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EFFECT OF CONCOMITANT ORAL ADMINISTRATION OF SOME ADSORBING DRUGS ON THE BIOAVAILABILITY OF METRONIDAZOLE

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ABSTRACT

The bioavailability of metronidazole was evaluated when administered alone and in presence of an antidiarrheal mixture, an antacid or in the presence of th e anion exchange resin cholestyramine. A previously developed method for bioavailability evaluation from urinary excretion data for drugs exhibiting linear pharmacokinetics has been used in this study. It is based upon careful collection of urine samples over 12 hr starting after one half-life of the drug. Through mathematical treatment of the cumulative amount excreted after different time intervals, a straight line relationship is obtained. from which the total amount of the drug excreted in urine is calculated. Good agreement between experimental and estimated total amounts of drug excreted unchanged in urine was obtained. While the effect of the antidiarrheal mixture on metronidazole bioavailability was found to be insignificant, a reduction of 14.5% and 21.3% in bioavailability was observed in presence of the antacid mixture and cholestyramine respectively. In agreement with a previous report, about 14% of the drug was found to be excreted unchanged in urine.

INTRODUCTION

Metronidazole (M) is an antibacterial, antiprotozoal agent widely used systemically against a variety of anaerobic bacteria, and in the treatment of trichomoniasis, giardiasis, amaebiasis and other conditions[1]. Several published reports deal with the bioavailability and pharmacokinetics of M[2-7]. A wide intersubject variations in excretion of unchanged M was reported[2]. The oral route of administration showed much better bioavailability when compared with the rectal or the vaginal route[3]. The bioavailability of the suppositories was about 90% of the corresponding tablet dose as judged by the area under the serum curves and amounts excreted in urine[4]. The mean recovery in urine of unchanged M within 36 h was 7-14% of the orally administered dose[4]. Food intake was found to have no consistent effect on the bioavailability of M[5-6]. Differences in M bioavailability in fasting and nonfasting volunteers were found to be insignificant[6].

The present study is concerned with the influence of concomitant oral administration of an antacid, an antidiarrheal mixture or the anion exchange resin, cholestyramine, on the bioavailability of M from its tablets. These agents are used oftenly and in large doses. They have tendency to bind many drugs in the gastrointestinal tract and interfere with their availability. Bioavailability evaluation was carried by analysing urine excretion data of the unchanged drug according to the method of Niebergall et.al.[8].

MATERIALS AND METHODS

Commercial M tablets were administered to five healthy volunteers. A single oral dose of 500 mg was given with enough water after an overnight fast. The bladder was emptied before each dose and some urine was kept for control. Drinks were allowed during the experiment but food was continued to be withheld for three hours after drug administration. Urine was then collected at predetermined time intervals over 17 hrs. In some randomly selected experiments, urine collection was continued for 48 hours. For

TABLE 1

Drug Combinations and Doses

-A- Drug	-B- Drug/Antidiarrheal Mixture	-C- Drug/Antacid Mixture	-D- Drug/Cholestyramine
-2 tablets contain 500 mg M	-2 tablets contain 500 mg M -30 ml suspension contain 5916 mg Kaolin, 132 mg Pectin.	-2 tablets contain 500 mg M -30 ml suspension contain 1290 mg Aluminum Hydroxide, 150 mg Simethicone.	-2 tablets contain 500 mg M -1 powder sachet contain 4 gm Cholestyramine.

model application and statistical estimation of total drug excreted unchanged in urine, during the period 7-17 hrs (10 hrs after the first half-life), urine samples were collected every two hours and subjects were advised to completely empty the bladder for each sample. This procedure was repeated every two weeks with the same subjects administering the assigned dose of one of the drug combinations listed in Table 1.

The urine samples were refrigerated after collection and drug assay was carried by a sensitive HPLC method. The procedure which is a modification of that of Gulaid et. al.[9] involved twice extraction of 2 ml urine each with 10 ml chloroform. Exactly 18 ml of the separated chloroform extract were evaporated to dryness in a rotavapor at 30°C. The residue was then reconstituted in 1 ml mobile phase (methanol 7.5%, acetonitrile 7.5% and water 85%). An exact volume of 20-40 µl solution was used for HPLC determination. The instrument was a Waters Associates (Milford, MA) equipped with a 6000 A pump; U6K injector, 481 Lambda Max detector; M730 Data Module and a MCH 10 column (Varian, California). The flow rate was

adjusted at 1.8 ml/min and sensitivity was set at 0.02. Ultraviolet absorption was measured at a λmax of 316 μm.

Theory

A previous measurement of M kinetics[7] has indicated that the drug exhibits linear pharmacokinetics, hence, the model independent, urinary excretion measurement to evaluate the drug bioavailability[8] is possible. Accordingly, after the absorption phase for drugs conforming to the one-compartment or the two-compartment open models is completed, the cumulative amount of drug excreted in urine may be given by:

$$U = U_\infty - P\, e^{-K_e t} \qquad \text{(Eq. 1)}$$

where U, is the cumulative amount of drug excreted unchanged in the urine up to time t; U_∞, is the total amount of drug excreted unchanged in the urine, K_e, is the overall elimination rate constant and P is a constant related to both the absorption and the elimination rate constants. When urine samples are collected at uniform time intervals Δ, eq. 1 becomes:

$$U' = U_\infty - P\, e^{-K_e (t+\Delta)} \qquad \text{(Eq. 2)}$$

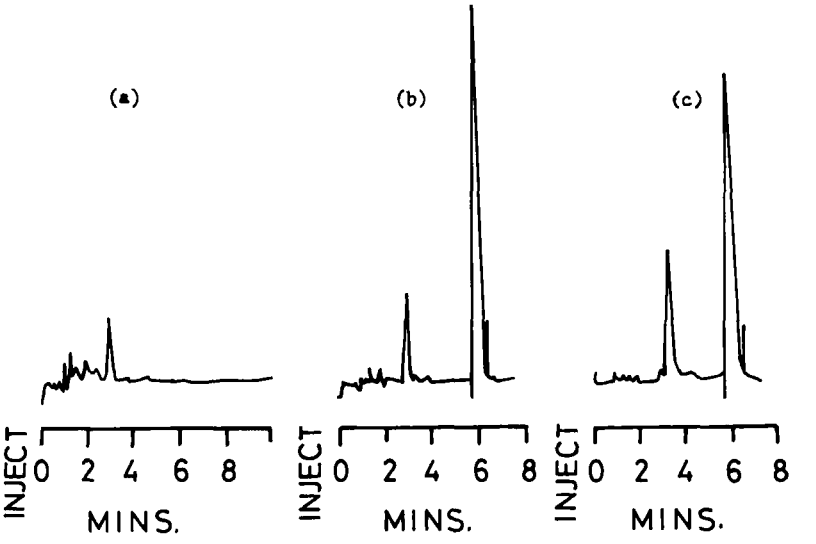
where U' is the cumulative amount of drug excreted after time t+Δ. By rearranging eq. 1 and substituting for P in eq. 2, U' becomes:

$$U' = U\, e^{-K_e \Delta} + U_\infty (1 - e^{-K_e \Delta}) \qquad \text{(Eq. 3)}$$

A plot of U' versus U should yield a straight line. The value of U_∞ can thus be calculated from the slope and the intercept of the line. A comparison between the estimated U_∞ when the drug was administered alone and those when the drug was coadministered with adsorbing agents should reflect any bioavailability changes.

RESULTS

Fig. 1 shows representative chromatograms for M as obtained for a blank urine sample excreted before and after addition of M and



FIGUR E 1

Typical Metronidazole Chromatogram , a, extracted blank urine; b, extracted urine spiked with M; c, extracted urine from an experiment.

an extracted urine sampe collected during one of the experiments. Similar chromatograms were obtained for all runs with retention time for M of 5.99-6.02 min. The chromatograms showed no interference from other urinary contents. A plot of M peak area versus its concentration in standard solution was linear in the range of 0.5-25 µg/ml and essentially passed through the origin (r^2=0.99). Metronidazole recovery from five spiked samples of urine was in the range of 98.5-100%. Concentrations down to 0.05 µg/ml were measurable. These results indicate that the extraction procedure and the instrumental method of analysis are accurate and reproducible.

Table 2 presents the urinary excretion results of one of the experiments in which M was coadministered with the antidiarrheal mixture (combination B) and urine collection was continued for 48 h. Results of samples withdrawn between the 7-17 hours were used for the estimation of the total amount of M excreted (U_∞). From the

TABLE 2

Experimental Amounts of M Excreted in Urine

Sample No.	Collection Time t(hr)	Amount Excreted (mg)	Cumulative Amount after Time t(U) (mg)	Cumulative Amount Excreted after Time t+Δ (U') (mg)
1	1	0.89	0.89	-----
2	2	4.57	5.46	-----
3	3	7.75	13.21	-----
4	5	9.32	22.53	-----
5	7	6.49	29.02	34.90
6	9	5.88	34.90	39.11
7	11	4.21	39.11	43.09
8	13	3.98	43.09	46.98
9	15	3.89	46.98	49.58
10	17	2.60	49.58	-----
11	24	7.68	57.26	-----
12	27.25	1.95	59.21	-----
13	31.50	1.36	60.57	-----
14	37	.90	61.47	-----
15	41	.42	61.89	-----
16	48	.44	62.33	-----

plot of U' versus U, U_∞ was calculated and found for this experiment to be 64.58 mg. When compared with the experimental value for U (62.33 mg), a less than 4% difference was noticable. Results of experiments in which urine collection was continued for 48 hours showed a difference between experimental and estimated U_∞ of less than 6%.

Table 3 presents the estimated total amounts of M excreted unchanged in urine as well as the means and standard deviations for all tested drug combinations. On analysing the results by the t-test of significance at (P=0.05) and using the proper degrees of

TABLE 3

Total Amounts of M Excreted Unchanged in Urine

Estimated U_∞ / Subject	Drug Combination			
	A	B	C	D
1	68.14	65.92	69.00	54.29
2	63.06	57.21	50.04	43.50
3	78.31	73.13	57.47	65.30
4	70.45	*	61.32	56.03
5	68.20	64.58	59.76	*
Mean ± S.D	69.63±5.56	65.21±6.52	59.52±6.84	54.78±8.94

* Experiments were not completed.

freemom, it was found that the difference in bioavailability between administering M alone or coadministering it with the antidiarrheal mixture is insignificant. However, the differences in bioavailability after administering M with the antacid mixture or the anion exchange resin was significant under the same statistical conditions. The estimated total amount of M excreted unchanged in urine was 14.5% less when administered with the antacid mixture and 21.3% less when administered with the anion exchange resin.

The subject-subject variations which are noticable from Table 3 were not related to subjects sex, weight or daily routine. Such variations may be referred to differences in metabolism and/or excretion among the subjects. In agreement with a previous report[4], about 14% of M were found to be excreted unchanged in urine.

DISCUSSION

Urine excretion data of unchanged metronidazole have been used to evaluate the effect of concomitant administration of some adsorbing agents on the drug bioavailability. The method used to

estimate total urinary excretion of the unchanged drug allowed for relatively less number of samples collected and a conveniency in completing the experiment in less than one day. The comparison between the estimated and the experimental total urinary excretion of unchanged M conducted in few experiments showed good agreement and differences of less than 6% were observed.

The antidiarrheal mixture containing pectin and kaolin was found to affect M bioavailability insignificantly. However, significant reduction in M bioavailability was observed with the antacid mixture containing aluminum hydroxide and magnesium hydroxide and with the anion exchange resin cholestyramine. This result would recommend for the separation between these adsorbing agents and M if simultaneously prescribed for oral administration.

The data presented in this paper agree with previous reports on the extent of urinary excretion of unchanged M and on the apparent subject-subject variations. It illustrates the possible use of the urinary excretion data in evaluating bioavailability changes associated with drug environmental conditions at the absorption site.

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