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# Lowering of theophylline clearance by isoniazid in slow and rapid acetylators

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The effect of isoniazid (INH) pretreatment (400 mg daily for 2 weeks) on the elimination kinetics of theophylline (given intravenously as aminophylline equivalent to 151.2 mg theophylline) was investigated in 13 healthy male non-smokers. Amongst the 13 subjects studied, seven were rapid and six were slow acetylators. The mean clearance of theophylline was significantly lowered after INH ($2.20 \pm 0.24$ l $h^{-1}$) (mean ± s.e. mean) compared with the baseline value ($2.80 \pm 0.24$ l $h^{-1}$). The volume of distribution at steady state was also lowered significantly after INH ($0.42 \pm 0.01$ l $kg^{-1}$ *vs* $0.47 \pm 0.02$ l $kg^{-1}$). Consequently, there was no significant prolongation of theophylline half-life after INH ($7.0 \pm 0.3$ h *vs* $6.7 \pm 0.4$ h control). The lowering of theophylline clearance by INH may be related to acetylator status since slow acetylators showed a greater interaction than rapid acetylators. However, this difference was not statistically significant.

**Keywords** theophylline isoniazid acetylator status

## Introduction

Isoniazid (INH) has been shown to impair the metabolism of other drugs by inhibition of mixed-function oxidase activity (Bacievicz & Self, 1985; Kutt *et al.*, 1970). However, there have been conflicting reports on the influence of INH on the elimination kinetics of theophylline. Thus, Thompson *et al.* (1982) showed that pretreatment with INH resulted in a 16% increase in the oral clearance of theophylline. In contrast, Hoglund *et al.* (1987) demonstrated a significant reduction of theophylline clearance after pretreatment with INH. The present study was designed to re-investigate this interaction and to examine whether or not any effect of INH is related to acetylator status.

## Methods

### *Subjects*

Thirteen healthy, male non-smokers were recruited (aged 20–39 years) and written informed consent was obtained from all subjects. The protocol of the study was approved by the Ethics Committee on Biomedical Research Involving Human Subjects, of the Faculty of Medicine, Gadjah Mada University. Prior to the study all subjects underwent a clinical examination and laboratory tests including measurements of serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), serum bilirubin, serum creatinine, haematology and routine urinalysis. All subjects were found to be normal and none had any history of serious diseases.

### *Procedures*

The volunteers received theophylline on two occasions, before and after pretreatment with INH. Isoniazid 400 mg was given daily for 14 days and on day 15, the second dose of theophylline was given 0.5 h after ingestion of the last dose of INH. No other medication was allowed during the study. Subjects were also

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requested to refrain from drinking coffee or tea throughout the study.

After an overnight fast, theophylline (given as aminophylline, equivalent to 151.2 mg theophylline) was injected intravenously over approximately 20 min. The midpoint of the injection time was taken as zero time. Serial venous blood samples were drawn at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h. The serum was separated immediately and frozen at −20° C until analysis which was carried out within 24 h.

*Determination of acetylator phenotype*

Acetylator phenotype was determined by the sulphadimidine test (Rao *et al.*, 1970), based on a measurement of the ratio of acetylsulphadimidine to total drug in the urine sample collected from 5 to 6 h after ingestion of 500 mg of the drug. Urinary sulphadimidine was assayed spectrophotometrically (Bratton & Marshall, 1937) in triplicate.

*Theophylline assay*

Serum theophylline concentrations were assayed by high-pressure liquid chromatography (Orcutt *et al.*, 1977). The lower limit of assay for theophylline was 0.1 $\mu g\ ml^{-1}$. The coefficient of variation for the measurement of theophylline standards (0.5, 5 and 15 $\mu g\ ml^{-1}$) was less than 5%.

*Data analysis*

Post-infusion serum concentrations ($C$) of theophylline were fitted by a biexponential function using a non linear least square regression programme (PCNonlin—Metzler & Weiner, 1986). Clearance (CL), volume of distribution at steady state ($V_{ss}$) and terminal elimination half-life ($t_{½}$) were calculated by standard methods.

Pharmacokinetic parameters obtained during the control period and after pretreatment with INH were compared using the paired Student's $t$-test. The relationship between acetylation ratio and the change in theophylline clearance following INH pretreatment was analyzed using the Spearman rank coefficient of correlation.

## Results

*Acetylator phenotype*

The 13 subjects in the study group comprised seven rapid and six slow acetylators. The acetylation ratio in the rapid group was 0.91 ± 0.02 (mean ± s.e. mean) and that in the slow acetylator group was 0.52 ± 0.03. The distribution of acetylator phenotype in the population is 65% for rapid and 35% for slow acetylators (Santoso, 1983). There was no difference in age (29.3 ± 2.3 years *vs* 28.5 ± 3.5 years) or body weight (53.4 ± 1.9 kg *vs* 53.2 ± 3.6 kg) between the rapid and slow acetylator subjects.

*Theophylline kinetics*

The mean serum theophylline concentration *vs* time curves during the control period (C) and after pretreatment with INH (+INH) are shown in Figure 1. After pretreatment with INH, serum theophylline concentrations were consistently higher than those obtained during the control study.

Irrespective of the acetylator phenotype, theophylline clearance (CL) after pretreatment with INH (2.20 ± 0.24 $l\ h^{-1}$) was significantly lower than that before INH pretreatment (2.80 ± 0.24 $l\ h^{-1}$) ($P < 0.01$—Table 1). The volume of distribution of theophylline at steady state ($V_{ss}$) after pretreatment with INH (0.42 ± 0.01 $l\ kg^{-1}$) was also significantly lower than that found during the control period (0.47 ± 0.02 $l\ kg^{-1}$) ($P < 0.05$—Table 1). The terminal elimination half-lives of theophylline on the two occasions were not significantly different, i.e. 6.7 ± 0.4 h before INH pretreatment and 7.0 ± 0.3 h after INH pretreatment ($P > 0.5$—Table 1).

The lowering of theophylline clearance after INH pretreatment in slow acetylators was 24.1% (± 9.0%) and that in rapid acetylators was 18% (± 5.5%). However, the difference between the two groups did not achieve statistical significance ($P > 0.05$). Similarly, no statistically significant correlation was found between the change in theophylline clearance after pretreatment with INH and the acetylation ratio ($r_s = -0.36$, $P > 0.05$).

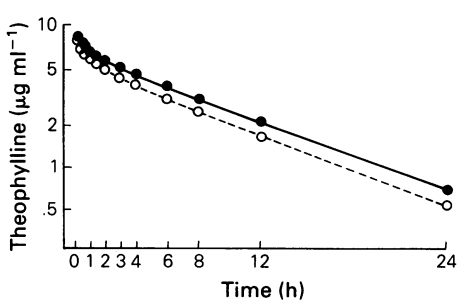


**Figure 1** Mean serum theophylline concentration *vs* time curves on the control day (○) and after pretreatment with isoniazid (●) in thirteen subjects.

**Table 1** Theophylline clearance (CL), volume of distribution at steady state ($V_{ss}$) and half-life ($t_{½}$) on the control day (C) and after pre-treatment with isoniazid (+INH)

| | $CL\ (l\ h^{-1})$ | | $V_{ss}\ (l\ kg^{-1})$ | | $t_{½}\ (h)$ | |
|---|---|---|---|---|---|---|
| *Subject* | *C* | *+INH* | *C* | *+INH* | *C* | *+INH* |
| *Rapid acetylator* | | | | | | |
| 1 | 2.58 | 2.06 | 0.47 | 0.40 | 6.1 | 7.0 |
| 2 | 2.47 | 2.18 | 0.46 | 0.40 | 6.6 | 6.0 |
| 3 | 2.45 | 2.34 | 0.40 | 0.40 | 6.5 | 6.6 |
| 4 | 2.35 | 2.26 | 0.78 | 0.38 | 9.0 | 6.9 |
| 5 | 2.19 | 1.94 | 0.36 | 0.42 | 8.1 | 6.2 |
| 6 | 3.27 | 1.89 | 0.48 | 0.37 | 5.9 | 7.5 |
| 7 | 2.63 | 1.77 | 0.41 | 0.39 | 5.5 | 7.4 |
| *Slow acetylator* | | | | | | |
| 8 | 2.29 | 1.80 | 0.47 | 0.39 | 8.8 | 8.5 |
| 9 | 4.64 | 4.82 | 0.51 | 0.55 | 5.4 | 4.7 |
| 10 | 2.14 | 2.05 | 0.48 | 0.50 | 8.8 | 8.2 |
| 11 | 4.56 | 2.76 | 0.61 | 0.42 | 5.3 | 5.9 |
| 12 | 2.02 | 1.46 | 0.43 | 0.40 | 5.3 | 7.7 |
| 13 | 2.84 | 1.26 | 0.49 | 0.40 | 5.4 | 8.2 |
| Mean | 2.80 | 2.20 | 0.47 | 0.42 | 6.7 | 7.0 |
| ±s.d. | 0.86 | 0.87 | 0.06 | 0.05 | 1.5 | 1.1 |

## Discussion

The results of the present study indicate that isoniazid does interfere with the disposition of theophylline, a drug which is metabolized extensively by hepatic mixed-function oxidases. Thus, our data are in agreement with those of Hoglund *et al.* (1987), who found a significant increase in plasma concentrations of theophylline after pretreatment with INH for 10 days. In man, pretreatment with INH has been reported to lower significantly the metabolic clearance of phenytoin (Kutt *et al.*, 1970), diazepam (Ochs *et al.*, 1981), vitamin D (Brodie *et al.*, 1981), carbamazepine (Valsalan & Cooper, 1982), primidone (Sutton & Kupferberg, 1975) and warfarin (Rosenthal *et al.*, 1977). Thus, significant interactions between INH and other drugs described so far have been inhibitory. These findings are difficult to reconcile with those of Thompson *et al.* (1982), who observed a 16% increase in the oral clearance of theophylline after INH pretreatment. However, this study was carried out in only four subjects. Although it has been demonstrated that INH can induce the metabolism of some volatile ether anaesthetics (Rice & Tallcot, 1979), it seems unlikely that theophylline metabolism is induced by INH. INH pretreatment selectively induces the activity of cytochromes P-451 and P-452, without elevating total cytochrome P-450 content (Rice & Tallcot, 1979), and theophylline is known to be metabolized by the cytochrome P-448 dependent mixed-function oxidase system.

It has been demonstrated *in vitro* that INH inhibits cytochrome P-450 dependent hepatic mixed-function oxidase activity. Thus, INH was found to decrease carbon monoxide binding to reduced cytochrome P-450 and to inhibit aniline hydroxylation and aminopyrine demethylation (Muakassah *et al.*, 1982). Since theophylline is metabolized by the cytochrome P-448 dependent mixed-function oxidase system, it is possible that such metabolism is also inhibited by INH. In man, INH is predominantly *N*-acetylated followed by oxidation of the acetylated product (Weber & Hein, 1979). Therefore, competitive inhibition may contribute to the interaction between INH and other drugs.

In conclusion therefore, INH 400 mg daily for 2 weeks significantly lowered the clearance of theophylline, suggesting caution when using the two drugs together in clinical practice.

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