

## Thinking Through Theophylline

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*The following is a contrived report that has been created as a teaching case in the area of medication error prevention.*

## INTRODUCTION

According to the U.S. Department of Health and Human Services, a medical error occurs in 1 out of every 25 hospitalized patients.<sup>1</sup> With these medical errors, there is an estimated cost of more than five million dollars per year within a large hospital and about 23 million dollars to the economy.<sup>1</sup> Kaushal et al. assessed rates of medication errors in hospitalized pediatric patients.<sup>2</sup> After reviewing medication orders and patient profiles, they found that 5.7% of orders had medication errors, or 55 errors per 100 admissions. Medication errors were defined as errors in drug ordering, transcribing, dispensing, administering, or monitoring. Comparing the results to a similar adult study,<sup>3</sup> the potential for adverse drug events (ADEs) was 3 times higher in the pediatric setting. Medication errors occur as a result of numerous factors that influence the health care system and have been discussed in depth in a paper jointly published by the Pediatric Pharmacy Advocacy Group and the Institute for Safe Medication

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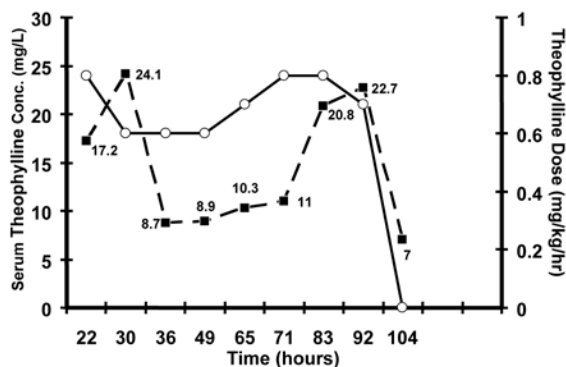
Practices.<sup>4</sup> Due to its narrow therapeutic range, many formulations, and difficulty in dosing,

**ABBREVIATIONS** ADE, adverse drug event

theophylline can pose many medication errors, as seen in this case report.

## CASE

A 3-year-old (16 kg) male with a previous diagnosis of asthma presented to the emergency department with wheezing, increased work of breathing, and was diagnosed with status asthmaticus. Prior to admission he only required albuterol as needed for his asthma. In the emergency department, he did not respond to continuous albuterol nebulization and intravenous steroids and was intubated and administered a continuous infusion of terbutaline at 0.1 µg/kg/min. While on mechanical ventilation, his heart rate was 210 beats/minute, respiratory rate was 15 breaths/minute, and oxygen saturation was 91%. His arterial blood gases were as follows: pH 7.48, pCO<sub>2</sub> 38, PO<sub>2</sub> 44, HCO<sub>3</sub> 29 and a base excess 5. After little improvement, he was given a 5-mg/kg loading dose of theophylline and was started on 0.8 mg/kg/hr continuous infusion of theophylline. The child improved over the next 8 hours and required less supplemental oxygen. A serum theophylline concentration (reference range 5-15 mg/L (27.5-82.5 µmol/L)) obtained 22 hours after the maintenance infusion was begun was 17.2 mg/L (94.6 µmol/L). Although the child had no evidence of toxicity, the serum



**Figure 1.** Serum theophylline concentration and theophylline dosage.

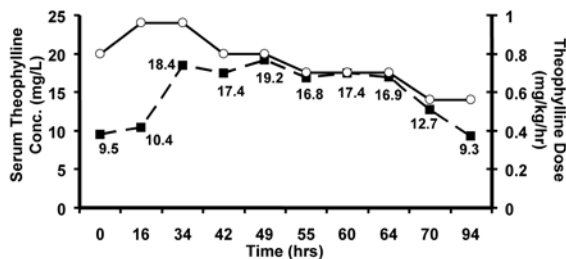
○ = theophylline dosage; ■ = serum theophylline concentration

concentration was higher than what would normally be expected and the dose of theophylline was reduced by 25% to 0.6 mg/kg/hr. Despite a decrease in dose, a follow-up serum concentration 8 hours later was supratherapeutic (24.1 mg/L) and the infusion was continued until another concentration was obtained. Six hours later the concentration had significantly decreased to 8.7 mg/L. Subsequent serum theophylline concentrations are noted in Figure 1. The child's overall status had improved and the theophylline infusion was discontinued because of concerns over unexplained variability in serum theophylline concentrations.

Although the child's condition initially improved, he remained intubated at day 10, when theophylline was again initiated. The patient was given a 5-mg/kg loading dose of theophylline and a standard maintenance infusion for age and weight (0.8 mg/kg/hr).

Serum theophylline concentrations are noted in Figure 2.

A post-bolus concentration allowed for the estimation of the patient's volume of distribution, which was calculated as 0.5 L/kg. There was essentially no change in the child's condition or serum concentration (10.4 mg/L) after 16 hours on the continuous infusion and the dose was increased to 0.96 mg/kg/hr. Using estimates for clearance determined via the Chiou equation,<sup>5</sup> one would have expected a serum concentration of less than 15 mg/L (82.5  $\mu$ mol/L); however, the concentration 18 hours later was 18.4 mg/L (101.2  $\mu$ mol/L). Despite decreasing the infusion twice (0.8 and 0.7 mg/kg/hr), subsequent serum concentrations con-



**Figure 2.** Serum theophylline concentration and theophylline dosage.

○ = theophylline dosage; ■ = serum theophylline concentration

tinued to be greater than 18 mg/L (99  $\mu$ mol/L) over the next 15 hours. The infusion was again decreased by 20% and the serum concentration decreased to 9 mg/L (54.5  $\mu$ mol/L).

## ASSESSMENT

Several possibilities were explored as plausible explanations for the significant variability in this patient's serum concentrations. The child's medical record was again reviewed. The weight (kg) and height were validated and both were normal for age per growth charts. A medication history was retaken and no alternative, prescription or over-the-counter medications known to affect theophylline clearance were taken prior to admission. A second likely reason for the fluctuating serum theophylline concentrations was error in intravenous administration of the medication. Had the infusion device been set incorrectly, the rate of administration could have led to administration of a smaller or larger dosage than expected. Each time a serum theophylline concentration was interpreted, the pharmacist validated by visual inspection that the infusion device was set at the correct rate and that the medication administration record noted that the rate had not been changed. Although unlikely, malfunction of the infusion device could have caused delivery of the wrong dose. This was eliminated as a contributing factor when the Biomedical Department of the hospital validated that the infusion device was accurate within manufacturer specifications. Infusing theophylline into a non-secure intravenous line could have also explained the low serum concentration; however, there was no notation of an infiltration and the catheter was not changed during the

course of therapy.

Another possible explanation for the aberrant serum concentrations was the phlebotomist sampling procedure. To eliminate the possibility of a theophylline contaminated sample due to collection through the catheter where theophylline was infusing or failure to adequately flush the port prior to collection, the pharmacist requested that a serum sample be obtained via venipuncture. The repeat serum theophylline concentration was within 10% of the previous value. Laboratory error in performing the assay or the assay itself was also a possible reason for the inconsistent theophylline concentrations. Upon checking with the clinical laboratory the standard curve for theophylline was within range. Additionally, the low, medium and high controls were run on each shift and were acceptable for within-day and between-day coefficients of variation for the assay. In viewing the actual serum samples there was no visual evidence of any factor that might interfere with the assay (e.g., hemolysis). Pharmacy and/or pharmacist error was the final explanation for the irregular serum concentrations. The institution uses only pre-mixed theophylline and does not carry a concentrated theophylline product; hence, there was not a possibility of a compounding error. Had a compounding error by either the pharmacist or manufacturer been in question the clinical laboratory would have been asked to assay a sample of the intravenous product that had been infused to determine its actual concentration. The final potential for error related to the wrong pre-mixed concentration being stocked in the pharmacy. This could have occurred when either the pharmacy or wholesaler inventoried the incorrect product. Upon investigating the possibility of this type error, the pharmacist found an 800 mg/500 mL theophylline infusion bag being administered to the patient instead of the hospital's standard 400 mg/500 mL pre-mixed infusion bag. It was then recognized that the patient had received two different concentrations of theophylline throughout the course of hospitalization. The pharmacy had, in error, ordered the 800 mg/500 mL pre-mixed theophylline infusion bags.

Since only the 400 mg/500 mL concentration was usually inventoried by the hospital, the pharmacist and nurse overlooked checking the concentration printed on the bag.

### RECOMMENDATIONS FOR PREVENTION OF THIS TYPE ERROR

In order to prevent this type error the hospital system should consider: 1) implementation of double checks throughout the medication process to ensure that the correct concentration is ordered, received, and stocked by the pharmacy; 2) checking all pre-mixed solutions even when only one concentration is routinely stocked within the hospital; 3) implementation of bar code technology throughout the medication use system; 4) increasing awareness of the potential for errors even with standard concentrations by educating pharmacists and pharmacy staff, nurses and physicians; 5) segregating storage when more than one concentration is inventoried; and 6) reviewing all the steps in the drug administration process when interpreting serum drug concentrations that do not correlate with dosing.

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