Mar.Üniv.Ecz.Der.,
8 (1), 13-21 (1992)

J.Pharm.Univ.Mar.,
8 (1), 13-21 (1992)

CO–TRIMOKSAZOL ORAL SUSPANSİYON FORMLARININ BİYOYARARLILIĞI

BIOAVAILABILITY OF CO–TRIMOXAZOLE ORAL SUSPENSIONS

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SUMMARY

In vivo absorption characteristics of co–trimoxazole (sulfamethoxazole–trimethoprim) from four commercially available oral suspensions have been studied. The absorption rate constanat ranges for trimethoprim were $21.3 \pm 2.8 \times 10^{-2}$ hr to $32.2 \pm 3.0 \times 10^{-2}$ hr while for sulfamethoxazole the ranges were $25.8 \pm 2.7 \times 10^{-2}$ hr to $32.1 \pm 2.2 \times 10^{-2}$ hr. variations between products were observed. However, it is possible that these variations reflect eitheir intersubject variations or variations in product performances.

ÖZET

Bu çalışmada piyasada bulunan sülfametoksozol ve trimetoprim oral suspansiyon formlarının in vivo absorbsiyon karakteristikleri araştırılmıştır. Trimetoprim için absorbsiyon hız sabiti $21.3 \pm 2.8 \times 10^{-2}$ saat ile $32.2 \pm 3.0 \times 10^{-2}$ saat arasında saptanırken bu değerler sulfametoksazol için $25.8 \pm 2.7 \times 10^{-2}$ saat ile $32.1 \pm 2.2 \times 10^{-2}$ saat arasında bulunmuştur. Ürünler arasında farklılıklar gözlenmiştir. Bu farklılıklar olgular arasındaki farklılıklardan veya ürünlerin performansları arasındaki farklardan ileri gelebileceği düşünülmektedir.

INTRODUCTION

Co–trimoxazole [sulfamethoxazole (SMZ) – Trimethoprim (TMP)] is widely used in the treatment of variety of gram–negative and gram–

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positive infections (1). The combination of these two drugs has a synergistic bactericidal effect (2). Welling et al (3) showed that SMZ and TMP revealed first order pharmacokinetic characteristics in humans.

Both SMZ and TMP are very slightly water soluble with aqueous solubilities of 0.5 μg/ml and 0.4 μg/ml, respectively at 25 C° (4).

Co–trimoxazole is available on the market in different dosage forms like tablet, suspension and, injection. Numerous studies have repoted the bioavailability characteristic of Co–trimoxazole when it is administered orally (3), or by intravenous infusion (5).

In our laboratory in vitro and in vivo evaluations of four Co–trimoxazole oral suspensions were performed (6). Rabbit was used as in vivo model. The results showed that in vitro dissolution and absorption profiles for both drugs were similar for all four products. While in the in vivo rabbit model, two to three–fold varitions in C_{max} and T_{max} values were observed.

Due to the lack of information on bioavailability of Co–trimoxazole in liquid oral suspensions, this study was conducted to evalute the bioavailability of these products in humans volunteers.

EXPERIMENTAL and METHODS

A. Materials

SMZ, TMP and glycine were obtained from S.D.I., Iraq. Sodium hydroxide and chloroform were obtained from (Merck, F.R.G.). Four oral suspensions, each containing 8 mg TMP and 40 SMZ ml, were procured commercially and are subsequently referred to as products A, B, C and D.

B. Equipment

UV SP6–550 (Pye Unicam uv/vis Spectrophotometer, England); Vortex (Heidolph Reax 1, W. Germany); Shaker (SM, Labsco, W. Germany); pH meter (WTW pH 530, W. Germany); Centrifuge (mlw T30, G.D.R).

C. Standards

Human urine were spiked with known amounts of TMP and SMZ to give certain concentrations (TMP range 1 – 10, μg/ml and SMZ range 50 – 500 μg/ml). These samples were subjected to extraction and analyses as described below.

D. Human studies

From each product 0.2 ml/kg, of well shaked suspension was orally administered to healthy men volunteers, weighing 70 – 88 kg. The urine was collected at the following time intervals : 1, 2, 4, 6, 9, 12, 21 and 24 hours and it's volume was recorded each time. Two ml of urine from each sample were transferred to an analytical stoppered–glass centrifuge tube, and subjected to the extraction procedure (6).

E. Extraction and analysis of SMZ and TMP (6)

The spectrofluorometric method of Lichtenwalner el al (7) was modified for the extraction and spectrophotometric analysis of SMZ and TMP in buffered aqueous solutions. Each 2 ml sample was transferred to a 15 ml glass–stoppered centrifuge tube and 0.3 ml of a 0.1 M glycine–sodium hydroxide buffer (pH 9.5) was added. Each solution was vortexed for several seconds followed by the addition of 4 ml of chloroform to each tube, and the tubes were shaken for 5 min on a horizontal mechanical shaker (S.M., Labsco, F.R.G.) at approximately 100 oscillations per min. The tubes were then centrifuged at 2000 x g for 10 min. The concentrations of SMZ and TMP in the upper aqueous and lower organic layers, respectively, were determined spectrophotometrically at their corresponding absorption wavelength maxima of 255 and 275 nm Ethanolic stock solutions containing 1 mg/ml TMP or SMZ were used to prepare a series of standard solutions for each drug in urine. Standard curves were prepared from combinations of known concentrations of the two drugs, using the same seperation and analysis methods described above. Concentrations of the drugs in the samples were determined from these working standard curves. Extraction efficiencies for both drugs were greater than 80 %.

RESULTS AND DISCUSSION

Four Co–trimoxazole oral suspensions found on the market were used in this study. The physical properties of these products were determined in our laboratory and is shown in Table 1 (6).

Fig (1), represents the calibration curves for TMP and SMZ extracted from human urine. The C.V. = 0.999. The standard curves are linear at concentration ranges studied (SMZ : 12 – 500 µg/ml and TMP : 1 – 10 µg/ml). Extraction efficiencies for both drugs are greater than 80 %.

Table – 1 : Physical properties of co–trimoxazole suspensions

Product	Viscosity (P)	Sedimentation volume after 24 h	Color
A	1.12	0.91	light pink
B	0.88	0.92	pink
C	1.65	0.90	milky white
D	1.43	0.92	pink

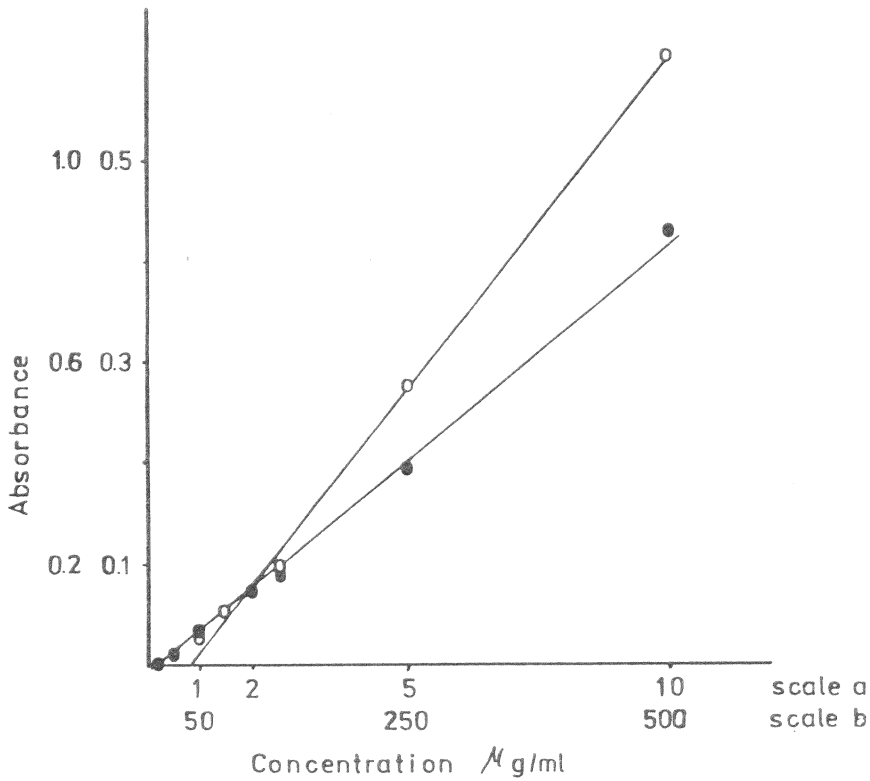

Fig. – 1 : Calibration curves of TMP (scale a) and SMZ (scale b) in human urine.
O : TMP ● : SMZ

Table 2, gives the urine output from human volunteers after taking the oral suspensions at different time intervals within 24 hr. The cumulative percent of SMZ and TMP excreted unchanged in urine within 24/hr is shown in Table 3.

Table – 2 : Urine output (ml) from human volunteers after taking different co–trimoxazole product

	PRODUCT											
	A			B			C			D		
Time	1	2	3	1	2	3	1	2	3	1	2	3
1	55	105	42	54	36	53	56	154	64	38	53	70
2	49	325	48	30	80	72	44	66	59	30	33	47
4	75	160	124	124	260	217	64	90	86	57	47	88
6	81	110	310	150	85	70	63	64	59	70	28	89
9	147	165	163	122	350	172	128	100	98	69	58	145
12	134	180	73	90	78	125	72	106	56	160	102	135
21	350	360	310	370	255	293	330	260	370	490	312	390
24	90	105	234	72	240	298	61	108	90	138	128	138

Table – 3 : Percentage of the drug excereted in urine within 24 hours.

Product	TMP	SMZ
Product A	19.5±1	52±10
Product B	21.5±2	55±10
Product C	9±4	65±4
Product D	11.5±2	31±6

The percentage amount of TMP excreted was between 21.5 ± 2 and 9 ± 4 while percentage amount of SMZ excreted was between 65 ± 4 and 31 ± 6. There is a large variation between products and these differences may bu due to biological variations or due to formulations. Large variations between products were observed also in our previous study using in vivo rabbit model (6).

The absorption and elimination rate constants (Ka and K) can be determined from urinary excretion data employing the sigma–minus method (9) according to the equation below.

$$X_u^{\infty} - X_u = \frac{X_u X_a}{K_a - K} - \frac{K_t}{2.303}$$

Where X_u^∞ is the amount of drug ultimately eliminated in the urine, X_u is the cumulative amount of drug eliminated in urine at time t.

In the common logarithmic form the equation becomes.

$$\log\left(X_u^\infty - X_u\right) = \log \frac{X_u^\infty - K}{K_a - K} - \frac{K_t}{2.303}$$

A plot of log ($X_u^\infty - X_u$) against t according to this relationship is illustrated in Fig 2,3, from which, the pharmacokinetic parameters K_a

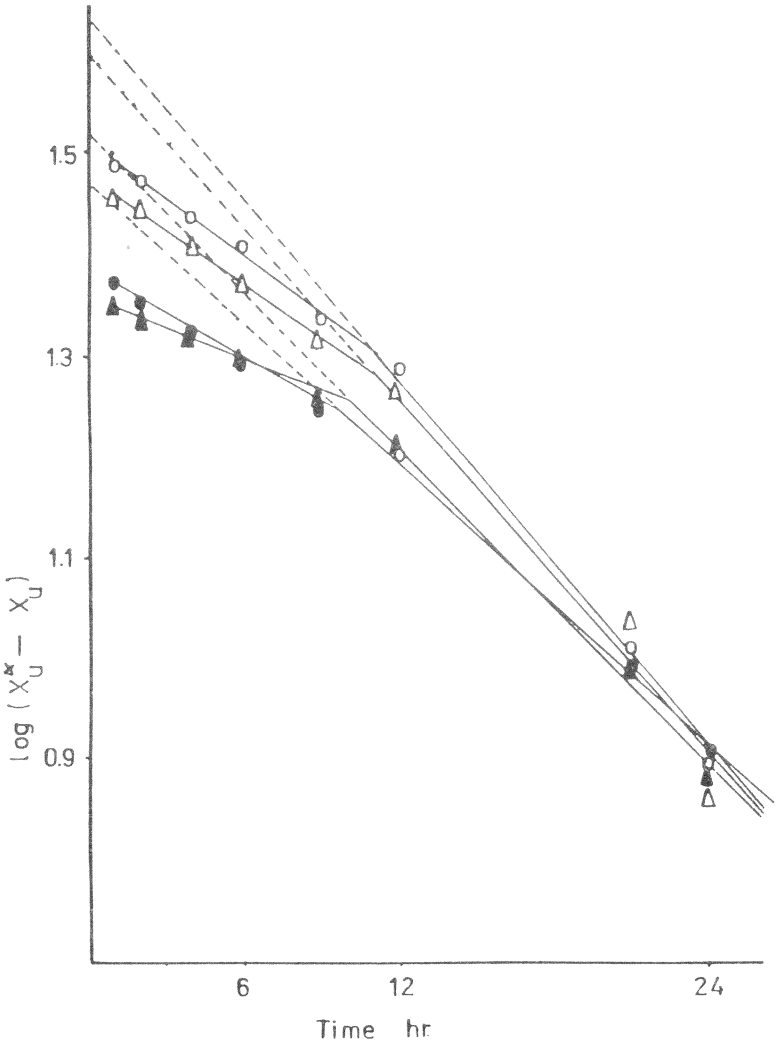

Fig – 2 : TMP in human urine (mean of three readings).
O : product A, Δ: product B, ● : product C, ▲ : product D.

and K are calculated. These parameters are given in Table 4. The K_a For TMP ranged between 21.31 ± 2.8 x 10^{-2} hr and 32.2 ± 3.0 x 10^{-2} hr while For SMZ this range was (25.8 ± 2.1 – 32.1 ± 2.2) x 10^{-2} hr.

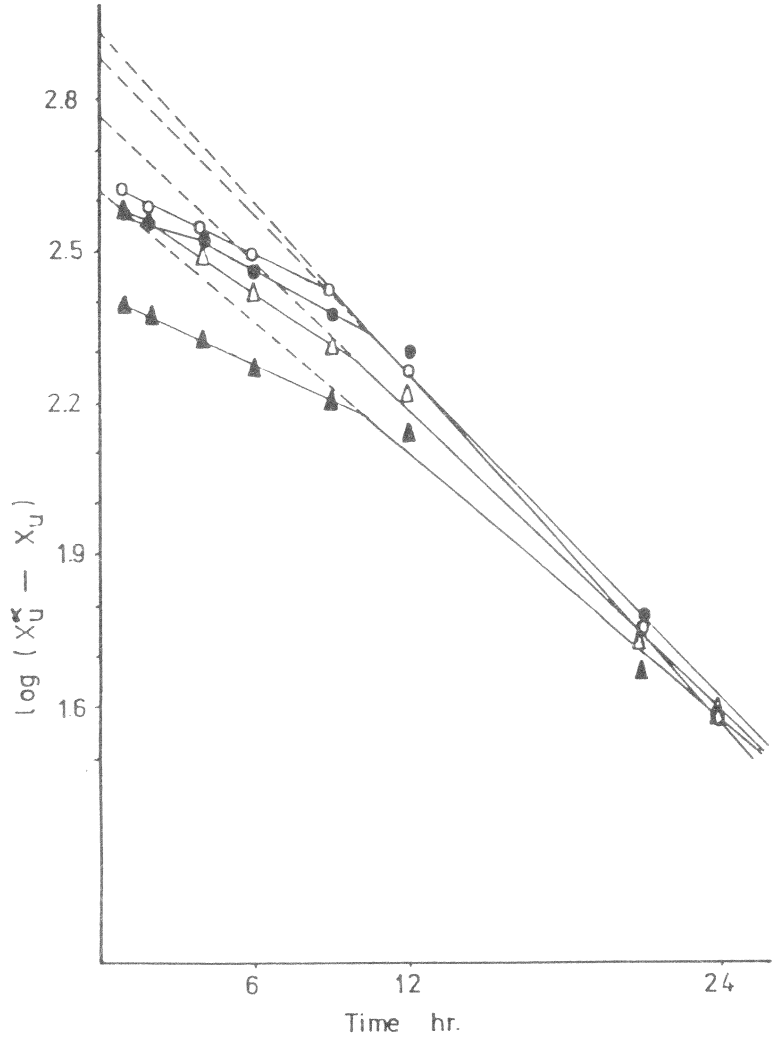

Fig – 3 : SMZ in human urine (mean of three readings).
O : product A, Δ: product B, ● : product C, ▲ : product D.

Table – 4 : Average urine parameters following oral administration of each product for three human volunteers ± s.d.

	Product			
Parameter	A	B	C	D
K_e hr. (x10-2)				
TMP	6.83±0.5	6.64±0.7	5.23±0.8	5.89±0.6
SMZ	12.97±0.4	11.28±0.4	12.3±1.8	10.06±0.5
$t_{1/2e}$ hr.				
TMP	10.2±0.7	10.43±1.3	13.6±1.9	11.92±1.38
SMZ	5.37±0.17	6.17±0.21	5.77±0.82	6.93±0.37
K_a hr. (x10-2)				
TMP	26.5±1.0	29.3±2.0	32.2±3.0	21.31±2.8
SMZ	26.55±3.9	32.1±2.2	25.8±2.7	25.97±4.3
$t_{1/2a}$ hr.				
TMP	2.63±0.2	2.57±0.69	2.3±0.5	3.33±0.39
SMZ	2.70±0.37	2.2±0.29	2.74±0.33	2.73±0.45

K_e : elimination rate constant, K_a : absorption rate constant

The values for absorption rate constants indicate a variation in absorption of the drug (TMP and SMZ) from different brands. However, it is possible that these large variations reflect inter–subject variations rather than variations in product performances. Considerable inter–subject variations in absorption rates of SMZ and TMP in human have been reported in the literature (8).

The results of this study are well correlated with our previous in vivo study using rabbit as an animal model (6).

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(Received February 5, 1992)