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This Week's Citation Classic®

Jenne J W, Wyze E, Rood F S & MacDonald F **M.** Pharmacokinetics of theophylline application to adjustment of clinical dose of aminophylline. *Clin. Pharm.* 13:349, 1972. [Pulmonary Disease Service, Minneapolis Veterans Hospital, and Department of Medicine, University of Minnesota Medical School MN]

In 1972, aminophylline (theophylline ethylenediamine) had been in use for years, but with only a few papers on its serum levels and potential for toxicity. Ours was one of the first two forma] studies of theophylline pharmacokinetics. It demonstrated that variable levels were a direct function of a wide variation in metabolic clearance, that side effects were common at trough levels over 20 µg/ml, and that dose adjustments should be made on the basis of monitoring serum levels. [The *SCI*® indicates that this paper has been cited in more than 675 publications.]

Pharmacokinetics and Drug Monitoring

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As a new staff member at the Minneapolis VA Hospital in 1959, my interest in pharmacokinetics really started with the tuberculosis drugs isoniazid and p-aminosaJicytic add, which I proceeded to study both in vivo and in vitro. By 1967, however, acetylation polymorphism was proving irrelevant to the successful treatment of tuberculosis and I needed to get back to something important to patient care.

One of my colleagues, Jim Lillehei, began measuring theophylline levels in his patients at the University of Minnesota, finding a large variation. I decided to study the problem with an intravenous T½ of only about four hours. At this time (1967-1968), the effect of smoking on liver enzyme induction was just breaking, and as I puzzled over our data, I realized that this outlier was the only one among us who smoked. Talk about serendipity! Sure enough, when we studied a group of young smokers and nonsmokers, the mean T½'s were 4.1 and 7.2 hours, respectively. Patients also had short T½'s, but most of them smoked. These studies were done with the considerable help of an Argentinean medical resident, Eduardo Wyse. We both have scarred veins to show for it

I then attended a brief, intense course in pharmacokinetics and drug metabolism developed by the J.M. Richards Lab. Sidney Riegelman was one of the prominent teachers. He kindly advised me to go about a formal pharmacokinetic analysis based on a single compartmentai model, and I shall be forever grateful. We used an infusion to steady state and subsequent decay curve to work out the parameters. We found that levels needed for a significant airway response ranged between 8 and 20 µg/ml. When we made major dose adjustments of maintenance therapy, we found suggestive evidence of dose-dependent kinetics. All these findings have been borne out Finally, we recommended a dosing approach based on monitoring levels. This was included in our first paper.

Research was fun again. Since now most of our patients had emphysema, chronic bronchitis, and asthma, theophylline dose-adjustment was immediately applicable. Herb T. Nagasawa, a pharmaceutical chemist, set about developing the first HPLC method for theophylline and its metabolites with Richard D. Thompson, his graduate student[1] A paper on the profile of urine metabolites vs. serum theophylline followed.[2] I hesitated for years to publish the smoking data with only the T½ data, but finally convinced myself that it was valid nevertheless.[3] This was fortunate, because a more complete study done independently came out in 1976 with almost the identical T½ values.[4] Wyse returned to Argentina, and I have had to live with the fact that I misspelled his name in our first paper. Cosio, our smoking index case, quit smoking and became a professor of pulmonary diseases at McGill University.

Other early workers must be acknowledged, particularly P.A. Mitenko and R.I. Ogirvie who published in the same issue using a two-comtmodel,[5]while Miles Weinberger, Myron Susan Lohmann and Ralph Miech, William Jusko, Elliot Ellis, and Leslie Hendeles all made important early contributions.

Despite theophylline's troublesome kinetics and narrow (10-20µg/ml) therapeutic range, it remains an important, if controversial, bronchodilator.[6] It certainly has alerted physicians to the role of pharmacokinetics and drug monitoring, as well as advancing all the careers of those studying its weird kinetics and drug interactions.

1. **Thompson R D, Nagasawa H T & Jenne J W.** The determination of theophylline and its metabolites in human urine and serum by high-pressure liquid chromatography. *J. Lab. Clin. Med.* 84:584-94,1974. (Cited 180 times.)
2. **Jenne J W, Nagasawa H T & Thompson R D.** The relationship of urinary metabolites of theophylline to serum theophylline levels. *Clin. Pharmacol. Ther.* 19:375-81, 1976. (Cited 145 times.)
3. **Jenne J W, Nagasawa H T, McHugh R, MacDonaid** F **M** & Wyse E. Decreased theophylline half-life in cigarette smokers. *Life Sri.* 17:195-8, 1975. (Cited 170 times.)
4. **Hunt S N, Jusko J W & Yonrchak A M.** Effects of smoking on theophylline disposition. *Clin. Pharmacol. Ther.* 19:546-51, 1976. (Cited 225 times.)
5. **Mitenko P A** & **Ogilvie R** L Pharmacokinetics of intravenous theophylline. *Clin. Pharmacol. Ther.* 13:329-35, 1972. (Cited 130 times.)
6. **Jenne J W.** Theophylline is DO more obsolete than "two puffs q.i.d." of current $beta_2$ agonists. (Editorial.) *Chest* 96:3-4, 1990.

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