Lack of effect of atenolol and nadolol on the metabolism of theophylline

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The effects of 7 days of pretreatment with atenolol, 150 mg day⁻¹, or nadolol, 80 mg day⁻¹, on the pharmacokinetics and metabolism of theophylline were determined in six male smokers. Theophylline clearance, volume of distribution, half-life and the urinary excretion of theophylline and its metabolites were unchanged during either treatment compared with control.

Keywords atenolol nadolol β -adrenoceptor theophylline

Introduction

β -adrenoceptor antagonists have been shown to inhibit oxidative drug metabolism. A lowering of clearance and a prolongation of the terminal half-life of model compounds metabolized by the liver (e.g. antipyrine and theophylline) provides evidence of such inhibition (Greenblatt & Huffman, 1978; Conrad & Nyman, 1980). Some *in vivo* and *in vitro* data suggest that the ability of β -adrenoceptor antagonists to exert this effect is dependent largely upon their lipid solubility (Bax *et al.*, 1981; Deacon *et al.*, 1981; Tucker *et al.*, 1982). However, other *in vivo* data do not appear to support this view (Adamska-Dyniewska *et al.*, 1986; Bax *et al.*, 1985; Daneshmend & Roberts, 1982; Kirch *et al.*, 1984; Parker *et al.*, 1984). Further studies (Miners *et al.*, 1984, 1985) suggest that the effects of various β -adrenoceptor antagonists on oxidative drug metabolism may be specific for different isozymes of cytochrome P-450. This specificity might be related to β -adrenoceptor selectivity in that cardioselective β_1 -adrenoceptor antagonists may not inhibit drug metabolism. In this study, we examined this question by comparing the effects of atenolol (a β_1 -selective adrenoceptor antagonist) and nadolol (a non-selective β -adrenoceptor antagonist) on theophylline metabolism in a population of young volunteers who were smokers. We chose to study smokers because

they have relatively high theophylline clearances (Grygiel & Birkett, 1981) and should, therefore, be more sensitive to a lowering of clearance by β -adrenoceptor antagonists. Atenolol and nadolol are similar in as much as they are both eliminated mainly by renal mechanisms and are highly hydrophilic.

Methods

The protocol was approved by the Committee for the Protection of Human Subjects of The Mary Imogene Bassett Hospital. Written informed consent was obtained. No subject was taking any medications and they were determined to be healthy by medical history, physical examination, electrocardiogram and liver function tests (aspartate transaminase, alanine transaminase, gamma glutamyl transpeptidase, total bilirubin, alkaline phosphatase, total protein and albumin). Six healthy smoking subjects (> 15 cigarettes per day) participated in this study. All subjects were male smokers (> 15 cigarettes per day) with an average age of 38.3 ± 9.8 years and body weight of 81.7 ± 14.2 kg. The average theophylline dose was 385 ± 64.7 mg.

Each subject participated in three separate study phases in a randomized crossover fashion.

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All three phases included a study day in which subjects were given an aminophylline infusion (6 mg kg^{-1}) intravenously over 20 min (aminophylline injection USP lot no. 058705C with 19.7 mg anhydrous theophylline/25 mg aminophylline; Invenex Laboratories, Orlando, FL), followed by a 50 ml 0.9% saline flush. Each subject took atenolol 150 mg by mouth once a day (Tenormin, lot no. 4281 F, 50 mg tablets; Stuart Pharmaceutical, Wilmington, DE) for 7 days prior to the study day in one phase (A). Each received nadolol 80 mg by mouth once a day (Corgard, lot no. 6C81722, 40 mg tablets, Princeton Pharmaceutical Products, Princeton, NJ) during another phase (N). In the control phase (C), no medication was taken prior to the study day. The subjects abstained from methylxanthine-containing foods and beverages during the 24 h around the time of each aminophylline dose. A minimum of 1 week separated each study phase. Compliance was ascertained by questioning the subjects and by tablet counts. The study day began at the same time in each phase.

Following an 8 h fast, indwelling i.v. catheters were placed in each arm. One catheter was used for the aminophylline infusion and was removed after the saline flush. Blood samples were drawn from the other catheter prior to and at 0, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, and 24 h following completion of the infusion. The catheter was kept patent by infusing with 3.0 ml of a dilute heparin solution (10 u ml^{-1}) after each blood sample was obtained. Following an initial urine void, the subjects collected and refrigerated all urine over a 24 h period. Blood samples were centrifuged and the harvested serum was stored at -70°C until analysis. Total urine volume was measured and an aliquot was stored at -70°C until analysis.

Serum theophylline concentrations were assayed in duplicate using a fluorescent polarization immunoassay technique (Abbott TDX, Abbott Laboratories, Diagnostics Division, Chicago, IL). This assay has a sensitivity range of 0.5 to 40.0 mg ml^{-1} with 95% sensitivity. The within-run coefficients of variation were 1.95% at $7.0 \text{ } \mu\text{g ml}^{-1}$, 1.41% at $12 \text{ } \mu\text{g ml}^{-1}$, and 1.29% at $26.0 \text{ } \mu\text{g ml}^{-1}$. The average between-run coefficient of variation was 2.8%. Urine samples were assayed for theophylline and three metabolites (3-methylxanthine [3MX], 1,3-dimethyluric acid [DMU], and 1-methyluric acid [1MU] using high-performance liquid chromatography (Muir *et al.*, 1980). The coefficient of variation (CV) for the assays of these compounds were as follows. For 3MX, the CVs over a concentration range of 2, 5, 10, 25, 50,

100, and $150 \text{ } \mu\text{g ml}^{-1}$ were 5.8, 6.2, 3.3, 2.2, 2.6, 3.9 and 3.5%. Over the same range of concentrations, the CVs for DMU were 11.1, 3.9, 4.5, 1.9, 2.8, 3.1, and 4.4%. For IMU, the CVs over the same concentration range were 17.6, 16.3, 14.2, 11.2, 10.7, 2.3, and 18.2%.

The area under the serum drug concentration vs time curve (AUC) and the area under the first moment curve (AUMC) were determined by the linear trapezoidal rule (Gibaldi, 1984). The terminal elimination rate constant (λ), was obtained by linear regression analysis of the log-linear portion of the serum drug concentration vs time curve. Both AUC and AUMC were extrapolated to infinity using the elimination rate constant and the last measured concentration. Total body clearance (CL) was calculated by dividing the intravenous dose of theophylline (D_{iv}) by the AUC. The volume of distribution at steady state (V_{ss}), corrected for infusion time (t), was calculated from:

$$V_{ss} = \frac{\text{Dose} \cdot \text{AUMC}}{\text{AUC}^2} - \frac{\text{Dose} \cdot t}{2 \cdot \text{AUC}}$$

Half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$ (Gibaldi, 1984).

Urinary theophylline and metabolite data were expressed in molar equivalents. Excretion of theophylline and each metabolite over 24 h is reported as a percentage of the total molar theophylline dose.

The data were subjected to an analysis of variance for repeated measures (ANOVA). A P value of < 0.05 was considered statistically significant. All data are presented as the mean $\pm$ s.d.

Results

Table 1 shows the half-life and clearance values obtained in each phase of the study. No significant difference was found in these parameters between either treatment phase and control. In addition, no change in volume of distribution at steady state was found.

Table 2 shows the recovery of each metabolite as a percentage of theophylline dose during the three phases. There were no significant differences in recovery compared with control. 1,3-dimethyluric acid accounted for the largest proportion of the dose followed by 1 MU, 3 MX and unchanged theophylline. These data are comparable with those of Grygiel & Birkett (1981) in smokers.

Table 1 Pharmacokinetic parameters of theophylline with and without coadministration of atenolol and nadolol

Subject	$t_{1/2}$ (h)			V_{ss} ($l\ kg^{-1}$)			CL ($ml\ min^{-1}\ 1.73\ m^{-2}$)		
	C	N	A	C	N	A	C	N	A
1	2.35	7.36	4.22	0.40	0.50	0.40	85.32	59.60	74.83
2	4.82	4.66	5.15	0.42	0.40	0.48	68.50	67.70	79.60
3	5.41	6.57	4.51	0.37	0.36	0.32	52.00	40.40	48.60
4	8.27	11.01	9.91	0.38	0.41	0.39	47.60	37.70	39.10
5	5.78	4.03	3.96	0.43	0.35	0.35	74.60	77.40	79.60
6	6.67	6.28	7.69	0.39	0.39	0.44	50.40	52.10	46.70
Mean	5.55	6.65	5.91	0.40	0.40	0.40	63.07	55.82	61.41
s.d.	1.97	2.47	2.38	0.02	0.05	0.06	15.36	15.50	18.55

$t_{1/2}$ = Half-life, V_{ss} = Volume of distribution at steady state, CL = Total body clearance, C = Control, N = Nadolol, A = Atenolol.

No significant differences in $t_{1/2}$, V_{ss} , or CL were observed during any phase of study.

Table 2 % Molar urinary recovery of total theophylline dose for theophylline and three metabolites with and without coadministration of nadolol and atenolol

Compound	C	N	A
Theophylline	16.3 ± 13.3	13.6 ± 9.0	12.6 ± 13.5
3MX	15.9 ± 4.8	10.7 ± 6.4	14.6 ± 5.8
DMU	46.7 ± 16.3	42.6 ± 23.2	41.9 ± 9.0
1MU	36.1 ± 14.6	22.6 ± 6.7	29.5 ± 15.1

All data expressed as mean ± s.d. No statistical differences were noted.

3MX = 3-methylxanthine, DMU = 1,3-dimethyluric acid, 1MU = 1-methyluric acid, C = Control phase,

N = Nadolol phase, A = Atenolol phase

Discussion

The results confirm previous work (Cerasa *et al.*, 1988) showing that atenolol, when administered in routinely used doses does not affect the metabolism of theophylline. In addition, this study indicates that nadolol is also without effect. Thus, the findings suggest that neither hydrophilic β -specific antagonists (e.g. atenolol) nor hydrophilic non-specific β -adrenoceptor antagonists (e.g. nadolol) have an effect on theophylline metabolism.

It has been shown previously that propranolol has a significantly greater inhibitory effect on theophylline clearance than metoprolol. This effect is particularly prominent in smokers (Conrad & Nyman, 1980). Furthermore, Miners *et al.* (1985) have shown a dose-dependent selective inhibitory effect of propranolol on the separate enzyme systems that hydroxylate and demethylate theophylline. We have noted a

33% decrease in theophylline clearance with propranolol, which could not be reversed by concurrent terbutaline administration (Lombardi *et al.*, 1987). In addition, our current, as well as our previous, findings show no effect of atenolol on theophylline pharmacokinetics (Cerasa *et al.*, 1988). This suggests that lipophilicity may be the important factor in determining inhibition of theophylline metabolism by β -adrenoceptor antagonists.

Data exist demonstrating an inhibitory effect of β -adrenoceptor antagonists on the pharmacokinetics of other drugs. Bax *et al.* (1981) showed a decrease in antipyrine clearance by metoprolol and propranolol. Other investigators have reported that atenolol, but not propranolol or labetalol, caused decreased antipyrine clearance in normal subjects (Daneshmend & Roberts, 1982). In this study, however, the atenolol dose ($200\ mg\ day^{-1}$) was significantly greater than the propranolol dose

(120 mg day⁻¹). Others have shown no effect of atenolol (100 mg day⁻¹) on antipyrine clearance (Tucker *et al.*, 1982). Adamska-Dyniewska *et al.* (1986) showed that atenolol and nadolol treatment, for 4.7 and 4.6 months, respectively, significantly prolonged antipyrine $t_{1/2}$, but did not significantly affect its clearance (Adamska-Dyniewska *et al.*, 1986). The data of Bax *et al.* (1985) showed that the lipid-soluble β -adrenoceptor blocker penbutolol did not inhibit antipyrine clearance, whereas propranolol did (Bax *et al.*, 1985). Greenblatt *et al.* (1978) also showed a significant reduction in antipyrine clearance by propranolol.

The results of our study suggest that selective β -adrenoceptor blockade with a hydro-

philic agent exerts no effect on theophylline metabolism. In addition, β -adrenoceptor blockade with a non-selective hydrophilic β -adrenoceptor agent did not inhibit theophylline metabolism significantly. Lipid solubility is probably the main factor determining the inhibitory effect of β -adrenoceptor antagonists on drug metabolism.

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