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COMPARATIVE BIOAVAILABILITY OF SULFAMETHOXAZOLE IN THREE FORMULATIONS OF COTRIMOXAZOLE SUSPENSIONS

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ABSTRACT:

The pharmacokinetic parameters and relative bioavailability of sulfamethoxazole were estimated using three commercially available cotrimoxazole suspensions on six human volunteers. Maximum concentration in plasma was shown by product 1, i.e., 89.6910.84 and were lower in products 2 and 3 i.e., 38.3330.58 and 16.50±0.89, respectively. The time for maximum concentration was 4 hours in products 1 and 3 while it was 3.50 in product 2. There was prolonged elimination half-life of formulation 2 (7.5030.94) than formulation 3 (7.4310.54) while product 1 (4.5410.15) showed lowest half-life. The values of absorption half-lives for formulations 1, 2 and 3 were 1.9230.05. 1.8030.41 and 2.7830.25, respectively. The volume of distribution was highest in formulation 1 (0.9+0.00) lower in formulation 3 (0.4030.03) and was lowest in formulation 2 (0.213003). The values for total body clearance was lowest i e., 0.2410.00 in formulation 1, higher in formulation 2 i.e., 0.353005 and still higher in formulation 3, i.e., 0.6210.02. By taking the formulation I, as standard (100%), the relative bioavailabilities of formulation 2 and 3 were 79.05 and 38.53% respectively.

INTRODUCTION

Cotrimoxazole combines the antimicrobial properties of sulfamethoxazole and trimethoprim. This product is being used against most of the infections like urinary tract infection, respiratory tract infection. Brucellosis, Staphylococcus infections, typhoid fever. Gonorrhea, Cholera and septicemia caused by Gram me bacteria. Sulfamethoxazole is well absorbed after oral administration. Peak blood levels are obtained within one hour in rats and 2.83-4.0 hours in dogs (Muzaffar *et al,* 1986) and 2 hours in humans (Kaplan *et al.,* 1973). The absolute bioavailability of sulfamethoxazole in human is approximately 85% (Reber *et al.*. 1963) and 80% in dogs (Lazaro *et al,* 1980). This product is being marketed by both International and National firms for a long period of time. Experience with the medical profession have shown that certain brands are more effective than others. The present study was, therefore, conducted to evaluate the difference in bioavailability of sulfamethoxazole in various formulations of cotrimoxazole suspensions being manufactured by National and Multinational pharmaceutical companies in Pakistan.

MATERIALS AND METHODS

Three different brands of colrixomazole suspensions (400mg SMZ + 80mg TMP/10m1) were taken from the market and designed as formulation 1, 2 and 3. Description of these formulations have been given below:

Formulation l:
Septran Suspension (Wellcome Pakistan Ltd., Karachi).

Formulation 2:
Mactran Suspension (Matter Pharmaceuticals (Pvt.) Ltd., Karachi-Pakistan.

Formulation 3:
Suptrex Suspension (The Schazoo Laboratories Ltd., Lahore-Pakistan).

The experimental subjects were six male healthy volunteers between 60-66 kg body weight and the age 27-30 years. All the volunteers were advised verbally not to take any kind of medicine one week before the experiment. On the day of experiment, the subjects were fasted over night and the drug was given on an empty stomach. Each volunteer was administered 10 ml suspension orally after thorough shaking of the bottle. Half a glass of water was allowed to drink after the dose. A light breakfast was then allowed after one hour of the dose. A washout period of atleast 10 days was given between each of the formulations. Samples of blood were collected from forearm vein immediately before dosing and thereafter at 0.5, 2.0, 3.0, 4.0, 8.0 and 12.0 hours with the help of disposable syringes after oral drug administration. The samples were centrifuged at 3000 rpm, plasma was separated and kept at 4^0C until analysis.

The spectrophotometer method for the estimation of sulfamethoxazole in biological fluids was used for the assay of sulfamethoxazole devised by Bratton and Marshall (1939). Using spectrophotometric method for in-vivo estimation of trimethoprim, the results could not obtained as this method works only if the volume of the sample is large.

The plasma sulfamethoxazole time data were analyzed for each subject for the calculation of various parameters, using non- linear least square regression implemented in PK-II, a software for phannacokinetic analysis, ran on IBM compatible computer (PK-II, 1988).

Mean values, standard errors of mean (SEM) for each parameter using a computer programme of "SPSS" for window 6 (release 1993). A $P<0.05$ being taken as statistically significant (SPSS, 1993).

RESULTS AND DISCUSSIONS

The mean ± SEM plasma concentration - time data were determined for sulphamethoxazole in all of the three cotrimoxazole suspensions and are presented in table I. These results have been graphically shown in Fig I. The pharmacokinetic parameters of sulphamethoxazole in humans after a single oral dose can be best described by one compartment open model which is in agreement with the results reported by Notle and Bottler (1974). The disposition kinetic parameters of sulphamethoxazole which describes absorption, distribution and elimination in normal human subjects are given in table 2. This table also reflects the statistical difference among all the brands examined. The mean peak plasma concentration of sulphamethoxazole 89.6730 84 and 1650±0.89 was obtained in 4 hours for brands 1 and 3, respectively while the value for the same parameter for brand 2 was 38.3330.50 reached half hour earlier than both of the brands examined. Thus the t_{max} values for brands 1 and 3 are statistically different from that of the brand 2. As indicated from the results the dung was rapidly released from the formulation of brand 2. All the three brands demonstrated statistical difference in the measured values for peak plasma concentration (C_{max}), total body clearance (Cl_B) and Va. the brand 1 have the highest values as compared to the brand 2 and 3. Reverse in the case for the Cl_B values where brand 3 has the highest values (0.62±0.02) as compared to brand 2 and 1 (035±0.05) and 0.24±0.00), respectively. When brand 2 and 3 were compared to brand I. a statistically significant difference was observed for mean residence time and elimination half-life. With respect to area under the plasma level-time curve and absorption half-life. brand 3 demonstrated statistical difference while no difference was observed between brand I and that of 3. In case of first moment plasma level-time curve, brand 2 was observed to be different from that of brand 3.

Area under the plasma level time-curves were used as measure of bioavailability. Taking formulation 1 as standard relative bioavailability of brand 2 and 3 was observed to be 79.05% and 38.53%, respectively.

In current practice, a drug is considered equivalent if the absorption lies within a range no more than 320% of the standard dung. In this context brand 3 can not be considered to be bioequivalent to brand 1.

Table 1

Plasma drug concentration-time data for sulphamethoxazole given orally in the form of cotrimoxazole suspension to six human volunteers at the dosage level of 10 ml to each individual

Formulation 1

Time (Hr)	0.5	2.0	3.0	4.0	8.0	12.0
Mean±SEM	33.75 ±0.42	41.67 ±0.81	47.25 ±0.60	89.67 ±0.84	31.75 ±0.74	25.67 ±0.89

Formulation 2

Time (Hr)	0.5	2.0	3.0	4.0	8.0	12.0
Mean±SEM	20.17 ±1.86	28.92 ±4.12	36.83 ±6.29	36.50 ±5.41	24.50 ±4.45	20.67 ±4.27

Formulation 3

Time (Hr)	0.5	2.0	3.0	4.0	8.0	12.0
Mean±SEM	9.50 ±1.10	12.08 ±1.0	14.25 ±1.20	16.50 ±0.89	13.67 ±0.87	10.83 ±0.48

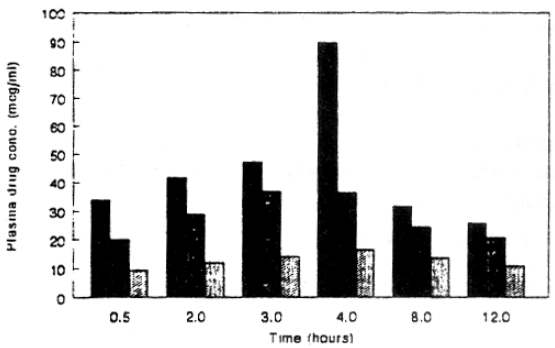

Figure 1: Plasma concentration of sulfamethoxazole in six volunteers after an oral dose of 10 ml suspension.

Formula 1 Formula 2 Formula 3

Table 2

Mean±SEM values for the disposition kinetics and bioavailability parameters of sulphamethoxazole after a single oral administration of cotrimoxazole suspension (400 mg SMZ + 80 mg TMP)

Kinetic Parameters	Formulation 1	Formulation 2	Formulation 3
$t_{1/2}$ abs (hours)	1.92 ± 0.05	1.80 ± 0.41^{ns}	2.78 ± 0.25*
$t_{1/2}$ elim (horus)	4.54 ± 0.15	7.50 ±0.94*	7.43 ± 0.25*
Cl_B (ml/min/kg)	0.24 ± 0.00	0.35 ± 0.05*	0.62 ± 0.02*
V_d (lit./kg)	0.90 ± 0.00	0.21 ± 0.03*	0.40 ± 0.03*
T_{max} (Hours)	4.00 ± 0.00	3.50 ± 0.22*	4.00 ± 0.00^{ns}
C_{max} (µg/ml)	89.67 ± 0.84	38.33 ± 0.59*	16.50 ± 0.89*
$AUC_{o-\infty}$ (µg/h/lit)	704.52 ± 11.83	556.92 ± 103.95^{ns}	271.50 ± 9.99*
$AUMC_{o-\infty}$ (µg/h^2/lit)	5936.37 ± 265.19	7469.21 ± 1765.82^{ns}	3567.24 ± 191.01^{ns}
MRT (hours)	8.41 ± 0.24	12.76 ± 1.42*	13.19 ± 0.71*
Relative Bioavailability	100%	79.05%	38.53%

* - Statistical significant ($P<0.05$), when formulation 1 is kept as standard.

ns - Statistical nonsignificant ($P<0.05$), when formulation 1 is kept as standard.

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