; and 3) intractable seizures or cardiac arrhythmias, regardless of serum theophylline concentration. It was recommended that all interventions continue until the serum theophylline concentration decreased to below 110 μmol/L (20 mg/L).

Patients were monitored via telephone three to eight times daily, at which times vital signs and clinical events, particularly the appearance of electrolyte disturbances, seizures, or arrhythmias, were recorded. Minor toxicity was defined as vomiting, cardiac disturbances without hemodynamic compromise, or muscle tremor. Major toxicity was defined as seizures or cardiac arrhythmias associated with hemodynamic instability. Patients were monitored until hospital discharge or death.

The Student *t*-test or analysis of variance with the Scheffe post hoc multiple-comparisons procedure was used for the analysis of continuous variables having a Gaussian distribution, and the chi-square or two-tailed Fisher exact test was done when appropriate. Risk ratios and 95% CIs were calculated using the method of Rothman and Boice (33). For each group of patients, a forced-entry logistic regression model was constructed using the MULTLR software program to identify factors associated with the development of major toxicity (34). Independent variables studied included serum potassium, glucose, and bicarbonate levels; peak serum theophylline concentration; time from ingestion of theophylline to peak serum concentration; minor toxicity; age; and concurrent drug use. Four categories of concurrently used drugs were analyzed as dichotomous independent variables: These categories included cardiac agents (for example, digoxin and calcium-channel blockers), neuroexcitatory drugs (for example, cocaine and tricyclic antidepressants), diuretics, and beta-adrenergic agonists. Sensitivity and specificity were calculated according to standard equations. Receiver-operating characteristic curves were generated to analyze the diagnostic accuracy of selected cutoff values (35). Data are expressed as mean ± SD unless otherwise indicated. Statistical significance was established at $P \leq 0.05$.

Results

During the study period, 254 eligible patients with theophylline intoxication were referred to the Massachusetts Poison Control System. Five of these patients were excluded from the study because their clinical course could not be closely monitored. Among enrolled patients, the mean age was 37.0 ± 24.5 years. Twenty-three percent of patients were 65 years or older; 12% were older than 75 years. One hundred nineteen patients (48%) had acute theophylline poisoning but were not receiving therapy, whereas 92 (37%) had been chronically overmedicated and 38 (15%) had acute intoxication while on therapy. All cases of acute intoxication were intentional, occurring in the context of a suicide attempt. Among patients who had been chronically overmedicated with theophylline, suspected mechanisms of intoxication included patient or caretaker dosing error (28 patients [30%]), physician or nurse dosing error (7 patients [8%]), hepatic or cardiac disease (15 patients [16%]), and drug interaction (8 patients [9%]). Twenty-four patients had a past medical history of cardiac disease, 4 had a seizure disorder, and 3 had hepatic disease.

The mean interval from last dose of theophylline to measurement of the serum theophylline concentration for the total sample was 7.7 ± 4.6 hours. The mean peak recorded serum theophylline concentration was 339 ± 189 μmol/L. Twenty-eight patients (11%) had a peak serum theophylline concentration of 555 μmol/L or greater.

Patient characteristics are summarized by group in Table 1. Intergroup differences were found in patient age and peak serum theophylline concentration: Patients having acute intoxication in the absence of theophylline therapy or acute intoxication while on therapy were younger and had a greater peak serum theophylline concentration than those who had been chronically overmedicated. No intergroup differences were observed in the interval from ingestion to presentation (7.85 hours, 7.85 hours, and 7.1 hours for the patients with acute intoxication but not receiving therapy, patients who were chronically overmedicated, and patients who had acute intoxication while receiving therapy, respectively [$P > 0.2$]).

Eighty-eight patients (35%) were taking other drugs concurrently. Fifteen patients were taking cardiac agents (digoxin [8 patients], propranolol [2 patients], verapamil [2 patients], cocaine [2 patients], and nifedipine [1 patient]). No patient receiving digoxin had toxic digoxin concentrations. Thirteen patients were taking diuretics (furosemide [7 patients] and hydrochlorothiazide [6 patients]), and 13 patients were taking beta-adrenergic agonists (albuterol [8 patients], terbutaline [3 patients], and metaproterenol [2 patients]).

Mean serum potassium and bicarbonate levels were lower and the serum glucose level was higher among

Table 1. Patient Characteristics and Complications*

Variable	Acute Theophylline Intoxication in the Absence of Therapy (n = 119)	Intoxication Due to Chronic Overmedication (n = 92)	Acute Intoxication While Receiving Therapy (n = 38)	P Value
Characteristics				
Age, *y*	22.8 ± 12.3	58.7 ± 23.8	29.1 ± 17.4	<0.04†;<0.01‡
Peak theophylline level, *μmol/L*	375 ± 219	279 ± 106	381 ± 192	<0.04†;<0.01‡
Time from theophylline ingestion to presentation, *h*	7.85 ± 5.43	7.85 ± 3.32	7.10 ± 4.74	>0.2
Concurrent drug use, *n(%)*				
Cardiac agent	4 (3)	9 (10)	2 (5)	0.15
Central nervous system agent	4 (3)	2 (2)	1 (3)	>0.2
Diuretic	3 (3)	8 (9)	2 (5)	<0.04†
Beta-agonist	4 (3)	7 (8)	2 (5)	0.11
Other	25 (21)	26 (28)	7 (18)	>0.2
Complications				
Metabolic disturbances				
Potassium, *mmol/L*	3.00 ± 0.42	3.66 ± 0.78	3.18 ± 0.44	<0.04†;<0.01‡
Bicarbonate, *mmol/L*	18.7 ± 4.0	25.5 ± 6.4	18.5 ± 4.9	<0.04†;<0.01‡
Glucose, *mmol/L (mg/dL)*	11.0 ± 3.8 (198 ± 69)	8.3 ± 2.6 (150 ± 4.9)	11.3 ± 4.9 (204 ± 88)	<0.04†;<0.01‡
Minor toxicity, *n(%)*				
Vomiting	87 (73)	28 (30)	29 (76)	<0.0001†‡
Tremor	45 (38)	15 (16)	16 (42)	<0.0001†‡
Cardiac	6 (5)	18 (20)	2 (5)	<0.04†
Total§	100 (84)	61 (66)	35 (92)	<0.0001†;<0.01‡
Major toxicity, *n(%)*				
Seizures	6 (5)	13 (14)	3 (8)	<0.04
Cardiac arrhythmias	9 (8)	36 (39)	4 (11)	<0.0001†;<0.01‡
Total§	12 (10)	45 (49)	5 (13)	<0.0001†;<0.01‡
Death	4 (3)	9 (10)	0	0.07

* Means are expressed ± SD.
† Comparison of patients with acute intoxication who were not receiving therapy and patients with intoxication due to chronic overmedication.
‡ Comparison of patients with intoxication due to chronic overmedication and patients with acute intoxication who were receiving theophylline therapy.
§ Totals represent total number of patients.

patients in both acute intoxication groups when compared with those who had been chronically overmedicated.

The frequency of minor toxicity was similar in all groups (84%, 83%, and 92%). Major toxicity occurred at a higher rate in patients with intoxication due to chronic overmedication compared with patients who had acute intoxication in the absence of theophylline therapy (49% compared with 10%; risk ratio, 4.85 [95% CI, 2.96 to 7.94]). Moreover, the mean peak serum theophylline concentration at which major toxicity occurred in patients with intoxication due to chronic intoxication was lower than that at which major toxicity occurred in patients in either of the acute intoxication groups (283, 777, and 566 μmol/L, respectively; P = 0.01).

Of the 13 patients who died, 4 had acute intoxication in the absence of therapy (mean age, 47.5 ± 18.7 years; mean peak serum theophylline concentration, 882 ± 316 μmol/L) and 9 had intoxication due to chronic overmedication (mean age, 80.4 ± 8.0 years; mean peak serum theophylline concentration, 300 ± 83 μmol/L).

Complications

At admission, 91 patients (37%) had abnormal serum potassium, glucose, or bicarbonate levels. The mean serum potassium level at admission was 3.26 ± 0.64 mmol/L (reference range, 3.50 to 5.50 mmol/L); 53% of patients had hypokalemia. The mean glucose level was 10.2 ± 3.9 mmol/L (184 ± 70 mg/dL) (reference range, 3.9 to 6.7 mmol/L [80 to 120 mg/dL]); hyperglycemia was present in 85%. Although the mean bicarbonate level was 21 ± 6 mmol/L, 24% of patients had an admission serum bicarbonate level of 18 mmol/L or less (reference range, 18 to 25 mmol/L).

Manifestations of minor toxicity included spontaneous vomiting (144 patients [58%] and muscle tremor (76 patients [31%]).

Cardiac disturbances associated with theophylline poisoning are listed in Table 2. Sinus tachycardia occurred in all 249 patients (mean pulse, 127 ± 30 beats/min). Twenty-six patients (10%) had other minor cardiac disturbances: These included ventricular premature beats (14 patients), supraventricular tachycardia (4 patients), premature atrial contractions (3 patients), and a combination of these events (5 patients).

Major toxicity developed in 62 patients (25%) (*see* Table 1): Twenty-two patients had generalized convulsions, and 49 had severe cardiac arrhythmias. Major toxicity was more common in elderly patients, occurring in 65% of those 60 years or older but in only 11% of patients less than 60 years of age (risk ratio, 5.48; 95% CI, 3.67 to 8.19). Among patients developing seizures, 4 had a known seizure disorder. Ten patients had only a single seizure, 7 had recurrent seizures, and 5 had status epilepticus.

Major cardiac disturbances included sustained su-

Table 2. Cardiac Arrhythmias after Theophylline Intoxication

Variable	Total (n = 249)	Acute Intoxication in the Absence of Therapy (n = 119)	Intoxication Due to Chronic Overmedication (n = 92)	Acute Intoxication While Receiving Therapy (n = 38)
	← n(%) →			
Minor cardiac manifestations*				
Supraventricular				
Supraventricular tachycardia	4 (2)	2 (2)	2 (2)	0
Premature atrial contractions	3 (1)	0	3 (3)	0
Ventricular				
Ventricular premature beats	14 (6)	4 (3)	9 (10)	1 (3)
Combination	1 (1)	0	1 (1)	0
Total	22 (9)	6 (5)	15 (16)	1 (3)
Major cardiac manifestations				
Supraventricular				
Supraventricular tachycardia	14 (6)	2 (2)	11 (12)	1 (3)
Atrial fibrillation or flutter	13 (5)	1 (1)	11 (12)	1 (3)
Multifocal atrial tachycardia	2 (1)	0	2 (2)	0
Ventricular				
Ventricular tachycardia	9 (4)	1 (1)	6 (7)	2 (5)
Multifocal premature ventricular beats	3 (1)	1 (1)	2 (2)	0
Bigeminy	3 (1)	0	3 (3)	0
Electromechanical dissociation	4 (2)	3 (3)	1 (1)	0
Combination	1 (1)	0	1 (1)	0
Total	49 (20)	8 (7)	37 (40)	4 (11)

* Excludes sinus tachycardia.

praventricular tachycardia (14 patients [6%]), atrial fibrillation or flutter with rapid ventricular conduction (13 patients [5%]), and ventricular tachycardia (9 patients [4%]) (Table 2). Among patients developing arrhythmias, 15 had previously known cardiovascular disease (recurrent atrial tachycardia, congestive heart failure, or essential hypertension). Myocardial infarction was diagnosed by positive enzyme fractionation in 5 patients while their serum theophylline concentrations were in the toxic range. Thirteen patients died within 72 hours of hospitalization, all of intractable cardiac arrhythmias.

In addition to supportive care and multiple-dose activated charcoal, hemoperfusion or hemodialysis was done in 38 patients (18 with acute intoxication in the absence of theophylline therapy, 12 with chronic intoxication, and 8 with acute intoxication while on therapy). Of the 21 patients who received extracorporeal drug removal before the appearance of major toxicity, 1 (5%) developed seizures during the procedure. Of the 17 patients who received extracorporeal intervention because of major toxicity, 12 (71%) continued to have toxic manifestations (P = 0.00001 compared with patients receiving prophylactic extracorporeal drug removal).

Acute Intoxication Compared with Chronic Intoxication

Of the 119 patients who had acute intoxication but were not receiving therapy, 12 (10%) developed major toxicity; these 12 patients had a higher mean peak serum theophylline concentration (777 μmol/L compared with 333 μmol/L, P = 0.001) and a lower serum bicarbonate level (15.2 mmol/L compared with 19.9 mmol/L, P = 0.004) than patients with acute poisoning who did not develop major toxicity.

Of the 92 patients with chronic intoxication due to overmedication, 45 (49%) developed major toxicity. No differences were found in the mean peak serum theophylline concentration (283 μmol/L compared with 272 μmol/L, P = 0.58) or in the serum electrolyte level between patients with major toxicity and those without major toxicity. However, those with major toxicity were older than those who remained well (mean age, 71.5 and 45.6 years, respectively [P = 0.001]).

Five patients who had acute intoxication while receiving therapy had major toxicity. When patients with and without major toxicity were compared, no differences were found in the peak serum theophylline concentration; however, patients with major toxicity were older (49.2 years compared with 26.1 years, P = 0.004) and had a lower serum bicarbonate level (14.6 mmol/L compared with 19.5 mmol/L, P = 0.04).

Risk Factors for Major Toxicity

In patients with acute theophylline intoxication, only the peak serum theophylline concentration was significantly associated with the development of major toxicity by logistic regression analysis (r = 0.83, P = 0.0001). A univariate logistic regression model predicted an increasing probability of major toxicity for increasing serum theophylline concentration (Table 3). For this calculation, patients who received prophylactic hemoperfusion or hemodialysis were excluded. A 50% probability of major toxicity was found at a peak serum theophylline concentration of 611 μmol/L (110 mg/L). A receiver-operating characteristic curve was constructed to evaluate the sensitivity of the peak serum theophylline concentration in identifying patients who developed major toxicity (Figure 1, *top*). A peak serum theophylline concentration of more than 555 μmol/L (100 mg/L) had a sensitivity of 0.67 and a false-positive rate of 0.03 in identifying all patients who developed

major toxicity. Using a peak serum theophylline concentration of greater than 444 μmol/L (80 mg/L) increased the false-positive rate to 0.08, with sensitivity remaining at 0.67.

For patients with chronic intoxication, logistic regression analysis showed only increasing age to be associated with the development of major toxicity (r = 0.51, P = 0.001). Calculations of the probability of major toxicity based on chronologic age are found in Table 4.

Receiver-operating characteristic curves were constructed that analyzed peak serum theophylline concentration and age as predictors of major toxicity after chronic overmedication (Figures 1 and 2). The peak serum theophylline concentration had no discriminant value in identifying patients who developed major toxicity (Figure 1, *bottom*). In contrast, an age of more than 60 years, independent of the peak serum theophylline concentration, was associated with a sensitivity of 0.85 and with a false-positive rate of 0.38 (Figure 2). Lowering the age cutoff to greater than 40 years increased sensitivity to 0.98 but increased the false-positive rate to 0.43.

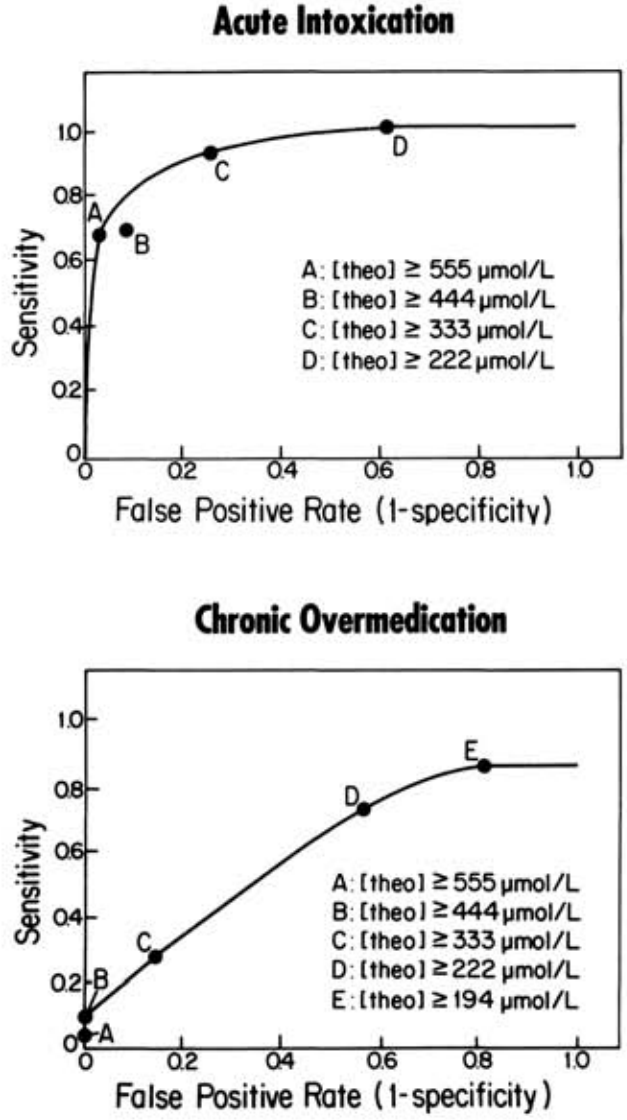

Figure 1. Receiver-operator characteristic curve for patients with acute theophylline intoxication (*top*) and patients with intoxication due to chronic overmedication (*bottom*). Curve shows the discriminant value of the peak serum theophylline concentration.

Discussion

This study reconciled apparently discrepant findings from studies that examined the association between peak serum theophylline concentration and the appearance of major toxicity. The major findings of this study were as follows: 1) the risk for major toxicity is influenced by method of intoxication; 2) patients with chronic theophylline intoxication have a greater risk for major toxicity, at lower serum theophylline concentrations, than those with acute intoxication; 3) the risk for major toxicity in cases of acute theophylline intoxication is best predicted by peak serum theophylline concentration; 4) the risk for major toxicity in cases of chronic overmedication cannot be predicted by the peak serum theophylline concentration; and 5) age provides the best predictor of major toxicity in cases of chronic theophylline overmedication.

Method of intoxication was first clearly shown to be a modulator of major toxicity after theophylline intoxication in a study by Olson and colleagues (27). That study received criticism because of its retrospective nature, a skewed distribution in patient age, and the conclusion that even among patients with chronic theophylline intoxication, some correlation between peak serum theophylline concentration and major toxicity existed. Subsequent studies by Aitken (17) and Bertino and colleagues (32) suggested that the peak serum theophylline concentration was not associated with major toxicity, particularly in cases of chronic overmedication (17, 32). The current study is more consonant with the findings of these investigators, showing the limited value of serum theophylline concentrations in patients who were chronically overmedicated.

The results of this study indicate that after theophylline intoxication has occurred, the approach to management must be initially influenced by whether the patient has acute intoxication in the absence of theophylline therapy, intoxication due to chronic overmedication, or acute intoxication while on theophylline therapy. For those with acute theophylline intoxication, high-risk pa-

Table 3. Probability of Major Toxicity after Acute Theophylline Intoxication according to Peak Serum Theophylline Concentration*

Peak Serum Theophylline Concentration, *μmol/L*	Probability of Major Toxicity (95% CI)
167	0 (0 to 0.04)
333	0.04 (0.01 to 0.11)
444	0.12 (0.05 to 0.26)
555	0.36 (0.13 to 0.67)
611	0.50 (0.18 to 0.96)
722	0.78 (0.30 to 0.97)

* Probability = $1/1 + e^{-z}$, where $z = -0.328 + 0.0056$ (peak serum theophylline concentration).

Table 4. Probability of Major Toxicity after Intoxication due to Chronic Theophylline Overmedication according to Age*

Age, *y*	Probability (95% CI)
25	0.11 (0.04 to 0.28)
40	0.23 (0.12 to 0.41)
50	0.36 (0.23 to 0.51)
60	0.50 (0.38 to 0.63)
70	0.65 (0.52 to 0.76)
80	0.77 (0.63 to 0.87)
90	0.87 (0.73 to 0.94)

* Probability = $1/1 + e^{-z}$, where $z = -0.155 + 0.0106$ (age).

tients can be readily identified using the peak serum theophylline concentration.

In contrast, for patients with chronic theophylline intoxication, the peak serum theophylline concentration has no predictive value and should not be the primary factor in making decisions for more aggressive intervention such as hemoperfusion. However, age does appear to have prognostic utility for clinical decision making (Table 4). An age of more than 60 years has the greatest diagnostic accuracy in identifying patients at highest risk. Unfortunately, age does not provide the same degree of prognostic accuracy in cases of chronic overmedication as the peak serum theophylline concentration does in cases of acute intoxication. For example, regarding the use of an age greater than 60 years as a criterion for hemoperfusion, the receiver-operating characteristic data suggest that 38% of such patients may not need the procedure but can be treated by supportive care and multiple-dose activated charcoal without the development of major toxicity.

Although not a primary intent of this investigation, data on the efficacy of hemoperfusion are notable. In our cohort, prophylactic hemoperfusion reduced the incidence of major toxicity from 71% to 5%. Hemoperfusion increases theophylline clearance two- to sixfold and appears to be highly effective in preventing seizures and cardiac arrhythmias (19, 20, 22, 28). Because the decision to do this procedure was based on factors such as its availability and its perceived risks and benefits, it is likely that the magnitude of the procedure's benefit was influenced by selection bias. Nonetheless, the results are consistent with those from previous studies of the prophylactic efficacy of hemoperfusion. The exact role of hemoperfusion after theophylline poisoning remains to be determined by a randomized clinical trial. In addition, it is important to note that hemoperfusion is associated with such complications as hypotension, hypocalcemia, platelet consumption, and bleeding diatheses. Therefore, the observation that hemodialysis appeared to be as effective as hemoperfusion in preventing major toxicity suggests that this safer, alternative therapy should be more fully explored.

On the basis of these findings, we recommend that enhancement of drug elimination be confined to the administration of multiple-dose activated charcoal in patients with acute theophylline intoxication who have a peak serum theophylline concentration of less than 555 μmol/L (100 mg/L). In patients with a peak serum theophylline concentration of 555 μmol/L or greater or with a serum theophylline concentration of less than 555 μmol/L and intractable vomiting, hemoperfusion (or hemodialysis) should be done immediately. The importance of instituting aggressive antiemetic therapy in ensuring the successful administration of activated charcoal has been previously emphasized (25).

Patients with chronic theophylline intoxication should initially receive multiple-dose activated charcoal (19). Because elderly patients appear to be at the highest risk for major toxicity, previous recommendations by other investigators to do prophylactic hemoperfusion in patients older than 60 years who have a peak serum theophylline concentration of 222 μmol/L (40 mg/L) or greater are supported by this study (10, 12, 14, 17, 28, 36). In fact, the findings of the current study suggest that hemoperfusion should be done in all such patients if the peak serum theophylline concentration is 167 μmol/L (30 mg/L) or greater, as has been previously suggested by Park and colleagues (20). However, hemoperfusion presents the greatest technical difficulty and risk in patients at the extremes of age (the elderly and neonates) (28).

This study's strength was the prospective enrollment of a large number of patients with theophylline intoxication. The study design, however, also presented the potential problems of referral bias and the heterogeneity that accompanies patient referrals from many different health care facilities. However, because all patients were managed in part by a consulting toxicologist who provided consistent recommendations and close monitoring, the effects should have been minimized. Nonetheless, this method may prevent generalizability of the results to all patients who seek treatment for theophylline poisoning.

Like our previous study of clinical toxicity after chronic theophylline intoxication, this investigation confirms the high rate of morbidity and mortality in elderly patients with theophylline intoxication due to chronic overmedication (31). If theophylline is to have continued use in this population, the importance of close monitoring is underscored by our findings. These data

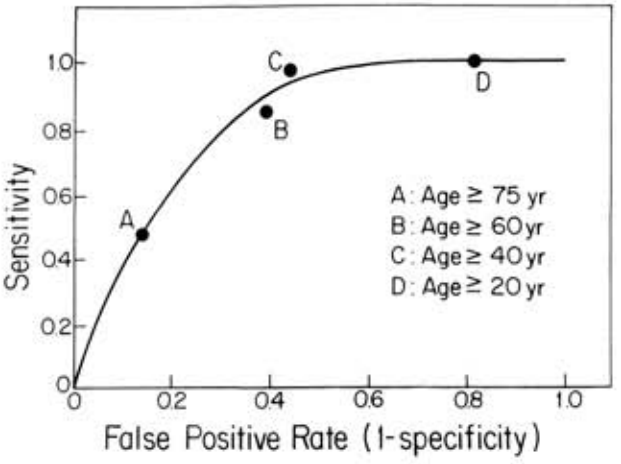

Figure 2. Receiver-operator characteristic curve for patients with intoxication due to chronic overmedication. Curve shows the discriminant value of increasing chronologic age.

further support admonitions that theophylline should be used cautiously, if at all, in elderly patients.

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