Table 1. Kinetic parameters[a] of D-α-tocopherol 500 iu following oral administration (means ± s.e.m.). n = 10.

V/F litres	$t_{\frac{1}{2}}$ h	K abs h^{-1}	K elim h^{-1}	T lag h	AUC_0^∞ μmol litre^{-1}	KV/F[b] ml min^{-1}
14·3 ±2·8	21·3 ±4·1	0·87 ±0·19	0·0032 ±0·002	1·92 ±0·29	433 ±79	160 ±40

[a] Standard nomenclature used.
[b] Estimated clearance.

The kinetic parameters computed with the subsequent analysis are presented in Table 1.

Most of the kinetics and absorption studies of vitamin E have been with rats and monkeys. However, Baker et al (1980), examined plasma tocopherol levels in three male and three female normal adults given single doses of D-α-tocopherol acetate. They found that a dose of 400 iu D-α-tocopheryl acetate in vegetable oil significantly increased plasma tocopherol (50%) from base line levels 8 h after ingestion. Kinetic analysis was not performed.

The vehicle in which the vitamin E is dissolved dramatically affects the vitamin's uptake into the blood stream (Schmandke & Schmidt 1965). In mammals, absorption of vitamin E dissolved in fixed oils is thought to take place mainly through lymphatic pathways where it is transported as part of a lipo-protein complex (Machlin & Gabriel 1983).

The high slope of serum levels vs time in Fig. 1 shows a rapid uptake of vitamin E into the blood stream after oral administration. It could be that the water soluble form of vitamin E is being absorbed across the gut mucosa through a mechanism that does not necessitate its emulsification with bile and incorporation into mixed micelles (Bateman & Uccellini 1984). Normally when taken up from the intestine into the lymph, vitamin E being fat soluble, is transported as a chylomicron sized particle which rapidly equilibrates with serum lipoproteins, predominantly the low density lipo-protein. The absorption of the water-soluble vitamin E formulation shown by Bateman & Uccellini (1984) over 8 h against a tablet and two capsule preparations is obviously sustained, and suggests its use in patients with fat malabsorption or lymphatic stasis.

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Effect of phenobarbitone on the pharmacokinetics and tissue levels of amiodarone in the rat

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Phenobarbitone pretreatment has been shown to increase amiodarone total clearance and decrease amiodarone elimination half-life after a single intravenous amiodarone dose in the rat. Coadministration of phenobarbitone with amiodarone for 7 days resulted in decreased tissue amiodarone levels compared to controls. These results may have implications for patients undergoing therapy with amiodarone and concomitant potent enzyme inducing drugs.

Amiodarone is a long acting, oral antiarrhythmic drug that is efficacious in the therapy of resistant supraventricular and ventricular tachyarrhythmias (Heger et al 1981). Phenobarbitone is a potent inducer of hepatic cytochrome P-450 monooxygenase activity (Conney 1967), and clinically significant drug interactions are well described between phenobarbitone and liver metabolized drugs (Greim 1981). Since amiodarone is presumed to be primarily eliminated by hepatic metabolism (Siddoway et al 1983), patients receiving concomitant phenobarbitone and amiodarone may have lower than expected plasma and tissue amiodarone concentrations, possibly leading to decreased drug efficacy. The present study examines this potential drug interaction in rats treated with single dose and chronic amiodarone.

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Methods

Male, Sprague-Dawley rats (270–300 g) received either 80 mg kg^{-1} sodium phenobarbitone or 1 ml kg^{-1} saline as a single daily intraperitoneal dose for 4 consecutive days. On the fifth day, all rats had a single catheter (Silastic, Dow Corning, Midland, MI) placed in the right jugular vein under ether anaesthesia. Two hours later, a 50 mg kg^{-1} intravenous bolus of amiodarone (Cordarone) was given through the jugular catheter followed by a 2 ml saline flush. Blood samples (0·5 ml)

for the determination of amiodarone plasma concentrations were collected through the jugular catheters into heparinized syringes at 0·25, 1, 2, 4, 8, 12 and 24 h after drug administration. Blood volume was replaced at each time point with 0·5 ml of heparinized saline.

For a chronic dosing study, male Sprague-Dawley rats (90–110 g) were anaesthetized with ether and had subcutaneous implantations of osmotic minipumps (Alzet, Model 2ML1) containing 2 ml of 25 mg ml^{-1} amiodarone hydrochloride in saline (Cordarone : saline—1 : 1). The pumps were predetermined by the manufacturer to continuously deliver 9·61 µl of solution subcutaneously per hour over 7 days. Thus, the rats received a constant subcutaneous infusion of 5·77 mg of amiodarone hydrochloride daily. The pumps were allowed to remain implanted for 7 days, and during each of these days the animals received a single intraperitoneal injection of either sodium phenobarbitone (50 mg kg^{-1}) or saline (1 ml kg^{-1}). On the seventh day post pump insertion, all animals were killed by cranial concussion, blood was obtained through puncture of the abdominal aorta, and tissue samples (heart, liver, kidney, lung) were homogenized in iced saline (¼ w/v). All plasma and tissue homogenate samples were stored at −20 °C until assay.

Amiodarone and *N*-desethylamiodarone concentrations in plasma and tissue homogenates were analysed by a previously reported high pressure liquid chromatographic procedure (Rotmensch et al 1984). Model independent pharmacokinetic parameters of plasma clearance (CL), volume of distribution at steady state (V_{ss}), and elimination half-life ($t_{\frac{1}{2}}$) were calculated using the LAGRAN program for pharmacokinetic area and moment analysis (Rocci & Jusko 1983). All data were compared by the unpaired Student's *t*-test using a $P < 0·05$ as being statistically significant.

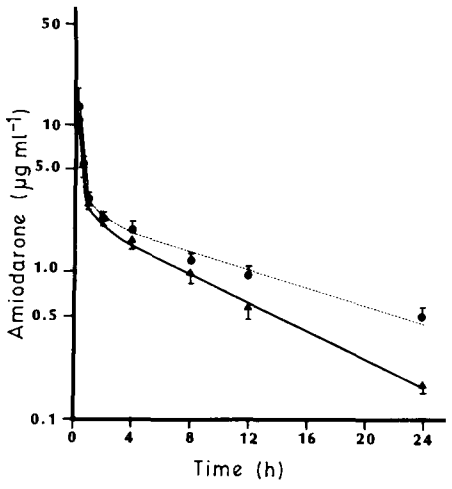

FIG. 1. Average plasma disappearance curves in rats pretreated for 4 days with 80 mg kg^{-1} phenobarbitone i.p. ▲——▲ or 1 ml kg^{-1} saline i.p. ●- - -● after a 50 mg kg^{-1} i.v. bolus of amiodarone. Values are mean ± s.e. with n = 5 at each point.

Table 1. Comparison of the i.v. pharmacokinetics of amiodarone in rats pretreated with either saline or phenobarbitone.

Parameters	Saline (n = 5)‡	Phenobarbitone (n = 5)
CL (litre h^{-1} kg^{-1})	1·47 ± 0·49†	2·35 ± 0·64*
V_{ss} (litre kg^{-1})	21·10 ± 4·0	20·50 ± 5·2
$t_{\frac{1}{2}}$ (h)	10·66 ± 1·99	6·10 ± 0·38*

‡ *n indicates number of animals in group.*
† Mean ± s.d.
* Significantly different from saline group mean ($P < 0·05$).

Table 2. Plasma and tissue amiodarone and *N*-desethylamiodarone concentrations in rats receiving a continuous subcutaneous amiodarone infusion for 7 days and concomitant daily i.p. injections of saline or phenobarbitone.

	Amiodarone†		*N*-Desethylamiodarone†	
Tissue	Saline (n = 6)‡	Phenobarbitone (n = 5)	Saline (n = 6)	Phenobarbitone (n = 5)
Plasma	0·52 ± 0·15	0·22 ± 0·05**	trace	trace
Heart	6·31 ± 3·10	2·66 ± 0·37*	trace	trace
Liver	15·20 ± 3·4	10·30 ± 1·5*	2·4 ± 1·6	2·6 ± 0·4
Kidney	12·30 ± 4·6	6·00 ± 1·4*	3·3 ± 2·3	2·7 ± 0·9
Lung	18·80 ± 6·7	12·00 ± 3·6*	6·1 ± 3·8	7·6 ± 3·8

† Mean values ± s.d. expressed as µg ml^{-1} or µg g^{-1}.
‡ n indicates number of animals in group.
* Significantly different from saline group ($P < 0·05$).
** Significantly different from saline group ($P < 0·01$).

Results

Fig. 1 illustrates the mean plasma disappearance curves for amiodarone in rats pretreated with either phenobarbitone or saline, and Table 1 lists the derived pharmacokinetic parameters for these same animals. Phenobarbitone produced a 43% decrease ($P < 0·05$) in amiodarone elimination half-life and a corresponding 60% increase in total amiodarone clearance ($P < 0·05$), without significantly affecting amiodarone's volume of distribution at steady state.

Plasma and tissue amiodarone and *N*-desethylamiodarone concentrations for the two experimental groups that received a continuous subcutaneous infusion of amiodarone are shown in Table 2. Phenobarbitone caused a significant decrease in the amiodarone content of all measured tissues and plasma when compared to saline treated animals 7 days post pump implantation. *N*-Desethylamiodarone levels were lower than the parent compound in liver, kidney and lung and did not significantly differ between saline or phenobarbitone treated groups. Only trace amounts of this metabolite were detectable in the heart and plasma samples for both groups.

Discussion

Phenobarbitone has been shown to increase amiodarone elimination in rat models for single dose and chronic amiodarone therapy. Although the exact metabolic disposition of amiodarone in the rat is not thoroughly characterized, recent studies in rats have demonstrated absent urinary amiodarone excretion, formation of an *N*-desethyl metabolite, negligible biliary amiodarone excretion, and an intermediate hepatic extraction ratio of 0·49 (Riva et al 1982; Fruncillo et al 1983). Phenobarbitone is well known to induce a wide spectrum of hepatic drug metabolizing enzymes in the rat (Conney 1967), and also to increase liver blood flow (Nies et al 1976). Thus, both enzyme induction and increased hepatic blood flow may have contributed to the increased amiodarone clearance in the phenobarbitone-treated rats observed in this study.

Pharmacokinetic studies in man have revealed differences in amiodarone's kinetic profile following single and multiple doses, with an elimination half-life as long as 3 months on chronic therapy (Kannan et al 1982; Holt et al 1983). Despite large loading doses, there is always a lag period of 5 to 30 days before arrhythmia control is achieved, and the antiarrhythmic effect can persist from 45 to 270 days after drug discontinuation (Rosenbaum et al 1983). An extension of the findings of this study to man would suggest that patients beginning concomitant amiodarone and phenobarbitone therapy may have lower initial plasma and tissue amiodarone levels, with a possible longer latency period between initiation of therapy and arrhythmia control.

Hepatic dysfunction and pulmonary alveolitis are two severe adverse effects of amiodarone that may be related to the respective liver and lung amiodarone concentrations (Harris et al 1983; Rakita et al 1983). In those patients with very long amiodarone elimination half-lives, toxicity could persist for weeks after drug discontinuation before tissue concentrations would fall to a non-toxic level. If it can be definitively shown that drug toxicity is related to elevated amiodarone and not metabolite levels, then initiation of phenobarbitone therapy to accelerate drug clearance, alone with amiodarone discontinuation may be of benefit to patients with dose related toxicity.

In conclusion, clinicians should closely monitor the dosage, plasma level and efficacy of amiodarone in patients receiving concomitant phenobarbitone or other potent enzyme-inducing drugs, so that further insight into this possible drug interaction in man could be obtained.

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