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Kinetics of D-α-tocopherol in a water soluble base in man

N. E. BATEMAN*, D. A. UCCELLINI, *R.P. Scherer Research Laboratory, Department of Biopharmacy, 39–47 Stafford Street, Huntingdale 3166, Victoria, Australia*

The kinetics of D-α-tocopherol (vitamin E) were investigated in 10 healthy, adult volunteers following a single dose of 500 iu D-α-tocopherol. Plasma concentration/time curves fitted using a one compartment open model, showed a rise to 12 ± 1·9 μmol litre^{-1} above endogenous values over 8–9 h and then a tailing away to 7 ± 1·1 μmol litre^{-1} after 24 h.

At present little is known about the absorption and disposition of vitamin E administered exogenously. It is absorbed by a specialized transport mechanism similar to fats (Blomstrand & Forsgren 1968).

We have previously examined the effect of formulation on the bioavailability of vitamin E from various dosage forms. It was found to be more bioavailable than a tablet and two capsule preparations after 2 h when formulated in a water soluble base consisting of polysorbate 80–ethanol–propylene glycol (80:10:10 w/w) (Aqua-Biosorb, R. P. Scherer Australia Pty. Ltd (Bateman & Uccellini 1984). However, in that study plasma levels were only monitored for 8 h and may not have peaked. We have now monitored the absorption for 24 h in an attempt to understand fully the disposition and kinetics of the vitamin in plasma when absorbed from the water-soluble base.

Materials and methods

The instrumentation and methods were as described by Bateman & Uccellini (1984).

The procedure was standardized by chromatographing six standard mixtures containing known mass ratios of α-tocopherol. A linear relation between peak-height ratios (peak-height of α-tocopherol/peak-height of internal standard) and mass ratios (mass of α-tocopherol/mass of internal standard) for concentrations ranging from 2 to 20 μmol litre^{-1} was found. The regression line was y = (0·0600 ± 0·0004) × (0·011 ± 0·005), the correlation coefficient 0·99. With use of this calibration curve, the concentration of α-tocopherol in a serum sample is easily determined after calculation of its peak-height ratio.

Five adult males and five adult females (22–39 years) in good health participated. All gave written informed consent and refrained from taking drug and vitamin preparations for two weeks before the study.

All subjects after fasting for a minimum of 12 h, received orally a single 500 iu dose of the water soluble D-α-tocopherol formulation in soft gelatin capsules and 200 ml of water.

Blood samples (10 ml) were withdrawn into heparinized vials from the left anticubital vein before and 1,2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 20 and 24 h after dosing. Within 1 h the plasma was separated by centrifugation and stored at −20 °C until analysed in duplicate.

Data analysis and pharmacokinetics. C_{max} and T_{max} were estimated visually. The other pharmacokinetic parameters were obtained using the computer program 'Applefitter' in which the Simplex algorithm runs as a suite of compiled programs on an 'Apple IIe' microcomputer. All data analysed were individual subject data fitted to a one compartment open model with first order absorption, extra vascular route of administration, and using weights proportional to the reciprocal of concentration squared.

The program requires initial estimates of the rate constants as input. These were determined by graphical analysis of the data.

Results

After subtraction of endogenous vitamin E from each subject (12·0 μmol litre^{-1} ± 1·05 s.e.m.) the mean plasma concentrations were calculated for the 10 subjects after administration of the 500 iu soft gelatin capsules and are presented in Fig. 1.

Two volunteers exhibited dramatic responses to the administered dose form in that one was a very bad absorber and one a very good absorber. The balance of the other eight patients exhibited a much smaller deviation in response. For complete analysis, the data from all ten patients were included both graphically and in the kinetic parameters.

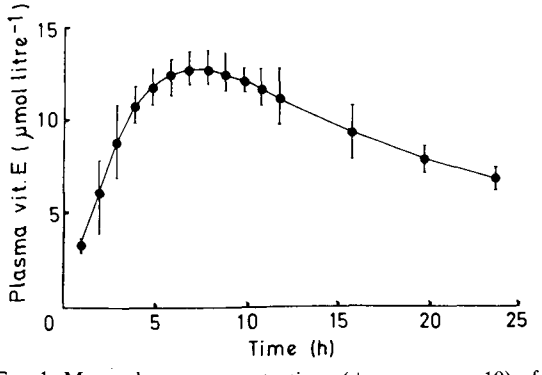

FIG. 1. Mean plasma concentrations (±s.e.m., n = 10) of vitamin E (D-α-tocopherol) as function of time following oral administration of a single vitamin E (500 iu) SEG capsule. Endogenous vitamin E subtracted.

* Correspondence.

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

RICHARD J. FRUNCILLO*, RONALD BERNHARD, BRIAN N. SWANSON, PETER H. VLASSES, ROGER K. FERGUSON, *Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA 19107, USA*

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.

* Correspondence.

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)