Plasma and salivary concentrations of erythromycin after administration of three different formulations

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Summary

In a 6-volunteer cross-over study the pharmacokinetics of 3 erythromycin preparations were compared. A single oral dose of 500 mg of each preparation was administered at each occasion and the levels measured in timed samples of plasma and saliva. Markedly higher blood concentrations of the estolate and propionate were obtained compared to the stearate. Comparison of serum and plasma concentration of the drugs from each split sample showed no significant differences. Plasma concentrations always exceeded those in saliva but for any one preparation a similar ratio was obtained at different times. This may be useful to ascertain compliance and to measure concentration of the compounds where direct measurement in plasma is not practicable.

Introduction

Erythromycin has an important place in treating many infections, particularly those due to Gram positive organisms, *Mycoplasma*, *Chlamydia* and anaerobes and in general, apart from the estolate ester, has a relatively wide safety margin (Lacey, 1977). Several esters as well as the base have been used clinically, some giving earlier, higher and more consistent plasma concentrations than others. The authors have compared the absorption of erythromycin in normal human subjects following administration of identical doses of the estolate, propionate and stearate, and have measured the plasma/salivary ratios of erythromycin in order to determine if salivary estimations provide a reliable guide to its plasma concentrations.

Experimental methods

Six volunteers (3 female, 3 male) aged 20-30 years whose weights and heights were within normal

limits took part in the study. Clinical examination and laboratory tests of haematology, liver and renal function had shown no abnormality, and pregnancy tests in females were negative. No drugs had been taken for one week before the dates of administration of the test substances and no alcohol was permitted during the study period. Subjects were allowed a light breakfast, following an overnight fast, at least 2 hr before drug ingestion and no food was then permitted until 3 hr after. Subjects remained supine during the first 4 hr after ingestion of the drug, and during the remainder of the day abstained from strenuous or athletic activities.

Three test preparations were used: erythromycin estolate capsules (Ilosone) 2×250 mg, erythromycin propionate capsules (Propiocrine) 1×500 mg and erythromycin stearate tablets (Erythrocin) 1×500 mg. Treatment was assigned randomly on the basis of 2 Latin squares so that each volunteer received each treatment separately on one of 3 occasions at weekly intervals at 9 a.m. Plasma samples were collected before and 20, 40, 60, 90 min, and 2, 4, 6, 8, 12 and 24 hr after administration.

Each of the timed blood samples was divided into 2 groups. One was centrifuged at 4°C immediately for 15 min at 4000 rev/min and the separated plasma removed and frozen at -25°C . The remainder of the sample was allowed to coagulate at room temperature and then centrifuged for 15 min at 4°C at 4000 rev/min and the extracted serum frozen at -25°C .

Unstimulated saliva was collected at 1, 2, 4, 6, and 8 hr after ingestion of the drug.

Assay

Erythromycin activity was determined on the

various samples by a cup plate assay using *Bacillus subtilis* ATCC 6633 as test organism. The samples (plasma, serum and saliva) as well as a standard sample of erythromycin base were diluted in 0.1 mol/l phosphate-buffered saline pH 8.0. Standard curves were established by serial dilution of standard erythromycin base, with a sensitivity range of 0.04 to 0.32 µg/ml.

Statistical methods

The pharmacokinetic evaluations were made using a one-compartment open model, with first-order absorption and elimination processes. A programme package of the Department of Informatique Roussel Uclaf (DIRU) was used to fit individual serum/plasma concentrations. The following pharmacokinetic parameters, peak level, time

TABLE 1. Plasma and saliva concentrations of erythromycin (µg/ml) mean ($\pm$ s.e. mean) ($n=6$)

	Propionate	Estolate	Stearate
Plasma			
Saliva			
at hr after			
2	3.14 (0.56) 0.71 (0.28)	3.03 (0.41) 0.40 (0.18)	0.91 (0.28) 0.20 (0.09)
4	2.31 (0.40) 0.21 (0.06)	2.69 (0.31) 0.25 (0.08)	0.87 (0.15) 0.16 (0.04)
6	1.47 (0.32) 0.12 (0.02)	1.82 (0.34) 0.15 (0.04)	0.35 (0.07) 0.09 (0.02)
8	0.89 (0.22) 0.09 (0.02)	1.02 (0.19) 0.09 (0.02)	0.13 (0.02) 0.07 (0.01)
12	0.28 (0.07) 0.06 (0.00)	0.42 (0.07) 0.07 (0.01)	0.06 (0.001) 0.07 (0.01)

Plasma and serum concentrations mean ($\pm$ s.e. mean) kinetic parameters for the 3 compounds

Peak level (µg/ml)	3.40 (0.78)	3.00 (0.55)	1.23 (0.37)
Time to peak (hr)	1.58 (0.15)	2.08 (0.97)	2.92 (0.49)
Area under curve (mg/ml hr)	17.98 (5.04)	18.64 (4.37)	4.70 (1.63)
Elimination half-life (hr)	2.63 (0.29)	2.95 (0.28)	1.18 (0.19)

TABLE 2. Ratio of plasma to saliva concentrations (mean % $\pm$ s.e. mean). Results subjected to computer analysis

	2 hr	4 hr	6 hr	Overall mean	<i>r</i>
Propionate	12.54 $\pm$ 3.00 (4.3–20.8)	7.62 $\pm$ 1.20 (4.3–10.9)	8.29 $\pm$ 1.80 (3.3–13.3)	10.3 $\pm$ 1.3 (7.5–13.1)	0.69 <i>P</i> < 0.01
Estolate	7.38 $\pm$ 1.42 (3.4–11.3)	6.46 $\pm$ 1.00 (3.7–9.3)	7.28 $\pm$ 0.65 (5.5–9.1)	7.5 $\pm$ 0.7 (5.9–9.0)	0.86 <i>P</i> < 0.01
Stearate	24.88 $\pm$ 6.42 (7.1–42.7)	17.10 $\pm$ 3.61 (7.1–27.1)	28.52 $\pm$ 6.20 (11.3–45.7)	23.5 $\pm$ 3.2 (16.6–30.4)	0.90 <i>P</i> < 0.01

The figures in brackets show the limits of 95% confidence interval. *r* correlation coefficient between saliva and plasma values

to peak, area under curve and elimination half-life were subjected to statistical comparisons.

The one-factor analysis of variance with repeated measures was used to compare the pharmacokinetic parameters of the drugs. Since a suitable choice of 2 Latin squares provided a balanced design with respect to residual effects, the analysis followed the method of Williams, where the direct effect of a treatment is adjusted so as to remove residual effects from the previous period (Cochran and Cox, 1957).

Results

Table 1. This shows plasma and salivary concentrations of the 3 preparations.

Erythromycin propionate reached a peak of $3.4 \mu\text{g/ml}$ 1.58 hr after ingestion, the estolate peaking at a lower concentration of $3.0 \mu\text{g/ml}$ and requiring a longer time to reach this value, with a mean of 2.08 hr. The stearate showed markedly lower blood concentration with a mean peak of $1.23 \mu\text{g/ml}$ and 2.92 hr to this concentration. The area under curve values for the antibiotics were comparable for the propionate and estolate

with a mean of $17.98 \mu\text{g/ml/hr}$ and $18.64 \mu\text{g/ml/hr}$ respectively, whereas the stearate was only $4.7 \mu\text{g/ml/hr}$. Mean elimination half-lives were 2.63 hr, 2.95 hr and 1.18 hr for the propionate, estolate and stearate respectively.

Table 2. The ratio of plasma/saliva and serum/saliva concentrations for the propionate and estolate showed a mean maximum value at 2 hr of 12.54 and 7.38 dropping to 8.29 and 7.28 at 6 hr respectively. The stearate ratio was markedly higher, 24.88 at 2 hr and rising to 28.52 at 6 hr.

The mean values for the 3 compounds in plasma, serum and saliva are compared in Figures 1 and 2.

Discussion

These results confirm those of previous investigations and demonstrate the markedly higher systemic availability of erythromycin from the estolate and propionate compared with the stearate esters. It has been shown in the literature that, using erythromycin esters, the drug circulates in the blood partly as ester and partly as base. Therefore, the *in vivo* activity must not be considered in terms

FIG. 1. Mean plasma erythromycin concentrations. ○—○ propionate, □ . . . □ estolate, △ --- △ stearate.

of that found in *in vitro* (Tardrew, Mao and Kenny, 1969).

The kinetic constants obtained are similar to those demonstrated in earlier studies (Stephens *et al.*, 1969; Wiegand, 1972; Griffith, 1958).

The serum/plasma ratios of erythromycin concentrations showed a reasonable degree of consistency with those in the literature, i.e. approximately

10% after administration of each of the 3 preparations. The stearate ratio was greater than that of the other esters although the total count was smaller, partly owing to the fact that erythromycin propionate and estolate circulate as the esters and that there may therefore be a difference in their distribution in the tissues.

The above indicates not only that satisfactory therapeutic concentrations are reached in the saliva, particularly after administration of the propionate and estolate but also that salivary drug concentrations may be used as an alternative to plasma concentration when monitoring the course of treatment with erythromycin in conditions where it is imperative rapidly to achieve adequate therapeutic concentrations of drug in tissues. This is subject to the important limitation, however, derived from observations with the lipid soluble drug propranolol (Kaye *et al.*, 1977), that buccal contamination by a drug may invalidate salivary estimations carried out on samples collected less than 2 hr after oral ingestion.

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FIG. 2. Mean salivary erythromycin concentrations. O—O propionate, □...□ estolate, △---△ stearate.