Decreased Tetracycline Bioavailability Caused by a Bismuth Subsalicylate Antidiarrheal Mixture

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Received April 3, 1978, from *The Upjohn Company, Kalamazoo, MI 49001.* Accepted for publication August 3, 1978.

Abstract □ Oral coadministration of a single 250-mg tetracycline capsule and 60 ml of a bismuth subsalicylate antidiarrheal mixture reduced tetracycline absorption by 34% without appearing to perturb its absorption or disposition rate. A pronounced increase in intersubject tetracycline absorption variability also was noted. Apparently, the reduction in tetracycline bioavailability previously reported with a kaolin–pectin suspension is not peculiar to kaolin–pectin but can be expected with almost any antidiarrheal whose mechanism of action is adsorptive in nature.

Keyphrases □ Tetracycline—bioavailability, decreased by coadministered bismuth subsalicylate antidiarrheal □ Bismuth subsalicylate—antidiarrheal mixture, interference with bioavailability of coadministered tetracycline □ Antibiotics—tetracycline, bioavailability decreased by coadministered bismuth subsalicylate □ Antidiarrheals—bismuth subsalicylate, interference with bioavailability of coadministered tetracycline □ Drug-antibiotic interactions—bismuth subsalicylate interference with tetracycline bioavailability

Several studies (1–8) demonstrated that kaolin–pectin-containing antidiarrheal mixtures[1] interfere with the absorption of some concomitantly administered oral drugs. Retrospective *in vitro* experiments[2] suggested that drugs that can exist as cations in solution (*e.g.*, clindamycin, lincomycin, and tetracycline) are most susceptible to irreversible adsorption by negatively charged components of the antidiarrheal, but neutral molecules that can hydrogen bond (*e.g.*, digoxin, which contains a large sugar molecule) also may interact in an untoward way.

This paper describes the effect of a bismuth subsalicylate antidiarrheal mixture[3] on the bioavailability of the cationic drug tetracycline. Concomitant administration of both products markedly decreased the antibiotic bioavailability, suggesting that, in general, any antidiarrheal whose mechanism of action is adsorptive may interfere with the absorption of coadministered cationic and hydrogen-bonded drugs.

EXPERIMENTAL

The 16 normal, nonobese adult volunteers, whose average age was 26 years (range of 20–37 years) and whose average weight was 79 kg (range of 69–90 kg), exhibited normal vital signs and selected laboratory parameters and were without evidence of cardiac, renal, or GI abnormalities. These subjects did not receive any antibacterial medication for 30 days before initiation of the protocol. During the study, volunteers received only the medication prescribed, with 7 days separating each administered treatment.

Subjects were fasted (food and beverage) from 10:00 pm the night before their allocated treatment until 4 hr after drug administration. To ensure adequate urine output, subjects were required to drink at least 360 ml of water with their noon meal. Smoking was permitted if it was the usual custom of a subject. Volunteers did not engage in strenuous or athletic activities during the days the drug was given.

Each subject received a 250-mg tetracycline capsule[4] with and without bismuth subsalicylate suspension in crossover fashion (Table I). Serum samples were obtained at 0, 0.5, 1.0, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, and 24.0 hr. Urine specimens were collected at the following time intervals during each treatment period: predose (to serve as a urine blank), 0–12, 12–24, 24–48, and 48–72 hr. All samples were kept frozen until assayed microbiologically for tetracycline-like activity (9).

RESULTS

The bismuth subsalicylate antidiarrheal preparation effect on average tetracycline serum levels and urinary excretion for the 15 subjects who completed the study is summarized in Tables II and III, respectively; Fig. 1 shows the serum tetracycline time course through 24 hr. It is evident from Table II and the figure that, at every sampling, significantly lower serum antibiotic levels were found following coadministration with the antidiarrheal mixture. With the exception of the 24–48-hr interval, Table III shows that the urinary tetracycline excretion was reduced as well.

The average times of individual peak serum levels were comparable for the two treatments, which suggests that absorption rates were similar (Table II). In contrast, Table II shows that, following the bismuth subsalicylate treatment, the individual peak average concentration was decreased by 27% and the average 24-hr area under the antibiotic curve

Table I—Dosage Schedule and Treatments

Group	Subjects in Group	Treatment for Phase Number[a] I	II
I	1, 3, 6, 9, 10, 12, 14, 16	A	B
II	2, 4, 5, 7, 8, 11, 13, 15	B	A

[a] Treatment A was 60 ml of Pepto-Bismol (lot 830547, Norwich Products) followed immediately by one Panmycin H.F.C., 250 mg (lot 532EK, Upjohn), administered orally with 90 ml of water. Treatment B was one Panmycin H.F.C., 250 mg (lot 532EK, Upjohn), administered orally with 90 ml of water.

Table II—Effect of Bismuth Subsalicylate Antidiarrheal Mixture on Mean Serum Tetracycline Levels

Parameter	Treatment Average[a] A	B	Level of Significance between Treatments, *p*
Serum tetracycline level, μg/ml, at:			
0.5 hr	0.08	0.53	<0.0001
1.0 hr	0.84	1.30	<0.001
1.5 hr	1.25	1.69	<0.01
2.0 hr	1.45	1.92	<0.0025
2.5 hr	1.50	1.98	<0.001
3.0 hr	1.54	2.04	<0.001
4.0 hr	1.44	1.97	<0.001
5.0 hr	1.22	1.85	<0.0001
6.0 hr	1.07	1.64	<0.0001
7.0 hr	1.02	1.55	<0.001
8.0 hr	0.91	1.40	<0.0001
10.0 hr	0.80	1.23	<0.0001
12.0 hr	0.68	1.02	<0.0001
16.0 hr	0.47	0.73	<0.0001
24.0 hr	0.30	0.47	<0.001
Average of individual peak serum levels, μg/ml	1.60	2.18	<0.001
Time of individual peak serum levels, hr	2.80	3.03	NS[b]
AUC through 24 hr, μg/ml × hr	17.5	26.1	<0.0001
Half-life, hr	8.38	9.13	<0.05
Renal clearance, ml/min	79.6	80.7	NS

[a] See Table I. [b] NS = not significant.

[1] Kaopectate or Kaopectate Concentrate, The Upjohn Co., Kalamazoo, MI 49001.
[2] Unpublished data.
[3] Pepto-Bismol, Norwich Products, Norwich, NY 13815.
[4] Panmycin H.F.C., 250 mg, The Upjohn Co., Kalamazoo, MI 49001.

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Table III—Effect of Bismuth Subsalicylate Antidiarrheal Mixture on Mean Urinary Tetracycline Excretion

Time Interval, hr	Amount Excreted[a], mg A	Amount Excreted[a], mg B	Level of Significance between Treatments, p
0–12	56.7	86.7	<0.001
12–24	26.2	45.5	<0.001
24–48	18.3	21.0	NS[b]
48–72	3.72	5.38	<0.005
0–72	105	159	<0.001

[a] See Table I. [b] NS = not significant.

(*AUC*) was reduced 33%, while Table III shows that the 72-hr urinary tetracycline recovery was reduced by 33%. These results indicated that the antidiarrheal disturbed either the absorption or the disposition of the antibiotic. All 15 subjects showed lower 24-hr serum antibiotic *AUC* values in the presence of the antidiarrheal, while 14 of 15 subjects showed the same trend in 72-hr urinary recoveries (Table III).

Two parameters free from absorption influences, renal clearance and half-life, also were evaluated to ascertain whether the bismuth subsalicylate product altered tetracycline disposition. Mean renal clearances were virtually identical while treatment half-lives differed by only 8% (Table II). Apparently, the interaction between the antidiarrheal and the antibiotic affected only absorption, not disposition.

An estimate of the antidiarrheal influence on absorption can be made utilizing a model-independent method described previously (10). This technique bases bioavailability assessment on total urinary recovery (U_∞) and renal clearance ($\dot{V}_{cl,r}$) and assumes that changes in serum clearance ($\dot{V}_{cl,s}$) would be manifested as observed differences in renal clearance among treatments.

Individual relative bioavailability estimates utilizing this approach are summarized in Table IV. Even though average treatment renal clearances were virtually equal, individual subject values did vary between study days. To compensate for these observed differences, adjustments in serum clearance were made on the assumption that individual nonrenal elimination components did not change. With the exception of Subject 8, bioavailability ratios were less than unity, indicating that the antidiarrheal had an adverse effect on absorption. On the average, tetracycline bioavailability when coadministered with bismuth subsalicylate was only 66% ($F^A/F^B = 0.66$, $p < 0.001$).

The effect of the bismuth subsalicylate antidiarrheal mixture on intersubject tetracycline variability is summarized in Table V. Except for time to peak, the data show that the variabilities exhibited by the parameters peak maximum, area under the curve, and urinary recovery were greater for the bismuth subsalicylate treatment. Since the two disposition parameters (renal clearance and half-life) exhibited similar ranges and percent standard deviations between treatments, the greater variation

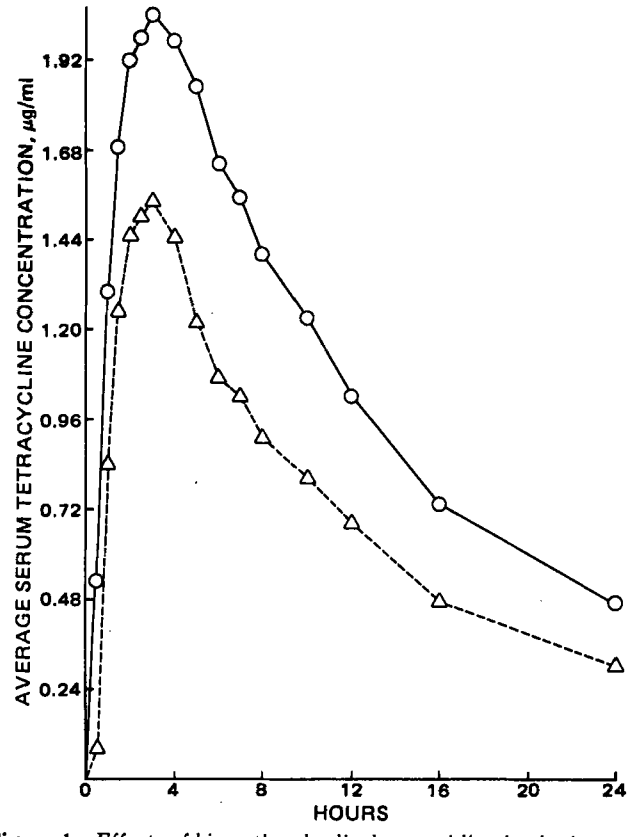

Figure 1—*Effects of bismuth subsalicylate antidiarrheal mixture on serum tetracycline levels following concomitant administration of both drugs. Key: ○, tetracycline alone; and △, tetracycline plus bismuth subsalicylate.*

associated with antidiarrheal coadministration can be attributed predominantly to a perturbation in tetracycline absorption. These results parallel the findings on absorption efficiency already described.

DISCUSSION

The only previous studies of antidiarrheal effect on coadministered oral drug absorption involved kaolin–pectin products (1–8). These studies

Table IV—Model-Independent Relative Bioavailability Estimate[a]

Subject[b]	Clearances, ml/min A $\dot{V}_{cl,r}$	Clearances, ml/min A $(\dot{V}_{cl,s})'_{ex}$	Clearances, ml/min B $\dot{V}_{cl,r}$	Clearances, ml/min B $(\dot{V}_{cl,s})_{ex}$	Urinary Recovery, mg A	Urinary Recovery, mg B	Relative Amount Absorbed, F^A/F^B
1	89.3	124.0	85.2	119.9	97.7	175.8	0.560
2	93.0	111.4	125.7	144.1	84.2	216.0	0.330
4	53.3	111.8	81.2	139.7	88.5	143.7	0.629
5	72.2	133.2	77.8	138.8	108.6	137.4	0.796
6	70.3	111.3	82.3	123.3	122.1	164.6	0.730
7	82.4	129.8	95.5	142.9	94.8	166.9	0.556
8	89.9	165.6	95.0	170.7	173.4	121.4	1.44
9	56.8	126.5	64.1	133.8	80.8	156.7	0.513
10	84.8	123.7	100.7	139.6	103.0	178.3	0.557
11	64.1	129.5	64.9	130.3	42.2	122.9	0.344
12	80.9	113.2	25.8	58.1	96.3	108.4	0.720
13	54.2	74.2	74.1	94.4	148.3	193.4	0.685
14	81.5	126.4	93.5	138.4	140.3	168.0	0.820
15	70.6	124.2	67.4	121.0	58.8	137.7	0.426
16	151.1	175.9	77.3	102.1	135.0	187.2	0.809
Mean	79.6	125.4	80.7	126.5	104.9	158.6	0.661[c]
CV, %	37.3	18.6	33.8	20.7	32.8	18.8	40.5

[a] Calculated according to the method of Kwan and Till (10) where:

$$(\dot{V}^B_{cl,s})_{ex} = \frac{(\dot{V}^B_{cl,r})(D^B)}{U^B_\infty}$$

$$(\dot{V}^A_{cl,s})'_{ex} = \dot{V}^A_{cl,r} + (\dot{V}^B_{cl,s})_{ex} - \dot{V}^B_{cl,r}$$

$$F^A/F^B = \frac{U^A_\infty (\dot{V}^A_{cl,s})'_{ex}}{(D^A)(\dot{V}^A_{cl,r})}$$

[b] Subject 3 did not complete the study. [c] Statistically significantly different from unity using t test ($p < 0.001$).

Table V—Bismuth Subsalicylate Antidiarrheal Mixture Effect on Tetracycline Product Variability

Parameter	Range A	Range B	SD, % A	SD, % B
Peak serum level, μg/ml	0.69–2.29	1.79–2.52	24.4	9.34
Peak time, hr	2.50–4.0	2.50–5.0	18.9	37.6
AUC through 24 hr, μg/ml × hr	7.13–27.9	21.1–30.5	28.9	11.0
Urinary recovery through 72 hr, mg	42.2–173	108–216	32.8	18.8
Half-life, hr	7.09–10.8	7.58–11.8	11.4	15.1
Renal clearance, ml/min	53.3–151	25.8–126	29.7	27.3

suggested that the antidiarrheal influence on antibiotic absorption is dose dependent.

In the present study, 60 ml of a bismuth subsalicylate antidiarrheal product was administered concomitantly with a 250-mg tetracycline hydrochloride capsule. Since the "active" bismuth subsalicylate concentration was not given on the package, molar comparisons of "active" bismuth subsalicylate antidiarrheal to "active" kaolin–pectin products were impossible. Nonetheless, the 34% decrease in relative tetracycline bioavailability was consistent with the kaolin–pectin with tetracycline data and indicated that similar drug interactions are likely with any antidiarrheal whose mechanism of action is adsorptive.

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ACKNOWLEDGMENTS

The authors thank Ms. Mariann Holthouse for secretarial assistance and W. L. Lummis for performing the microbiological assays.

Molecular Weight Determination of Commercial Heparin Sodium USP and Its Sterile Solutions

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Received June 19, 1978, from *Control Analytical Research and Development, The Upjohn Company, Kalamazoo, MI 49001.* Accepted for publication September 8, 1978. *Present address: Waters Associates, Milford, MA 01757.

Abstract □ A liquid chromatographic assay for the characterization of heparin sodium USP and heparin sterile solutions was developed. The method employs size exclusion chromatography and computer-based data collection and manipulation. An examination of commercially available heparin showed only minor differences between the heparins extracted from beef lung and porcine intestinal mucosa. The molecular weight averages of the material and its sterile solutions were 9000–12,000 daltons. A correlation was observed between average molecular weight and anticoagulant activity for the heparin sodium samples examined.

Keyphrases □ Heparin sodium—molecular weight determination of commercial products and sterile solutions using liquid chromatography □ Molecular weight determination—commercial heparin sodium USP and its sterile solutions, liquid chromatography □ Liquid chromatography—molecular weight determination of commercial heparin sodium USP and its sterile solutions □ Anticoagulants—heparin sodium, molecular weight determination, liquid chromatography

Several methods for the molecular weight fractionation of heparin sodium have been reported (1–3), gel filtration being most commonly used (4). In most cases, analysis requires several hours per sample and complicated detection procedures. Recently, a fast and reliable method was developed (5, 6) using high-performance liquid chromatography (HPLC) with refractive index detection for the determination of molecular weight averages of heparin sodium USP and injectable heparin sodium solutions (6).

The literature contains conflicting reports regarding the relationship of molecular weight and anticoagulant activity (7–9). There are also significant differences in the reported molecular weights of commercially available heparin (5, 6, 10). This paper presents the results of an examination of sterile injectable heparin sodium from commercial sources. The liquid chromatographic method recently developed (5) was modified and used to determine if any relationship exists between molecular weight and anticoagulant activity.

EXPERIMENTAL

A liquid chromatograph[1] was equipped with a refractive index detector and a syringe loop injector. A minicomputer[2] was used to monitor the refractive index detector signals and to run the molecular weight calculation programs. The detector–computer interface is shown in Fig. 1.

Chromatographic Conditions—Two sets of columns were used. The hand-packed set was used initially to compare molecular weight fractions for their relationship to anticoagulant activity. Commercially available columns were used for the comparative study on heparin sterile solutions.

A set of three columns was tap packed with various pore sizes of 5–10-μm glycophase-controlled porous glass. These columns were packed

[1] Waters Associates model ALC/GPC 244 equipped with a RI (R-404) and a U6K injector.

[2] PDP-11/40, Digital Equipment Co.; the interfacing was developed in-house.

0022-3549/79/0500-0588$01.00/0