COMPARATIVE STUDY OF THE BIOAVAILABILITY AND DISSOLUTION BEHAVIOR OF FIVE BRANDS OF TETRACYCLINE CAPSULES

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INTRODUCTION

STABILITY AND SAFETY are some of the qualities that define a good drug product. Equally important and frequently ignored is the efficiency by which the product delivers the drug. The availability of drug defines the efficiency of drug products and clearly then a reduction in drug availability can be considered equivalent to a reduction in dosage. Studies made on blood and/or urine levels or other body fluids following the administration of a drug product in order to ascertain a significant concentration in these fluids where its presence is understood to be effective is termed biological availability or bioavailability.

Barr *et al.* (1972) studied three commercial tetracycline preparations and found them to be significantly different in bioavailability. Lovering *et al.* (1975) undertook study involving nine brands of tetracycline preparations available in Canada and found there were significant differences in bioavailability. Both studies showed the validity of either measuring the blood level or urine level for studies of tetracycline bioavailability, confirming earlier work of Chulski *et al.* (1961). Present work involved the comparative study of five brands of commercial tetracycline capsule available in Malaysia (some manufactured locally) and correlations were made between bioavailability and dissolution rates. Bioavailability was obtained from cummulative urine concentration following its oral administration. This is considered as justified as the rate of excretion of tetracycline correlates extremely well with area under the curve (AUC) of blood level, hence a good indication of bioavailability (Barr *et al.*, 1972; Lovering *et al.*, 1975).

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MATERIALS AND METHOD

Samples from one Lot of the commercial product of each of the five brands of tetracycline capsules were obtained from a retail pharmacy. Each claimed to contain 250 mg tetracycline base per capsule. Each brand of the tetracycline HCl had been designated as brand A, B, C, D and E respectively. Five capsules from each brand were analysed to ascertain the amount of tetracycline present by comparison to the reference standard curve prepared using standard tetracycline HCl powder obtained from Sigma Chemical Co.

In-vitro dissolution rates of all the five brands of tetracycline capsules were performed according to the method described in USP XVIII (1970) at 37°C and the rotating basket kept at 50 r.p.m. for a period of 30 min. Simulated gastric fluid was as the dissolution medium and samples were analysed spectrophotometrically at 270 nm for tetracycline by the method of Kohn (1961) on five capsules for each brand. Mean values were taken and dissolution profiles were plotted by plotting percentage of tetracycline dissolved against time.

In-vivo studies: Ten healthy volunteers (aged 21–25 yrs.) with no history of allergy to drugs, and no evidence of kidney and liver diseases were chosen

for the study. The ten volunteers were divided into two groups of 5. One group underwent single dose study while the other group followed the multiple dose study. Volunteers received no drugs affecting liver enzyme activity in 30 days period before the trial and no drug of any kind or alcohol, in the 48 hr prior to or during the test period. Each volunteer whether following single dose study or multiple dose study received each brand of tetracycline capsule(s) at weekly intervals according to the scheme shown in Table 1.

Dosing scheme for 5 different brands of tetracycline given to volunteers for both single and multiple dose study

	Test periods				
Subject	Week 1	Week 2	Week 3	Week 4	Week 5
1	A	B	C	D	E
2	B	C	D	E	A
3	C	D	E	A	B
4	D	E	A	B	C
5	E	A	B	C	D

Each volunteer fasted for at least 8 hr prior to receiving the capsule (first capsule for multiple dose study). Tetracycline 250 mg capsule was administered orally at 7.00 a.m. in the fasting state accompanied by 50 ml water. Food was withheld for the next 4 hr after tetracycline administration, but 50 ml of water was given every two hours after administration of tetracycline until the volunteers went to bed at night. This was to ensure an adequate urine flow. For the next day, volunteers were asked to drink 50 ml water every three hours until they went to bed. Urine samples were collected at 0 (at time of administration), 3, 6, 9, 12, 24 and 48 hr. The urinary volume measured and samples frozen for the assay of tetracycline concentration.

For multiple dose study a total of 3 tetracycline capsules were taken by each volunteer. The capsule was taken at an interval of 8 hr. There is no change in protocol as that in single dose study except collection of urine sample was made at 3, 6, 9, 12, 15, 18, 24, 32 and 48 hr after oral administration of first capsule. No attempt was made to collect urine sample longer than 48 hr for it had been shown previously that 48 hr is more than adequate for tetracycline administered orally to be cleared into the urine (Barr *et al.*, 1972).

RESULTS

The dissolution behaviour of the 5 brands of tetracycline was shown in Figure 1. The values obtained were the mean ± standard error of six capsules from each brand. Brand E possessed the fastest dissolution rate. This was followed by brands B and D (comparable in dissolution rate) which in turn followed by brand A. Brand C ranked the lowest in terms of dissolution rate.

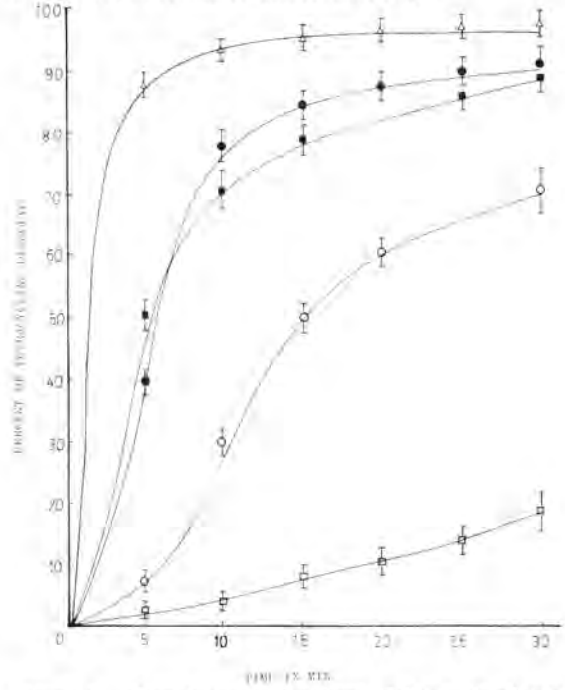

Figure 1. Dissolution behaviour of 5 brands of tetracycline. Value obtained are mean ± S.E. of 6 capsules for A (○), B (●), C (□), D (■), and E (△).

The cummulative urinary concentrations of tetracycline in 48 hr period were plotted in Figure 2 for single dose study and Figure 3 for multiple dose study. In both studies, brand C ranked the lowest in terms of bioavailability as reflected from the cummulative urinary concentration of tetracycline. In both studies again, brand E appeared to be most available, although in multiple dose study (Figure 3), the availability of brand E was only marginally above that of brands B, D and A. While the availabilities of brands B, D and A appeared to be comparable and insignificantly difference, there were definite differences in bioavailability between brands E and C. Brand E being very much more bioavailable than brand C. Good correlations were seen between single dose and multiple dose study for the cummulative urinary concentration of tetracycline measured during the 48 hr period for the 5 brands under study.

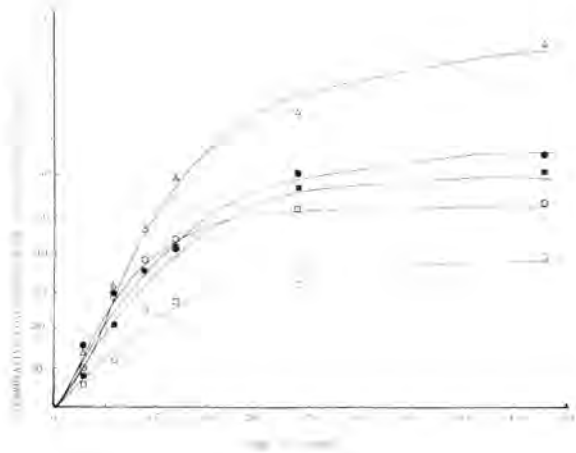

Figure 2. Cummulative concentration of tetracycline in urine for single dose study for 48 hr. A (○), B (●), C (□), D (■), and E (△). For simplicity the standard error bars had been omitted.

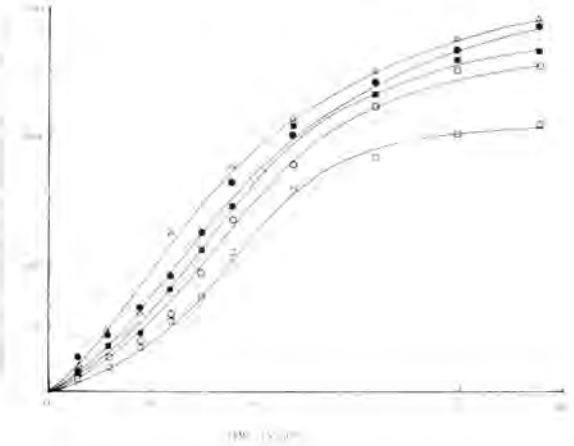

Figure 3. Cummulative concentration of tetracycline in urine for multiple dose study for 48 hr. period. A (○), B (●), C (□), D (■), and E (△). For simplicity the Standard errors bars had been omitted.

DISCUSSION

There were differences in bioavailability in the 5 brands of tetracycline both in single dose and in multiple dose studies. In single dose study urinary data showed that brand E was most bioavailable. Brand B appeared to be comparable in bioavailability to brands D and A. Brand C was the least bioavailable. Good correlation was observed between differences in bioavailability seen in single dose and in multiple dose studies. This infered that single dose study can be used to predict the bioavailability of tetracycline for volunteers that followed multiple dose regimen confirming earlier observation (Barr *et al.*, 1972).

The order of dissolution rate carried out in *in-vitro* on the 5 brands of tetracycline was in good agreement with the bioavailability data both for single and for multiple dose study. Thus dissolution rate of the tablets could be wholly if not mainly responsible for the differences in bioavailability seen in the 5 brands under study.

So far no study had been undertaken on the failure of tetracycline therapy in Malaysia. From data provided it is possible that decrease in absorption from the gastro-intestinal tract due to the low availability could be responsible for some of the therapeutic failure for this widely used drug, in particular brand C whose availability proved to be relatively low. Moreover, it is common knowledge that antacids containing polyvalent cations (e.g. magnesium hydroxide) decrease tetracycline absorption (Harcourt & Hamburger, 1957; Kunin, 1961). Iron tablets taken together with tetracycline and dairy product like milk and cheese (that contain the di or polyvalent cations) can reduce the absorption of tetracycline. Decrease in absorption of tetracycline will not only decrease the amount of tetracycline which reach the systemic circulation and hence the site of infection, but also will increase the amount of drug remaining in the gastrointestinal tract. If more tetracycline remains in the gastrointestinal tract as a consequence of decrease absorption this will increase the possibility of nausea, mucosal irritation and alteration of normal flora at gastrointestinal tract which are all common untoward effects of tetracycline.

Finally it must be mentioned that these studies were made on normal healthy individuals and what effect an infection had (under which tetracycline is indicated) on the absorption of tetracycline is not known. Moreover only one lot of each brand was studied, they should not be taken as identical to others of the same brand.

SUMMARY

Comparative study was made on the bioavailability and dissolution behaviour of five commonly used brands of tetracycline capsules available in Malaysia. Significant differences were detected both in bioavailability and in dissolution behaviour amongst the five brands. *In-vitro* dissolution rate correlated well with both single dose and multiple dose bioavailability *in-vivo* involving healthy volunteers.

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