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# Cigarette Abstinence, Nicotine Gum, and Theophylline Disposition

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When cigarette smokers with chronic lung disease become acutely ill or require surgery, they are often forced to stop smoking and may use nicotine gum. Smoking is known to accelerate the metabolism of theophylline, but the effects of short-term abstinence or nicotine gum on theophylline metabolism have not been reported. We studied the effects of brief tobacco abstinence and nicotine gum on theophylline elimination in healthy volunteers. Abstinence from smoking for 1 week resulted in a 37.6% decrease in clearance and a 35.8% increase in half-life. Nicotine gum had no effect on theophylline clearance. Our data indicate that at least partial normalization of the enzyme-inducing effects of smoking can be seen after brief cigarette abstinence. For smokers who are taking theophylline chronically, their dose of theophylline will need to be reduced by one fourth to one third after brief tobacco abstinence. Plasma concentration monitoring may be necessary for optimal dosing of theophylline in such patients.

HABITUAL CIGARETTE smoking accelerates the biotransformation of some drugs (1, 2). What happens to drug metabolism after short-term tobacco abstinence is not known. Theophylline, a bronchodilator with a narrow therapeutic index, is commonly prescribed to smokers with chronic pulmonary disease. When such smokers are hospitalized for acute illness or surgery, they are often required to stop smoking, but their prehospital dosages of theophylline are often maintained in the hospital. To determine whether theophylline dosages should be adjusted in such circumstances, we studied the effects of short-term cigarette abstinence on the metabolism of theophylline.

Nicotine polacrilex gum (Nicorette; Merrell Dow Pharmaceuticals, Inc., Indianapolis, Indiana) is widely used as an adjunct to smoking cessation. Animal studies indicate that nicotine may inhibit drug metabolism (3, 4). Because the effects of nicotine gum on drug metabolism in humans have not been reported, we also studied the influence of nicotine gum on theophylline metabolism.

## Methods

### SUBJECTS

Fourteen healthy men, 22 to 61 years of age, who were regular cigarette smokers participated in the study. They smoked at least one pack of cigarettes per day (average, 31 cigarettes per day). Nine subjects had smoked marijuana in the past, but only 1 had smoked marijuana in the month before the study. The Federal Trade Commission (FTC) yields for the smokers' usual cigarette brands averaged 1.1 mg of nicotine, 16.3 mg of tar, and 13.8 mg of carbon monoxide. The level of cotinine (the

major metabolite of nicotine) before admission averaged 404.7 ng/mL. The subjects were hospitalized in the General Clinical Research Center at San Francisco General Hospital Medical Center. They ate a normal diet except that caffeine-containing beverages and alcohol were prohibited. None of the subjects had a history of liver disease, and all had normal liver function tests. Written informed consent was obtained from each subject and the study was approved by the University of California, San Francisco, Committee on Human Research.

### EXPERIMENTAL DESIGN

Subjects were hospitalized for 24 days. The first group of seven subjects freely smoked cigarettes of their choice for the first 6 days. On the morning of the seventh hospital day, aminophylline (Elkins-Sinn, Inc., Cherry Hill, New Jersey), equivalent to theophylline, 0.2 mg/kg body weight · min, was infused intravenously over 30 minutes. Plasma samples for theophylline determination were collected from each subject at frequent intervals before and for 24 hours after the infusion. From days 8 to 14, subjects abstained from smoking. Abstinence was confirmed by frequent measurement of expired carbon monoxide levels. On the morning of day 14 (after 7 days of abstinence), theophylline infusion was repeated. From days 15 to 22, the subjects resumed smoking and the same theophylline infusion was repeated on day 22. The second group of seven subjects were studied the same way as the first group, except that from days 8 to 14, and days 15 to 22 the subjects chewed either placebo or 4-mg nicotine gum (Nicorette) once hourly for 12 hours per day. The order of placebo and nicotine gum was balanced.

Theophylline concentrations were determined using a modification of the method of Shah and Riegelman (5). Aliquots of 100 µL plasma and internal standard, 3-isobutyl-1-methyl xanthine (100 µL of 10 µg/mL), were added to 0.5 mL of 1 M potassium phosphate monobasic buffer (pH 8) and extracted with 2.5 mL of methyl-tert-butyl ether: isopropyl alcohol (80:20). The extracts were evaporated, reconstituted with 0.5 mL of 0.1 M triethylsulfonium hydroxide isoamyl alcohol, and analyzed by gas chromatography on a 25-m 5% phenylmethylsilium capillary column, with a temperature program from 90 °C to 275 °C. The sensitivity of the method is 0.5 µg/mL. Coefficients of variation for samples with concentrations of 5 µg/mL and 20 µg/mL were 2.2% ( $n=5$ ) and 3.9% ( $n=6$ ), respectively.

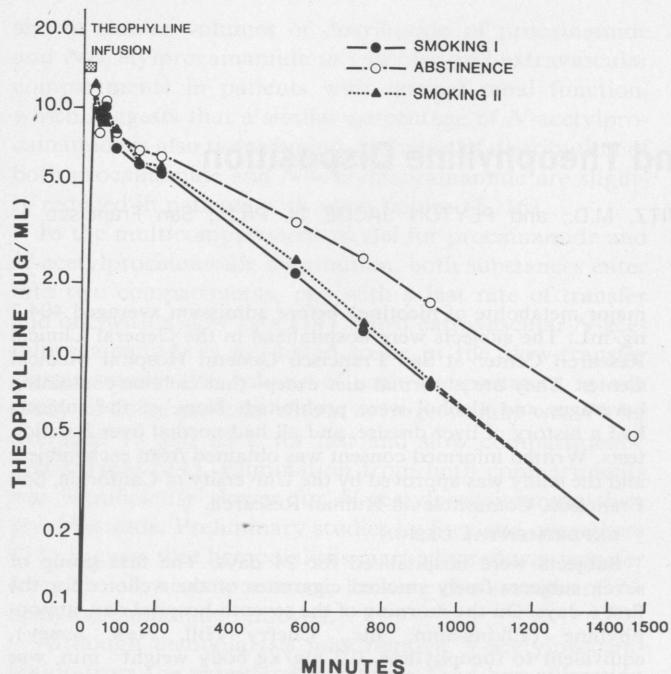
### DATA ANALYSIS

Terminal half-life and elimination rate constants were computed by linear regression of the log plasma theophylline concentrations versus time in the terminal log linear phase. The area under the plasma concentration-time curve for theophylline (AUC) was computed by the trapezoidal rule. Total theophylline clearance was computed as  $CL_f = \text{Dose}/\text{AUC}$ . Steady-state volume of distribution was computed using a model-independent method with appropriate correction for constant infusion (6). Pharmacokinetic comparisons were analyzed by repeated measures analysis of variance comparing smoking, abstinence, and smoking in the first group and smoking, placebo gum, and nicotine gum in the second group. Specific treatment comparisons were made using the Tukey post-hoc test.

## Results

Examples of plasma theophylline concentration-time

► From the Medical Service, San Francisco General Hospital Medical Center, University of California, San Francisco, California.



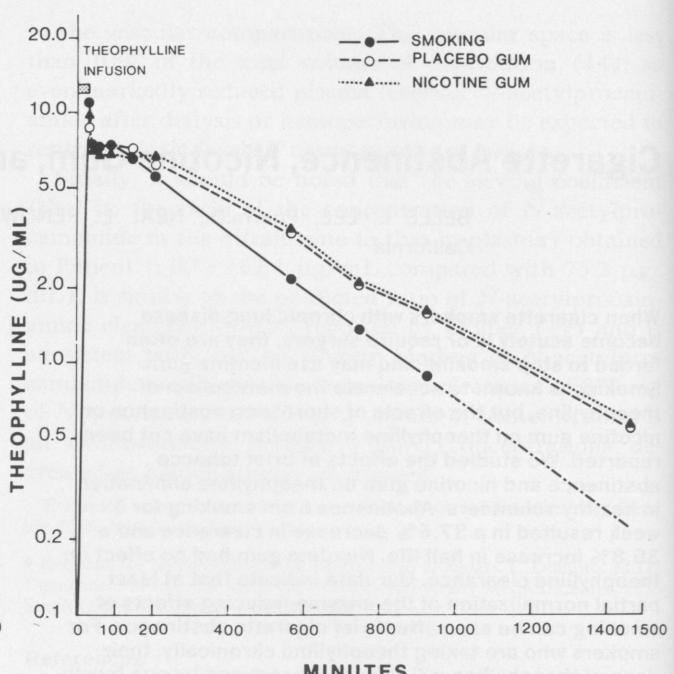
**Figure 1.** Plasma theophylline concentration-time curves in individual subjects. **Figure 1 Left.** One subject received 0.2 mg/kg body weight · min theophylline intravenously for 30 minutes while smoking, abstaining for 1 week, and smoking again. **Figure 1 Right.** A second subject received a similar infusion of theophylline while smoking, chewing placebo gum, and chewing nicotine gum. In the smoking conditions, plasma theophylline concentrations at 1500 minutes were less than 0.5 µg/mL. The dashed line represents an extrapolation of the terminal slope from 900 to 1500 minutes.

curves from one subject studied while smoking, abstaining, and smoking again and another subject while smoking, chewing nicotine gum, and chewing placebo gum are shown in Figure 1.

On the average, the total clearance for Group 1 decreased by 37.6% and half-life increased by 35.8% after 1 week of cigarette abstinence, and returned to baseline after smoking was resumed (Figure 2). Average values (mean  $\pm$  SD) for smoking, abstinence, and resumption of smoking, respectively, were  $130 \pm 36$ ,  $95 \pm 31$ , and  $118 \pm 26$  mL/min for total clearance ( $p < 0.001$ ) and  $280 \pm 90$ ,  $380 \pm 117$ , and  $301 \pm 129$  minutes for half-life ( $p < 0.05$ ). In Group 2, total clearance decreased by 32% and half-life increased by 39.5% while chewing placebo gum compared to values obtained while smoking. Clearance values while chewing nicotine gum and placebo were similar. Average values for smoking, chewing placebo gum, and chewing nicotine gum, respectively, were  $132 \pm 41$ ,  $100 \pm 24$ , and  $98 \pm 28$  mL/min for total clearance ( $p < 0.05$ ) and  $265 \pm 56$ ,  $369 \pm 98$ , and  $376 \pm 130$  minutes for half-life ( $p < 0.05$ ). The mean volumes of distribution of theophylline before, during, and after cigarette abstinence were  $46.5 \pm 9.7$ ,  $46.8 \pm 8.3$ , and  $46.0 \pm 12.4$ , and while smoking, chewing placebo gum, and chewing nicotine gum were  $49.7 \pm 14.9$ ,  $52.3 \pm 16.2$ , and  $50.8 \pm 14.0$ . Volume of distribution of theophylline was unaffected by tobacco abstinence or nicotine gum.

#### Discussion

Our study shows that total clearance of theophylline decreases and half-life increases substantially after 1 week



of cigarette abstinence. By using subjects as their own controls, we excluded many variables that may affect rates of hepatic metabolism. Clearance of theophylline in our subjects was similar to that reported in other studies of smokers (7-9). Clearance after abstinence was still higher than values reported for nonsmokers (7-11).

For patients receiving theophylline therapy, determining the proper dosage is critical because of the potential side effects (12, 13). The elimination of theophylline from the body is primarily via hepatic metabolism (14, 15). Because theophylline is commonly used for smokers with chronic lung disease, and cigarette smoking is known to accelerate the elimination of theophylline (7-10, 16-18), it is conceivable that toxicity might result when theophylline dosages are kept constant after patients abstain from smoking.

Little is known about the time course of normalization of the drug metabolizing enzyme activity after cessation of smoking. Powell and associates (8) reported that the average theophylline half-life of smokers who abstained for 2 years was intermediate between those of nonsmoker and smoker groups. Piafsky and coworkers (11) found that light smokers who abstained for a minimum of 3 weeks had theophylline half-lives similar to those of nonsmokers. Hunt and colleagues (9) suggested that, upon cessation of smoking, the clearance of theophylline returned to normal very slowly. They concluded that a period of 3 months to 2 years may be necessary for normalization of the effects of smoking on theophylline elimination. These studies involved ambulatory patients and did not control for diet or environment, and did not document changes in smoking behavior. Our study with a

carefully controlled environment shows substantial normalization of drug metabolism within 1 week of abstinence. We estimated that clearance in our subjects was midway between the smoker's value and that expected after long-term abstinence. Our data suggest that for smokers who stop smoking, even for a brief period of time, doses of theophylline should be decreased by one fourth to one third to avoid development of theophylline toxicity. Plasma concentration monitoring may be necessary for optimal dosing of theophylline in such patients.

In-vitro and in-vivo studies have shown that nicotine may inhibit drug metabolism (3, 4). However, in our study, chewing 4-mg nicotine gum (which results in higher nicotine levels than the 2-mg gum currently available in the United States) for 1 week had the same effect on theophylline clearance or half-life as abstinence without gum. This finding suggests that the accelerated metabolism of theophylline in smokers is related to the effects of polycyclic aromatic hydrocarbons or other combustion products in tobacco smoke (19, 20). Our data suggest that when smokers stop smoking and begin chewing nicotine gum, their rate of metabolism of theophylline responds as if they had stopped smoking without using gum, and theophylline dosages should be adjusted accordingly.

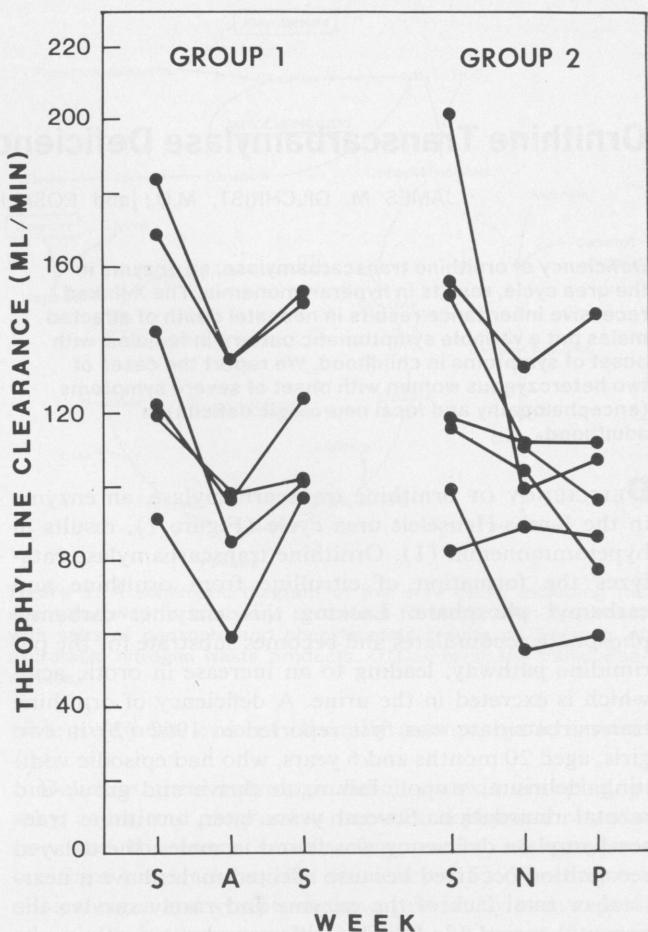
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## References

- JUSKO WJ. Influence of cigarette smoking on drug metabolism in man. *Drug Metab Rev.* 1979;9:221-36.
- DAWSON GW, VESTAL RE. Smoking and drug metabolism. *Pharmacol Ther.* 1982;15:207-21.
- WEBER RP, COON JM, TRIOLO AJ. Nicotine inhibition of the metabolism of 3,4-benzopyrene, a carcinogen in tobacco smoke. *Science.* 1974;184:1081-3.
- STALHANDSKA T, SLANINA P. Effect of nicotine treatment on the metabolism of nicotine in the mouse liver *in vitro*. *Acta Pharmacol Toxicol (Copenh).* 1970;28:75-80.
- SHAH VP, RIEGELMAN S. GLC determination of theophylline in biological fluids. *J Pharm Sci.* 1974;63:1283-5.
- BENET LZ, GALEAZZI RL. Noncompartmental determination of the steady-state volume of distribution. *J Pharm Sci.* 1979;68:1071-4.
- JENNE J, NAGASAWA H, MCHUGH R, MACDONALD F, WYSE E. Decreased theophylline half-life in cigarette smokers. *Life Sci.* 1975;17:195-8.
- POWELL JR, THIERCELIN JF, VOZEH S, SANSOM L, RIEGELMAN S. The influence of cigarette smoking and sex on theophylline disposition. *Am Rev Respir Dis.* 1977;116:17-23.
- HUNT SN, JUSKO WJ, YURCHAK AM. Effect of smoking on theophylline disposition. *Clin Pharmacol Ther.* 1976;19:546-51.
- JUSKO WJ, SCHENTAG JJ, CLARK JH, GARDNER M, YURCHAK AM. Enhanced biotransformation of theophylline in marijuana and tobacco smokers. *Clin Pharmacol Ther.* 1978;24:406-10.
- PIAFSKY KM, SITAR DS, OGILVIE RI. Effect of phenobarbital on the disposition of intravenous theophylline. *Clin Pharmacol Ther.* 1977;22:336-9.
- JACOBS MH, SENIOR RM, KESSLER G. Clinical experience with theophylline: relationships between dosage, serum concentration and toxicity. *JAMA.* 1976;235:1983-6.
- MOUNTAIN RD, NEFF TA. Oral theophylline intoxication: a serious error of patient and physician understanding. *Arch Intern Med.* 1984;144:724-7.
- JENNE JW, NAGASAWA HT, THOMPSON RD. Relationship of urinary metabolites of theophylline to serum theophylline levels. *Clin Pharmacol Ther.* 1976;19:375-81.
- CORNISH HH, CHRISTMAN AA. A study of the metabolism of theobromine, theophylline, and caffeine in man. *J Biol Chem.* 1957;228:315-23.
- GRYGIEL JJ, BIRKETT DJ. Cigarette smoking and theophylline clearance and metabolism. *Clin Pharmacol Ther.* 1981;30:491-6.
- HENDELES L, WEINBERGER M, BIGHLEY L. Disposition of theophylline after a single intravenous infusion of aminophylline. *Am Rev Respir Dis.* 1978;118:97-103.
- PFEIFER HF, GREENBLATT DJ. Clinical toxicity of theophylline in relation to cigarette smoking: a report from the Boston Collaborative Drug Surveillance Program. *Chest.* 1978;73:455-9.
- WELCH RM, HARRISON YE, GOMMI BW, POPPERS PJ, FINSTER M, CONNEY AH. Stimulatory effect of cigarette smoking on the hydroxylation of 3,4-benzopyrene and the N-demethylation of 3-methyl-4-monomethyl-aminoazobenzene by enzymes in human placenta. *Clin Pharmacol Ther.* 1969;10:100-9.
- CONNEY AH, PANTUCK EJ, HSIAO KC, KUNTZMAN R, ALVARES AP, KAPPAS A. Regulation of drug metabolism in man by environmental chemicals and diet. *Fed Proc.* 1977;36:1647-52.



**Figure 2.** Influence of cigarette abstinence and nicotine gum on plasma clearance of theophylline. S = week of smoking; A = week of abstinence; N = week of nicotine gum; P = week of placebo gum.