previous reports (16), absorption of temazepam from the hard gelatin capsule utilized in the United States occurs relatively slowly, with peak plasma concentrations an average of 2.0–2.1 h after dosage. Temazepam elimination half-lives ranged from 6 to 21 h, and total metabolic clearances ranged from 0.9 to 2.6 mL/min/kg. None of these kinetic variables were significantly influenced by cimetidine coadministration, nor was the extent of temazepam binding to plasma protein altered by cimetidine. Furthermore, for any given individual, the kinetic profile for temazepam was highly consistent between the two treatment trials.

The clinical implications of an interaction or noninteraction with cimetidine for any particular benzodiazepine cannot at present be determined. The present study nonetheless suggests that, consistent with its biotransformation pathway mainly involving glucuronide conjugation, the pharmacokinetic profile of temazepam is not influenced by concurrent treatment with cimetidine.

REFERENCES

(1) M. M. Mitler, *Pharmacotherapy*, **1**, 3 (1981).

(2) W. Finkelstein and K. J. Isselbacher, *N. Engl. J. Med.*, **299**, 992 (1978).

(3) R. N. Brogden, R. C. Heel, T. M. Speight, and G. S. Avery, *Drugs*, **15**, 93 (1978).

(4) U. Klotz and I. Reimann, *N. Engl. J. Med.*, **302**, 1012 (1980).

(5) P. V. Desmond, R. V. Patwardhan, S. Schenker, and K. V. Speeg, *Ann. Intern. Med.*, **93**, 266 (1980).

(6) D. R. Abernethy, D. J. Greenblatt, M. Divoll, L. J. Moschitto, J. S. Harmatz, and R. I. Shader, *Psychopharmacology*, **80**, 275 (1983).

(7) M. Divoll, D. J. Greenblatt, D. R. Abernethy, and R. I. Shader, *J. Am. Geriat. Soc.*, **30**, 684 (1982).

(8) U. Klotz and I. Reimann, *Eur. J. Clin. Pharmacol.*, **18**, 517 (1980).

(9) D. R. Abernethy, D. J. Greenblatt, M. Divoll, B. Ameer, and R. I. Shader, *J. Pharmacol. Exp. Ther.*, **224**, 508 (1983).

(10) R. V. Patwardhan, G. W. Yarborough, P. V. Desmond, R. F. Johnson, S. Shenker, and K. V. Speeg, *Gastroenterology*, **79**, 912 (1980).

(11) H. J. Schwarz, *Br. J. Clin. Pharmacol.*, **8**, 23s, (1979).

(12) M. Divoll and D. J. Greenblatt, *J. Chromatogr.*, **222**, 125 (1981).

(13) E. Woo and D. J. Greenblatt, *J. Pharm. Sci.*, **68**, 466 (1979).

(14) M. Divoll and D. J. Greenblatt, *J. Pharm. Pharmacol.*, **34**, 122 (1982).

(15) B. Lorenzo and D. E. Drayer, *J. Lab. Clin. Med.*, **97**, 545 (1981).

(16) M. Divoll, D. J. Greenblatt, J. S. Harmatz, and R. I. Shader, *J. Pharm. Sci.*, **70**, 1104 (1981).

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Dissolution Rates of Corticoid Solutions Dispersed on Silicas

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Abstract □ Two nonporous and three porous amorphous silicas were used as dispersion media to convert corticoid solutions into free-flowing powders. The corticoids (prednisone, prednisolone, and hydrocortisone) were dissolved in *N,N*-dimethylacetamide–polyethylene glycol 400 (7:3 v/v) and their 10% (w/v) solutions were mixed with the silicas (1:3 v/w). Dissolution rates of the corticoids from such powdered solutions were more rapid than their micronized powders in various aqueous media.

Keyphrases □ Dissolution rate—corticoid solutions dispersed on silicas, prednisone, prednisolone, hydrocortisone, free-flowing powders □ Corticoids—solutions dispersed on silicas, dissolution rates, prednisone, prednisolone, hydrocortisone, free-flowing powders □ Powders, free-flowing—corticoid solutions dispersed on silicas, dissolution rates, prednisone, prednisolone, hydrocortisone

The USP (1) requires that ≥60% of the prednisone or prednisolone from their respective tablets must dissolve within 20 min in deaerated water. These water-insoluble neutral drug molecules could exhibit poor dissolution rates from improperly prepared capsule or tablet dosage forms. Oral absorption efficiency of the corticoids from such solid dosage forms could be impaired.

Concentrated solutions of three corticoids (prednisone, prednisolone, and hydrocortisone) had been prepared in *N,N*-dimethylacetamide, a high-boiling, water-miscible liquid (2). These earlier studies had shown that the addition of 30% (v/v) polyethylene glycol 400 to the *N,N*-dimethylacetamide would prevent the softening effect of the latter on hard gelatin capsules. As a consequence, this mixture of solvents was used to prepare 10% (w/v) solutions of the three corticoids.

Simple admixture of the corticoid solutions with amorphous, porous, or nonporous silicas converted them to free-flowing powders. The corticoids in such powdered solutions are thus in a molecular state of subdivision. Dissolution rates of such water-insoluble, neutral compounds should be instantaneous if localized dilution with simulated GI media does not cause their precipitation.

The purpose of this study was to convert solutions of corticoids to free-flowing powders by dispersing them on various silicas. Dissolution rates in simulated GI media are compared with those of micronized powders. A comparison of the dissolution rate with ball-milled or solvent-deposited prednisone–silica dispersions is also presented (3).

Table I—UV Wavelengths Used in the Development of Calibration Curves for the Three Drugs in Various Solvents

Solvent	Wavelength of Light, nm I	II	III
Simulated gastric fluid (without pepsin)	248	243	247
Simulated intestinal fluid (without pancreatin)	248	243	247
Ethanol	248	243	247

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Table II—Dissolution in Simulated Gastrointestinal Media of Solutions of Prednisolone, Prednisone, and Hydrocortisone Dispersed on Various Silicas

Sample	Solvent: Simulated Gastric	Solvent: Simulated Intestinal	Amount Dissolved, %: 5 min	10 min	20 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
1. I[a]	+		62.0	74.7	79.5	81.9	84.8	86.4	88.6	88.7	90.0	90.0
2. I[a]		+	67.9	79.0	83.1	85.7	87.5	89.4	90.3	91.2	92.5	93.1
3. I–IV	+		87.5	97.0	99.8	100						
4. I–V	+		92.1	95.1	96.4	96.4	96.5	97.0	97.0	97.3	97.8	97.8
5. I–VI	+		91.5	94.9	96.0	96.5	97.5	97.6	98.0	98.0	98.4	98.4
6. I–VII	+		84.2	86.5	89.5	90.1	91.1	91.6	91.8	92.0	92.2	92.5
7. I–VIII	+		84.2	86.5	89.5	90.1	91.1	91.6	91.8	92.0	92.2	92.5
8. I–IV		+	85.0	86.2	89.5	90.1	90.8	91.9	92.3	94.1	—	95.0
9. I–V		+	84.8	88.8	92.0	93.2	94.1	94.1	94.8	95.1	95.3	95.3
10. I–VI		+	89.3	93.6	94.2	94.5	94.9	95.1	95.2	96.2	96.6	96.6
11. I–VII		+	75.3	86.8	91.7	94.9	96.2	96.8	97.0	97.3	97.6	98.1
12. I–VIII		+	87.7	93.8	96.6	97.6	99.1	100				
13. I–VI[b]	+		80.2	87.2	91.5	92.5	93.6	93.8	94.2	94.6	94.6	94.7
14. I–V[b]	+		74.5	80.9	85.1	86.9	89.7	91.2	92.1	93.2	92.8	92.8
15. I–VI[b]	+		74.0	79.1	82.6	87.6	89.5	89.5	89.8	90.8	91.8	93.1
16. I–IV[b]		+	51.5	57.9	64.5	67.9	71.2	73.8	83.3	86.3	87.7	88.9
17. I–V[b]		+	60.2	68.4	73.3	77.0	80.2	81.8	83.2	84.7	86.2	87.5
18. I–VI[b]		+	61.5	66.7	73.1	75.0	77.2	79.7	80.3	81.0	82.3	83.0
19. II[a]	+		22.6	36.8	55.1	62.5	68.5	73.3	76.9	79.4	81.6	83.3
20. II[a]		+	19.5	30.0	57.3	65.4	71.1	73.3	75.9	81.4	83.1	85.1
21. II–IV	+		73.7	79.3	86.4	93.7	95.3	96.6	98.9	99.0	99.2	99.4
22. II–V	+		76.0	84.0	89.4	93.5	95.9	97.8	99.4	99.6	100	
23. II–VI	+		70.8	75.6	82.0	91.4	95.7	96.1	96.7	97.6	99.3	99.3
24. II–VII	+		48.4	58.7	63.1	67.7	72.1	73.9	76.1	78.2	79.7	80.2
25. II–VIII	+		43.0	49.9	59.9	65.3	68.4	71.7	75.6	78.3	79.3	80.6
26. II–IV		+	62.4	71.6	80.7	86.2	91.6	93.5	96.5	98.6	99.0	100
27. II–V		+	70.5	83.9	91.5	92.7	96.0	97.1	97.8	98.3	99.1	99.8
28. II–VI		+	57.9	68.5	81.5	84.9	90.5	93.9	96.6	98.7	99.9	100
29. II–VII		+	48.4	58.7	63.1	67.7	72.1	73.9	76.1	78.2	79.7	80.2
30. II–VIII		+	43.9	49.9	58.5	64.4	69.1	74.9	84.0	87.9	91.3	93.1
31. III[a]	+		25.0	34.9	52.5	59.4	66.1	77.7	82.8	86.7	89.5	91.6
32. III[a]		+	60.5	72.4	80.0	84.9	88.6	89.8	91.3	91.8	92.8	92.8
33. III–IV	+		96.9	100								
34. III–V	+		96.4	100								
35. III–VI	+		98.5	100								
36. III–VII	+		98.2	99.6	100	100						
37. III–VIII	+		94.3	98.3	98.3	98.3	98.4	98.4	99.0	99.1	100	
38. III–IV		+	81.8	93.0	98.3	99.1	100					
39. III–V		+	94.8	98.3	99.3	99.7	99.9	100				
40. III–VI		+	90.2	95.9	98.5	99.2	99.7	99.7	100			
41. III–VII		+	90.2	93.8	96.6	96.7	96.8	96.8	96.8	96.8	96.8	96.8
42. III–VIII		+	92.8	96.9	97.3	97.5	97.5	97.5	97.5	97.5	97.5	97.5

[a] Micronized powder. [b] Corticoid was solvent-deposited on the surface of the silica by the method of Yang *et al.* (3).

EXPERIMENTAL

Materials—The following were obtained from commercial sources: anhydrous micronized prednisolone[1] (I); micronized prednisone, USP[1] (II); micronized hydrocortisone[2] (III); three grades of porous silicas[3]; two types of nonporous silicas[4]; *N,N*-dimethylacetamide[5]; polyethylene glycol 400[6]; anhydrous ethanol (UV grade)[7]; hydrochloric acid[7]; sodium chloride[7]; monobasic potassium phosphate (AR)[7]; sodium hydroxide pellets[7]; phosphate buffer, pH 7[8]; phosphate buffer, pH 4[8]; and distilled water. The following equipment was used: double-beam spectrophotometer[9]; pH meter (Model DB-GT)[8]; analytical balance[10]; USP XIX dissolution test basket assembly[11]; polytherm constant-temperature water bath[12]; 13-mm Swinny adapter[13]; filter paper, 0.45-μm porosity[13]; plastic syringe[13]; and quartz electric stopwatch[14].

Methods—Corticoid solutions were prepared by dissolving 1 g of corticoid in a sufficient quantity of *N,N*-dimethylacetamide–polyethylene glycol 400 (7:3 v/v) to make 10 mL of solution. The weights of mixed solvent used are: for I, 9.2031 g; for II, 9.2067 g; for III, 9.2086 g.

Corticoid–silica dispersions were prepared by placing 1 mL of corticoid solution (1 mL of prednisolone solution weighs 1.01 g) in a mortar and adding 3 g of silica. Simple admixture with a pestle produced a homogeneous free-flowing powder. Aliquots of 0.401 g should contain 10 mg of prednisolone. All corticoid solution–silica samples were prepared in duplicate.

Spectrophotometric absorption and calibration curves were obtained by diluting the corticoid solutions with simulated GI media, without enzymes (4), and wavelengths for maximum absorbance were determined (Table I). Absorbance *versus* concentration plots (concentration range 3–12 μg/mL) revealed that Beer's law was followed (regression coefficient, 0.999). To blank out interference from the organic solvents present, stock solutions of simulated GI fluids were used which contained identical quantities of mixed solvent without the corticoid.

The assay of the corticoid solution–silica dispersions involved the extraction of 1 g of corticoid solution–silica dispersion with 15 mL of ethanol four times. The ethanol extracts were combined and centrifuged. Three milliliters of supernatant was diluted to 200 mL with ethanol, and the absorbance was measured at the wavelength shown in Table I.

Dissolution rates of the corticoid solution–silica dispersions were determined by the USP basket method (1) using 1000 mL of simulated gastric juice without pepsin (pH 1.2) or simulated intestinal fluid without pancreatin (pH 7.4). Dispersions which contained the equivalent of 10 mg of corticoid were placed in the basket, which was lowered to a depth 2 cm from the bottom of the vessel and rotated at 150 rpm. All dissolution studies were conducted at 37 ± 0.5°C.

Five-milliliter aliquots were withdrawn midway between the surface

[1] Lots 314GR (prednisolone) and 7A566 (prednisone); The Upjohn Co., Kalamazoo, Mich.
[2] Lot 8X371; Pfizer Inc., New York, N.Y.
[3] Syloid 63 (IV), Syloid 72 (V), and Syloid 244 (VI); Davison Chemical Div., W. R. Grace & Co., Baltimore, Md.
[4] Cab-O-Sil EH-5 (VII); Cabot Corp., Boston, Mass. Aerosil 380 (VIII); Degussa Inc., Pigments Div., New York, N.Y.
[5] Eastman Kodak Co., Rochester, N.Y.
[6] Ruger Chemical Co., Inc., Irvington, N.J.
[7] J. T. Baker Chemical Co., Phillipsburg, N.J.
[8] Beckman Instruments, Fullerton, Calif.
[9] Model 124; Coleman Instruments Div., Maywood, Ill.
[10] Mettler Instrument Corp., Hightstown, N.J.
[11] Hanson Research Corp., Northridge, Calif.
[12] Bench Scale Equipment Co., Inc., Dayton, Ohio.
[13] Millipore Corp., Bedford, Mass.
[14] Citizen Watch Corp., Tokyo, Japan.

of the dissolution medium and the bottom of the vessel, filtered through 0.45-μm membrane, and assayed spectrophotometrically. The volume of the dissolution medium was maintained at 1000 mL by the addition of the appropriate medium and cumulative corrections were made for the previously removed samples in determining the total amount of drug in solution. The results of all the dissolution studies, which were run in duplicate, are shown in Table II.

RESULTS AND DISCUSSION

The data in Table II clearly show the more rapid presence of I, II, or III in either dissolution medium when the corticoid solutions were dispersed on the five silicas used. As a micronized powder, II (samples 19 and 20) dissolved very slowly in either GI medium; after 20 min <60% had dissolved. However, when a solution of II was dispersed on IV, V, or VI, >70% of II was in solution within 5 min (samples 21, 22, and 23) in simulated gastric juice. In simulated intestinal juice, the rate was not as large; within 10 min >68.5% of II had dissolved (samples 26, 27, and 28).

Silicas IV, V, and VI were consistently more efficient in releasing the drug solutions dispersed on them than were VII and VIII. When silicas VII and VIII were used with a solution of II <100% of II had dissolved in the simulated GI media after 120 min (samples 24, 25, 29, and 30).

A comparison of solvent-deposited I with its silica-dispersed solution is also of interest. In every instance the silica-dispersed solutions were superior (samples 3 *versus* 13, 4 *versus* 14, 5 *versus* 15; 8 *versus* 16, 9 *versus* 17, and 10 *versus* 20). Ball-milled samples were not prepared. However, Yang *et al.* (3) reported that after ball-milling prednisone with a 20-fold excess of IV, V, or VI, a maximum of 65% of II had dissolved after 120 min in simulated GI media. Their dissolution studies were conducted at 100 rpm. Narurkar and Jarowski (5) also reported similar slow dissolution rates for I that had been ball-milled with various ratios of IV, V, VI, or VII. When solutions of I or II were dispersed on IV, V, VI, VII, or VIII and their dissolution rates studied at 100 rpm, all but one sample released 83–99% within 120 min. The exception was a solution of II dispersed on VI; only 60% had dissolved in simulated intestinal fluid after 120 min.

Such reduction in dissolution rate resulting from reduced basket speed is of concern since the anticipated superiority in the *in vivo* performance of silica-dispersed solutions over micronized powders is suspect. A preliminary *in vivo* experiment with salicylamide indicates that more rapid oral absorption does occur when the compound is dissolved and dispersed on silica. This data will be published elsewhere.

REFERENCES

(1) "The United States Pharmacopeia," 19th rev., U.S. Pharmacopeial Convention, Rockville, Md., 1975, pp. 398, 404.

(2) T. H. Nguyen, Master's Thesis, St. John's University (1978).

(3) K. Y. Yang, R. Glemza, and C. I. Jarowski, *J. Pharm. Sci.*, **68**, 560 (1979).

(4) "The United States Pharmacopeia," 19th rev., U.S. Pharmacopeial Convention, Rockville, Md., 1975, p. 765.

(5) A. N. Narurkar, Doctoral Thesis, St. John's University (1979).

Synthesis of New 8-(5-Substituted Amino-1,3,4-oxadiazol-2-yl) and 8-(5-Substituted Amino-1,3,4-thiadiazol-2-yl) Methoxyquinolines with Antibilharzial Activity

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Received November 8, 1982, from the **Department of Pharmaceutical Chemistry, Faculty of Pharmacy* and the ‡*Department of Chemistry, Faculty of Science, University of Alexandria, Alexandria, Egypt.* Accepted for publication February 1, 1983. §Present address: College of Pharmacy, University of Florida, J. Hillis Miller Health Center, Gainesville, FL 32610.

Abstract □ Several 5-substituted amino-1,3,4-oxadiazol-2-yl and 5-substituted amino-1,3,4-thiadiazol-2-yl derivatives with different 8-hydroxyquinoline moieties in the 2-position were prepared and tested for their antiparasitic activity. Preliminary biological tests on mice experimentally infested with *Schistosoma mansoni* revealed that the new compounds show moderate schistosomicidal activity.

Keyphrases □ 8-(5-Substituted amino-1,3,4-oxadiazol-2-yl) methoxyquinolines—synthesis, antibilharzial activity against *Schistosoma mansoni* □ 8-(5-Substituted amino-1,3,4-thiadiazol-2-yl) methoxyquinolines—synthesis, antibilharzial activity against *Schistosoma mansoni* □ Antischistosomal agents—synthesis of 8-(5-substituted amino-1,3,4-oxadiazol-2-yl) and 8-(5-substituted amino-1,3,4-thiadiazol-2-yl) methoxyquinolines

The fact that lucanthone (1) and its active metabolite hycanthone (2) were the first metal-free compounds to show clinical activity against bilharziasis initiated the synthesis of a distantly related compound 6-chloro-5-(2-diethylaminoethylamino)-8-methylquinoline. The latter exhibited outstanding activity against experimental schistosomiasis (3, 4). Unfortunately, preclinical toxicity studies indicated wide differences among various species of laboratory animals, precluding early clinical trials of this compound (3). A new entry in bilharzial chemotherapy is 1,2,3,4-tetrahydro-2-[[(1-methylethyl)amino]methyl]-7-nitro-6-quinolinemethanol (oxamniquine). It has potent schistosomicidal activity against *Schistosoma mansoni* by causing worms to shift from the mesenteric veins to the liver, where they are destroyed (5).

In our previous work (6) several 3-mercaptotriazoles with the 8-hydroxyquinoline moiety were prepared by cyclization of their corresponding substituted thiosemicarbazides by the action of hot sodium hydroxide solution. Preliminary biological tests revealed that those mercaptotriazoles showed potent schistosomicidal activity. These observations prompted the synthesis of several 5-substituted amino-1,3,4-oxadiazol-2-yl and 5-substituted amino-1,3,4-thiadiazol-2-yl derivatives with different 8-hydroxyquinoline moieties in the 2-position. Contrary to the mercaptotriazoles, the incorporation of the potent antiparasitic drug iodochlorhydroxyquinoline in the 2-oxadiazole or 2-thiadiazole rings produced compounds with moderate or low schistosomicidal activity.

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