Multi-Drug Theophylline Overdose

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Theophylline, one of the most often prescribed pharmacologic agents, continues to be the source of challenging issues in clinical practice.[1] Perhaps one reason lies in its availability in single-entity and combination, as well as rapid-release and sustained-release, dosage forms. Depending on the product formulation and the individual, there may be variable lengths of time required for total theophylline release. Variability in product formulation may account for specific clinical findings, particularly in circumstances in which more than one product type is used simultaneously, as in the case of multi-drug overdose.

Accounts of theophylline overdose and toxicities have been recently reviewed.[2] Of the 399 cases of theophylline toxicity evaluated in this compilation of 89 citations in the English language literature, 122 patients were presumed to be suffering from drug overdose. Within this group, when information could be determined, 60% were female and the mean age was 26 years. The mean value of the highest recorded serum theophylline concentration (STC) for these overdose patients was 599.5 μmol/L (109 mg/L). Interestingly, 22 patients had ingested a sustained-release theophylline product. In ten of these patients the time to peak concentration ranged from 2 to 18 hours. Four patients had STCs during observation that substantially exceeded admission values.

This report describes a patient who was seen following overdose with multiple theophylline products, each having different dosage release characteristics and accounting for different features of the documented serum theophylline concentration curve.

CASE REPORT

A 27-year-old nonsmoking woman weighing 61.4 kg came to her local emergency room following attempted suicide by the ingestion of 50 200-mg timed-release theophylline capsules (Slo-bid Gyrocaps), 20 50-mg sustained-action theophylline capsules (Theo-Dur Sprinkles), and 15 tablets of a combination of 130 mg of theophylline and 24 mg of ephedrine (Primatene), representing a total of 12.95 g of anhydrous theophylline (Table 1). The patient had no history of asthma and had been prescribed no medicines (the ingested medicines belonged to her son). She also claimed to have consumed 1.5 fifths of whiskey. Before this episode, there had been no documented drug misuse or substance abuse. Approximately 2 hours after ingestion and before transport to the Medical College of Georgia (MCG) Emergency Department, blood was obtained for theophylline evaluation. Assay for the presence of theophylline revealed a serum concentration of 203.5 μmol/L (37 mg/L). An assessment of the patient's blood alcohol was not performed. A review of the medical record documented that one dose each of ipecac, charcoal, and magnesium citrate was administered prior to transport; however, additional details of these measures were missing, including the exact amounts administered or the results obtained.

Upon arrival at MCG, the patient was oriented and cooperative. By her own assessment and physician observation, she appeared quite nervous. She had no additional complaints. Based on the referral information, another sample of blood was obtained, and a second theophylline evaluation revealed a 6-hour postingestion STC of 489.5 μmol/L (89 mg/L). Her pulse was 136 beats per minute, respirations 22/min, and blood pressure 122/60 mmHg. Other than tachypnea and tachycardia, the physical examination was unremarkable. Although no electroencephalogram was obtained, the neurological examination, except for the observed nervousness, was within normal limits. Additional laboratory evaluation included an arterial blood gas determination on 2 L of oxygen, which revealed pH 7.43, pO_2 126 mmHg, pCO_2 13 mmHg. The serum sodium was 141 mmol/L (mEq/L), potassium 2.3 mmol/L (mEq/L), chloride 103 mmol/L (mEq/L), bicarbonate 22 mmol/L (mEq/L), glucose 12.3 mmol/L (221 mg/dL), and urea nitrogen 1.8 mmol/L (5 mg/dL). The white cell count was 16.5×10^9/L ($16.5 \times 10^3/\mu L$).

The patient was admitted for observation and telemetry. She received 50 g of charcoal and 1 bottle of magnesium

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TABLE 1. MEDICATIONS INGESTED IN OVERDOSE

Brand Name	Contents	Quantity Ingested	Total Ingested Theophylline
Slo-bid Gyrocaps	Theophylline 200 mg	50	10,000 mg (10 g)
Theo-Dur Sprinkles	Theophylline 50 mg	20	1,000 mg (1 g)
Primatene M	Theophylline 130 mg Ephedrine 24.3 mg Pyrilamine 16.6 mg	15	
	or		
Primatene P	Theophylline 130 mg Ephedrine 24 mg Phenobarbital 8 mg	15	1,950 mg (1.95g)
Total			12,950 mg (12.95 g)

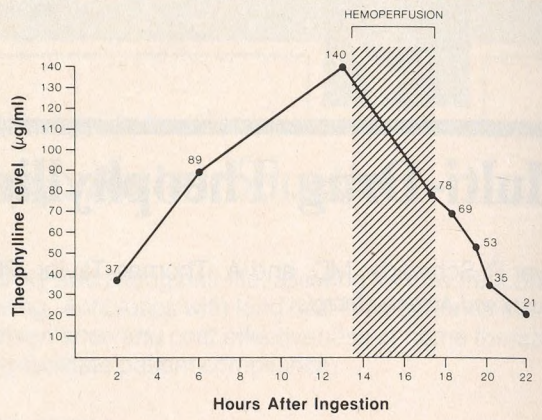

Figure 1. Serum theophylline concentration curve showing a peak at approximately 13 hours after ingestion.

citrate every 4 hours over the first day. Thirteen hours after ingestion, the STC was documented, and confirmed by a repeat assay, as 770 μmol/L (140mg/L). The patient was transferred to the intensive care unit, where hemoperfusion was begun. The patient exhibited no seizure activity, cardiac dysrhythmias, or loss of consciousness. She underwent hemoperfusion with 2 charcoal cartridges over 4 hours. The STC decreased to 110 μmol/L (20 mg/L) over the next 9 hours (Figure 1). She left the hospital the next day without apparent sequelae and was referred to the local mental health clinic.

DISCUSSION

Other authors have documented that life-threatening theophylline toxicity is not well correlated with serum levels.[3–6] This case, however, represents one of the highest reported theophylline serum concentrations in a patient who not only survived but also remained relatively asymptomatic during her recovery period.

The risks from overdose with sustained-release theophylline products have been previously addressed.[7–9] This patient, however, ingested two sustained-release theophylline formulations, each having different drug release characteristics. Although the high initial STC of 203.5 μmol/L (37 mg/L) was likely due to the 1,950 mg of rapidly available theophylline contained in Primatene, the remainder of the absorption and distribution phase of the STC curve was probably a result of the large amount of sustained-release theophylline. As can be noted in the evaluation of this curve in Figure 1, the total absorption of theophylline appeared to continue beyond the usual 4 to 8 hours of most appropriately administered sustained-release products. In fact, this patient's STC appeared to have peaked at 770 μmol/L (140 mg/L) approximately 13 hours after ingestion.

By performing standard pharmacokinetic calculations for this case, the contributions to the total STC curve provided by each drug's ingestion can be assessed. For example, the predicted STC for the rapid-release Primatene formulation can be separated from the total STC as follows.

$$Cp = (Dose \times S \times F)/Vd$$

Where:

- Cp = predicted serum concentration (mg/L)
- Dose = total dose administered in this form (mg)
- S = fraction of anhydrous theophylline (1.0)
- F = fraction absorbed (1.0)
- Vd = volume of distribution (0.48 L/kg); in this patient Vd = 29.5 L (or 61.4 kg × 0.48 L/kg)

For Primatene (rapid-release):

$$Cp = (1{,}950 \text{ mg} \times 1.0 \times 1.0)/29.5 \text{ L}$$

$$Cp = 66 \text{ mg/L, or } 363 \text{ μmol/L}$$

Total for all theophylline products ingested:

$$Cp = (12{,}950 \text{ mg} \times 1.0 \times 1.0)/29.5 \text{ L}$$

$$Cp = 440 \text{ mg/L, or } 2{,}420 \text{ μmol/L}$$

Through these separated calculations, one can appreciate that the actual STC peak produced by such an overdose should have been expected between 363 μmol/L and 2,420 μmol/L (66 and 440 mg/L, respectively). Although the initial STC of 203.5 μmol/L (37 mg/L) was probably a result primarily of the rapid-release Primatene, the peak STC achieved should have been higher than 363 μmol/L (66 mg/L) because of the contributions of the sustained-release products. The actual STC did not reach the predicted 2,420 μmol/L (440 mg/L), however, probably as a result of the aggressive use of magnesium citrate, a saline

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laxative aimed at decreasing the transit time of theophylline through the gastrointestinal tract and thereby reducing its absorption. Hemoperfusion was not begun until after the 770-μmol/L (140-mg/L) peak STC was known.

There are two commercially available Primatene products, one of which contains 8 mg of phenobarbital per tablet. Since it is unknown which product was ingested, the possible anticonvulsant benefits from the phenobarbital 120 mg are unknown; however, the 360 mg of ephedrine contained in these tablets probably contributed to this patient's tachycardia.

CONCLUSIONS

This case report illustrates the need to be mindful of the differences among product formulations that account for variations in the STC curve and the associated clinical presentations of the overdose patient. An important point in the management of this patient was the observed increase in the serum concentration from 203.5 μmol/L (37 mg/L) to 770 μmol/L (140 mg/L) over a period of 11 hours. This increase, as well as the period required for it to occur, was primarily the result of sustained-release formulations. It is essential, therefore, that clinicians continue to observe the clinical status of overdose patients until the STC not only ceases to increase, but falls to an acceptable and safe serum concentration.

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