

This Week's Citation Classic®

Zwillich C W, Sutton F D, Jr., Neff T A, Cohn W M, Matthey R A & Weinberger M M. Theophylline-induced seizures in adults: correlation with serum concentrations. *Ann. Intern. Med.* 82:784-7, 1975.

[Divs. Pulmonary Medicine and Clinical Pharmacology, Dept. Medicine, Univ. Colorado Medical Ctr., and affiliated hospitals, Denver, CO]

Seizures with high mortality occurred in hospitalized patients treated with intravenous theophylline, which resulted in high serum concentrations. Hospitalized patients with similar underlying illnesses but with lower theophylline plasma concentrations did not display clinical seizure activity. [The SCI® indicates that this paper has been cited in over 300 publications.]

Clifford W. Zwillich
Pulmonary Division
College of Medicine
Milton S. Hershey Medical Center
Pennsylvania State University
Hershey, PA 17033

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In 1972 we pulmonary fellows in Tom Petty's unit at the University of Colorado met weekly to share ideas and observations for the purpose of organizing and conducting clinically based research. The group members hoped to achieve through this research effort two goals during the course of the clinical training year. The first was simply to critically evaluate our individual desires to pursue an academic career; the second, to answer some relevant questions related to clinical medicine. Our meetings were highly animated and charged affairs where everyone got, or attempted to get, their "pearls" heard. Four separate projects were proposed and subsequently completed as a result of these meetings.

I recall from an early research meeting that one of us reported anecdotally observing a high frequency of new-onset grand mal seizures in patients receiving intravenous theophylline. Surprisingly, a literature review at that time suggested that this complication was very rare, since only two case reports describing

this complication in adults could be found.^{1,2} Our initial research plan was simply to obtain serum theophylline concentrations in our subsequent patients who displayed seizure activity during intravenous theophylline administration.

We very rapidly collected data on eight such patients and reached the alarming conclusion that this complication was correlated with theophylline serum concentrations and was associated with a high degree of mortality. We hastily attempted to publish our observations but the manuscript was rejected as an "uncontrolled observation." However, we were strongly encouraged by the reviewers to obtain data in a control group of equally ill patients receiving intravenous theophylline but displaying no seizure activity. This was done and resulted in a paper that more convincingly suggested that high serum theophylline concentrations were the likely cause for the seizure disorder.

In retrospect, I believe that the peer review system was working at its best during the various phases of this study's development. We young investigators were initially crushed by the rejection clearly outlined on the pink sheets. However, the constructive criticism was eventually perceived by all of us as being truly helpful and educational.

I believe this paper has been frequently cited for a number of reasons. Other clinicians were also observing severe toxicity, including seizures, in a similar setting.³ A need, therefore, was recognized for a more thorough understanding of theophylline pharmacokinetics and, in particular, a more complete analysis of the relationship between liver disease and altered drug metabolism.⁴ Also, we and others pointed out that premonitory symptoms of drug toxicity may not be present before serious complications such as seizures occur. The fact that these features of serious toxic effects often correlated with serum concentrations may have been a stimulus for the development of rapid and accurate methods for the determination of serum theophylline concentration and their current wide use in monitoring theophylline therapy.⁵

1. Jenne J W, Wyze E, Rood F S & MacDonald F M. Pharmacokinetics of theophylline: application to adjustment of the clinical dose of aminophylline. *Clin. Pharmacol. Ther.* 13:349-60, 1972. (Cited 565 times.)
2. Nicholson D P & Chick T W. A re-evaluation of parenteral aminophylline. *Amer. Rev. Resp. Dis.* 108:241-74, 1973. (Cited 105 times.)
3. Yarnell P R & Chu N S. Focal seizures and aminophylline. *Neurology* 9:819-22, 1975.
4. Piatzky K M, Sitar D S, Rangno R E & Ogilvie R I. Theophylline disposition in patients with hepatic cirrhosis. *N. Engl. J. Med.* 296:1495-7, 1977. (Cited 180 times.)
5. Hendeles L & Weinberger M. Improved efficacy and safety of theophylline in the control of airway hyperactivity. *Pharmacol. Ther.* 18:91-105, 1982.

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