Table VI—Predicted Effects of Chain Length on Activity Coefficients

Solvent	γ, dynes/cm²	Factor by which Room Temperature Activity Coefficient Decreases with Addition of Methylene Unit to Solute: Predicted	Observed
Water	51.9	3.46	3.31
Glycerin	35.2	2.19	2.13
Formamide	31.1	2.11	1.73
Ethylene glycol	19.3	1.59	1.69
Propylene glycol	12.5	1.35	1.33
Methanol	4.2	1.10	1.24
Ethanol	0	1.00	1.13

phobic surface area (Eqs. 1 and 12).

An interesting and important consequence of Eq. 16 is that the relative ability of the various cosolvents to solubilize a drug is independent of the drug (provided that it is sufficiently hydrophobic for this treatment to be applicable) and is related only to $\Delta\gamma^0$. Therefore, for any very insoluble drug, ethanol will be the most efficient solubilizer of the solvents considered, with the other solvents following in the order listed in Table IV.

SUMMARY AND CONCLUSIONS

The solubility of poorly water-soluble compounds in mixed aqueous solvents is treated as a linear combination of terms representing the pairwise interactions of each solvent component with each topographical component of the drug.

The interactions involving the hydrophobic portion of the solute are the major factors that determine how well it can be solubilized, and these interactions can be related directly to the interactions of a pure liquid hydrocarbon with the solvent components.

On this basis, an equation is derived that explains the exponential increase in the aqueous solubility of insoluble drugs with the addition of a cosolvent. This equation further predicts that the magnitude of the increase in solubility produced by the cosolvent is exponentially related to the surface (interfacial) properties of the solvent components and the hydrophobic surface area of the solute.

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Bioavailability of 11 Sulfisoxazole Products in Humans

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Abstract □ Single lots of 11 commercially available 500-mg sulfisoxazole tablets were evaluated *in vitro* and *in vivo*. All products tested met USP XVIII specifications for weight variation and product assay. However, three products failed to meet the USP XVIII dissolution requirement. The only statistically significant difference observed between the 11 products was a lower peak plasma level exhibited by one product. No useful correlation was observed between the *in vivo* and *in vitro* studies for the dosage forms tested.

Keyphrases □ Sulfisoxazole—weight variation, dissolution, and bioavailability, *in vivo* and *in vitro* evaluation, commercial dosage forms □ Weight variation product assay—USP test, sulfisoxazole, commercial dosage forms □ Dissolution—USP test, sulfisoxazole, commercial dosage forms □ Bioavailability—sulfisoxazole, *in vivo* and *in vitro* evaluation, commercial dosage forms □ Antibacterial agents—sulfisoxazole, weight variation, dissolution, and bioavailability, commercial dosage forms

Sulfisoxazole is a sulfonamide antibacterial agent employed in the treatment of urinary tract infections. Although the metabolism, distribution, and elimination of sulfisoxazole have been studied in animals and humans (1–4), few studies have been undertaken to evaluate the bioavailability of commercially available

products. Earlier studies (5–8) of a limited number of sulfisoxazole products failed to detect significant differences in bioavailability and reported only a moderate to poor correlation between *in vitro* dissolution rates and *in vivo* performance.

The present study of 11 sulfisoxazole products, manufactured by 10 companies, sought to determine if differences in bioavailability existed and if any differences could be related to the dissolution or disintegration properties of the dosage form.

EXPERIMENTAL

Analysis of Plasma Samples—A method similar to the Bratton–Marshall (9) procedure was employed in the determination of the free, unmetabolized sulfisoxazole present in the plasma. One-half milliliter of plasma, 4.0 ml of water, and 2.5 ml of 15% trichloroacetic acid were gently agitated and centrifuged for 30 min. Five milliliters of the supernate was transferred to a clean tube, 1.0 ml of 4 *N* HCl and then 1.0 ml of a freshly prepared 0.1% aqueous solution of sodium nitrate were added, and the mixture was vortexed. After 4 min, 1.0 ml of a 0.5% aqueous ammonium sulfamate solution was added and the tube was vigorously shaken by hand.

Upon standing for 3 additional min, 1.0 ml of a freshly prepared 0.1% aqueous solution of *N*-(1-naphthyl)ethylenediamine dihydrochloride was added and mixed. After the samples were stored in the dark for 15 min, the absorbance of each was determined at 546 nm against a distilled water blank. Blank plasma samples, collected prior to drug administration, also were analyzed. Each drug absorbance reading was corrected for the blank plasma values.

***In Vitro* Tests**—The USP XVIII (10) tablet weight variation, product assay, and dissolution tests were performed on each product[1]. Disintegration tests[2] were determined according to the USP XVII (11) procedure. More recent editions of the USP do not contain a disintegration specification for this drug.

Selection of Sulfisoxazole Products—Table I summarizes the sulfisoxazole products that were evaluated. Ten manufacturers were represented. In each case, the products tested were purchased directly from a local pharmacy or supplied by the FDA field offices.

Clinical Study Protocol—Seven healthy adult male volunteers were recruited from the staff and student body of this University. The average age of the subjects was 24 years (range 21–28), the average height was 177.4 cm (range 167.6–187.9), and the average weight was 75.6 kg (range 65.8–93.0). Each subject underwent a urine analysis as well as a hematologic and blood enzyme analysis[3] to ensure inclusion of only subjects in good health.

The bioavailability study of 11 products was divided into two separate parts, designated Groups 1 and 2. Each group consisted of six subjects who received a single 500-mg sulfisoxazole tablet in each of 6 consecutive weeks with a 7-day "washout" period between each dose. The administration of each drug to each subject every week was based on a crossover sequence designed to minimize the influence of any residual or cumulative effects of preceding doses (12).

Five subjects were common to both Groups 1 and 2. The Group 2 study was initiated following completion of the Group 1 study. Product 1 was included in both groups as a reference standard to facilitate comparison of data between groups.

Each subject was instructed to adhere to a standard protocol and abstain from taking any medication during the study. The subjects were given the tablets in the morning following an overnight fast. No food or liquid, other than water, was permitted until 4 hr following drug ingestion. Ten-milliliter blood samples were withdrawn from each subject prior to and 1, 2, 3, 4, 6, 8, 10, and 25 hr after drug ingestion. The blood samples were transferred to heparinized centrifuge tubes and the plasma was separated and frozen until assayed.

RESULTS AND DISCUSSION

Sulfisoxazole *In Vitro* Tests—Each of the 11 products tested met the USP XVIII (10) specifications for tablet weight variation. The product assays indicated that each product was within the 95–105% limits. However, three products failed to meet the USP XVIII dissolution requirement that 60% of the labeled content of the tablet must dissolve in not more than 30 min. The actual percent dissolved in 30 min ranged from approximately 12 to 97% (Table I). The three products that failed were approximately 12, 22, and 50% dissolved after 30 min.

Table I—*In Vitro* Test Data for Sulfisoxazole Bioavailability Study

Product[a] Code Number (Study Group)	Assay, % of Label	Mean Percent Dissolved in 30 min	Disintegration Time, min
1 (1, 2)	101.2	77.8	15
2 (1)	102.1	97.4	2
3 (1)	100.0	49.0	20
4 (1)	98.2	82.0	3
5 (1)	99.6	21.4	22
6 (1)	98.0	71.7	4
2 (2)	104.3	12.6	>30
3 (2)	99.7	⩾60[b]	7
4 (2)	100.0	⩾60[b]	5
5 (2)	102.6	⩾60[b]	4
6 (2)	100.2	⩾60[b]	>30

[a] Distributor (Manufacturer if different from distributor) and Lot No. are as follows: Group 1—1, Roche, 8453-02074; 2, Towne, Paulsen (Dow Chemical), 087459; 3, Arcum (Lannett), 16929; 4, Geneva Generics (Cord), 32813; 5, Ulmer Pharmaceuticals (Zenith), 2218-20; and 6, Zenith Labs, 2218-21; and Group 2—1, Roche, 8453-02074; 2, Harvey Labs, 18952; 3, Interstate Drug Exchange (Myland), 900910; 4, Upjohn, 563AT-C2; 5, West-ward, 41229; and 6, Smith Kline and French, R151163. [b] More quantitative data were not provided by the FDA.

Neither USP XVIII nor XIX contains a disintegration time specification for sulfisoxazole tablets. However, since disintegration time requirements are currently official for several tablet products and since USP XVII (11) had such a requirement for sulfisoxazole tablets, samples of each lot were tested for disintegration properties (Table I). Nine of the 11 products met the USP XVII requirement of disintegration in distilled water at 37° within 30 min. Products 2 and 6 of Group 2 failed to disintegrate in distilled water. However, when dilute hydrochloric acid (1:25) was used as the test solvent, both products disintegrated within 12 min.

Plasma Levels—Tables II and III summarize the average plasma sulfisoxazole levels for each product at each sampling time. These results are shown graphically in Figs. 1 and 2. An analysis of variance for these data indicated that there were no significant differences ($p > 0.05$) between the 11 products studied in each group in terms of mean plasma levels obtained at each sampling time.

Time of Peak Plasma Levels—In each case, the time required to reach peak plasma sulfisoxazole levels was 3 hr or less, indicating relatively rapid absorption of the drug following oral administration.

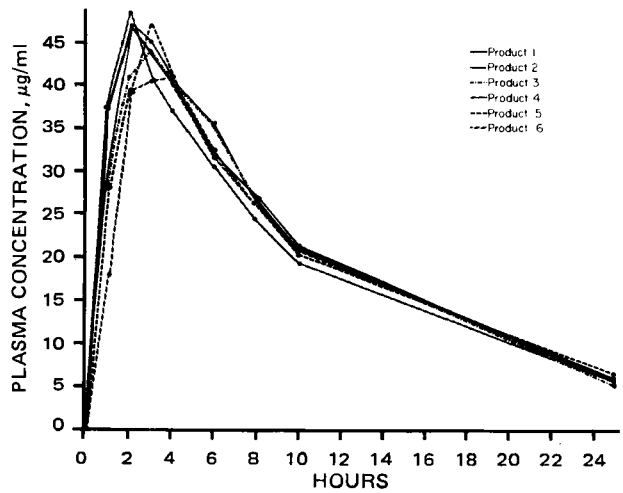

Figure 1—*Average plasma sulfisoxazole levels for Group 1. Each data point represents the mean of six subjects. (See Table I for product code numbers.)*

[1] In the laboratories of the U.S. Food and Drug Administration (FDA).
[2] In the laboratories of the University of Tennessee Center for the Health Sciences.
[3] SMA 12/60.

Table II—Average Plasma Sulfisoxazole Levels, Group 1

Product Code[a]	Average Plasma Sulfisoxazole Levels, μg/ml[b]							
	1 hr	2 hr	3 hr	4 hr	6 hr	8 hr	10 hr	25 hr
1	37.18 (9.59)	46.70 (6.70)	43.59 (3.26)	40.20 (1.91)	35.38 (2.36)	26.43 (1.18)	21.43 (1.13)	6.01 (0.54)
2	30.82 (8.21)	47.06 (9.58)	45.25 (2.63)	40.91 (2.52)	32.65 (2.07)	27.12 (1.62)	21.60 (1.02)	6.16 (0.66)
3	28.81 (7.69)	40.97 (7.79)	44.21 (2.18)	40.80 (2.17)	33.18 (1.68)	26.57 (1.36)	21.65 (1.19)	5.61 (0.72)
4	38.77 (8.33)	48.32 (2.29)	41.92 (2.43)	37.13 (2.32)	30.67 (1.99)	24.50 (1.71)	19.76 (1.37)	5.74 (0.60)
5	28.45 (10.88)	38.55 (7.13)	47.32 (4.19)	41.20 (3.17)	32.55 (3.02)	25.73 (2.49)	20.91 (2.12)	6.40 (0.95)
6	17.88 (4.90)	39.50 (8.39)	40.49 (3.50)	40.44 (2.63)	31.46 (2.31)	25.56 (1.91)	21.06 (1.83)	5.48 (0.82)

[a] See Table I. [b] Average of six subjects; standard error in parentheses.

Table III—Average Plasma Sulfisoxazole Levels, Group 2

Product Code[a]	Average Plasma Sulfisoxazole Levels, μg/ml[b]							
	1 hr	2 hr	3 hr	4 hr	6 hr	8 hr	10 hr	25 hr
1	45.21 (8.62)	48.78 (5.22)	47.81 (3.54)	43.69 (3.76)	33.77 (3.06)	26.77 (2.31)	22.17 (2.01)	7.16 (1.16)
2	7.35 (4.21)	33.14 (6.67)	43.71 (3.93)	42.50 (3.47)	35.45 (2.71)	27.89 (2.43)	24.02 (2.33)	7.22 (0.99)
3	31.82 (10.96)	36.67 (7.89)	43.12 (3.61)	43.51 (4.57)	35.44 (3.48)	29.05 (3.35)	24.43 (3.49)	7.75 (1.67)
4	29.86 (9.12)	42.13 (5.17)	44.35 (3.84)	40.86 (3.79)	32.68 (3.40)	27.25 (2.82)	22.38 (2.77)	6.64 (1.52)
5	40.49 (6.63)	44.78 (4.40)	47.18 (3.61)	40.72 (3.51)	33.79 (2.95)	27.51 (2.12)	22.99 (1.57)	7.42 (0.88)
6	32.34 (10.35)	38.28 (7.37)	40.46 (4.91)	44.02 (3.75)	36.33 (3.92)	29.80 (3.33)	25.08 (3.43)	8.74 (2.19)

[a] See Table I. [b] Average of six subjects; standard error in parentheses.

The average peak times ranged from 1.7 to 2.7 hr in Group 1 and from 2.2 to 3.0 hr in Group 2. These values are in agreement with a mean value of 2.5 hr reported previously (7, 8). There was no statistically significant ($p > 0.05$) difference in the time of peak level between any of the products in each group.

Peak Plasma Concentration—Reports in the literature (5–7) indicate that the average peak plasma levels achieved following the oral administration of sulfisoxazole may vary widely. If the previously reported peak plasma levels following 2–4-g doses are normalized to a 1-g dose, the levels range from a low of 32.2 μg/ml to a high of 84.4 μg/ml. For example, Kaplan *et al.* (7) reported a peak plasma sulfisoxazole level of 168.7 μg/ml for averaged data obtained in a study of seven subjects receiving a 2.0-g dose of the drug, with the individual peak levels ranging from 121 to 210 μg/ml.

In the present study, the average of the peak levels for each of the 11 products, obtained by averaging the individual peak levels observed for each subject, ranged from 45.5 to 57.5 μg/ml in Group 1 and from 47.6 to 56.8 μg/ml in Group 2 following administration of a single 500-mg tablet. When the average peak plasma levels observed for Products 2–6 in Groups 1 and 2 were expressed as a percentage of the average peak plasma level observed for Product 1, the values ranged from 80 to 101% in Group 1 and from 84 to 100% in Group 2. The analysis of variance indicated that Product 3 in Group 1 was significantly lower ($p < 0.05$) than the other five products in the group in terms of peak plasma level.

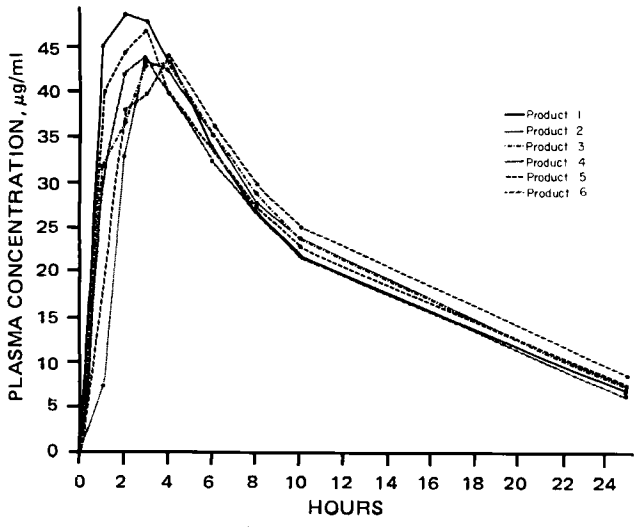

Figure 2—*Average plasma sulfisoxazole levels for Group II. Each data point represents the mean of six subjects. (See Table I for product code numbers.)*

Area under Plasma Level–Time Curve (*AUC*)—Table IV summarizes the average "uncorrected" *AUC* values computed from the individual plasma sulfisoxazole level–time curves obtained following administration of each of the 11 products. These values were estimated, using the trapezoidal rule, for the interval of 0–25 hr postadministration. For the 11 products evaluated, the average uncorrected *AUC*'s, expressed relative to Product 1, ranged from 91.0 to 100% in Group 1 and from 95 to 104% in Group 2. The analysis of variance indicated that there were no significant differences ($p > 0.05$) observed between the *AUC* values for the 11 products.

In cases where the plasma sulfisoxazole level had not reached zero at the terminal 25-hr sampling time, a "corrected" *AUC* was also calculated using:

$$(AUC)_{0-\infty} = (AUC)_{0-25\text{ hr}} + (AUC)_{25\text{ hr}-\infty} \qquad \text{(Eq. 1)}$$

and:

$$(AUC)_{25\text{ hr}-\infty} = \frac{(C_p)_{25\text{ hr}}}{K_e} \qquad \text{(Eq. 2)}$$

where $(C_p)_{25\text{ hr}}$ is the plasma level at the 25-hr sampling time, and K_e is the elimination rate constant determined from the slope of the terminal portion of a semilog plot of plasma concentration *versus* time.

Table IV—Summary of Average Areas under the Plasma Level–Time Curve (*AUC*), Uncorrected

Product Code[a]	Average *AUC*, μg/ml × hr[b]	*CV*, %[c]	Percent Relative to Product 1
	Group 1		
1	537.28 (14.8)	6.7	100.0
2	528.81 (21.7)	10.0	98.3
3	521.31 (28.3)	13.3	97.0
5	520.99 (31.8)	15.0	97.0
4	502.95 (33.5)	16.3	93.6
6	488.61 (26.8)	13.4	91.0
	Group 2		
6	583.96 (56.3)	23.6	104.6
3	575.09 (74.5)	31.7	103.1
1	558.44 (48.1)	21.1	100.0
5	555.68 (44.5)	19.6	99.5
2	533.46 (45.3)	20.8	95.5
4	532.62 (62.4)	28.7	95.4

[a] See Table I. [b] Average of six subjects per group; standard error in parentheses. [c] (Standard deviation) (100)/(mean).

Table V—Summary of Average Areas under the Plasma Level–Time Curve (*AUC*), Corrected

Product Code[a]	Average *AUC*, μg/ml × hr[b]	*CV*, %[c]	Percent Relative to Product 1
	Group 1		
1	606.98 (23.7)	9.6	100.0
5	606.94 (47.8)	19.3	99.9
2	605.60 (30.6)	12.3	99.8
3	585.90 (36.9)	15.4	96.5
4	573.45 (43.1)	18.4	94.5
6	555.89 (36.1)	15.9	91.6
	Group 2		
6	716.91 (98.1)	33.5	109.8
3	686.16 (105.6)	37.7	105.2
5	654.23 (60.4)	22.6	100.2
1	653.04 (71.2)	26.7	100.0
2	625.69 (61.0)	23.9	95.8
4	620.76 (91.1)	36.0	95.1

[a] See Table I. [b] Average of six subjects per group; standard error in parentheses. [c] (Standard deviation) (100)/(mean).

Table V summarizes the corrected average area under the plasma level–time curve. For the 11 products evaluated, the average corrected *AUC*'s, expressed relative to Product 1, ranged from 91.6 to 100% in Group 1 and from 95 to 110% in Group 2. No statistically significant differences ($p > 0.05$) were found between any of the products in terms of the corrected area under the plasma level–time curve.

Between Group Differences—Table VI summarizes the *AUC* values and peak concentrations observed following the repeat administration of Product 1 to the five subjects who were common to both Groups 1 and 2. These data indicate the reproducibility of the *in vivo* studies, since the mean uncorrected *AUC*, corrected *AUC*, and peak plasma level differed by only 4.6, 4.5, and 2.1%, respectively, between the two groups. When the data from all six subjects in each group were included in the average data for Product 1, the mean values differed by only 3.8, 7.0, and 0.04% for the uncorrected *AUC*, corrected *AUC*, and peak plasma concentration, respectively.

Differences between Subjects—Individual subjects appeared to be consistent from week to week. Subject 2, who was common to both Groups 1 and 2, exhibited the lowest *AUC* of any subject. Subject 5 exhibited the largest *AUC* of the five subjects common to both groups. The average apparent half-life for sulfisoxazole elimination, estimated from the terminal portion of a semilog plot of plasma level *versus* time for each product in each subject, was 8.5 hr. Subject 2 had an average half-life of 7.8 hr. Subject 6 of Group 2, who had the largest *AUC* values of any of the seven subjects, exhibited an average apparent half-life of 11.1 hr. In addition to possible differences in the rate and extent of GI absorption, differences in rates of elimination may have contributed to the observed differences in *AUC*'s found for the individual subjects.

Product Variability—Examination of the coefficients of variation failed to reveal any apparent deficiency in any of the 11 products. The Group 2 study yielded higher coefficients of variation readings than were observed in Group 1. This finding could be related to the fact that Subject 6 of Group 2 consistently exhibited plasma levels that were substantially greater than those observed in the other subjects.

Table VI—Comparison of Product 1 in the Group 1 and Group 2 Studies

Subject Number	Uncorrected *AUC*, μg/ml × hr		Corrected *AUC*, μg/ml × hr		Peak Plasma Level, μg/ml	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
1	527	494	583	551	55.94	61.40
2	485	409	538	457	58.23	51.17
3	568	545	639	635	57.77	57.02
4	563	599	655	701	49.34	45.16
5	572	542	677	607	54.06	54.71
Mean	543	518	618	590	55.07	53.89

Table VII—*In Vitro–In Vivo* Correlations

Correlation	Degrees of Freedom	Correlation Coefficient	*t* Value	*p* Level
Disintegration *versus* dissolution[a]	5	−0.90973	4.899	$p = 0.01$
Disintegration *versus* peak plasma level	10	−0.04621	0.103	NS
Disintegration *versus AUC*	10	+0.3271	0.774	NS
Dissolution *versus* peak plasma level	5	+0.1830	0.4162	NS
Dissolution *versus AUC*	5	−0.0859	0.1928	NS
Peak level *versus AUC*	10	+0.0737	0.2337	NS

[a] Disintegration time *versus* percent dissolved after 30 min.

Lot-to-lot variations were examined for Products 5 and 6 of the Group 1 study. Both lots were manufactured by the same company. The mean time of peak plasma level was 2.0 hr for Product 5 and 2.7 hr for Product 6. There was a difference of 9% in the peak plasma level between the two lots as well as differences of 6 and 8% in uncorrected *AUC* and corrected *AUC* values, respectively. The two lots of this product exhibited similar bioavailability parameters, although they had significantly different dissolution and disintegration characteristics, with Product 5 failing the USP XVIII dissolution test.

***In Vivo–In Vitro* Correlations**—Table VII summarizes the relationship observed between the various *in vitro* and *in vivo* parameters. There was a good correlation between disintegration and dissolution rate. However, no correlations were found that would be of value in predicting *in vivo* performance. A similar lack of relationship between dissolution rate and bioavailability for sulfisoxazole was noted by Solomon (6). It is significant that three lots tested in the present study failed to meet current compendial specifications for dissolution but exhibited adequate bioavailability. However, as recently discussed by Feldmann (13), this observation does not necessarily negate the validity of the USP test for the detection of products that may exhibit inadequate bioavailability.

SUMMARY AND CONCLUSIONS

Eleven lots of 500-mg sulfisoxazole tablets, manufactured by 10 companies, were evaluated in seven subjects. The study was divided into two groups, with five subjects common to both groups. All products met USP XVIII specifications except that three products did not meet the dissolution rate requirement.

The only statistically significant difference observed between the 11 products was in terms of a lower peak plasma level for Product 3 in Group 1. The peak plasma level for this product was 20% lower than that observed for the reference standard product. In view of the lack of any other statistically significant differences ($p > 0.05$) between any of the products in terms of *AUC*, time of peak plasma level, or plasma levels 1, 2, 3, 4, 6, 8, 10, and 25 hr postadministration, it was concluded that the 11 lots of sulfisoxazole could be considered as bioequivalent. It was further concluded that the current USP dissolution specifications may be of limited value in the prediction of bioavailability.

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Effect of Certain Drugs in Perfused Human Placenta XII: Autacoid Antagonism by Phenothiazines

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Abstract □ The effects of chlorpromazine, prochlorperazine, and trifluoperazine on the pressor actions of serotonin, angiotensin, and bradykinin in the perfused vessels of full-term human placentas were investigated. A significant inhibition of the effect of serotonin was observed with trifluoperazine and chlorpromazine but not with prochlorperazine. This inhibition is attributed to the ability of phenothiazines to cause adrenergic blockade. Because both bradykinin and angiotensin could not be consistently antagonized, it is concluded that they must act primarily *via* musculotropic mechanisms and only secondarily by stimulation of adrenergic receptors.

Keyphrases □ Chlorpromazine—effects on pressor actions of serotonin, angiotensin, and bradykinin in perfused human placenta □ Prochlorperazine—effects on pressor actions of serotonin, angiotensin, and bradykinin in perfused human placenta □ Trifluoperazine—effects on pressor actions of serotonin, angiotensin, and bradykinin in perfused human placenta □ Serotonin—pressor actions in perfused human placenta, effects of chlorpromazine, prochlorperazine, and trifluoperazine □ Angiotensin—pressor actions in perfused human placenta, effects of chlorpromazine, prochlorperazine, and trifluoperazine □ Bradykinin—pressor actions in perfused human placenta, effects of chlorpromazine, prochlorperazine, and trifluoperazine □ Autacoid antagonism—effects of chlorpromazine, prochlorperazine, and trifluoperazine on pressor actions of serotonin, angiotensin, and bradykinin in perfused human placenta □ Phenothiazines—chlorpromazine, prochlorperazine, and trifluoperazine, effects on pressor actions of serotonin, angiotensin, and bradykinin in perfused human placenta

It is well established that the endogenous autacoids serotonin, angiotensin, and bradykinin are present and that their levels fluctuate in human placental and/or related tissues (1–8). Several investigations linked high blood levels of angiotensin (9), renin (10), and serotonin (11) to the pathogenesis of the toxemias of pregnancy. Increased pressor response to angiotensin was observed in preeclamptic women (9); increased renin levels were reported in eclamptic and preeclamptic women (12), and decreased angiotensinase levels were found in toxemic women (13).

Serotonin, angiotensin, and bradykinin share two noticeable actions on the perfused placental vasculature: vasoconstriction with an associated increase in blood vessel pressure and increased blood vessel permeability (14–20). They also share similarities in their mechanisms of action in that they all cause α-receptor stimulation in these vessels (16, 20). Serotonin and angiotensin cause direct vascular smooth muscle stimulation, while bradykinin causes release of norepinephrine from unspecified storage sites in the placenta.

Chlorpromazine antagonizes the vasoconstrictor action of serotonin in the perfused human placental blood vessels by approximately 67.8% (21). Chlorpromazine also inhibits the ability of serotonin to cause intrauterine deaths (22). In addition, chlorpromazine and other phenothiazines block the increased vascular permeability of serotonin injections in the hindpaw of rats (23).

The phenothiazines are presently prescribed for anxiety states, tranquilization, motion sickness, night sedation, and preanesthetic medication. They are used as analgesics in labor and to prevent nausea and vomiting during labor and morning sickness (24). These compounds have strong adrenergic blocking activity and weaker cholinergic blocking activity, and they can block the actions of serotonin both *in vivo* and *in vitro* (25). The phenothiazines and the previously mentioned autacoids are capable of crossing the "placental barrier," since their molecular weight is less than 1000. Furthermore, the phenothiazines are suspected of con-