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Report

The Effect of Amiodarone on Theophylline Pharmacokinetics in the Rat

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Amiodarone is an investigational antiarrhythmic agent which has been implicated in reducing the activity of the hepatic mixed-function oxidase system. To evaluate this effect further, two groups of six male Sprague–Dawley rats each received theophylline (6 mg/kg, iv) preceded by either normal saline or amiodarone HCl (100 mg/kg, iv). Blood samples were obtained serially for a period of 6 hr and the sera were assayed for theophylline by high-pressure liquid chromatography (HPLC). In rats pretreated with amiodarone, a significant 45% reduction in the mean (± SD) systemic clearance [0.057 (0.010) vs 0.031 (0.004) liter/hr/kg, $P < 0.001$] and a greater than 100% increase in the mean elimination half-life [2.03 (0.46) vs 4.29 (0.71) hr, $P < 0.001$] of theophylline were observed. These data demonstrate an acute inhibitory effect of amiodarone on the hepatic microsomal enzyme system.

KEY WORDS: amiodarone; theophylline; pharmacokinetics; drug interaction.

INTRODUCTION

Amiodarone, a benzofuran derivative with potent antiarrhythmic properties, has been recently released in the United States for the treatment of supraventricular and ventricular arrhythmias (1). Although its therapeutic effectiveness for the treatment of life-threatening arrhythmias resistant to standard therapy is well documented, little is known about its pharmacokinetics in animals or in humans (2–4).

Amiodarone has been demonstrated to decrease cytochrome *P*450 activity and antipyrine clearance in rats (5). Consistent with these animal data is a human study demonstrating decreases in antipyrine clearance with concomitant amiodarone therapy (6). Amiodarone has also been implicated in reducing the hepatic clearance of drugs such as phenytoin (7,8), warfarin (9), quinidine, and procainamide (10).

Theophylline is a widely prescribed bronchodilator and continues to be one of the most effective agents for the treatment of asthma (11). Theophylline is extensively metabolized in humans and rats through similar hepatic biotransformation pathways (12). Only a small percentage of the administered dose is excreted unchanged into the urine (11). The extensive, cytochrome-mediated, metabolic clearance of theophylline is likely to be sensitive to reductions in the intrinsic metabolic activity of the liver induced by amiodarone.

The purpose of this investigation was to evaluate the influence of amiodarone on the pharmacokinetics of theophylline using the rat as an animal model.

MATERIALS AND METHODS

Twelve male Sprague–Dawley rats (300 to 400 g), under light ether anesthesia, had both jugular veins cannulated with silastic catheters which were exteriorized to the back of their necks. Two to three hours after the catheterization, when all animals were awake and alert, the rats were randomly assigned to receive one of the two study treatment sequences. In one group ($N = 6$), a single dose of normal saline was administered intravenously (iv) followed in 1 min by a single iv dose of theophylline (6 mg/kg). The second group ($N = 6$) received a single iv dose of amiodarone HCl (100 mg/kg) dissolved in 10% polysorbate 80 followed in 1 min by a single iv dose of theophylline (6 mg/kg).

All injections were made through the same jugular vein catheter. Blood samples (0.4 ml) were obtained through the opposite catheter at 0.25, 0.5, 1, 2, 3, 4, 5, and 6 hr following the administration of theophylline. Blood samples were replaced by an equal volume of normal saline after each sampling. Following the centrifugation of the blood samples, the serum was removed and stored at −20°C until analysis. The samples were assayed within a month following their collection for theophylline using the high-pressure liquid chromatography (HPLC) method of Adam *et al.* (13). Amiodarone did not interfere with the theophylline assay. The sensitivity of this assay is 0.5 μg/ml, with a day-to-day coefficient of variation of 1.5 and 2% at 25 and 0.5 μg/ml.

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The initial serum concentration (C_0) and the elimination rate constant (λ_Z) of theophylline in each rat were determined by least-squares linear regression. A minimum of five data points was used for the determination of λ_Z. Using the C_0 and λ_Z values, the pharmacokinetic parameters described below were determined by the LAGRAN computer program, which performs area and moment analysis of serum concentration–time data (14).

The systemic clearance of theophylline (CL) was computed using Eq. (1):

$$CL = \frac{dose}{AUC_{0\to\infty}} \quad (1)$$

where dose is the theophylline dose administered and AUC is the total area under the theophylline serum concentration–time curve.

The volume of distribution at the steady state of theophylline (V_{ss}) was computed using Eq. (2):

$$V_{ss} = \frac{dose \cdot AUTC_{0\to\infty}}{(AUC)^2_{0\to\infty}} \quad (2)$$

where AUTC is the first moment of the theophylline serum concentration–time curve.

Theophylline serum half-life ($t_{1/2}$) was computed using Eq. (3):

$$t_{1/2} = \frac{\ln(2)}{\lambda_Z} \quad (3)$$

The mean residence time (MRT), which is a reflection of the *in vivo* persistence of theophylline, was computed using Eq. (4):

$$MRT = \frac{AUTC_{0\to\infty}}{AUC_{0\to\infty}} \quad (4)$$

Statistical Analysis

A statistical comparison of the pharmacokinetic parameters for theophylline following pretreatment with normal saline vs amiodarone was performed using an unpaired t test (two tailed). A $P < 0.05$ was considered significant. When the differences between the two groups did not reach statistical significance, a power analysis was performed to evaluate the potential for a type II statistical error. All results are expressed as the mean (± SD).

RESULTS

The mean (± SD) theophylline serum concentrations as a function of time following either normal saline or amiodarone administration are shown in Fig. 1. The decline in theophylline serum concentrations in the saline-treated rats was characterized by a mean (± SD) λ_Z of 0.36 (0.08) hr^{-1}. The decline in theophylline serum concentrations in the amiodarone-treated group was more prolonged when compared to the control, with a mean (± SD) λ_Z of 0.17 (0.03) hr^{-1}. In addition, an apparent increase in the mean theophylline serum concentration occurred for 1 hr after the dose. Examination of the time course of theophylline in individual rats treated with amiodarone revealed that the serum concentrations of theophylline were either relatively constant ($N = 3$) or increasing ($N = 3$) for the first hour following its administration. The reason for these increases is currently unknown. Other selected pharmacokinetic parameters for theophylline are presented in Table I. In the rats pretreated with amiodarone, the systemic clearance of theophylline was reduced by an average of 45% [0.057 (0.010) vs 0.031 (0.004) liter/hr/kg, $P < 0.001$]. This reduction in the systemic clearance of theophylline was accompanied by a prolongation in the mean elimination half-life by an average of 110% [2.03 (0.46) vs 4.29 (0.71) hr, $P < 0.001$]. The MRT of theophylline was also significantly prolonged in rats pretreated with amiodarone [3.07 (0.69) vs 5.98 (0.96) hr, $P < 0.001$]. There was no significant difference in the mean steady-state volume of distribution of theophylline between the two groups. Power analysis revealed that these data had a greater than 90% chance of detecting a 20% difference or more in the volume of distribution between the two groups.

Table I. Selected Pharmacokinetic Parameters of Theophylline During Coadministration of a Single Dose of Normal Saline or Amiodarone

Rat No.	Systemic clearance (L/hr/kg)	Half-life (hr)	Mean residence time (hr)	Volume of distribution at steady state (L/kg)
		Normal-saline treated group		
1	0.047	1.93	2.86	0.136
2	0.067	1.51	2.30	0.155
3	0.055	1.92	2.92	0.159
4	0.049	2.74	4.13	0.203
5	0.071	1.67	2.58	0.183
6	0.050	2.43	3.65	0.183
Mean (± SD)	0.057 (0.010)	2.03 (0.46)	3.07 (0.69)	0.17 (0.024)
		Amiodarone-treated group		
1	0.032	3.98	5.45	0.175
2	0.035	3.54	4.96	0.174
3	0.029	4.80	6.57	0.189
4	0.025	5.31	7.34	0.186
5	0.030	4.53	6.48	0.192
6	0.037	3.58	5.09	0.187
Mean (± SD)	0.031 (0.004)*	4.29 (0.71)*	5.98 (0.96)*	0.18 (0.008)

* $P < 0.001$ compared to the normal saline-treated group.

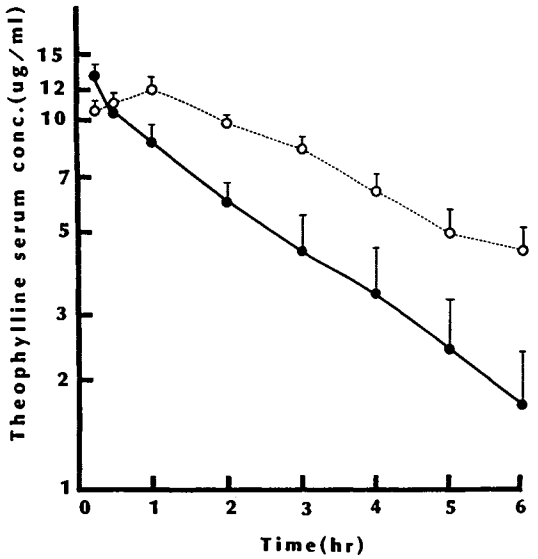

Fig. 1. Mean (± SD) serum theophylline concentrations versus time during concomitant administration of normal saline (filled circles) or a single 100-mg/kg dose of amiodarone HCl (open circles).

DISCUSSION

In a recent study in rats, Grech-Bilanger (5) demonstrated dose-dependent depressive effects of amiodarone on the activity of the cytochrome *P*450 system. This decrease in activity resulted in inhibition of antipyrine clearance during concomitant amiodarone treatment. Staiger *et al.* (6) has also shown significant reductions in the systemic clearance and prolongations in the elimination half-life of antipyrine in three men treated with amiodarone for 2 to 6 weeks. No significant changes in the volume of distribution of antipyrine were observed in these two studies. Each of these reports demonstrates inhibition of the cytochrome *P*450 system with chronic doses of amiodarone. The present investigation suggests that this effect occurs following single doses of the drug. A single-dose study was selected to minimize any contribution of the metabolites of amiodarone to the metabolic depressant effects of this drug. The differences in the vehicle used in the amiodarone-treated rats versus the control group is not likely to explain the alterations in the systemic clearance of theophylline observed. Polysorbate 80 has been shown to *increase* dramatically the activity of certain hepatic microsomal enzymes (15). This might tend to make it more difficult to detect an amiodarone-induced depressant effect on the hepatic metabolism of theophylline.

The magnitude of the systemic clearance of theophylline in the present study is low in comparison to estimates of hepatic plasma flow in the rat (0.057 vs 2.2 liters/hr/kg) (16), yielding an apparent hepatic extraction ratio (CL/hepatic plasma flow) of 0.026. This inefficient extraction of theophylline implies that its systemic clearance is sensitive to changes in intrinsic hepatic enzyme activity. Assuming that amiodarone has no effect on the serum binding of theophylline, the results of the present study tend to support the hypothesis that some form of hepatic enzyme inhibition is responsible for the observed effect of amiodarone on theophylline pharmacokinetics. Further studies are warranted to assess the effect of amiodarone on theophylline disposition in humans.

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