time of aprindine. None of the eight compounds tested interfered with the aprindine peak (Table I).

Duplicate injections of five 50-mg raw material samples, extracted by a single analyst, gave a standard deviation (*SD*) of 0.01 and a relative standard deviation [*RSD* = (*SD* × 100)/mean] of 1.48%. Duplicate injections of five capsule samples containing 25 mg/capsule gave a relative standard deviation of 1.04%. The relative error calculated for this formulation was +0.2%. Duplicate injections of five solution samples (1 mg/ml) gave a relative standard deviation of 0.79%.

No extra peaks were observed in the chromatograms of the refluxed or heated samples. Table II summarizes the results of the various degradation studies. With the exception of samples irradiated with UV light, the data indicate that aprindine is stable to these artificial degradation conditions. Analysis of the UV-irradiated solution showed detectable extra peaks. These were identified on the basis of their retention times to be *N*-phenyl-2-indanamine (II) and *N,N*-diethyl-*N'*-phenyl-1,3-propanediamine (III).

The formation of II and III may be due to a UV light-catalyzed homolytic cleavage of the appropriate carbon–nitrogen bond. Compounds II and III were reported previously as metabolites of aprindine (1, 4). None of the degraded solutions showed any interference with the assay of aprindine. Due to the light sensitivity of aprindine, ampul formulations must be protected from light. Natural shelflife stability data on raw material and capsule formulations for 2 years and on ampuls for 1 year indicate that the material is stable.

REFERENCES

(1) *Acta Cardiol., Suppl.*, **18**, 131, 177, 195, 233(1974).

(2) H. Kesteloot, W. Van Mieghem, and H. De Geest, *Acta Cardiol.*, **28**, 145(1973).

(3) M. F. Rousseau, L. A. Brasseur, and J. M. Detry, *ibid.*, **28**, 456(1973).

(4) L. Dodion, J. M. De Suray, M. Deblecker, and A. Georges, *Therapie*, **29**, 221(1974).

(5) J. P. Van Durme, M. G. Bogaert, and M. T. Rosseel, *Br. J. Clin. Pharmacol.*, **1**, 461(1974).

(6) J. P. Van Durme, M. G. Bogaert, and M. T. Rosseel, *Eur. J. Clin. Pharmacol.*, **7**, 343(1974).

(7) F. Verdonck, J. Vereecke, and A. Vleugels, *Eur. J. Pharmacol.*, **26**, 338(1974).

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Comparative Plasma Concentrations of Quinidine following Administration of One Intramuscular and Three Oral Formulations to 13 Human Subjects

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Abstract □ Three oral dosage forms of quinidine sulfate (*i.e.*, tablet, capsule, and solution) and one intramuscular formulation of quinidine gluconate were administered to 13 healthy volunteers in a randomized complete crossover design. The plasma concentration of quinidine following each dose (equivalent to 167 mg of quinidine) was determined at 0.25, 0.50, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hr following dosing. Three conclusions were derived from analysis of the plasma concentration *versus* time data. First, the intersubject and intrasubject variability in the half-life of quinidine is large and should be considered in evaluating the bioavailability of quinidine. Second, the intramuscular quinidine gluconate gives a greater bioavailability than the quinidine sulfate tablet. And finally, the relative bioavailability of the quinidine sulfate capsule and solution administered orally as compared with the intramuscular quinidine gluconate depends on the methods employed to evaluate the plasma concentration *versus* time data.

Keyphrases □ Quinidine—pharmacokinetics and bioavailability of different dosage forms compared □ Pharmacokinetics—quinidine, different dosage forms compared □ Bioavailability—quinidine, different dosage forms compared □ Dosage forms—tablets, capsules, solutions, and intramuscular quinidine, pharmacokinetics and bioavailability compared □ Antiarrhythmic agents—quinidine, pharmacokinetics and bioavailability of different dosage forms compared

Quinidine is widely recognized as a clinically useful antiarrhythmic agent (1, 2). The plasma concentration *versus* time plots following both single and multiple doses were studied in several species of laboratory animals (3, 4) and in a relatively small number of humans (5–8). Intravenously administered quinidine hydrochloride gave varying plasma half-life values, depending on the species of laboratory animal (3).

Three different salts of quinidine (*i.e.*, sulfate, gluconate, and polygalacturonate) and dihydroquinidine gluconate were administered by mouth to 11 patients in both single- and multiple-dose studies (5). Following a single dose of quinidine sulfate, the maximum mean plasma concentration was 4.02 ± 0.74 (*SD*) μg/ml 2 hr after dosing. With multiple dosing, the gluconate and sulfate salts (in doses equivalent to 400 mg of quinidine sulfate every 8 hr) were most effective and gave steady-state plasma levels between 4 and 7 μg/ml.

The serum quinidine concentrations were determined in 17 patients taking 1–3 g of quinidine sulfate/day (6). The serum quinidine concentration following a single 664-mg dose of quinidine sulfate was measured at frequent intervals over 24 hr. The maximum serum concentration ranged from about 4 to 6 μg/ml, and the time to reach the maximum serum concentration ranged from 2 to 5 hr.

Three different oral quinidine preparations were administered to seven healthy volunteers in a comparative bioavailability study (7). The mean steady-state

Table I—Treatment Schedule

Subject	Time Period 1	2	3	4
1	Capsule	Tablet	Injection[a]	Solution[b]
2	Capsule	Solution	Injection	Tablet
3	Capsule	Injection	Tablet	Solution
4	Tablet	Capsule	Solution	Injection
5	Tablet	Solution	Capsule	Injection
6	Tablet	Injection	Solution	Capsule
7	Injection	Tablet	Solution	Capsule
8	Injection	Capsule	Tablet	Solution
9	Solution	Injection	Capsule	Tablet
10	Solution	Tablet	Capsule	Injection
11	Solution	Capsule	Injection	Tablet
12	Tablet	Capsule	Solution	Injection
13	Tablet	Capsule	Solution	Injection

[a] Intramuscular injection. [b] Orally administered solution.

serum concentrations of quinidine were determined following a dosage regimen of 330 mg of quinidine base as the bisulfate salt in rapidly dissolving tablets, in a slowly dissolving form, and in a slowly dissolving arabogalactone sulfate form. A higher mean serum level was found for the more rapidly dissolving form than for the slow dissolving sustained-release forms.

Serum quinidine concentrations also were determined following a single 600-mg quinidine sulfate dose to each of 10 healthy subjects, 10 patients with congestive heart failure, and 10 patients with renal insufficiency (8). This study demonstrated the great variability of serum quinidine levels among subjects within each group as well as the differences between serum levels of the normal subjects and those with one of the diseases.

In the present study, the plasma quinidine concentration following administration of single doses of four different preparations was measured in a randomized complete crossover design. Three preparations contained quinidine sulfate and were administered by mouth; the fourth was an intramuscular injection of quinidine gluconate. In addition to comparing the bioavailability of the four dosage forms, two other objectives were designed into the study. First, numerous blood samples were drawn to describe the plasma concentration–time plot more accurately than had been done in previous studies while clearly defining the plasma quinidine half-life. Second, because of the large number of subjects being dosed at four different times, the intersubject and intrasubject variabilities can be assessed accurately.

EXPERIMENTAL

Subjects—Sixteen male and two female healthy adult volunteers between the ages of 22 and 40 were admitted to the study. All subjects were within 10% of ideal body weight. Each subject gave a medical history and received a medical examination. Values for the following tests were determined prior to the study and were required to be within the normal range: ECG, chest X-ray, creatinine, blood urea nitrogen, lactic dehydrogenase, alkaline phosphatase, serum glutamic oxalacetic transaminase, blood sugar, calcium, phosphorus, bilirubin, total protein, albumin, cholesterol, uric acid, urinalysis, hematocrit, hemoglobin, platelet count, and prothrombin time. In addition, the following tests were run during each treatment period and were required to be normal: white blood cell count, differential, platelet count, and urinalysis.

Dosage Forms—Four different dosage forms were administered, three by mouth and one by injection into the gluteus maximus. The three oral dosage forms were a tablet[1], capsule[1], and solution[1], each containing 200 mg of quinidine sulfate USP (equal to 167 mg of quinidine base). The oral solution was 1% quinidine sulfate, 1.3% sucrose, and 25% glycerin in water. Quinidine gluconate injection USP[1] was used for the intramuscular injections. All four dosage forms were assayed for potency by USP XVIII methods.

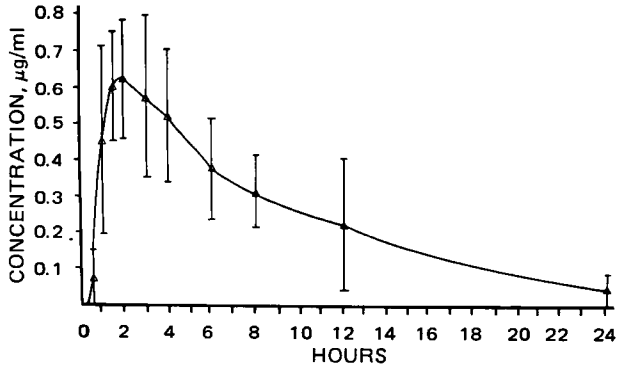

Figure 1—*Plasma concentration (mean ± SD) for 13 subjects following administration of a single capsule containing 200 mg of quinidine sulfate.*

Protocol—Subjects were permitted no food or drink for 10 hr prior to dosing and then were given only 100 ml of water with the quinidine and 100 ml of water each hour for 4 hr. A uniform lunch was provided 4 hr after dosing; after lunch, water was permitted *ad libitum*. All subjects were required to remain upright (standing, sitting, or walking) during the observation period (*i.e.*, 12 hr after dosing).

Blood (10 ml) was taken from the forearm vein *via* a heparin lock immediately prior to dosing and then at 0.25, 0.50, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hr following dosing. The blood samples were drawn into heparin-containing vacutainer tubes and centrifuged at 2500 rpm within a few minutes of collection. The plasma samples were immediately frozen (−20°), and they remained frozen until analyzed.

Treatments and Schedules—The study was originally designed to contain four replications of a basic 4 × 4 Latin square with two extra subjects. A single dose (equal to 167 mg of quinidine) was to be administered to each subject each week over 4 successive weeks. However, only 13 of the original 18 subjects completed the schedule[2]. The resulting randomized complete crossover design is shown in Table I.

Because two subjects experienced chills, fever, arthralgia, and mild tachycardia 12 hr after the third treatment, the fourth treatment period was delayed 2 weeks so that the possible adverse drug reaction could be investigated. Therefore, the first three treatments were separated by 7-day intervals while the fourth was separated by a 21-day interval.

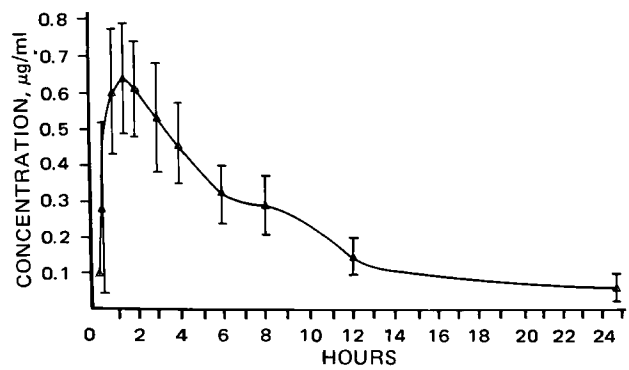

Figure 2—*Plasma concentration (mean ± SD) for 13 subjects following administration of a single tablet containing 200 mg of quinidine sulfate.*

[1] Supplied by Eli Lilly Co.

[2] The five subjects did not complete the study for the following reasons: two experienced chills, fever, arthralgia, and mild tachycardia after the third dose; the platelet count of one subject fell to 169,000; and two others developed conflicts with their work schedules.

Table II—Analysis of Variance for All Four Treatments (Randomized Complete Block, Two-Way Analysis)[a]

Parameter	Mean[b] Injection	Solution	Capsule	Tablet	df[c]	SS[d]	MS[e]	F Ratio
AUC_0^{24}, $\frac{\mu g \times min}{ml}$	472.6	305.4	337.9	318.7	3	231,986	77,328	16.05+
Subject					12	409,236.5	34,103	7.08+
Error					36	173,370	4,816	
Total					51	814,592.7		
C_p^{max}, $\frac{\mu g}{ml}$	0.908	0.673	0.721	0.692	3	0.455	0.1515	7.81+
Subject					12	0.959	0.0798	4.114+
Error					36	0.699	0.0194	
Total					51	2.11		
t_{max}, min	101	84.8	97.3	88.4	3	2,279	759.9	0.43 ns
Subject					12	44,129	3,677	2.12*
Error					36	62,299	1,730	
Total					51	108,707		
$(AUC_0^{\infty})(\beta)$, $\frac{\mu g}{ml}$	0.846	0.774	0.721	0.598	3	0.426	0.142	3.732*
Subject					12	2.010	0.168	4.401+
Error					36	1.370	0.038	
Total					51	3.807		

[a] ns = not significant at 0.05 level, * = significant at 0.05 level, and + = significant at 0.01 level. [b] Underlined values are not significantly different from each other when using Duncan's new multiple range test ($p < 0.05$). [c] Degrees of freedom. [d] Sums of squares. [e] Means squares.

Plasma Quinidine Analysis—The plasma concentration of quinidine was determined by the fluorometric method of Cramer and Isaksson (9). Each plasma sample was assayed in triplicate, and the mean value was used in the data treatment.

Treatment of Data and Statistical Analysis—The plasma concentration, C_p, *versus* time, t, was plotted for each dose administered. The maximum plasma concentration, C_p^{max}, and the time required to reach the maximum plasma concentration, t_{max}, were determined directly from the graphs. By using the trapezoidal method, the area under each plasma concentration–time plot for the first 24 hr following dosing, AUC_0^{24}, was calculated. For each dose, a plot of ln C_p *versus* t was made using the data at 6, 8, 12, and 24 hr.

The least-squares value of the slope, β, and the correlation coefficient, r, was calculated for each semilog plot. The biological half-life, $t_{1/2}$, for each dose was calculated using the equation $t_{1/2} = 0.693/\beta$. An adjustment of the area under the curve to add the area beyond 24 hr was calculated as:

$$AUC_0^{\infty} = AUC_0^{24} + (C_p{}^{24}/\beta) \qquad \text{(Eq. 1)}$$

where $C_p{}^{24}$ is the plasma concentration at 24 hr. Due to the relatively large variability in the biological half-lives among and within subjects, a "normalized area under the curve," $(AUC_0^{\infty})(\beta)$, was computed for each dose in each subject. The rationale and equations for correcting the area under the curve data for variability in the biological half-life were described by Wagner (10).

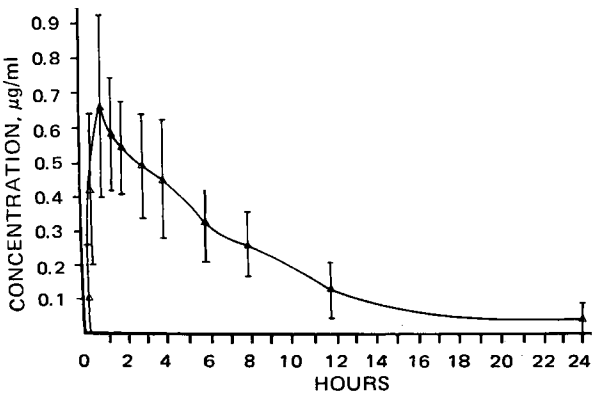

Figure 3—*Plasma concentration (mean ± SD) for 13 subjects following administration of a single oral solution containing 200 mg of quinidine sulfate.*

Each parameter [*i.e.*, C_p^{max}, t_{max}, AUC_0^{24}, and $(AUC_0^{\infty})(\beta)$] was evaluated for statistical significance using a two-way analysis of variance[3] and Duncan's new multiple range test. The sources of variation in the analysis included treatments, subjects, and residual.

RESULTS

Figures 1–4 present the mean plasma concentration–time plots for each treatment in 13 subjects. The standard deviation for the plasma concentration at each sampling time is indicated. Figure 5 presents the mean plasma concentration–time plots for comparison of all four treatments. An analysis of variance among the parameters determined [*i.e.*, C_p^{max}, t_{max}, AUC_0^{24}, and (AUC_0^{∞}) (β)] for all four treatments is shown in Table II. Table III presents the biological half-lives, $t_{1/2}$, and the least-squares values for the slopes, (β), of the ln C_p *versus* t plots along with their correlation coefficients, r.

DISCUSSION

The relatively large standard deviations shown in Figs. 1–4, the variability in the biological half-lives of Table III, and the large F-values for subject variability in Table II indicate a substantial vari-

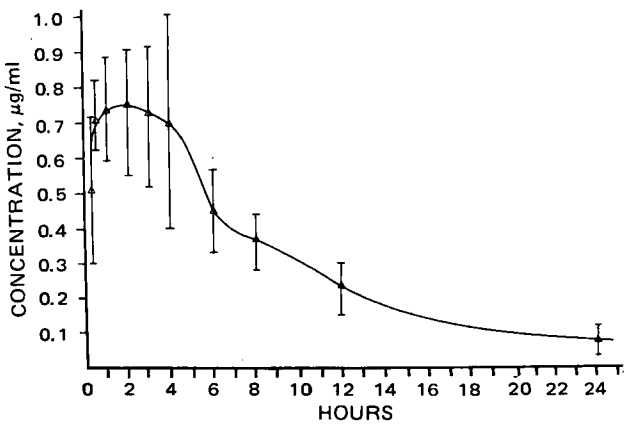

Figure 4—*Plasma concentration (mean ± SD) for 13 subjects following intramuscular injection of 321 mg of quinidine gluconate.*

[3] Monroe calculator program 2001-B.

Table III—Elimination Rate Constants[a] and Biological Half-Lives

	Treatment Period											
	1			2			3			4		
Subject	β, hr^{-1}	$t_{1/2}$, hr	r^b	β, hr^{-1}	$t_{1/2}$, hr	r^b	β, hr^{-1}	$t_{1/2}$, hr	r^b	β, hr^{-1}	$t_{1/2}$, hr	r^b
1	0.104	6.66	0.980	0.163	4.25	0.997	0.105	6.60	0.980	0.131	5.29	0.999
2	0.120	5.78	1.00	0.155	4.47	0.997	0.126	5.50	1.00	0.163	4.25	0.997
3	0.083	8.35	0.990	0.112	6.19	0.990	0.097	7.14	0.985	0.205	3.38	0.979
4	0.059	11.75	0.983	0.082	8.45	1.00	0.131	5.29	0.990	0.076	9.12	1.00
5	0.044	15.75	0.966	0.046	15.1	0.977	0.083	8.35	0.980	0.057	12.16	0.980
6	0.068	10.19	0.993	0.090	7.70	1.00	0.150	4.62	0.920	0.220	3.15	0.980
7	0.091	7.14	0.980	0.146	4.75	0.999	0.217	3.19	0.990	0.115	6.03	0.980
8	0.084	8.25	0.970	0.099	7.00	1.00	0.073	9.49	0.970	0.284	2.44	0.996
9	0.067	10.34	0.970	0.071	9.76	1.00	0.161	4.30	0.939	0.086	8.06	0.995
10	0.085	8.15	0.957	0.153	4.53	0.995	0.135	5.13	0.990	0.123	5.63	1.00
11	0.096	7.22	0.934	0.173	4.01	0.956	0.211	3.28	0.990	0.142	4.88	0.988
12	0.134	5.17	0.998	0.154	4.50	0.972	0.213	3.25	0.985	0.137	5.06	1.00
13	0.129	5.37	0.991	0.239	2.90	0.990	0.596	1.16	0.950	0.177	3.92	0.990

[a] Determined by least-squares fit of the natural logarithm of the plasma concentration plotted against time for the 6-, 8-, 12-, and 24-hr points. [b] Correlation coefficient.

ability in plasma levels attained for quinidine within and among subjects receiving the same dose. Specifically, the range in the biological half-life was 15.75–1.16 hr. Although the variability within a single subject was less than the variability among subjects, it was still considerable. With such significant intrasubject and intersubject variability, utilization of pharmacokinetic methods to "normalize" the data and the use of a complete crossover design become quite important (10).

From the statistical data in Table II, it is apparent that the parameters determined directly from the data (*i.e.*, C_p^{max}, AUC_0^{24}, and t_{max}) show the differences among the three oral dosage forms not to be significant ($p < 0.05$). These data also indicate that the relative amount of quinidine reaching the general circulation is greater from the intramuscular route than from the oral route. However, when the areas under the curve are corrected for the variability in the biological half-life [*i.e.*, (AUC_0^{∞}) (β)], the F-values decrease substantially for both the treatments and the subject variance. This result indicates that the bias produced by the variability in the half-life accentuated any differences among the four dosage forms.

Data from Duncan's new multiple range test support the assertion that the intramuscular route results in greater quinidine availability when only the C_p^{max} and AUC_0^{24} parameters are considered. However, the difference between oral and intramuscular routes decreases greatly when compensation is made for the variability in the biological half-life. Indeed, for the parameter $(AUC_0^{\infty})(\beta)$, only the oral tablet differs significantly from the intramuscular injection ($p < 0.05$).

The statistical analysis indicates that there is no difference ($p < 0.05$) in the time required to reach the maximal plasma concentration among the four treatments. Thus, the rate of absorption is not different for the three oral and one intramuscular preparations.

CONCLUSIONS

The plasma concentration of quinidine following a single dose may differ significantly from person to person and within the same person at different times. Much of this variability is due to the intersubject and intrasubject variabilities in biological half-life. This information points to the importance of individualization of dosage regimens for patients taking quinidine and the possible use of plasma levels in assessing quinidine therapy.

The data presented in this study show no significant differences ($p < 0.05$) in the bioavailability of quinidine from the three oral dosage forms tested. However, depending upon the treatment of the plasma level data, one may or may not conclude that the relative amount of quinidine available from an intramuscular injection is greater than from an equimolar oral dose in the capsule or solution dosage form. This possible difference between the oral and intramuscular routes of administration requires further study. The intramuscular quinidine gluconate does give a greater bioavailability than the quinidine sulfate tablet administered by mouth.

An important conclusion one can draw from these data on quinidine is the necessity for careful evaluation of bioavailability data. In this study, the variability in the biological half-life is sufficient to bias the data and lead one to conclude that the intramuscular route gives a greater bioavailability than any of the oral dosage forms tested; however, if the data are corrected for the variability in the half-life, only the tablet is significantly ($p < 0.05$) less bioavailable than the intramuscular injection.

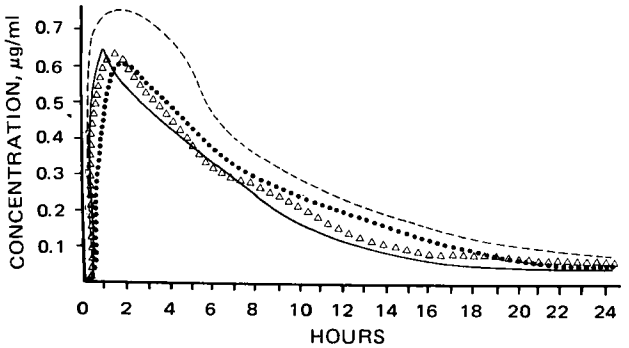

Figure 5—*Comparison of the mean plasma concentration–time curves for the four dosage forms of quinidine administered to 13 subjects. Key: △, tablet; - - -, intramuscular injection; . . ., capsule; and —, oral solution.*

REFERENCES

(1) S. S. Bloomfield, D. W. Romhilt, T. Chou, and N. O. Fowler, *Circulation*, **47**, 967(1973) and *N. Engl. J. Med.*, **285**, 979(1971).

(2) J. Koch-Weser, *N. Engl. J. Med.*, **285**, 1024(1971).

(3) C. A. Neff, L. E. Davis, and J. D. Baggot, *Am. J. Vet. Res.*, **33**, 1521(1972).

(4) J. Nakano and R. B. McCloy, Jr., *Arch. Int. Pharmacodyn. Ther.*, **168**, 400(1967).

(5) W. M. Goldberg and S. G. Chakrabarti, *Can. Med. Assoc. J.*, **91**, 991(1964).

(6) H. E. Archer, D. Weitzman, and H. L. Kay, *Br. Heart J.*, **17**, 534(1955).

(7) R. Henning and G. Nyberg, *Eur. J. Clin. Pharmacol.*, **6**, 239(1973).

(8) S. Bellet, L. R. Roman, and A. Boza, *Am. J. Cardiol.*, **27**, 368(1971).

(9) B. Cramer and B. Isaksson, *Scand. J. Clin. Lab. Invest.*, **15**, 553(1963).

(10) J. G. Wagner, "Biopharmaceutics and Relevant Pharmacokinetics," 1st ed., Drug Intelligence Publications, Hamilton, Ill., 1971, chap. 25.

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GLC Determination of Methotrimeprazine and Its Sulfoxide in Plasma

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Abstract □ A GLC method, based on flame-ionization detection, was developed for the assay of methotrimeprazine and its sulfoxide in plasma. For a 6-ml aliquot, the sensitivity was 2–3 ng/ml for the unchanged drug and 4–5 ng/ml for the sulfoxide. The coefficient of variation, calculated from duplicate analyses of plasma samples, was 8–15% for concentrations between 10 and 100 ng/ml. Patients treated with orally administered methotrimeprazine had higher plasma levels of the sulfoxide than of unmetabolized drug. The method also was applied to the analysis of promazine and chlorpromazine in patient plasma.

Keyphrases □ Methotrimeprazine—base and sulfoxide, GLC analysis, plasma □ GLC—analysis, methotrimeprazine base and sulfoxide, plasma □ Analgesic agents—methotrimeprazine base and sulfoxide, GLC analysis in plasma

Methotrimeprazine[1] (I) has been widely used in Europe as a neuroleptic for the past 15 years. It is usually administered orally as tablets or syrup but occasionally is given intramuscularly. In the United States, the drug is mainly used as an analgesic and only is recognized for intramuscular use. The molecular formula resembles that of chlorpromazine (III), but unmetabolized methotrimeprazine has no electron-capturing groups or positions suitable for introduction of such groups. No sufficiently sensitive and specific assay for the drug in plasma is available, and information about the biological half-life and plasma levels was lacking when this study was undertaken.

Three metabolites have been identified and quantitated in urine from psychiatric patients after oral doses of methotrimeprazine: methotrimeprazine sulfoxide (II), monodesmethyl methotrimeprazine, and monodesmethyl methotrimeprazine sulfoxide (1). The urine contained II in considerably higher concentrations than the other two metabolites.

The pharmacological effects of methotrimeprazine are similar to those of chlorpromazine. A fall in the sitting systolic and diastolic blood pressure produced by chlorpromazine has been correlated with the plasma drug level (2). Sedation and orthostatic hypotension are the most important side effects of methotrimeprazine (3, 4). A method for analysis of this drug in plasma provides an opportunity to examine whether these and other adverse reactions are related to plasma drug concentrations and perhaps to establish a more rational dosage scheme.

[1] Known as levomepromazine in Europe.

A sensitive and specific method for quantitation of chlorpromazine and some of its metabolites in plasma was reported by Curry (5) and has since been modified to improve its sensitivity and accuracy (6–9). The method is based on GLC with electron-capture detection, which permits quantitation of absolute amounts down to 2 ng of chlorpromazine/sample. The method described in this report is based on a modification of the extraction procedure described by Curry (5). By a more extensive purification and concentration of the extract, absolute amounts down to 10–15 ng of methotrimeprazine and 20–25 ng of its sulfoxide/sample can be quantitated by GLC with flame-ionization detection.

By a check on whether other phenothiazines could interfere with the analysis, it became apparent that the method could be used for chlorpromazine and its sulfoxide (IV) in plasma and, by a slight reduction of the column temperature, for promazine (V) in plasma.

Sulfoxidation and *N*-demethylation are two of the known pathways of promazine metabolism in humans (10, 11). Peak concentrations of unchanged promazine in blood shortly after an intravenous injection were measured by a spectrophotometric method (12), but the