COMPARISON OF THE PHARMACOKINETICS OF METRONIDAZOLE IN HEALTHY FEMALE VOLUNTEERS FOLLOWING EITHER A SINGLE ORAL OR INTRAVENOUS DOSE

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1 The plasma pharmacokinetics of metronidazole following a single dose (500 mg) of metronidazole have been investigated in a crossover study in healthy female volunteers, using assays specific for metronidazole and its metabolites 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole (metabolite I) and 2-methyl-5-nitroimidazole-1-acetic acid (metabolite II).

2 No systematic differences, which could be related to the route of metronidazole administration, were observed in the area under the plasma metronidazole concentration against time curve, elimination half-life, apparent volume of distribution, or total urinary excretion of metronidazole. Following a single oral or intravenous dose, the half-life estimates were 7.0 h and 7.3 h respectively.

3 No metabolite II was detected in plasma following the administration of metronidazole by either route. Urinary elimination of this metabolite appeared to be independent of the route of administration.

4 No systematic differences, which could be related to the route of administration, were observed in the apparent half-life or total urinary excretion of metabolite I. However, the area under the plasma concentration against time curve for metabolite I was significantly greater (+27%) following oral administration than following intravenous administration.

5 A single dose of metronidazole (500 mg) produced a peak plasma concentration for the drug which was in excess of the minimum inhibitory concentration of most susceptible anaerobic bacteria, and in several of the volunteers such an inhibitory concentration of metronidazole was maintained in plasma for more than 8 h following a single dose.

Introduction

Metronidazole [1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole, Figure 1] is an antibacterial agent used systemically against a variety of anaerobic bacteria (Ingham, Rich, Selkon, Hale, Roxby, Betty, Johnson & Uldhall, 1975), and in the treatment of trichomoniasis (McGill & Black, 1962), giardiasis (Khan & Muazzam, 1964), amoebiasis (Powell, 1969) and other conditions (Templeton, 1977).

Metabolism in man has been shown to occur by oxidative mechanisms. The principal metabolic products detected in human urine are 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole (metabolite I, Figure 1), 2-methyl-5-nitroimidazole-1-acetic acid (metabolite II, Figure 1) and glucuronide conjugates of metronidazole (Stambaugh, Feo & Manthei, 1968).

The pharmacokinetics of metronidazole administered by the oral route, together with the limited information available following intravenous or rectal dosings have been reviewed by Templeton (1977).

However, many of these studies have used

non-specific assay procedures, which measure both metronidazole and one or more of its oxidative metabolites, and none have involved the separate quantitative measurement of the plasma concentrations of metronidazole and these metabolites.

Recently, a specific and sensitive high-pressure liquid chromatographic method has been reported for the simultaneous quantification of metronidazole and its two major oxidative metabolites in plasma and urine (Gulaid, Houghton, Lewellen, Smith & Thorne, 1978). This HPLC method was used to determine the plasma and urinary levels of metronidazole and these metabolites following oral or intravenous administration of metronidazole.

Methods

Study design

Nine healthy female volunteers (age range 19 to 50 years, mean 30 years; weight range 46 to 69 kg, mean

Figure 1 Metronidazole and its principal oxidative metabolites in urine (from Stambaugh *et al.*, 1968). M = metronidazole; I = 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole; II = 2-methyl-5-nitroimidazole-1-acetic acid.

56 kg) were admitted to the study. For 2 weeks preceding and during the study, no other medication was taken by the volunteers. On the days of dosing, a light breakfast of coffee and toast was consumed at 06.30 h, and a standard lunch was taken 3 h after dosing. Thereafter, food, drink and tobacco were allowed *ad lib*, but alcohol was excluded. Metronidazole was administered either orally as a tablet formulation (Flagyl® 2.5 tablets, each containing 200 mg metronidazole), or as an intravenous infusion administered over 20 min (Flagyl® injection; containing 500 mg metronidazole in 100 ml of aqueous medium). Each volunteer received each preparation, thereby acting as her own control. The order in which the formulations were administered was randomized according to an incomplete latin square design.

Heparinized blood (10 to 20 ml) was withdrawn at the times indicated on Figure 2. Urine samples were collected over a bacteriostat during the time intervals indicated on Figure 3.

The standard procedure used to halve the metronidazole tablets was studied and found to produce half tablets containing 100 ± 6 (s.d.) mg of metronidazole.

Extraction and assay procedures

The plasma and urinary levels of metronidazole and of the two major oxidative metabolites (I and II) were measured using the specific HPLC methods which may be used to quantify these compounds at concentrations of 50 ng/ml in plasma and 2.5 µg/ml in urine.

Analysis of results

The elimination half-life of metronidazole from plasma and the apparent elimination half-life of metabolite I from plasma were estimated for each subject after oral and intravenous doses using the method of least squares for a regression of $\log_e$ plasma concentration against time. The elimination

half-life of metronidazole was calculated using the data points between 4 and 48 h after dosing. The apparent elimination half-life of metabolite I was calculated on the four points between 24 and 48 h after dosing.

The area under the plasma concentration against time curve from the time of dosing to infinity (AUC) was calculated by the trapezoidal rule. The fraction of the dose absorbed following oral administration and the apparent volume of distribution (V_d) were calculated using equations 1 and 2, respectively:

$$F = \frac{AUC_o \cdot D_{i.v.}}{AUC_{i.v.} \cdot D_o} \quad 1$$

$$V_d = \frac{F \cdot D}{K \cdot AUC} \quad 2$$

where AUC is the area under the plasma concentration against time curve (mg h l^{-1}); D is the dose (mg) following intravenous (i.v.) or oral (o) administration; F is the fraction of the dose absorbed and K is the elimination rate constant (h^{-1}).

Student's *t*-test for pair differences was used to compare the pair differences observed between individual pharmacokinetic parameters following oral or intravenous dosing in the same subject.

Results

Plasma pharmacokinetics of metronidazole and its major oxidative metabolites

The plasma concentrations of metronidazole and metabolite I in each individual were obtained following both oral and intravenous administration of metronidazole (500 mg) and the mean data calculated (Figure 2). However, all pharmacokinetic parameters were calculated by manipulation of the individual plasma level data. No metabolite II was found in the plasma of any volunteer, at any time interval, although with the analytical method

Figure 2 Mean plasma concentrations of metronidazole (●) and 1-(2-hydroxyethyl)-2-hydroxy-methyl-5-nitroimidazole (○) in nine healthy female volunteers following intravenous (a) and oral (b) administration of metronidazole (500 mg).

employed, levels down to 200 ng/ml would have been quantified.

Several pharmacokinetic parameters were calculated for each individual following oral and intravenous dosing with metronidazole. The means and standard deviations of these parameters are given (Table 1). In one volunteer there were insufficient points on the terminal portion of the metabolite I elimination curve to allow the determination of an apparent half-life for metabolite I, or the area under the plasma concentration against time curve.

The mean value for the areas under the metabolite I curves were 71 ± 17.2 (s.d.) mg h l^{-1} following oral dosing and 56 ± 16.0 (s.d.) mg h l^{-1} following intravenous dosing. The pair differences between AUC values, after oral and intravenous dosing in the same subject, were analysed using a paired *t*-test ($t = 3.0$ with 7 degrees of freedom). There was a significantly higher AUC value ($P = 0.02$) following oral administration than following intravenous administration.

Urinary excretion of metronidazole and its major oxidative metabolites

The mean values were obtained for the cumulative urinary excretion of metronidazole and metabolites I and II, and the total of these three compounds during each collection period (Figure 3). Approximately 33% of the administered dose was excreted in urine as metronidazole and metabolites I and II. No systematic difference due to the route of metronidazole administration was observed in the proportion of metronidazole and its metabolites in urine. The majority of the metronidazole and metabolite II eliminated in urine was excreted within 12 h after the administration of a single dose of metronidazole, and excretion was complete within 48 h. The rate at which metabolite I was excreted appeared to remain constant for the first 24 h after a single dose. Subsequently, this rate decreased and excretion was complete within 72 h of dosing.

Discussion

The plasma and urinary concentrations of metronidazole and its oxidative metabolites have been

Table 1 Pharmacokinetic parameters (mean $\pm$ s.d.) observed in nine healthy female volunteers following oral or intravenous administration of metronidazole (500 mg)

Pharmacokinetic parameter	Oral administration	Intravenous infusion
Plasma elimination half-life of metronidazole (h)	7.0 ± 1.1	7.3 ± 1.0
Area under the plasma metronidazole concentration against time curve (mg h l^{-1})	159 ± 48	151 ± 42
Apparent volume of distribution of metronidazole (l)	34 ± 8.2	36 ± 7.9
Plasma elimination half-life of metabolite I (h)*	$9.5 \pm 2.1^\dagger$	$9.8 \pm 1.3^\dagger$
Area under the plasma metabolite I concentration against time curve (mg h l^{-1})	$71 \pm 17^\dagger$	$56 \pm 16^\dagger$

*Apparent elimination half-life calculated from the terminal portion of the plasma metabolite I concentration against time curve.

†Mean of eight volunteers. In one volunteer, the terminal half-life could not be estimated.

Figure 3 Mean cumulative urinary excretion of metronidazole (■), 2-methyl-5-nitroimidazole-1-acetic acid (□), 1-(2-hydroxyethyl)-2-hydroxy-methyl-5-nitroimidazole (○) and the total (●) of these three compounds by nine healthy female volunteers following intravenous (a) and oral (b) administration of metronidazole (500 mg).

determined and compared following oral or intravenous administration of metronidazole.

The systemic availability of metronidazole has been shown, in this study, to be similar following oral or intravenous dosing. No systematic differences, which could be attributed to the route of administration, were seen in the elimination half-life, apparent volume of distribution, or total urinary clearance of metronidazole.

Limited data are available on the pharmacokinetics of metronidazole administered by routes other than the oral one. However, Welling & Munro (1972) and Schwartz & Jeunet (1976) have determined phar-

macokinetic parameters of metronidazole, assayed specifically, following oral administration. The values which they reported for the elimination half-life (6.2 h and 8.4 h, respectively) were in close agreement with those (7.0 ± 1.1 h (s.d.)) obtained following the oral administration of metronidazole (500 mg) in this study.

Metabolite II was not detected in plasma following the administration of metronidazole by either route. Since this metabolite was detected, in both cases, as a major metabolite in urine, these data suggest that it was rapidly cleared from the plasma. The total urinary excretion of this metabolite appeared to be independent of the route of administration.

Metabolite I was detected in plasma. However, the peak plasma concentration achieved following a single oral or intravenous dose was considerably lower than that of the parent compound. The area under the plasma concentration against time curve for metabolite I was significantly smaller following an intravenous infusion of metronidazole than following oral administration. However, both the apparent plasma elimination half-life and the total urinary excretion of this metabolite showed little tendency to vary with the route of metronidazole administration. These data indicate that the increase, following oral dosing rather than intravenous, observed in the area under the plasma concentration against time curve for metabolite I, is not due to a change in the clearance parameters of this metabolite. It is not possible, using only the data collected in this study, to explain clearly the reason for the small but significant difference between the AUC values following oral and intravenous administration.

The data presented in this paper show that a single dose of metronidazole (500 mg), administered either by the oral or intravenous route, reached a peak level which is in excess of the minimum inhibitory concentration of most susceptible anaerobic bacteria (approximately $6.2 \mu\text{g/ml}$; Finegold & Sutter, 1972) and several of the volunteers maintained an inhibitory concentration of metronidazole in their plasma for more than 8 h following a single dose.

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