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Report

Effect of Amiodarone and Desethylamiodarone on the Pharmacokinetics of Antipyrine in the Rat

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The effect of amiodarone on hepatic drug metabolism *in vivo* was examined in the rat using antipyrine as a model substrate. Pretreatment with oral amiodarone hydrochloride, 100 mg/kg/day, for 5 days resulted in a 19% reduction in antipyrine clearance and a 22% increase in half-life. The administration of single oral doses of amiodarone hydrochloride, 100 mg/kg, 1 or 5 hr prior to antipyrine administration had no significant effect on antipyrine pharmacokinetics. The administration of a single intravenous dose of amiodarone hydrochloride, 50 mg/kg, reduced antipyrine clearance by 32% and increased the half-life by 46%. The desethyl metabolite of amiodarone was also found to reduce antipyrine clearance (21%) after a single oral dose of 100 mg/kg.

KEY WORDS: amiodarone; antipyrine; desethylamiodarone; drug metabolism; drug interactions; pharmacokinetics.

INTRODUCTION

Amiodarone is a potent antiarrhythmic agent effective in the management of a variety of resistant arrhythmias. During clinical trials with this agent, a number of drug interactions have been reported (1). Elevations in the serum concentrations of several drugs, including digoxin (2,3), flecainide (4), quinidine (5,6), phenytoin (7), and warfarin (8,9), have been reported when amiodarone was added to the regimen of patients receiving these agents. It was suggested that amiodarone may interact with other drugs by decreasing hepatic drug metabolism (1). Subsequently, chronic amiodarone treatment has been shown to reduce cytochrome P-450-dependent metabolism in humans (10,11) and the rat (12,13).

To characterize further the effect of amiodarone on drug metabolism, we have examined the effect of single- and multiple-dose administration on *in vivo* drug metabolism in the rat. Antipyrine was used as the model substrate for cytochrome P-450-dependent metabolism (14). In addition, we have examined the effect of the desethyl metabolite of amiodarone on drug metabolism *in vivo*.

MATERIALS AND METHODS

Animals and Treatment. Male Sprague–Dawley rats (weighing 170 to 216 g) had an indwelling cannula implanted in the right jugular vein under light ether anesthesia 1 day prior to antipyrine administration (15). Antipyrine (20 mg/kg) was infused through the cannula and blood samples (0.25 ml) were obtained over a 5-hr period. Plasma was separated by centrifugation and stored at −20°C until analyzed by an HPLC method described previously (16). Direct injection of amiodarone or desethylamiodarone onto the chromatographic system did not result in any interfering peaks. Furthermore, plasma from animals pretreated with amiodarone or desethylamiodarone that did not receive antipyrine also did not exhibit any interfering peaks.

Animals received amiodarone hydrochloride orally or intravenously as indicated in the Results. Other animals received desethylamiodarone hydrochloride, 100 mg/kg orally, 1 hr prior to antipyrine administration. Amiodarone hydrochloride and desethylamiodarone hydrochloride were dissolved in a solution of 40% propylene glycol in saline to a final concentration of 40 mg/ml just prior to administration. A control group that received the diluent only was studied in parallel to each treatment regimen.

Data Analysis. To obtain an estimate of the initial plasma concentration (i.e., concentration at time 0), the antipyrine plasma concentration–time curves were fitted using an unweighted nonlinear least-squares regression program (17). The data were then subjected to statistical moment analysis using the LAGRAN program (18) to obtain the model independent pharmacokinetic parameters. Pharmacokinetic parameters between control and treatment groups were compared using the two-tailed Student's t test. A value of $P < 0.05$ was considered statistically significant. Data are presented as mean ± standard deviation.

RESULTS

The pharmacokinetic parameters of antipyrine after oral amiodarone pretreatment are shown in Table I. The mean antipyrine plasma concentration versus time profile in control animals and those pretreated with amiodarone hydrochloride, 100 mg/kg/day, for 5 days (the last dose of amio-

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Table I. Effect of Oral Amiodarone Hydrochloride Pretreatment on the Pharmacokinetics of Antipyrine in the Rat[a]

Treatment		Pharmacokinetic parameter		
		CL (ml/min/kg)	$t_{1/2}$ (min)	V_{dss} (ml/kg)
Control	6	9.13 (1.19)	62.2 (9.3)	811 (34)
A, 100 mg/kg/day × 5 days	6	7.36 (0.83)**	75.7 (9.4)*	798 (65)
Control	6	10.03 (0.55)	58.3 (7.4)	858 (52)
A, 100 mg/kg 1 hr prior to antipyrine administration	6	10.24 (0.94)	58.1 (5.6)	867 (34)
Control	7	9.04 (0.82)	59.4 (5.0)	776 (46)
A, 100 mg/kg 5 hr prior to antipyrine administration	9	8.44 (1.78)	63.6 (15.4)	757 (63)

[a] Values are means (±SD). A, amiodarone hydrochloride; CL, total plasma clearance; $t_{1/2}$, half-life; V_{dss}, steady-state volume of distribution.
* $P < 0.05$.
** $P < 0.02$.

darone was administered 1 hr prior to antipyrine administration) is illustrated in Fig. 1. The administration of this regimen resulted in a mean 19% reduction in antipyrine clearance (from 9.13 ± 1.19 to 7.36 ± 0.83 ml/min/kg) and a 22% increase in half-life (from 62.2 ± 9.3 to 75.7 ± 9.4 min). The administration of amiodarone for 5 days also caused a significant weight loss in these animals. While control animals gained an average of 10 g over the study period, those which received amiodarone lost an average of 7 g. A weight loss with chronic amiodarone treatment has been noted previously in the rat, accompanied by a decrease in food and water consumption (19). Studies in our laboratory have demonstrated that a more extensive dietary restriction has no significant effect on the pharmacokinetics of antipyrine in the rat (16).

The administration of a single oral dose of amiodarone hydrochloride, 100 mg/kg, 1 hr prior to antipyrine administration had no significant effect on the pharmacokinetics of

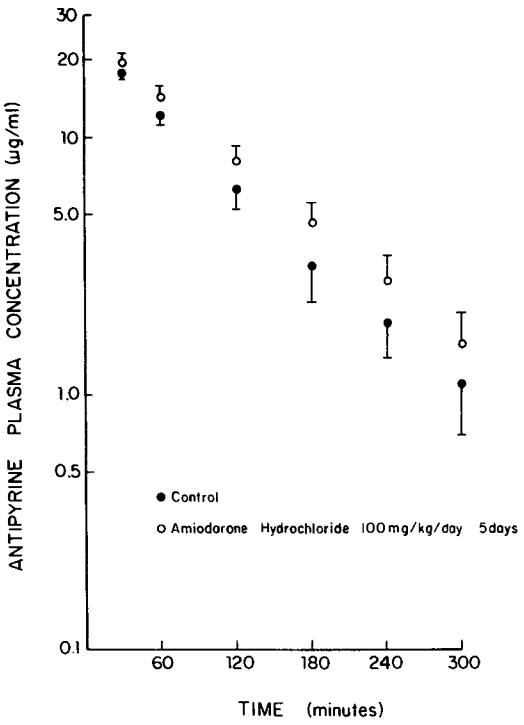

Fig. 1. Mean antipyrine plasma concentration versus time profile in animals receiving diluent (●) or amiodarone hydrochloride, 100 mg/kg/day (○), for 5 days orally. Bars represent 1 SD.

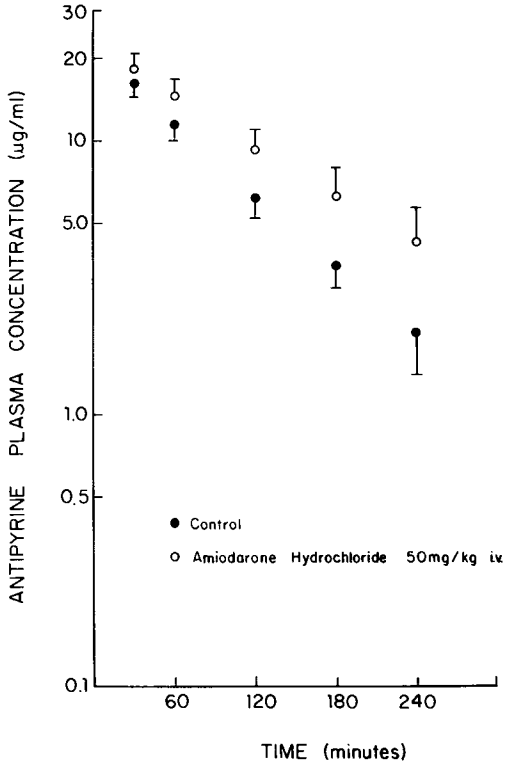

Fig. 2. Mean antipyrine plasma concentration versus time profile in animals receiving a single intravenous dose of diluent (●) or amiodarone hydrochloride, 50 mg/kg (○). Bars represent 1 SD.

Table II. Effect of Intravenous Amiodarone Hydrochloride, 50 mg/kg, on the Pharmacokinetics of Antipyrine in the Rat[a]

Treatment[b]	Pharmacokinetic parameter		
	CL (ml/min/kg)	$t_{1/2}$ (min)	V_{dss} (ml/kg)
Control	9.12 (1.22)	71.4 (7.7)	923 (53)
Amiodarone	6.18 (1.35)*	104.3 (18.3)*	909 (44)

[a] Values are means (± SD), with $N = 6$. Abbreviations as in Table I, footnote *a*.

[b] Amiodarone or diluent was given 15 min prior to antipyrine administration.

* $P < 0.01$.

antipyrine (Table I). The administration of the same oral dose of amiodarone hydrochloride 5 hr prior to antipyrine administration also had no significant effect on the elimination of antipyrine (Table I).

The lack of effect of single-dose oral amiodarone hydrochloride on antipyrine disposition may have been secondary to delayed or incomplete absorption. To examine this possibility, the effect of acute intravenous amiodarone on antipyrine disposition was studied. We found, however, that the animals did not tolerate the same dose of amiodarone intravenously. In the first three animals administered 100 mg/kg intravenously, one died within 10 min of administration and the remaining two developed gross hematuria and marked ataxia. Administering the drug as a slow infusion did not alleviate the development of hematuria. When the dose was reduced to 50 mg/kg all animals tolerated the dosage but several developed mild hematuria. None of the control animals (which received the diluent) exhibited any adverse effects.

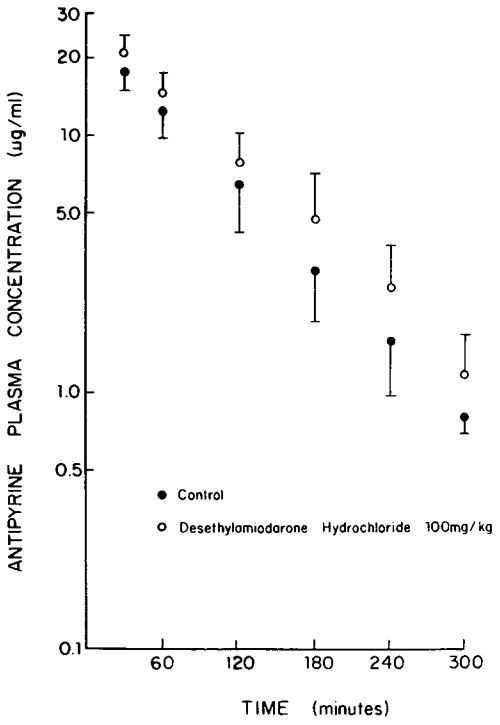

Fig. 3. Mean antipyrine plasma concentration versus time profile in animals receiving a single oral dose of diluent (●) or desethylamiodarone hydrochloride, 100 mg/kg (○). Bars represent 1 SD.

Figure 2 illustrates the mean plasma concentration versus time profile for the single-dose intravenous study. The data in Table II indicate that a single intravenous dose of amiodarone hydrochloride, 50 mg/kg, given 15 min prior to antipyrine administration caused a 32% reduction in antipyrine clearance (from 9.12 ± 1.22 to 6.16 ± 1.35 ml/min/kg) and a 46% increase in half-life (from 71.4 ± 7.7 to 104.3 ± 18.3 min).

Figure 3 illustrates the mean plasma concentration–time profile for antipyrine in control animals and those receiving a single dose of desethylamiodarone hydrochloride, 100 mg/kg orally. The administration of a single dose of desethylamiodarone hydrochloride 1 hr before antipyrine administration reduced the clearance of antipyrine (see Table III) by 21% (from 10.42 ± 2.16 to 8.21 ± 1.67 ml/min/kg) and increased the half-life by the same magnitude (from 58.4 ± 11.6 to 70.6 ± 20 min).

DISCUSSION

The results of this study confirm previous observations that amiodarone is an inhibitor of drug metabolism *in vivo* (12,20). This effect is seen after both single and multiple doses. The differential effect of the acute oral and intravenous doses of amiodarone is most likely due to slow absorption and/or poor bioavailability after oral administration. While the absorption of amiodarone in the rat has not been reported, the compound demonstrates delayed and erratic absorption after oral administration in humans (21). The decrease in antipyrine clearance after acute intravenous administration suggests that the effect of amiodarone on drug metabolism is most likely a direct effect of the parent compound and not mediated soley by a metabolite. Furthermore, in view of the turnover time of P-450 cytochromes (22,23), this effect occurs too rapidly to be caused by inhibition of cytochrome P-450 synthesis. Thus, amiodarone must cause its effect by either a direct interaction with or destruction of the enzyme system.

The effect of desethylamiodarone on drug metabolism has not been previously reported. The results obtained in this study indicate that, like the parent compound, the desethyl metabolite is capable of inhibiting oxidative drug metabolism. Since this metabolite is present in plasma of patients receiving the drug chronically at concentrations comparable to that of the parent compound (21), it is quite probable that it makes a significant contribution to the reduction of drug metabolism observed after chronic amiodarone therapy. Additionally, since the metabolite inhibited drug metabolism after an acute oral dose, while the parent compound did not, its absorption may be more rapid and/or complete than the parent compound.

In summary, amiodarone and its desethyl metabolite have been shown to inhibit oxidative drug metabolism *in vivo* after both single- and multiple-dose administration. This indicates that the effect of amiodarone on drug metabolism occurs rapidly. The ability of amiodarone to inhibit drug metabolism suggests the potential for interaction with a number of important therapeutic agents. Furthermore, as suggested by others (24), amiodarone may inhibit its own

Table III. Effect of Oral Desethylamiodarone Hydrochloride, 100 mg/kg, on the Pharmacokinetics of Antipyrine in the Rat[a]

Treatment[b]	Pharmacokinetic parameter		
	CL (ml/min/kg)	$t_{1/2}$ (min)	V_{dss} (ml/kg)
Control	10.42 (2.16)	58.4 (11.6)	861 (73)
Desethylamiodarone	8.21 (1.67)*	70.6 (20.0)	810 (95)

[a] Values are means (± SD), with $N = 7$ for control and $N = 8$ for desethylamiodarone group. Abbreviations as in Table I, footnote *a*.
[b] Desethylamiodarone or diluent was given 1 hr prior to antipyrine administration.
* $P < 0.05$.

metabolism and thereby exhibit time-dependent pharmacokinetics.

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