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Lack of effect of erythromycin on the pharmacokinetics of single oral doses of phenytoin

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The effect of erythromycin on the pharmacokinetics of phenytoin was studied in eight healthy volunteers using a balanced randomised cross-over design. Volunteers received a single oral dose of 400 mg of phenytoin sodium during each phase. During the treatment phase, the phenytoin sodium dose was administered 4.5 days after the commencement of a 7 day course of erythromycin base (250 mg every 6 h). There was no significant difference between the control and treatment phases ($P > 0.05$) with respect to the area under the plasma phenytoin concentration-time curve, the fraction of phenytoin unbound in plasma, the area under the unbound phenytoin concentration-time curve, the elimination half-life of phenytoin or the fraction of the dose excreted in urine as free and conjugated hydroxyphenylphenylhydantoin. This single dose study indicated that the intrinsic clearance of unbound phenytoin was unaffected by the concurrent administration of erythromycin.

Keywords phenytoin erythromycin pharmacokinetics interaction

Introduction

Phenytoin is one of the most commonly used drugs for the management of epilepsy. The drug is cleared predominantly by hepatic metabolism via the mixed function oxidase system. Within the therapeutic plasma concentration range (10 to 20 mg l^{-1}), this enzyme mediated oxidation displays non-linear kinetics (Martin *et al.*, 1977). Urinary recovery of the metabolic product, hydroxyphenylphenylhydantoin (HPPH), and its glucuronide conjugate accounts for 60 to 90% of an oral dose (Glazko *et al.*, 1982). Other drugs have been shown to reduce the clearance of phenytoin (Perucca, 1982). Because of the non-linear kinetics, changes in clearance will produce disproportionate changes in plasma concentrations and, given the narrow therapeutic range of phenytoin, there is an increased likelihood of poor seizure control or toxicity.

We undertook this study following a case in which an eleven year old child, previously stabilised on phenytoin, was admitted to hospital with symptoms of phenytoin toxicity, confirmed by plasma phenytoin concentrations of up to 54 mg l^{-1}. The patient had commenced a course of erythromycin approximately 5 days prior to admission. Erythromycin, a macrolide antibiotic, has been shown to reduce the clearance of and/or precipitate clinical toxicity for a number of drugs which are extensively metabolised by the liver (Ludden, 1985). The aim of this study was to determine whether erythromycin had similar effects on the metabolism of phenytoin.

Methods

Subjects and study design

Eight non-smoking male volunteers, age 20 to 41 years and weighing 70 to 110 kg were selected. After being assessed as healthy following a physical examination, a clinical history and

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routine biochemical, haematological and microurine analyses, all the subjects gave written consent to be admitted into the study. None was taking chronic medication and alcohol consumption was not controlled during the study. Approval was given by the Institutional Ethics Committee.

A balanced randomised cross-over design was used. Each subject, after an overnight fast, received phenytoin sodium (Dilantin capsules, Parke Davis, 4 × 100 mg), at 07.00 h with 200 ml of water, in both a control and treatment phase separated by 3 weeks. A standard breakfast was given at 10.00 h and a standard lunch at 13.00 h. During the treatment phase the phenytoin was given 4.5 days after starting a 7 day course of erythromycin base (Eryc, F. H. Faulding, 250 mg at 00.00, 06.00, 12.00 and 18.00 h) given 1 h before food and 5 h after the evening meal.

Sample collection

Blood samples (7 ml), withdrawn via an indwelling venous catheter on the first day at 0, 1, 2, 4, 6, 8, 10 and 12 h, and subsequently by venepuncture at 26, 33, 50, 57, 74 and 81 h after phenytoin administration, were collected into tubes containing lithium heparin. After centrifugation, the plasma was removed and stored at −20°C until analysed. The volume of urine collected up to 72 h after phenytoin administration was measured and aliquots stored at −20°C. During the treatment phase, finger-prick blood samples were taken during the first 4 days of the erythromycin course. Plasma from these samples together with selected plasma samples collected after phenytoin administration in the treatment phase, enabled the determination of the concentration of erythromycin in a total of ten plasma samples for each subject spanning the 7 day course of erythromycin. Each sample was collected at approximately 1.5 h after any 250 mg dose of erythromycin.

Analytical techniques

Phenytoin in plasma was measured by a specific reversed phase h.p.l.c. method after the precipitation of protein by the addition of 10 parts of acetonitrile containing internal standard. The coefficient of variation (n = 5) was 5.1% and 1.5% at 0.5 and 5 mg l^{-1}, respectively. For the determination of the unbound phenytoin concentration in plasma, six of the samples collected from each volunteer during each phase (at 1, 4, 8, 12, 33 and 57 h) were subjected to ultrafiltration at 37°C using an MPS-1 Micropartition System (Amicon). An aliquot of the ultrafiltrate was injected into the h.p.l.c. The coefficient of variation (n = 5) for the unbound concentration was 3.4% and 1.5% for plasma samples containing phenytoin at a concentration of 1 mg l^{-1} and 5 mg l^{-1}, respectively. Total HPPH in urine was determined by h.p.l.c. after hydrolysis of the HPPH conjugate with β-glucuronidase and extraction with ethyl acetate. The extraction recovery of HPPH was greater than 90%. Erythromycin concentrations in plasma were determined using an agar diffusion technique with *Micrococcus lutea* ATCC 9341 as the test organism.

Pharmacokinetic and statistical analysis

The elimination rate constant, the half-life and the area under the plasma phenytoin concentration time curve for total drug to infinite time (AUC) were determined (Gibaldi & Perrier, 1982). The unbound fraction (f_u) was calculated by dividing the concentration of phenytoin in the plasma ultrafiltrate by the plasma phenytoin concentration and an average of the six f_u values for each volunteer in each phase was obtained. The area under the curve of unbound phenytoin (AUC_u) was obtained from the product of mean f_u and AUC. A two-tailed Student's t-test for paired data was used to compare the pharmacokinetic parameters obtained during the control and treatment phases.

Results

From 26 h after the phenytoin dose the decline in plasma phenytoin concentrations appeared to be log-linear for all subjects ($r > 0.98$). There was no significant difference between the two phases ($P > 0.05$) with respect to the C_{max}, elimination half-life, AUC, AUC_u or the fraction of the dose excreted as HPPH in urine (Table 1). The power of the study to detect a 25% difference in AUC_u between the phases was 90% (Bolton, 1984).

For seven of the eight subjects, the concentrations of erythromycin in plasma were in the range of 0.4 to 2.0 mg l^{-1}. For the other subject, five of the plasma samples had concentrations of erythromycin which were below the minimum detectable concentration of 0.1 mg l^{-1}. The concentrations of erythromycin in the other five samples were similar to those achieved for the other subjects in this study.

Discussion

Phenytoin is restrictively cleared primarily by hepatic metabolism. For such a drug, the area

Table 1 Effect of erythromycin on the pharmacokinetics of phenytoin (mean ± s.d.)

	Control phase	*Treatment phase*	
C_{max} (mg l^{-1})	4.1 ± 0.7	4.1 ± 0.6	NS[1]
$t_{½}$ (h)	18.6 ± 3.1	18.7 ± 2.2	NS
f_u	0.103 ± 0.011	0.109 ± 0.018	NS
AUC (mg l^{-1} h)	176 ± 47	169 ± 31	NS
AUC_u (mg l^{-1} h)	17.4 ± 5.3	18.4 ± 3.8	NS
Fraction of dose as HPPH in urine	0.55 ± 0.10	0.51 ± 0.08	NS

[1]NS = $P > 0.05$ ($n = 8$)

under the curve of unbound drug (AUC_u) is given by

$$AUC_u = f_G . \text{Dose}/CLu_{int}$$

where f_G is the fraction of an oral dose absorbed from the gut and CLu_{int} is the intrinsic clearance of unbound drug. The lack of any significant alteration in the observed AUC_u between the two phases could be explained either by no change in f_G or CLu_{int}, or compensatory changes in f_G and CLu_{int}. If it is assumed that greater than 90% of an absorbed dose of phenytoin is cleared via a saturable metabolic pathway involving an epoxide intermediate (Winter & Tozer, 1986), then at plasma concentrations significantly below the reported K_m (± s.d.) in normal subjects of 11.5 ± 5.0 mg l^{-1} (Martin *et al.*,1977), the fraction of the dose excreted as the major metabolite, HPPH, will give an indication of the relative fraction of the oral dose that has been absorbed during each phase of the study. Since no significant difference in the urinary recovery of total HPPH was found, this indicates that f_G did not differ between the control and treatment phases. Consequently it may be concluded that CLu_{int} also was not affected by concurrent administration of erythromycin. While Bachmann *et al.* (1984) reached a similar conclusion, their study suffers from a number of limitations, in particular the assumption that there was no difference in the extent of absorption of phenytoin in either phase and also that a constant value of 0.069 for f_u was assigned to all subjects during both phases. In addition, Bachmann *et al.* (1984) did not report the plasma concentrations of erythromycin that were achieved in their study. The erythromycin concentrations obtained in our study are consistent with those reported by Josefsson *et al.* (1986) after administration of the same product.

Erythromycin both directly induces and indirectly inhibits microsomal enzyme activity (Pessayre, 1983) and this may in part explain the reported variable effects of concurrent erythromycin on the clearance of other drugs such as theophylline, warfarin and carbamazepine (Ludden, 1985). Since erythromycin is usually given over a period of 7 days, the design of this study allowed an acceptable pretreatment of 4.5 days and continued treatment for a further 2.5 days after the phenytoin dose. As with any single dose study in volunteers, whether the conclusions reached from this study would apply to patients on chronic phenytoin therapy is yet to be resolved. For ethical reasons, it was not possible to conduct a study in patients stabilised on phenytoin.

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