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# A Curious Cause of Seizures

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**Fatal Forty DDI:** ketamine, theophylline

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## Abstract

This case discusses a ketamine/theophylline interaction of unknown etiology resulting in decreased seizure threshold.

## Case

A 24-year-old, 65 kg woman presented to the hospital for diagnostic abdominal laparoscopy. Because she had a history of severe asthma requiring hospitalization and intubation, she was admitted to the hospital on the night before her surgery for optimization of her asthma before planned general anesthesia.

She was given a loading dose of aminophylline (5.9 mg/kg), followed by an aminophylline maintenance infusion (1 mg/kg/hr). The following morning, she was taken to the operating room, anesthesia was induced with ketamine (100 mg) over 2 minutes. Within minutes, ventilation became impossible due to jaw rigidity, and her upper extremities developed extensor posturing. The patient's heart rate also increased from 80 to 120 beats per minute. Succinylcholine (80 mg) was given, and ventilation via mask became easy. The patient was intubated, and the rest of the intraoperative course was uneventful.

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## Discussion

### **This is an example of a drug–drug interaction of undetermined mechanism.**

Drug–drug interactions between ketamine and theophylline resulting in seizures have been reported.<sup>4,5</sup> The mechanism is not known. Aminophylline is a combined preparation of theophylline and ethylenediamine. Theophylline is a substrate for cytochrome P450 1A2 (primarily), and is secondarily a substrate for cytochromes 2E1 and 3A4, (it is important to note that some studies have shown that 3A4 does not contribute to theophylline metabolism.)<sup>1,2</sup> Ketamine has been thought of as primarily a substrate for cytochrome 2B6 and a minor substrate for 3A4 and 2C9 (although recent research suggests that at clinical concentrations 3A4 may be the principal enzyme responsible for ketamine metabolism in the liver).<sup>1,3</sup> Neither drug is an inducer or inhibitor of P450 enzymes.

There are several case reports of seizures with this drug combination.<sup>4,5</sup> Theophylline is rarely used in the United States, however, the drug is still commonly used in Africa, Asia, South America, and parts of Eastern Europe. In the cases that have been reported, ketamine was always given to someone who was already receiving theophylline, and the seizure began shortly after the ketamine was administered. A laboratory study in mice demonstrated that the combination of ketamine and theophylline did, in fact, lower the seizure threshold though no mechanism for this decrease in the threshold was postulated.

High concentrations of theophylline are associated with multiple deleterious side effects, one of which is seizures. Because ketamine was administered to a patient who was already getting theophylline, and the seizure occurred shortly after the ketamine was administered; the inference is raised that the addition of ketamine resulted in an increase of the fraction of theophylline available in the bloodstream. If so, the possible mechanisms could involve either displacement of theophylline by ketamine on the transport proteins in the bloodstream, or a change in the profile of which drug between the two is preferentially metabolized by 3A4.

## Take-Home Points

- Ketamine and theophylline are both metabolized by more than one cytochrome P450 enzyme.
- Ketamine administration to someone who is already receiving aminophylline (theophylline) has been reported to result in seizures.
- The mechanism for such seizures is unknown. Thus, it is prudent to avoid this combination of drugs.

## Summary

**Interaction:** unknown

**Substrates:** theophylline and ketamine

**Mechanism/site of action/enzyme:** unknown, possibly displacement of protein binding or differential metabolism at cytochrome 3A4

**Clinical effect:** decreased seizure threshold

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## References

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