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BIOAVAIL ABILITY OF SULFAMETHOXAZOLE-TRIMETHOPRIM FROM TABLETS: Comparison of In Vitro and In Vivo Results(การศึกษาชีวประสิทธิผลของยาเม็ด sulfamethoxazole-trimethoprim: เปรียบเท...

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ORIGINAL ARTICLE

BIOAVAILABILITY OF SULFAMETHOXAZOLE-TRIMETHOPRIM FROM TABLETS: Comparison of *In Vitro* and *In Vivo* Results

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ABSTRACT

Ten single lots of 400-mg sulfamethoxazole and 80-mg trimethoprim tablets, manufactured by various companies, were evaluated for their *in vitro* quality according to the specifications of the United States Pharmacopoeia and the British Pharmacopoeia. All ten products met the British requirements whereas only nine products conformed to the United States specifications. Five products the dissolution behaviours of which were appreciably different were selected for further *in vivo* study. The *in vivo* bioavailability studies were performed in 18 healthy volunteers following administration of single 800-mg sulfamethoxazole and 160-mg trimethoprim. The products were evaluated with respect to plasma levels at various times up to 24 h following dosing, areas under plasma level-time curve, peak plasma concentrations, times of peak level, lag times, mean residence times, and relative bioavailability. Only the product with the least dissolution showed a potential trimethoprim bioavailability problem as indicated by the significantly longer lag time and mean residence time and lower relative bioavailability as compared with the reference product. No bioavailability problem of sulfamethoxazole was observed in any products tested. The correlation between *in vitro-in vivo* data and the implications of the study have been discussed in details.
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KEY WORDS : Sulfamethoxazole Trimethoprim Bioavailability Dissolution *In vitro-in vivo* correlation

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INTRODUCTION

The combination of sulfamethoxazole and trimethoprim in a 5:1 ratio has been widely used for the treatment of various infections in man (1-3). The principal advantages claimed in the use of the drug combination, compared with single drug therapy, are the reduction in overall drug minimum inhibitory concentration (MIC) values, increase in antibacterial activity and decrease in risk of the emergence of resistant strains (4). The antibacterial synergism of these two compounds has been attributed to sequential blockades of the bacterial enzyme system associated with folate metabolism.

During the past few decades, much concern has been raised, both locally and internationally, regarding the bioavailability of a drug product since differences in the bioavailability of the drug products from different manufacturers may affect therapeutic results (5-6). Recently, the World Health Organization (WHO) has issued a proposed list of drug substances exhibiting problems in bioavailability (7). Trimethoprim-sulfamethoxazole combination is among those in the list. To date, there has been a study in Germany demonstrating the potential bioavailability problem of trimethoprim, but not sulfamethoxazole in sulfamethoxazole-trimethoprim tablets or capsules (8). In that study, three local products were compared with the original "Bactrim" product in eight healthy volunteers. No other study of the bioavailability problem of sulfamethoxazole or trimethoprim in this particular combination has been reported elsewhere. It is thus an aim of this study to investigate extensively the relative bioavailability of sulfamethoxazole and trimethoprim products locally manufactured in Thailand, in comparison with the so-called innovator product.

Since determination of the bioavailability of a dosage form is costly and involves use of human volunteers, there have been several attempts to develop an *in vitro* test, usually a dissolution test, as a predictive model for the *in vivo* bioavailability (9-10), as reflected in the proliferation of such test in the current version of the United States Pharmacopoeia (USP XXII) and of the British Pharmacopoeia (BP 1988). For sulfamethoxazole-trimethoprim tablets, the dissolution test is required by the USP XXII, but not by the BP 1988. In the previous report (8), the *in vitro-in vivo* correlation has been found for trimethoprim, indicating the need for the dissolution test requirement. However, the *in vitro* dissolution system used in that study was different from that in the USP XXII. Thus, this report also aimed to study the correlation between the existing USP XXII dissolution test and the *in vivo* bioavailability data of trimethoprim and sulfamethoxazole tablets.

METHODS

In-vitro studies

Material Ten single lots of 400-mg sulfamethoxazole and 80-mg trimethoprim tablets locally man ufactured by 10 different companies were purchased from a drug wholesaler. One of these product (Product No.1) which was the innovator product (Bactrim^{R}) manufactured by Olic (Thailand) Limited under the authority of Hoffmann-La Roche & Co. (Switzerland) was used as the reference product.

Procedure The official requirements of B.P. 1988 and USP XXII were followed. Each product was tested for contents of sulfamethoxazole and trimethoprim, uniformity of weight, disintegration, and dissolution. Tablet dissolution rates were determined by the USP paddle method (medium : 0.1 NHCl, stirring rate: 75 rpm) and expressed as times that about 50% of the active ingredients was released from the tablet (TD50). Mean dissolution time (MDT) for each component was also estimated using the model independent method of Tanigawara *et al.* (11).

In-vivo studies

Product selection Five products exhibiting different dissolution profiles were selected from the *in vitro* studies. (See Results and Discussion for detail.)

Subject selection Subjects were 18 healthy male volunteers between 25 to 39 years of age (mean of 30) and weighing between 48 to 85 kg (mean of 60.6) and height of 155 to 185 cm (mean of 167). Before participation in the study, each subject underwent physical examination and blood and urine biochemistry analyses to ensure their good health. All subjects were instructed to take no medications 1 week prior to and during the study.

Study design The study protocol was approved by the Ethical Committee on Human Research, Ministry of Public Health, Thailand. Each individual subject was given, in a randomized cross-over design, 2 sulfamethoxazole-trimethoprim tablets, on 5 occasions, with a minimum of 1-week interval between successive experiments. The tablets were administered in the morning with about 200 ml of water following overnight fasting. Food

was allowed after 3h of dosing. Venous blood samples (2 ml) were collected into heparinized glass tubes immediately before and at 10, 20, 40 min, and 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 h after oral dosing. Plasma samples were separated and stored frozen until analysis.

Analytical method Concentrations of sulfamethoxazole and trimethoprim were determined by an HPLC procedure. The method consisted of simple deproteinization of a plasma sample with acetonitrile (0.1 ml plasma : 0.2 ml acetonitrile) followed by a 25-μl injection of the supernatant onto a 10- μ C_{18} reversed phase column (30 cm x 3.9 mm, serial no. P8298 C31, Waters). The mobile phase was a mixture of acetonitrile and 0.03 M ammonium phosphate buffer, pH >6.4 (22 : 78 v/v) and flowed at the rate of 1.4 ml/min. The eluent was monitored with a UV detector at 232 nm. Peak heights were used for quantitation. The specificity of the method was confirmed by the absorbance-ratio procedure (12). This method has sensitivity of 0.5 μg/ml of sulfamethoxazole and 0.14 μg/ml of trimethoprim. The intra-day coefficients of variation ranged between 2-7%.

Data analysis The 5 products were compared on the following bases: the area under the plasma concentration time curve up to the last sample time point (AUCt) and extrapolated to infinity (AUCα), the maximum plasma concentration achieved (Cmax), the time to reach that maximum concentration (Tmax), the elapsed time between dosing and the first detectable concentration or higher (Tlag), the mean residence time (MRT), and the relative bioavailability (Frel). The AUCt was calculated using the trapezoidal rule and the AUCα was determined by adding Ct/kel to AUCt, where Ct is the concentration at the last sampling time and kel is the terminal elimination rate constant obtained by using linear regression analysis of the natural logarithm of the terminal portion of the concentration-time curve. The Cmax and Tmax were obtained directly from each individual plasma profile. The MRT was determined using the statistical moment theory (13). The Frel was estimated using AUCα values corrected for the intra-individual variation in the elimination rate constants.

$$Frel_i = \frac{AUC_{\alpha i} \cdot kel_i}{AUC_{\alpha 1} \cdot kel_1}$$

where i is either of product 2, 3, 4 or 5; and 1 is of the reference product.

Statistical analysis The multivariate analysis of variance (MANOVA) with randomized block design was performed on a digital computer using the SPSS^x (14). Contrast subcommands were used for multiple comparison tests. Statistical significance between products was defined at $p = 0.05$.

RESULTS AND DISCUSSION

In Vitro Studies

All ten products tested met the BP 1988 standard for sulfamethoxazole-trimethoprim tablets, whereas only nine products passed all the USP XXII specifications. The amounts of trimethoprim and sulfamethoxazole in all the products tested were within the officially acceptable limits of both BP 1988 and USP XXII. They also passed the specified BP 1988 and USP XXII tests for weight variation. All products complied with the BP 1988 disintegration test; the least disintegrating product, product 4, disintegrated within 4 minutes. With respect to the USP XXII dissolution test, nine products conformed to the specification; both sulfamethoxazole and trimethoprim dissolved more than 70% within 1 h. Product 5 failed the test, releasing only 37.4% of sulfamethoxazole and 57.7% of trimethoprim during the 1-h period. Thus, product 5 was classified either as a qualified product according to the BP 1988 or a substandard product according to the USP XXII.

Table 1 Results of *In Vitro* Dissolution

Product	Trimethoprim				Sulfamethoxazole			
	F10min (%)	F60min (%)	TD50 (min)	MDT (min)	F10min (%)	F60min (%)	TD50 (min)	MDT (min)
1	98.2 ± 1.6	-	< 2	1.7	93.4 ± 1.2	99.8 ± 0.8	3.5	4.2
2	102.1 ± 3.2	-	< 2	ND[a]	100.1 ± 1.5	-	< 2	ND
3	93.9 ± 2.4	-	2	3.3	51.2 ± 2.1	99.2 ± 3.0	9	14.7
4	74.5 ± 7.7	99.6 ± 6.1	5	7.6	36.9 ± 4.7	97.2 ± 3.8	14	15.9
5	30.6 ± 5.1	57.7 ± 7.6	40	90.2	12.5 ± 2.8	37.4 ± 8.7	> 60	145.4
6	99.7 ± 2.1	-	< 2	1.1	92.0 ± 2.7	96.5 ± 0.7	< 2	7.2
7	99.8 ± 2.2	-	< 2	ND	79.2 ± 1.0	96.8 ± 2.1	2	10.2
8	97.5 ± 1.6	100.3 ± 1.8	< 2	2.6	50.1 ± 4.4	98.5 ± 2.4	10	16.5
9	97.6 ± 0.9	101.0 ± 0.7	< 2	0.9	87.1 ± 1.6	100.5 ± 0.7	4	3.3
10	96.4 ± 2.5	101.2 ± 1.6	< 2	2.0	95.0 ± 1.8	99.9 ± 3.4	< 2	2.9

[a] Not determined.

Table 1 shows the dissolution characteristics of all 10 products under study. It appears that trimethoprim dissolved more rapidly than sulfamethoxazole. Within 10 min, more than 70% of trimethoprim was obtained in nine products, whereas approximately that of sulfamethoxazole obtained in only six products. According to all *in vitro* parameters, i.e. the amount dissolved within 10 min (F10), TD50 and MDT of both components, product 5 was evidently the product with the slowest dissolution rate. When only the parameters of sulfamethoxazole were used for classification, products 3, 4 and 8 could be grouped as products having intermediate dissolution rate. It is of interest to note that product 2 exhibited exceptionally fast dissolution, releasing virtually all trimethoprim and sulfamethoxazole within 2 minutes. Since it was desirable that products possessing markedly different *in vitro* dissolution characteristics were studied, in comparison with their *in vivo* bioavailability, products 2, 3, 4 , 5, and 1 were selected for further *in vivo* studies. The dissolution profiles of trimethoprim and sulfamethoxazole of these 5 products were depicted in Figures 1 and 2, respectively.

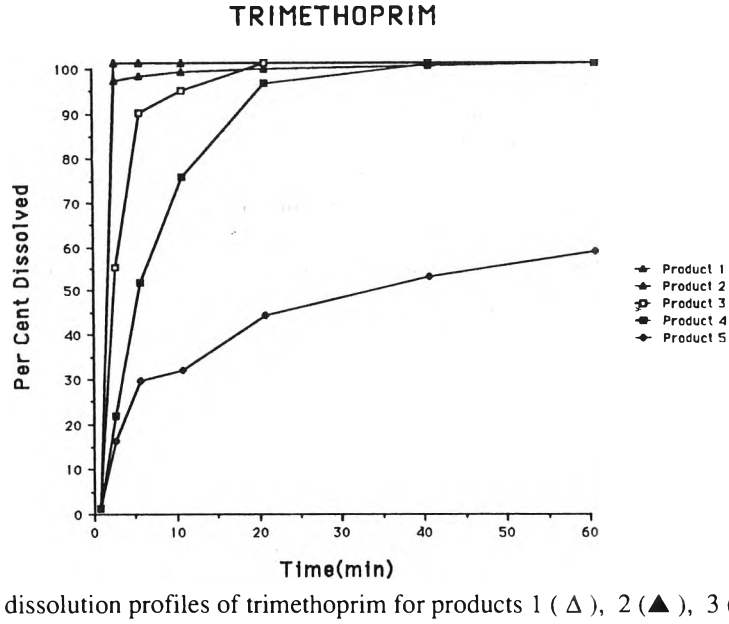

Fig. 1 Mean (n=6) dissolution profiles of trimethoprim for products 1 (Δ), 2 (▲), 3 (□), 4 (■), and 5 (○).

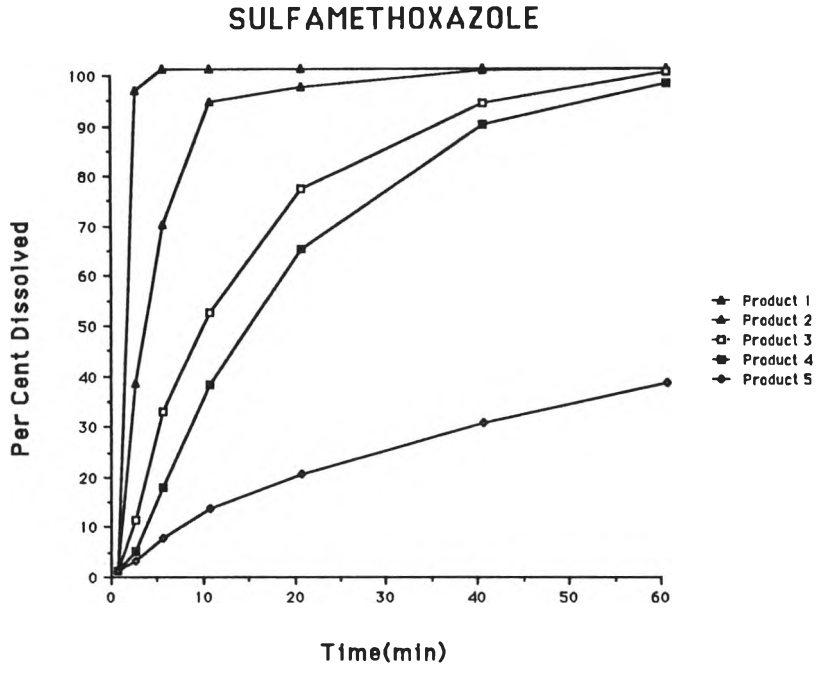

Fig. 2 Mean (n=6) dissolution profiles of sulfamethoxazole for products 1 (Δ), 2 (▲), 3 (□), 4 (■), and 5 (○).

In Vivo Studies

The mean plasma trimethoprim and sulfamethoxazole concentrations-time profiles following administration of 160 mg trimethoprim and 800 mg sulfamethoxazole from 5 different tablet products are shown in Figures 3 and 4. Unlike the *in vitro* dissolution profiles, only slight differences were observed among the plasma profiles of the 5 products. However, careful inspection of individual data revealed significant difference ($p < 0.05$) in the plasma levels obtained at certain sampling times. For trimethoprim, the significant difference was observed during the first 40 min of dosing and for sulfamethoxazole during 2 h (Table 2). At 10 min after dosing, the trimethoprim level was very low in most of volunteers following all 5 products. The measurable trimethoprim concentrations were only obtained in 2 volunteers following products 5 and 4, and in 4, 6 and 8 volunteers following products 3, 1 and 2, respectively. The trimethoprim level from product 5 was significantly lower than those from products 1 and 2 at 20 min after dosing and lower than those from products 3, 1 and 2 at 40 min. For sulfamethoxazole, the plasma levels from product 2 were significantly higher than those from the other 4 products during 20 min after dosing. From 40 min to 1.5 h after dosing, the sulfamethoxazole levels from product 2 were higher than those from products 5 and 1, but indistinguishable from those of products 4 and 3. No significant difference in sulfamethoxazole levels between product 1 and product 5 was observed during any sampling time.

Table 2 Statistic Differences Between Products at Each Sampling Time[a]

	Sampling Time						
	10 min	20 min	40 min	1 h	1.5 h	2 h	3-24 h
Trimethoprim	ND[b]	2 1 3 5 4	3 1 2 4 5	NS[c]	NS	NS	NS
Sulfamethoxazole	2 3 4 1 5	2 4 3 5 1	2 4 3 5 1	2 4 3 5 1	2 4 3 5 1	2 4 5 3 1	NS

a Products underlined by a common line were not found to differ significantly.

b Not determined.

c Not significant.

Table 3 shows the bioavailability parameters of trimethoprim: AUC24, AUCα, Cmax, Tmax, Tlag, MRT, and Frel obtained following 5 different products. The statistical analysis revealed no significant difference in AUC24, AUCα, Cmax, and Tmax among these products. If only these 4 parameters were used for evaluation of the bioequivalency, as usually employed, all 5 products would be bioequivalent, in consistent with the previous report (8). In that report, the bioavailability problem of trimethoprim among products was clearly shown by the differences in AUCα and Cmax. In the present study, the significant differences, although small, were found in the values of Tlag, MRT and Frel. As shown in Table 3 product 5 had the longest Tlag and MRT and the lowest Frel, agreeing with the significantly lower plasma levels found during the first 40 minutes after dosing. These results are indicative of potentially bioequivalent problem of trimethoprim.

Table 3 Bioavailability Parameters of Trimethoprim

Parameter	Product 1	2	3	4	5	Statistic[a]
AUC24	19.28	20.08	19.55	20.26	18.54	NS
(μg.h/ml)	(2.93)[b]	(2.87)	(3.58)	(2.87)	(2.83)	
AUCα	23.16	23.59	23.21	23.91	22.59	NS
(μg.h/ml)	(4.16)	(3.75)	(4.83)	(3.96)	(5.12)	
Cmax	2.0	2.0	2.1	1.9	1.9	NS
(μg/ml)	(0.55)	(0.54)	(0.54)	(0.32)	(0.40)	
Tmax	1.3	1.3	1.3	1.4	1.3	NS
(h)	(0.9)	(0.6)	(0.7)	(0.7)	(0.6)	
Tlag	0.30	0.28	0.34	0.38	0.40	2 1 3 4 5
(h)	(0.13)	(0.12)	(0.14)	(0.12)	(0.16)	
MRT	12.5	12.2	12.4	13.1	13.7	2 3 1 4 5
(h)	(2.5)	(2.2)	(2.1)	(2.3)	(3.8)	
Frel	1.00	1.04	1.01	1.01	0.88	2 3 4 5
		(0.15)	(0.17)	(0.15)	(0.13)	

[a] Products underlined by a common line were found not to differ significantly.

[b] Values in parentheses are standard deviations.

Shown in Table 4 are the bioavailability parameters of sulfamethoxazole from 5 products. All products yielded similar values of AUC24, AUCα, MRT, and Frel ($p > 0.05$). Values of Cmax from products 2 and 4 were significantly higher than those from the other products. In addition, the Tmax of the reference product was surprisingly the longest, suggesting the slowest absorption rate. These findings indicated that the reference product might not be totally bioavailable. As a result, the bioinequivalency of sulfamethoxazole, in relation to the innovator product, was not observed even in product 5 which was classified as substandard according to the USP XXII.

Table 4 Bioavailability Parameters of Sulfamethoxazole

Parameter	Product 1	2	3	4	5	Statistic[a]
AUC24	717.3	730.9	716.0	716.2	702.7	NS
(μg.h/ml)	(114.1)[b]	(108.7)	(122.9)	(103.8)	(88.8)	
AUCα	930.5	942.7	929.7	923.9	920.2	NS
(μg.h/ml)	(206.4)	(193.0)	(222.4)	(201.7)	(183.8)	
Cmax	57.8	62.1	59.1	62.0	58.4	2 4 3 5 1
(μg/ml)	(8.5)	(10.3)	(8.5)	(8.1)	(6.9)	
Tmax	2.9	1.9	2.3	2.0	1.9	2 5 4 3 1
(h)	(0.8)	(1.0)	(0.8)	(0.8)	(0.6)	
MRT	15.8	15.6	15.6	15.5	16.1	NS
(h)	(2.8)	(2.8)	(3.2)	(2.6)	(3.1)	
Frel	1.00	1.00	1.01	1.01	0.98	NS
		(0.15)	(0.17)	(0.16)	(0.13)	

a Products underlined by a common line were found not to differ significantly.

b Values in parentheses are standard deviations.

A summary of relevant pharmacokinetic parameters following the single dose of 800 mg of sulfamethoxazole and 160 mg of trimethoprim derived from 5 products presented in Table 5. Analysis of results of individual data of product 1 in terms of initial estimates of absorption half-times (t1-2a) using the STRIPE programme (15) is also shown. Wide individual variations in all parameters were observed for both compounds. During the absorption process, the variations became more evident; individual Cmax's ranging from 1.4 to 3.4 μg/ml and from 38.9 to 84.9 μg/ml were attained between 0.3 and 3 h and between 0.7 and 4 h for trimethoprim and sulfamethoxazole, respectively. Apparently, trimethoprim absorbed faster than sulfamethoxazole, consistent with earlier studies (16). The mean Cmax's obtained in this study, however, were slightly higher (2 μg/ml of trimethoprim and 60 μg/ml of sulfamethoxazole) as compared with those reported earlier, while the mean Tmax values were somewhat shorter (1 and 2 h of trimethoprim and sulfamethoxazole, respectively) (1,8). The reasons for these discrepancies are not known, but the difference in the body weights of volunteers participated among these studies may be one of possible explanations.

Table 5 Summary of Pharmacokinetic Parameters of Trimethoprim and Sulfamethoxazole Following a Single Oral Dose of 800 mg Sulfamethoxazole and 160 mg Trimethoprim Tablets.

Parameter	Trimethoprim		Sulfamethoxazole	
	Mean ±S.D.	Range	Mean ± S.D.	Range
t1/2a[a] (h)	0.26 ± 0.19	0.07 - 0.64	0.76 ± 0.27	0.36 - 1.22
Cmax (μg/ml)	2.0 ± 0.44	1.4 - 3.4	60.3 ± 9.2	38.9 - 84.9
Tmax (h)	1.3 ± 0.7	0.3 - 3.0	2.2 ± 0.9	0.7 - 4.0
kel (h^{-1})	0.080 ± 0.016	0.049 - 0.128	0.065 ± 0.011	0.041 - 0.098
t1/2 (h)	9.0 ± 1.8	5.4 - 14.2	10.9 ± 2.0	7.1 - 17.0
MRT (h)	12.8 ± 2.5	8.3 - 19.7	15.7 ± 2.8	10.8 - 24.3
C max sulfa / C max tri	31± 7	19 - 50		

a From product 1 only.

The elimination half-lives (t1/2) of trimethoprim and sulfamethoxazole ranged from 5.4 to 14.2 h and from 7.1 to 17 h, with the means of 9 and 10.9 h, respectively. These values were in agreement with those reported earlier (3, 17). The t1/2's of both compounds among the 5 products were found to be statistically comparable in this study. Thus, the difference in the MRT's of trimethoprim observed may be partly attributed to the difference in the absorption rates of these products since the MRT of a given compound reflects the overall behaviour of the compound molecules following an oral administration in the body, including in the GI tract. With faster absorption and elimination characteristic of trimethoprim as compared with those of sulfamethoxazole, the mean MRT of trimethoprim (12.8 h) was shorter than that of sulfamethoxazole (15.7 h).

In spite of the differences in the pharmacokinetic parameters discussed earlier, the plasma profiles of both compounds following any tested products were very similar in shape; their concentration-time profiles were almost parallel. As a consequence, relatively constant ratios of between 1:20 to 1:50 were maintained during the 1- to 24-h period of the single dose. The ratios of their maximum concentrations were also in this range (Table 5). These ratios have been shown to be favorable for the optimum synergistic activity of the combination against many organisms (4).

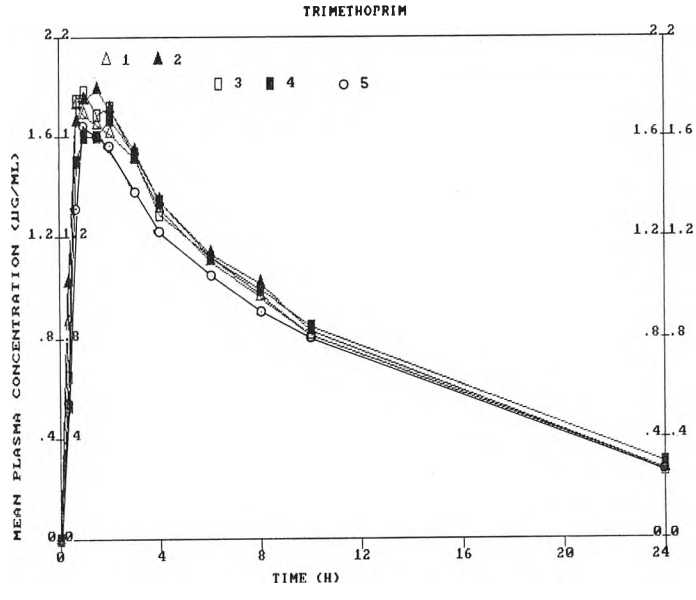

Fig. 3 Mean (n=18) trimethoprim levels as a function of time following products 1 (Δ), 2 (▲), 3 (□), 4 (■), and 5 (○).

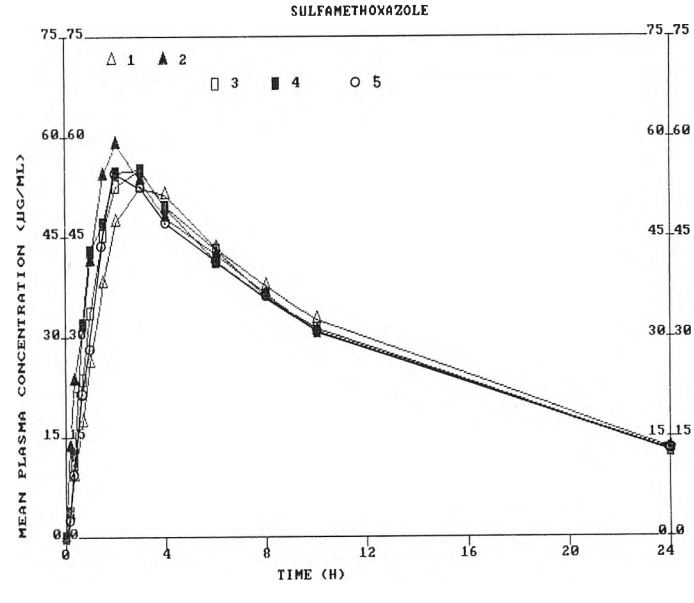

Fig. 4 Mean (n=18) sulfamethoxazole levels as a function of time following products 1 (Δ), 2 (▲), 3 (□), 4 (■), and 5 (○).

In Vitro - In Vivo Correlation

Generally, correlation between *in vitro - in vivo* is judged good when difference in *in vivo* bioavailability observed among products is reflected by similar difference in the *in vitro* test. From the present *in vitro* dissolution results, the *in vivo* bioinequivalency of both components following product 5, as compared with the reference product would be anticipated. For trimethoprim, there was a trend of this correlation, although the in vivo problem was not so prominent as the *in vitro* one. The very slow dissolution rate of trimethoprim caused merely sluggish absorption as reflected by the relatively longer Tlag, and somewhat slow absorption by the longer MRT. More studies on the bioavailability of trimethoprim in the products with poor dissolution rates may be needed before a definite conclusion could be drawn.

For sulfamethoxazole, no *in vitro - in vivo* correlation was found. The reference product the dissolution rate of which was appreciably faster than those of products 3, 4 and 5 was nevertheless the slowest absorption product. In the earlier report (8), products with different sulfamethoxazole dissolution behaviours were found to be bioequivalent. One of possible reasons for there being no correlation may be that the dissolution is not the rate-limiting step in the absorption process of sulfamethoxazole. It may also be possible that the dissolution systems of both the USPXXII which was used in this study and of the previous study (8) were inappropriate. It should be noted, however, that this current dissolution system of the USP XXII (75 rpm) would be better than the previous system in the USP XXI (50 rpm), as the latter would make the dissolution rates of all products become even slower (18), resulting in greater *in vitro - in vivo* discrepancy.

Implications

It is generally preferred that evaluation of bioequivalency of drug products be based on clinical judgement. In antimicrobial therapy, it is important that the MIC of drugs be achieved rapidly and maintained throughout or most of the course of therapy (19). Since the MIC's of trimethoprim and sulfamethoxazole for most susceptible organisms were reported to be 0.15 and 3 μg/ml, respectively, the time to reach and the duration that the concentration remains above these levels would be of particular interest. Based on the present results, all 5 products would present no therapeutic problem, in spite of some differences found in certain parameters. The MIC level of sulfamethoxazole was reached within 10 min after dosing and was maintained throughout 24 h following the single dose of any tested products. Although the times to reach the trimethoprim MIC level were found to be different among products, as indicated by the significant difference in Tlag in this study, the therapeutic inequivalence probably would not be observed since this combination is usually used for long-term treatment. In addition, the significant lower Frel of trimethoprim from product 5, accounting for more than 75% of the reference product in more than 75% of volunteers, may not be judged as bioinequivalent to the reference product according to the USFDA criteria "75/75 rule" (20).

It is thus uncertain that the sulfamethoxazole-trimethoprim tablets, as far as this study is concerned, will present a clinically significant bioavailability problem. The inclusion of this combination in the WHO proposed list of drugs exhibiting bioavailability problems cannot be firmly supported by this study. More studies may be warranted. Nevertheless, it appears that there is a theoretical basis in performing the *in vitro* dissolution test in the routine quality control of these products as it may indicate, to some extent, the bioavailability problem of trimethoprim. Although the current official dissolution test of the USP XXII may practically be used for this purpose, it is probably mostly desirable that a new dissolution test which can provide better *in vitro - in vivo* correlation be developed and employed instead.

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การศึกษาชีวประสิทธิผลของยาเม็ด sulfamethoxazole-trimethoprim: เปรียบเทียบคุณภาพด้าน *in vitro* และ *in vivo*

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บทคัดย่อ

จากการประเมินคุณภาพด้าน *in vitro* ของยาเม็ด sulfamethoxazole 400 มิลลิกรัม trimethoprim 80 มิลลิกรัม จำนวน 10 รุ่น ที่ผลิตจาก 10 บริษัท โดยใช้มาตรฐานของตำรายาประเทศสหรัฐอเมริกา และอังกฤษ พบว่ายาเม็ดทั้ง 10 บริษัท เข้ามาตรฐานตำรายาประเทศอังกฤษในขณะที่ 9 บริษัทเท่านั้นที่เข้ามาตรฐานตำรายาประเทศสหรัฐอเมริกา ได้คัดเลือกยาเม็ดจาก 5 บริษัท ที่มีการละลายตัวต่างกันมาศึกษาด้าน *in vivo* โดยศึกษาชีวประสิทธิผล (bioavailability) ในอาสาสมัครชายสุขภาพดีจำนวน 18 คน ซึ่งได้รับยาเม็ด sulfamethoxazole 800 มิลลิกรัม-trimethoprim 160 มิลลิกรัม จากการประเมินระดับยาในพลาสมาที่เวลาต่างๆ กันจนถึง 24 ชั่วโมง หลังจากได้รับยา, พื้นที่ภายใต้ส่วนโค้งของระดับยาในพลาสมาที่เวลาต่างๆ กัน, ความเข้มข้นสูงสุดของระดับยาในพลาสมา, เวลาที่ระดับยาในพลาสมาถึงจุดสูงสุด, lag times, mean residence times และ relative bioavailability พบว่ายาเม็ดที่มีการละลายตัวช้าที่สุด แสดงแนวโน้มว่าจะมีปัญหาด้านชีวประสิทธิผลของด้วยา trimethoprim ทั้งนี้จากค่า lag time และ mean residence time ที่ยาวกว่าและ relative bioavailability ที่ต่ำกว่าเมื่อเปรียบเทียบกับผลิตภัณฑ์ต้นแบบ ไม่พบปัญหาชีวประสิทธิผลของตัวยา sulfamethoxazole ในยาเม็ดชนิดใดเลย ได้วิจารณ์ความสัมพันธ์ระหว่างข้อมูลการทดลองด้าน *in vitro - in vivo* และการประเมินผลอย่างละเอียดไว้ด้วย (ไทยเภสัชสาร ปีที่ 15(3) : หน้า 187-197 (2533))

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