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# DECREASED THEOPHYLLINE HALF-LIFE IN CIGARETTE SMOKERS

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## Summary

In a group of 19 hospitalized patients, most of whom smoked, the half-life of theophylline following an I.V. aminophylline bolus was 3.6 ± 1.5 hours. When the young male control group was broken down by smoking history, 10 smokers had a theophylline half-life of 4.1 ± 1.2 hours, and 14 non-smokers a theophylline half-life of 7.2 ± 1.8 hours. The prolongation of half-life in the non-smokers was very significant ($p<0.0001$). These findings are consistent with observations that polycyclic hydrocarbons are strong inducers of microsomal enzymes involved in drug metabolism, and may help explain the individual variations of theophylline half-life.

It is now well established that theophylline is eliminated at widely differing rates among individual patients, thus influencing maintenance drug levels. In a panel of ten adult patients studied after infusion of theophylline to equilibrium, we reported half-lives ranging from 3.0 to 9.5 hours (mean 5.2) (1); Lampton reported a range of 1.3 to 9.6 hours (mean 6.0) (2); Ellis has observed a range of 3.0 to 8.3 hours (mean 5.4) in adults and a 40% mean shortening in children (3). In all probability these variations occur through variable drug metabolism, since renal clearance of theophylline is relatively small and constant (1). Furthermore, theophylline is almost wholly metabolized (4), a situation which invites differences in clearance rate.

Several years ago, we first explored possible differences in theophylline half-lives in patients and controls. We discovered a highly significant shortening of half-life in young cigarette smokers. Notwithstanding that these methods are not optimal by present standards, we feel that they are of acceptable quality and internal consistency to warrant publication, particularly because of their application to management of theophylline therapy and their broad application to the field of drug metabolism.

## Method

Initially, subjects consisted of nineteen hospitalized male patients averaging 58 years of age and fifteen healthy male controls averaging about 33 years of age. The strikingly shorter mean half-life in the patient group led us to suspect that induction of drug metabolism was responsible, but the inhomogeneity of the population, particularly with respect to age, inhibited our publication of the data barring further investigation. Reports of the

pronounced effect of cigarette smoking on induction of microsomal oxidative reactions (5) caused us to reassess our data in this light, and it was realized that only one of our controls smoked cigarettes. He also had the shortest half-life. Therefore, an additional nine normal smokers were investigated from the same young population, giving fourteen subjects in the non-smoking group and ten in the smoking group. Among the patients, eight were still smoking cigarettes and two had switched to cigars. Five had formerly smoked cigarettes but had stopped two to seven years previously. Eleven were on maintenance aminophylline and six were on or had recently taken sedatives. Habitual coffee intake of the group was not tabulated.

Theophylline half-life determinations were performed by bolus injection of 5 mg./kg. aminophylline intravenously over a five minute period. The incidence of annoying side effects during injection finally led us to administer the aminophylline in a 50 ml. D5/W drip over ten minutes with better results. Oxalated blood was collected immediately before, and at 1.0, 2.5, 4.0, and 6.0 hours. Subjects had been withdrawn from aminophylline and obvious xanthine-containing substances (coffee, tea, chocolate and cola beverages) at least 15 hours prior to testing. Other medications given in substantial quantities were also avoided. Subjects were not fasting. Blood theophylline was determined by the Schluger modification of the method of Schack and Waxler (6,7). The pre-injection blank value was substracted from each determination since separate experiments demonstrated essential constancy of blank over the six hour period. Although individual blanks showed appreciable variation, with extremes of 0.1 to 4.8 µg/ml. theophylline equivalents, the mean blank values for the three groups were very similar: 2.1 µg/ml. for patients, 2.0 µg/ml. for young smokers, and 2.0 µg/ml. for non-smokers. Likewise, there was no correlation between half-life and blank value within any group. Thus, an artifact created by a high blank, or a blank which fell during the half-life determination, could not be responsible for shorter individual or mean half-lives. Half-lives were calculated by a log-linear least square method.

## Result

Figure 1 shows the half-life data. The patient group has a half-life (mean ± S.D.) of 3.6 ± 1.5 hours; the smoking control group 4.1 ± 1 hours; the non-smoking control group 7.2 ± 1.8 hours. There is a significant differences between the smoking and non-smoking control groups ($p<0.0001$) but not between the smoking control group and the patient group ($p = 0.30$). Non-smoking controls also differs significantly from patients ($p<0.0001$). The shorter mean half-life in our patients compared to the series cited is possibly an artifact of the I.V. bolus method used, which might include a little of the alpha (distribution) phase superimposed on the actual beta phase. However, the mean half-life for the alpha phase of six minutes found by Mitenko and Ogilvie seems to eliminate this possibility (8). Another objection can be raised to our failure to determine serum levels through the terminal portions of the decay curves in all patients. The four points used did appear to be on the log-linear portion, and division of drug distribution into multiple compartments, or use of strictly terminal portions of the decay curves would strain the analytical methodology. Furthermore, the large intergroup differences in mean half-life outweigh this lack of precision in methodology.

Comparably short mean half-lives are in the literature, such as the 4.4 hours (beta phase) of Mitenko and Ogilvie (8), 3.0 hours in eleven subjects receiving I.V. bolus injections by Truitt et al. (9) and 4.2 hours calculated from the descending slopes of orally administered theophylline solutions by Schluger et al. (6). All three groups noted considerable individual variation. It is interesting that half-lives ranged from 0.6 to 9.9 hours in the present series.

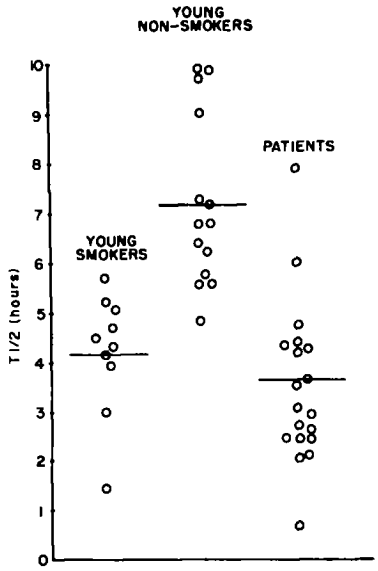


FIG. 1

Intravenous theophylline half-lives following bolus aminophylline injection in ten young normal smokers, fourteen young normal non-smokers and nineteen patients.

## Discussion

This study strongly suggests that cigarette smoking accelerates the metabolism of theophylline. To be absolutely certain of this, one needs to quantitate the metabolites of theophylline in urine. Although methods for such studies are now available (10), this work was completed prior to their development. Such large differences in half-lives do not seem likely on the basis of an effect on the small renal clearance of theophylline, and there is no precedent to suggest that polycyclic hydrocarbons or nicotine would affect protein binding or distribution volume.

However, there is substantial evidence that extremely small amounts of the polycyclic hydrocarbons found in cigarette smoke, such as benzo(a)pyrene and 3-methylcholanthrene, are capable of inducing the microsomal cytochrome P-450 enzymes that not only accelerate their own metabolism but also the oxidative metabolism of other compounds as well. More pertinent to this study, Welch et al. found striking variable elevations in the activity of the enzyme systems that hydroxylate benzo(a)pyrene and N-demethylate 3-methyl-4-monomethylaminoazabenzene in the placenta of cigarette smokers (5). Others have noted smoking effects on drug metabolism (11,12,13). The possible role of nicotine as an inducer substance must also be kept in mind (14).

In contrast, many drugs such as phenobarbital stimulate a broader range of microsomal reactions mediated by cytochrome P-450 but larger doses are required (15). The admixture of tobacco smoking and drug intake in our patients makes it impossible to evaluate the effects of drugs themselves on theophylline half-lives, and the patient data of Fig. 1 may likely reflect the combined effect; however, the effect of smoking seems clear cut, since all normals denied regular intake of medications. Caffeine intake was not tabulated, but is theoretically another factor if greater in smokers (16).

Cornish and Christman were the first to completely delineate the urinary metabolites of theophylline in man, finding 1,3-dimethyluric acid and the demethylated products, 3-methylxanthine and 1-methyluric acid (4). Unchanged

theophylline constituted 11 and 15% in two subjects studied. Brodie et al. had previously found about 10% unchanged theophylline and identified 1,3-dimethyluric acid as the major metabolite in a single subject. They also found that milk xanthine oxidase did not catalyze this oxidation (17). Using high pressure liquid chromatography (10), we have recently identified and quantitated theophylline metabolites in fifteen subjects given oral aminophylline. We found 7.8 ± 6.3% of the total urinary products as unchanged drug, 36.2 ± 7.1 % as 3-methylxanthine, 17.9 ± 6.0% as 1-methyluric acid and 38.0 ± 7.9% as 1,3-dimethyluric acid.

The enzymes responsible for the conversion of theophylline to the N-demethylated and 8-hydroxylated products have not been isolated. However, microsomal system are evidently involved, since Lohman and Miech have recently demonstrated that theophylline metabolism by rat liver slices is moderately enhanced by prior treatment of the rats with phenobarbital and markedly enhanced by feeding of 3-methylcholanthrene (18). Moreover, this metabolism *in vitro* was strongly inhibited by SKF-525A, a Type I inhibitor of liver microsomal enzymes.

Thus, there is now substantial *in vitro* evidence for anticipating the possibility that theophylline metabolism may be affected by polycyclic aromatic hydrocarbons, and the present data (Fig. 1) suggest that smoking accelerates theophylline metabolism *in vivo*. The actual reactions affected in man must be delineated by study of the nature and quantities of the urinary metabolites, but all reactions may be involved. One can perhaps generalize that non-smokers will tend to require less aminophylline for bronchodilation, at least initially. Obviously, the kinetics of induction and deinduction of theophylline metabolism as applied to clinical situations will be a fascinating area for pharmacokinetic study.

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