Absolute Bioavailability, Rate of Absorption, and Dose Proportionality of Sulpiride in Humans

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Abstract □ The pharmacokinetics of orally administered sulpiride was determined in a series of three studies. In the first study, 12 subjects received an oral solution (200 mg) and an iv dose (100 mg). The second study also included an iv dose, and examined the absorption of 200-, 300-, and 400-mg doses given as 50-mg capsules to six subjects. The third study compared the bioavailability of a 200-mg capsule dose with a 200-mg im dose in eight subjects. The concentration of sulpiride in plasma, red blood cells, and urine was measured by HPLC. The disposition of the drug was generally best described by a two-compartment pharmacokinetic model, with absorption appearing to occur by two sequential zero-order processes. The fraction of dose absorbed after oral administration was ~30% based on plasma and urine data. After the 200-mg dose, the mean elimination half-life was 7.0 h, and the mean residence time was 8.4 h. For each subject, total clearance, corrected for the fraction absorbed, and renal clearance were similar. The dose proportionality study demonstrated linear disposition kinetics.

Sulpiride belongs to a special class of antipsychotic drugs, the substituted benzamides, and possesses a more specific pharmacological profile than the conventional neuroleptics.[1-5] Sulpiride pharmacokinetics after iv or im administrations of a single dose have been investigated by Brès and Bressolle,[3] Bressolle et al.,[2,4] and Wiesel et al.[6,7] The concentration of unchanged drug in plasma versus time and the urinary excretion rate versus time were consistent with a two-compartment, open-body model, with first-order transfer rates among compartments and a first-order elimination rate. We have shown that, after im administration, sulpiride pharmacokinetic parameters are not dose dependent.[2]

Several studies have been conducted in humans following oral administration of the two most commonly prescribed formulations (50-mg capsules and 200-mg tablets) either after a single dose[5-11] or after repetitive dosing.[1,12,13] In almost all these studies, the relative bioavailability of several commercial sulpiride preparations was determined, but not the absolute bioavailability. Sulpiride absorption was relatively slow, with very large interindividual variations in the rate and the extent of absorption. It has been shown that sulpiride absorption does not follow a first-order process and could be a zero-order process.[6,7,8,11] Most of these studies were conducted at only one dose level for each subject,[6-10] and the linearity of the kinetics following oral administration was never demonstrated.

The studies presented here were conducted to obtain more information on the fate of sulpiride after a single oral dose. To this end, the pharmacokinetics of orally administered sulpiride (200 mg either as a solution or as capsules) was evaluated in healthy volunteers of both sexes, and its absolute bioavailability was determined with reference to an iv administration. The absorption profile of sulpiride and its zero-order rate of absorption were determined.[14,15] Plasma and red blood cell (RBC) pharmacokinetics of sulpiride were also evaluated at three dose levels (200, 300, and 400 mg) in order to explore the dose dependency of sulpiride absorption and disposition.

Experimental Section

Drug Products—Sulpiride (5-aminosulfamoyl-*N*-[(1-ethyl-2-pyrrolodinyl)methyl]-2-methoxy benzamide), sulpiride ampules for iv or im injection (100 mg/2 mL) and sulpiride capsules (50 mg/capsule) were obtained from Laboratoires Delagrange (Paris, France). The ampules contained an amount of sulpiride sulfate equivalent to 100 mg of sulpiride free base for each 2 mL.

Subjects—Healthy, nonobese subjects were enrolled in three studies after providing written, informed consent. The subjects were fully informed of the study design and were given all available data on sulpiride clinical and toxicological studies. For each of the three studies, the protocol was approved by the local Ethics Committee.

All subjects were free from cardiac, renal, hepatic, and respiratory diseases and from allergies, according to clinical and biological examinations. All laboratory parameters were monitored before and once during each study. The subjects were not allowed to take theophylline or common dietetary xanthines, caffeine, or theobromine 48 h prior to sulpiride administration and during sample collection. None of the subjects received any drugs for at least 15 days prior to the first sulpiride administration and during all the subsequent studies.

Study Design—In Study I, 12 subjects of both sexes (Subjects 1 to 12) received three different treatments, randomly allocated according to four 3 × 3 Latin squares, and at least 7 days were allowed between two treatments. Treatment 1 was 100 mg of sulpiride administered intravenously, Treatment 2 was 100 mg of sulpiride administered intramuscularly, and Treatment 3 was 200 mg of sulpiride, in the form of a solution, administered orally (the oral solution was prepared from sulpiride ampules for injection).

In Study II, six subjects of both sexes (Subjects 1, 4, 7, 11, 14, 15) received four different treatments: Treatment 1, 100 mg of sulpiride administered intravenously; Treatment 2, 200 mg of sulpiride base in 50-mg capsules administered orally; Treatment 3, 300 mg of sulpiride base in 50-mg capsules administered orally; Treatment 4, 400 mg of sulpiride base in 50-mg capsules administered orally. The three oral treatments were randomly allocated according to two 3 × 3 Latin squares. The period of iv injection was attributed by lot, before or between two oral administrations. At least 7 days were allowed between two treatments.

Study III was conducted in nine male subjects (Subjects 1, 2, 3, 6, and 16–19). Each subject received one dose (200 mg) by the im route, and 200 mg orally in a 50-mg capsule form. Each subject received the two administrations according to four series of 2 × 2 Latin squares. At least 7 days were allowed between two treatments.

In the three studies, the subjects fasted for 12 h prior to drug administration and 4 h after each drug administration; they were given 300 mL of water 1 h before receiving the drug. They were nonambulatory for 6 h after drug administration. A catheter was placed in a forearm vein and a continuous drip was maintained during a 6-h period, after which time blood samples were collected by venipuncture. Oral doses were administered with 100 mL of water. Blood samples (8 mL) were obtained immediately before and 15, 30, 45, 60, 75, 90, and 105 min, and 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 32, and 36 h after each administration. Urine specimens were collected before drug administration and every 1 h during the first 6 h, once every 2 h during the next 6 h, and once for the following intervals: 12 to 16, 16 to 24, 24 to 28, 28 to 32, 32 to 36, and 36 to 48 h.

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Sample Collection—Blood samples were collected in heparinized tubes, and immediately centrifuged to separate the plasma and RBC. Plasma and RBC samples were immediately frozen (−30 °C). The voided urine was collected, the total volume and the pH were recorded, and three 20-mL aliquots were placed in three vials and frozen until analysis.

Assay Method—Sulpiride concentration in plasma, RBC (Study II only), and in urine was assayed, as described in our previous studies,[2-5] using a selective and sensitive reversed-phase HPLC method.[16,17] The practical lower limit of detection was 5 ng/mL. Levels measured below this value were not taken into account for data analysis.

Pharmacokinetic Data Analysis—The plasma and RBC concentrations of sulpiride, as well as the urinary data (excretion rate plot and sigma minus plot), were modeled using the IGPHARM program on a SIRIUS microcomputer by the extended least squares method.[18-20] The exponential parameters, as well as the error model parameters, were estimated. Sulpiride plasma and RBC concentrations versus time curves were modeled for each subject using a one- or a two-compartment open model, with either a first-order (Model M1) or a zero-order (Model M0) rate of absorption. The choice of the order of the absorption kinetic was done with respect to several criteria to assess the goodness of fit of the models to the experimental data. These criteria were as follows: the correlation coefficient between observed and theoretical values; the coefficient of variation of each parameter, defined by the formula CV% = 100 × SD/P, where SD is the standard deviation and P is the mean parameter value (SD was computed using the variance–covariance matrix); the scatter of the plot of the residuals and of the standardized residuals (normalized to the variance model) against time and against computed values; and the correlation matrix. Comparison between competing models was made by using the 2 Log Likelihood, the Akaike test, the Leonard test, and the Schwartz test.[18-20]

The highest observed concentration is designated C_{max}. The value $C_{max}n$ is C_{max} normalized to a 1-mg/kg absorbed dose [i.e., $C_{max}n = (C_{max} \cdot \text{weight})/(\text{dose} \times F_U)$, where F_U is the fraction of the administered dose which is absorbed, as evaluated from urine data as follows: $F_U = U_\infty/\text{dose}$]. The value U_∞ was calculated from the amount recovered after 48 h as follows: $U_\infty = U_{48}/(1 - e^{-k_e \times 48})$. This determination of the fraction absorbed is possible since sulpiride is not metabolized in humans,[9] and its elimination occurs mainly by the renal route.[2-5] The time of the C_{max} concentration relative to the time of dosing was designated t_{max}. The duration of absorption, $t_{max}d$, was the difference between t_{max} and the apparent lag time (t_{lag}). The total area under the concentration versus time curve (AUC) was obtained by linear trapezoidal approximation with correction to time infinity by dividing the last observed data point by the elimination rate constant. The value AUC_n is the AUC normalized to a 1-mg/kg dose. The total clearance (*CL*) was evaluated by the following: $F_U \cdot \text{dose}/\text{AUC}$. The volume of distribution (*Vd*) was the ratio of the total clearance to the apparent rate constant of elimination; *CL* and *Vd* were corrected by F_U. The mean residence time (MRT), a model-independant parameter, was determined by the ratio of AUMC to AUC, where AUMC is defined as the area under the first moment curve.[21] The renal clearance (CL_R) of sulpiride was estimated from the ratio of the amount of unchanged drug excreted in urine to time infinity (U_∞) to the corresponding AUC. A pharmacokinetic analysis of the urinary excretion rate of sulpiride versus time curves (rate plot) or from the amount remaining to be excreted versus time curves (sigma minus plot) was undertaken for each subject using the same computer program.

The ratios of AUC_n and U_∞ after oral and iv administration were used to calculate the fraction of the administered dose which was absorbed or the absorption coefficient F_{AUC} (F_U). The absorption profile was determined using the Loo and Riegelman method.[14,15]

Statistical Analysis—In order to make comparisons across doses, the different parameters were first tested for normal distribution and variance homogeneity. In the case of normality of the distribution and homogeneity of variance, an analysis of variance (ANOVA) on a randomized 3 × 3 Latin square design was performed in Study II. Subject, sequence of administration, and dose were used as the grouping variables. A p value of <0.05 was considered significant.

A two-way analysis of variance was performed for the comparisons, along with symmetrical 95% confidence interval, for plasma versus RBC data.[22]

Results

Pharmacokinetic Parameters from Plasma Data—The detailed results for the iv and the im doses given as part of Study I,[3] Study II,[3] and Study III[2] have been published elsewhere. After oral administration, individual sulpiride concentrations in plasma were systematically interpreted according to two different pharmacokinetic models [i.e., with a zero-order (Model M0) or with a first-order input (Model M1)]. Model M1 underestimated the peak in all data sets. The good agreement between the simulated and experimental data, the correlation coefficient between observed and theoretical values, and the coefficient of variation of each parameter were consistent with a zero-order absorption rate. Model M0 typically produced a significant reduction in the four statistical tests performed compared with Model M1. After the absorption, a two-compartment open model with first-order distribution and elimination adequately described the observed data for the individual oral dose for 16 subjects. The sulpiride plasma concentration versus time curves for two typical subjects are presented in Figure 1.

The mean (±SD) model-independent and model-dependent pharmacokinetic parameters obtained for Study I are presented (Table I). The apparent elimination half-life was in the same range as that obtained after iv administration (F = 0.038, NS). The mean value of the steady-state volume of distribution (*Vd*) and the total clearance (*CL*) and CL_R were much higher after oral administration than after iv administration, with a statistically significant difference for *Vd* (F = 6.318; $p < 0.05$) and CL_R (F = 5.442; $p < 0.05$); no statistically significant difference was found for *CL*, with an F value of 4.456. Individual values showed that these differences between the two routes of administration were unimportant for half of the subjects, so the assay method for plasma and urine seems to yield equivalent results for the samples obtained during the duration of the studies and did not contribute to the same bias. For the six other subjects, both *CL* and CL_R were very much higher after oral administration; the creatinine clearance may have been modified between the two administrations.

Table I—Pharmacokinetic Parameters Determined in 12 Subjects (Study I)[a] from Plasma Levels and Urinary Excretion after Administration of Sulpiride

Parameter	Route of Administration	
	Intravenous	Oral as a Solution
Dose, mg	100	200
Lag time, h	—	0.210 ± 0.240
$t_{max}d$, h	—	1.47 ± 0.789
$C_{max}n$, mg/L	—	0.802 ± 0.440
Cumulative amount in urine (U_∞), %	91.7 ± 11.8	36.9 ± 19.8
AUC_n, mg · h/L	8.27 ± 1.53	2.41 ± 1.48
CL, mL/min[b]	135.3 ± 27.4	207.9 ± 106.6
CL_R, mL/min[c]	130.3 ± 31.1	208.6 ± 113.9
MRT, h	8.16 ± 1.67	8.79 ± 2.06
$t_{1/2}$, h		
Elimination[d]	6.63 ± 1.08	6.73 ± 1.48
Urinary[e]	6.38 ± 0.918	7.10 ± 1.78
Sigma minus[f]	6.48 ± 0.913	8.30 ± 3.58
Vd, L/kg[b]	1.19 ± 0.280	2.05 ± 1.02

[a] Values are means ± SDs; this study was conducted in six male (nos. 1 to 6) and six female (nos. 7 to 12) subjects; mean values (± SDs) of demographic characteristics were 27 ± 3 years for age, 66.0 ± 11.3 kg for weight, and 172 ± 9.6 cm for height. [b] *CL* and *Vd* were corrected by F_U. [c] Mean (± SD) creatinine clearance was 118 ± 30.0 mL/min. [d] Half-life evaluated from plasma data. [e] Half-life evaluated from urinary excretion rate. [f] Half-life evaluated from sigma minus plot.

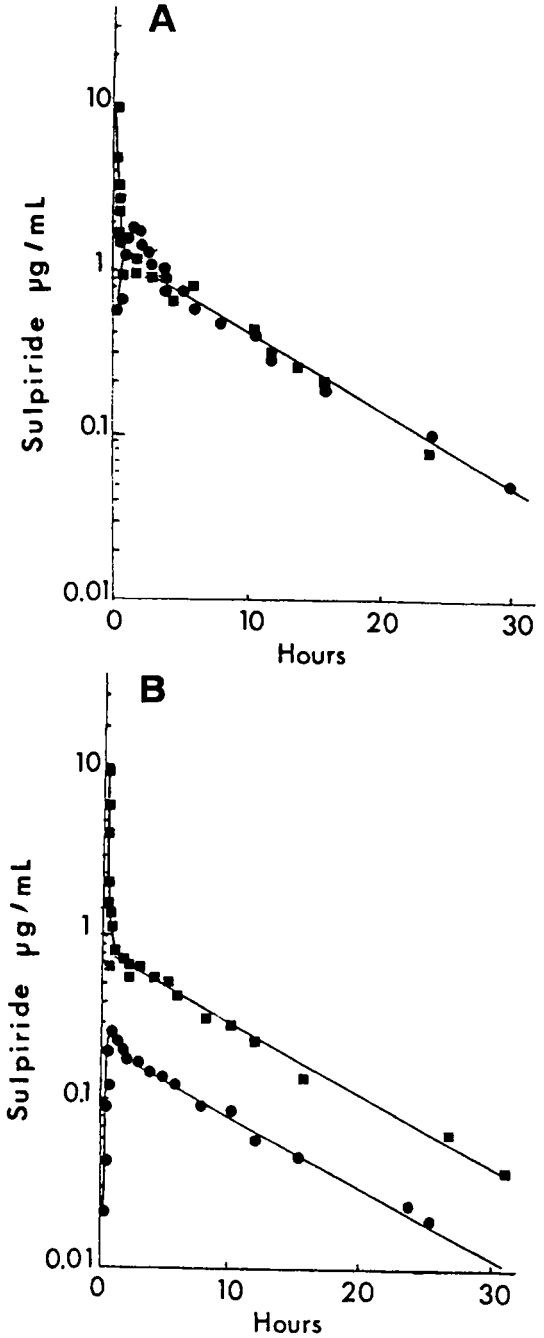

Figure 1—Plasma log concentration versus time curves for sulpiride in two subjects following (■) iv (100 mg) or (●) oral (200 mg) administration of a sulpiride solution: (**A**) Subject 1; (**B**) Subject 5. The lines were obtained when the data were fitted to a two-compartment body model and, for the oral dose, a zero-order absorption rate.

Sulpiride Excretion In Urine—The unchanged urinary sulpiride recovery accounted, in Study I, for 36.9 ± 19.8% of the administered dose (Table I). The mean apparent rate constant of elimination, determined from the variations with time of the urinary excretion rate (rate plot) or from the variations with time of the amount remaining to be excreted (sigma minus method), were close to the rate constant determined from the plasma data (Table I).

Bioavailability—After oral administration, the AUC and the percent of the administered dose recovered in urine were low. The absorption coefficient determined with reference to the iv administration was F_{AUC} = 0.325 ± 0.189 when determined from the AUC and F_U = 0.397 ± 0.201 when determined from the urinary data. Thus, the absolute bioavailability of a sulpiride sulfate solution was ~35%.

Dose Proportionality—For all subjects in Study II, sulpiride levels were determined at each sampling time in plasma and RBC. The observed sulpiride concentrations in plasma for one subject receiving three oral doses are shown in Figure 2. All oral doses led to a short lag time (0.133 to 0.183 h) prior to the beginning of absorption. The mean pharmacokinetic parameters are presented in Table II. For the three doses, the apparent elimination half-life, Vd, CL, CL_R, and the apparent rate constant of elimination determined from the urinary excretion rate versus time plot and from the sigma minus versus time plot were in the same range as those obtained after iv administration. The paired t test failed to show differences in these values. For the three dose levels, the MRTs were higher, as expected, than those observed after iv administration, since $MRT_{po} = MRT_{absorption} + MRT_{iv}$.[21]

There was no significant difference between the dose, subject, and period for the distribution and the elimination pharmacokinetic parameters (Table II). It can be concluded that the distribution and elimination of sulpiride are linear. This fact confirms the results obtained after im administration.[2]

No statistically significant difference in normalized C_{max} values among the three oral doses was detected, although the normalized mean C_{max} decreased with the dose. A statistically significant difference in t_{max}d ($p < 0.01$) was detected, although the mean values for the 300- and 400-mg doses were identical. For the normalized AUC, no significant difference appeared; large variations between subjects ($p < 0.001$) were observed.

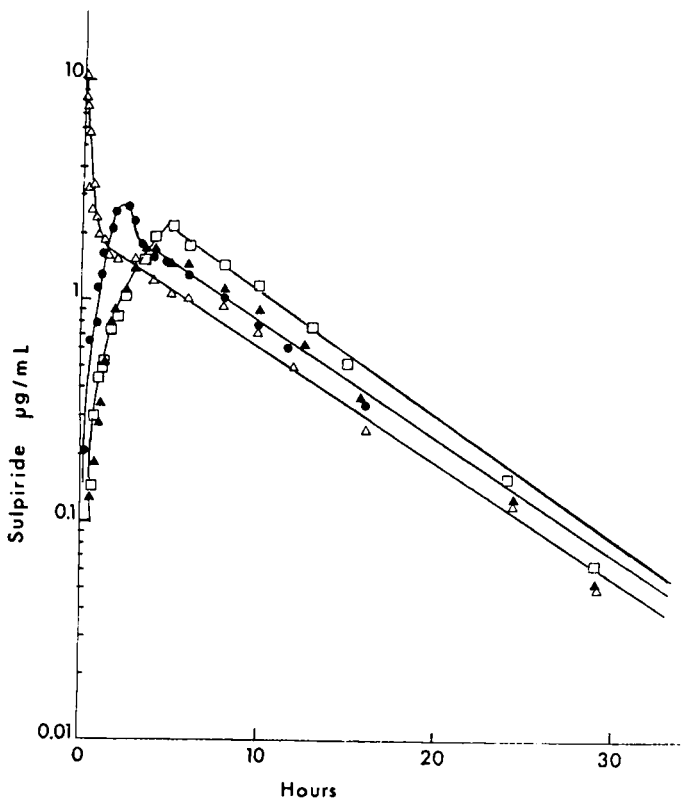

Figure 2—Plasma log concentration versus time curves for sulpiride in Subject 4 following (△) iv (100 mg) or oral administration of sulpiride capsules at three dose levels: (●) 200 mg, (▲) 300 mg, and (□) 400 mg. Absorption of the drug appeared to be higher for the lower dose in this subject.

Table II—Pharmacokinetic Parameters Determined in Six Subjects (Study II)[a] from Plasma Levels and Urinary Excretion after Administration of Sulpiride

Parameter	Route of Administration			
	Intravenous	Oral as Capsules		
Dose, mg	100	200	300	400
Lag time, h	—	0.183 ± 0.0983	0.150 ± 0.0548	0.133 ± 0.0816
t_{max}d, h	—	2.27 ± 0.372	3.17 ± 0.689	3.15 ± 1.20
C_{max}n, mg/L	—	1.10 ± 0.445	1.00 ± 0.281	0.982 ± 0.337
Cumulative amount in urine (U_∞), %	88.3 ± 9.17	24.0 ± 14.7	29.1 ± 8.41	24.8 ± 6.45
AUC_n, mg · h/L	10.4 ± 2.08	2.84 ± 2.18	3.11 ± 1.11	2.58 ± 0.708
CL, mL/min[b]	109.2 ± 20.2	120.8 ± 36.8	124.5 ± 27.4	122.5 ± 24.6
CL_R, mL/min[c]	97.0 ± 23.2	107.6 ± 38.4	111.1 ± 33.6	108.6 ± 26.9
MRT, h	7.48 ± 0.49	9.56 ± 1.99	8.20 ± 1.04	8.24 ± 1.86
$t_{1/2}$, h				
Elimination[d]	5.90 ± 0.370	6.84 ± 1.40	6.26 ± 0.866	6.39 ± 1.74
Urinary[e]	6.03 ± 0.874	7.48 ± 2.24	6.40 ± 1.79	7.16 ± 1.42
Sigma minus[f]	5.92 ± 0.841	6.96 ± 1.91	5.76 ± 1.62	6.75 ± 1.00
Vd, L/kg[b]	0.845 ± 0.165	1.12 ± 0.523	1.04 ± 0.324	1.08 ± 0.486
F_{AUC}	—	0.261 ± 0.175	0.303 ± 0.121	0.248 ± 0.057
F_U	—	0.275 ± 0.176	0.340 ± 0.125	0.280 ± 0.063

[a] Values are means ± SDs; this study was conducted in three male (nos. 1, 4, 14) and three female (nos. 7, 11, 15) subjects; mean values (± SD) of demographic data were 30.2 ± 4.1 years for age, 66.5 ± 8.8 kg for weight, and 175 ± 10.2 cm for height. [b] *Vd* and *CL* were corrected by F_U. [c] Mean (± SD) creatinine clearance was 111 ± 21.7 mL/min. [d] Half-life evaluated from plasma data. [e] Half-life evaluated from urinary excretion rate. [f] Half-life evaluated from sigma minus plot.

The amount of unchanged sulpiride recovered in urine leads to a mean apparent systemic absolute bioavailability of 27 to 34%. These values were of the same order of magnitude as the values found from the AUC values.

Distribution of Sulpiride between Red Blood Cells and Plasma—The RBC:plasma ratio of sulpiride concentration (D) was determined at each sampling time in Study II. The mean values were very close to 1, after either iv or oral administration and for the whole therapeutic range tested. The kinetic parameters determined either from RBC or from plasma levels were very similar, as expected based on this RBC:plasma ratio of 1.

Inter- and Intraindividual Variability—In order to enhance our knowledge of inter- and intraindividual variability, another study (Study III) was conducted in eight male subjects, after oral administration of 200-mg capsules, with reference to the im route (four of these subjects also took part in Study I). For all subjects the best fit was obtained with the two-compartment open model and a zero-order rate of absorption. The mean (±SD) pharmacokinetic parameters are presented in Table III. In these eight subjects, sulpiride plasma levels at 4 h post dosing and AUC values were significantly higher than those obtained in Studies I and II, after either the reference route or after oral administration. Thus, *CL* and CL_R were much lower. The absolute bioavailability with reference to the im route was $F_{AUC} = 0.320 \pm 0.130$ when determined from plasma data and $F_U = 0.280 \pm 0.008$ when determined from the urinary data.

The intraindividual variability can be compared with the interindividual variability since seven subjects received sulpiride on several separate occasions, sometimes with a one- or two-year interval between two administrations (Table IV). Sulpiride absorption parameters (t_{max}, C_{max}, k_o, and AUC) and sulpiride elimination parameters ($t_{1/2}$, CL_R, U_∞) showed an intrasubject variability almost as great as the intersubject variability (Subjects 1M and 11F).

Absorption Profile—Sulpiride absorption kinetics were characterized for all subjects in the three studies, by the construction and evaluation of a percent absorbed–time plot[14,15] (Figure 3). When this plot, on an arithmetic scale, contains linear segments, the slope of such a linear segment is the absorption rate in percent/hour; the absorption rate follows a zero-order process and a plot on a semilogarithmic scale gives a convex curve (Figure 4, inset). In 20 cases out of 30 (seven subjects in Study I and five subjects in Study II), two components were observed in the absorption phase. Sulpiride liberation from the capsules, followed by its dissolution, its absorption, and its penetration into the blood stream, can be described by two sequential zero-order processes with zero-order rates of ~17 mg/h (Study I) and 15 mg/h (Study II) during the first hour and with zero-order rates of ~40 mg/h (Study I) and 30 mg/h (Study II) up to 3–4 h (Table V and

Table III—Pharmacokinetic Parameters Determined in Eight Subjects (Study III)[a] from Plasma Levels and Urinary Excretion Data after Administration of Sulpiride

Parameter	Route of Administration	
	Intramuscular	Oral as Capsules
Dose, mg	200	200
Lag time, h	—	0.210 ± 0.131
t_{max}d, h	0.406 ± 0.129	1.86 ± 0.667
C_{max}n, mg/L	3.44 ± 0.664	3.67 ± 1.30
k_a, h^{-1}[b]	6.85 ± 2.99	—
Cumulative amount in urine (U_∞), %	90.83 ± 7.33	25.75 ± 8.09
AUC_n, mg · h/L	14.45 ± 4.12	4.44 ± 1.50
CL, mL/min[c]	84.4 ± 22.7	78.4 ± 28.7
CL_R, mL/min[d]	77.6 ± 22.5	71.8 ± 27.8
MRT, h	—	6.72 ± 1.09
$t_{1/2}$, h		
Elimination[e]	7.25 ± 3.15	7.50 ± 1.73
Urinary[f]	5.93 ± 1.40	6.79 ± 2.25
Sigma minus[g]	6.07 ± 1.64	6.28 ± 1.79
Vd, L/kg[c]	0.731 ± 0.224	0.732 ± 0.268

[a] Values are means ± SDs; this study was conducted in eight male subjects (nos. 1, 2, 3, 6, 16, 17, 18, 19); mean values (± SDs) of demographic characteristics were 25.8 ± 3.4 years for age, 68.8 ± 5.1 kg for weight, and 178.9 ± 6.1 cm for height. [b] Rate constant for a first-order rate of absorption from the muscle. [c] *Vd* and *CL* were corrected by F_U. [d] Mean (± SD) creatinine clearance was 135.1 ± 38.6 mL/min. [e] Half-life evaluated from plasma data. [f] Half-life evaluated from urinary excretion rate. [g] Half-life evaluated from sigma minus plot.

Table IV—Intraindividual Variability of Sulpiride Pharmacokinetic Parameters Determined from Plasma Levels after Oral Administration

Subject	Study	Time Table, months	Dose, mg	t_{max}d, h	C_{max}n, mg/L	AUC_n, mg · h/L	Vd, L/kg	$t_{1/2}$, h	CL_R, mL/min	U_∞, %
1M	I	0	205	1.60	1.12	3.94	1.26	6.74	133.2	45.3
	II	11	200	2.00	1.01	1.09	1.71	7.70	178.6	17.1
	II	10	300	2.50	0.807	1.07	1.30	5.92	175.4	16.9
	II	12	400	3.00	1.05	2.38	1.11	5.82	149.3	32.5
	III	24	200	1.21	2.78	6.59	0.576	6.85	64.6	36.0
2M	I	0	204	1.48	0.548	1.13	3.59	9.73	197.8	22.7
	III	22	200	2.15	4.09	4.53	0.385	5.50	45.3	20.5
3M	I	0	196	0.76	0.827	0.830	1.85	4.82	286.7	20.9
	III	24	200	1.97	5.21	4.67	0.941	10.52	52.6	21.4
4M	I	0	190	0.807	1.44	2.19	0.900	6.52	112.0	21.3
	II	12	200	2.50	1.50	6.00	0.648	4.71	67.6	49.5
	II	11	300	3.50	1.24	3.89	0.660	5.78	96.2	26.7
	II	10	400	5.00	1.36	3.71	0.526	5.37	92.6	22.7
6M	I	0	204	1.59	1.71	2.69	1.17	9.14	104.7	21.9
	III	22	200	2.44	1.98	3.26	0.672	6.70	82.2	21.7
7F	I	0	196	2.56	1.00	4.57	0.940	6.34	107.3	44.2
	II	11	200	3.00	0.980	4.35	0.980	7.29	75.0	33.0
	II	12	300	3.00	1.18	3.80	1.07	7.06	69.4	32.2
	II	10	400	3.00	0.938	2.38	0.846	5.46	108.7	20.7
11F	I	0	189	1.40	0.653	2.40	1.90	6.83	176.7	49.6
	II	12	200	3.00	0.835	1.34	1.00	6.73	66.7	11.3
	II	11	300	2.50	0.668	3.73	1.21	6.42	100.0	40.2
	II	10	400	3.50	0.627	1.32	1.66	7.18	100.0	16.6

Figure 4).

Only one zero-order process could be detected for one subject (Subject 7 in Study II) and for all the subjects in Study III (Table V). In some subjects, the absorption process might be more complex and could be described by a sigmoid curve, which suggests a three-step absorption process (Figure 3B). In three subjects (Subjects 1, 7, and 14 in Study II), the absorption rate was lower for the 200-mg dose and increased, although not systematically, with the administered dose.

Discussion

Sulpiride is a weak base with a very low water solubility. Its partition coefficients (K_p) between several organic solvents and pH 7.4 phosphate buffer, as determined by Alam et al.,[23] are very low. It would appear, therefore, that the poor solubility of sulpiride is not due exclusively to its marked lipophilic properties. Sulpiride exists mainly in the ionized form at physiological pH, with two pK_a values[24] (pK_{a_1} = 9.00; pK_{a_2} = 10.19). On the basis of the pH–partition hypothesis, sulpiride should be a poorly absorbable drug.[25]

Time to Reach Maximum Plasma Levels—Sulpiride was slowly absorbed after oral administration of a solution or capsules. A lag time of 0.05 to 0.4 h was observed, which may be related to gastric emptying time under fasting conditions. After a 200-mg dose, the mean t_{max} values, adjusted for lag time, were 1.47 h for the oral solution, with values ranging from 0.6 to 3.3 h, and 1.9 or 2.2 h for capsules, with values ranging from 1.0 to 3.2 h. These results are within the range reported by others.[6–11]

Maximum Plasma Level and Area Under the Plasma Concentration versus Time Curve—The mean C_{max} values normalized for a 1-mg/kg absorbed dose were similar in Studies I and II (0.8–1.1 mg/L). In Study III, the mean C_{max} was higher (3.7 mg/L). However, when the distribution was completed, 4 h after drug administration, the mean value was closer to the maximum value observed in subjects of Studies I and II, for which the distribution phase was not apparent.

Studies I and II gave values of total AUC_n close to those reported by Imondi et al.[9] and Sugnaux and Benakis,[11] with values from 2.40 to 3.10 mg · h/L, while we obtained much higher values in Study III (4.4 mg · h/L). The much lower value reported by Wiesel et al.[6,7] should be attributed to much lower levels due to the very large Vd of the subjects included in the study; it is also possible that the plasma assay contributed to some bias.

The large differences in C_{max} and AUC_n between Studies I and II and Study III can be related to variations either in elimination half-life or in distribution since the values for U_∞ indicated that a greater amount absorbed did not account for the increase in C_{max} and AUC_n. The larger elimination half-life for subject 3 in Study III versus Study I (Table IV) could partially explain the results for this subject. However the half-life could not explain the data obtained for Subjects 1 and 2. The higher values found in Study III can be linked to the apparent distribution phase seen after extravascular administration; the lower Vd observed in Study III could also explain these results.

Mean absorption coefficients in all the studies, realized after sulpiride extravascular administration, were of the same magnitude (0.30–0.35[7,11]) in spite of the differences in the population tested or in the protocols and the methods used.

Rate of Absorption—Drug absorption from the gastrointestinal tract (GIT) is generally considered to occur by passive diffusion throughout the gastrointestinal membrane, and the rate of appearance of drug in the systemic circulation can usually be described by simple first-order kinetics. Nevertheless, there are several exceptions, such as amino acids,[25] riboflavin,[25] thiamine,[25] erythromycin,[15] hydroflumethiazide,[15,26] cyclosporin A,[27] colchicine,[28] and chlorpromazine,[29] where active processes are involved and where the absorption may be better described by assuming zero-order (constant-rate) kinetics. These observations were done not only after oral administrations of different commercial dosage forms[26,28] but also after oral administrations of drug as drinking solution[27] and as syrup.[29] For sulpiride, the zero-order absorption rate demonstrated in this study (for the solution as well as for the capsules) is probably due to either a carrier-mediated transport system or to changes in solubility along the GIT (when an excess of dissolving solid maintains a saturated solution of drug), since the physicochemical properties of sulpiride do not allow its absorption by a single passive diffusion process (pH–partition hypothesis).

In previous studies,[9–11] the rate constant of the absorption phase was evaluated on the assumption of a first-order process. Values reported ranged from 0.90 to 1.90 h^{-1}, with

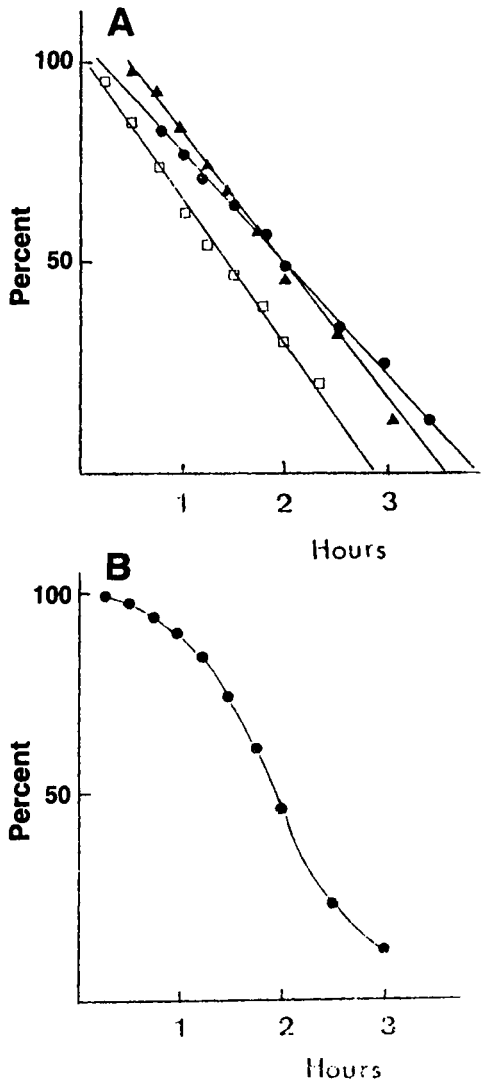

Figure 3—Plot of percent sulpiride remaining to be absorbed versus time after (**A**) oral administration of sulpiride capsules in Subject 7 [200 mg (●), 300 mg (▲), and 400 mg (□)], and (**B**) oral administration of sulpiride (200 mg) in Subject 1.

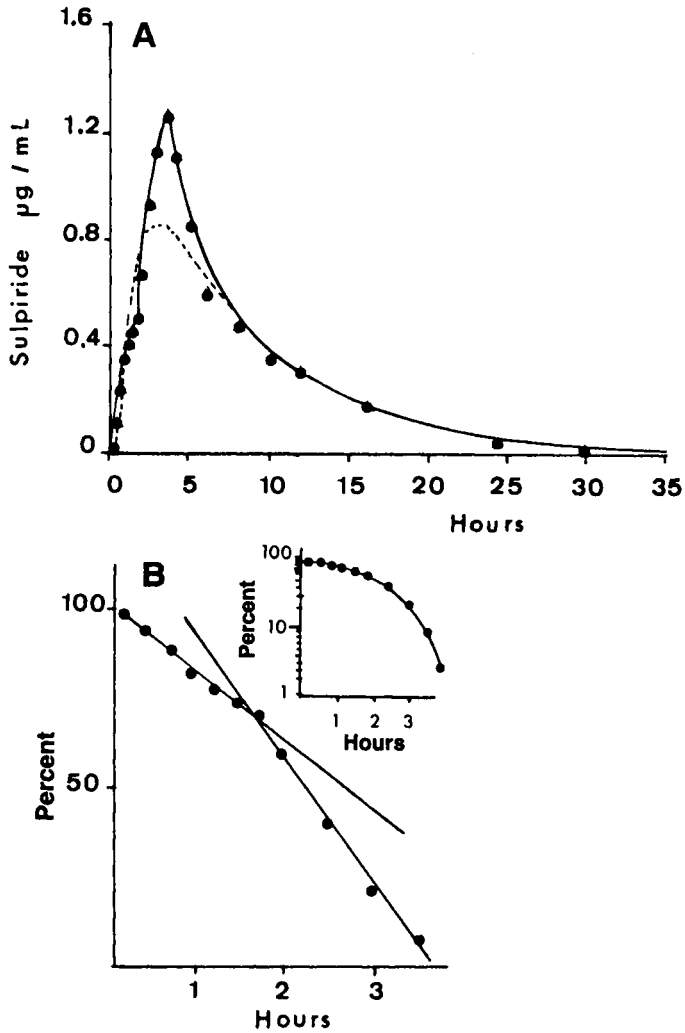

Figure 4—Sulpiride plasma concentration (●) versus time for subject 14 following a single oral 300-mg dose given as capsules: (**A**) best fit curves for a two-compartment model with first-order input (----) and with zero-order input (——); (**B**) percent sulpiride remaining to be absorbed (●) versus time (the inset is a semilogarithmic plot of the data).

half-lives for the absorption process ranging from 20 to 50 min.[9-11] When absorption is fast, the distribution phase is seen, higher maximum plasma levels are obtained, and the data fit a two-compartment model. Kleimola et al.[8] and Wiesel et al.[6,7] did not attempt to evaluate this model-dependent rate constant. Several observations have shown that sulpiride absorption does not follow a single first-order process and that in this case it is meaningless to determine an absorption rate constant.[6,7,8,10,11]

In the three studies presented here, we showed that sulpiride absorption can be described in half of the subjects by two sequential zero-order processes with a rate of 17 ± 13 mg/h during the first 1.5 h, and a rate of 40 ± 20 mg/h between 1.5 and 3 to 4 h. These rates are not related to the administered doses. The two components in the absorption phase were apparent for the solution and for capsules (Table V); thus, the first and lower zero-order rate could not be related to the liberation of sulpiride from the capsules or from its dissolution rate. For the other subjects, only one zero-order process was

Table V—Rate of Absorption for Sulpiride Administered Orally[a]

Study	Dose, mg	k_{o_1}, mg/h				k_{o_2}, mg/h			
		n	Mean	SD	Range	n	Mean	SD	Range
I	200	7	16.9	13.2	1.92–34.6	12	39.4	20.5	13.2–77.8
II	200	5	9.99	9.31	4.42–26.3	6	20.8	15.2	7.81–49.7
	300	5	17.8	11.5	6.18–33.3	6	33.8	14.3	16.1–51.3
	400	3	17.9	3.18	14.4–20.6	6	30.9	11.7	19.1–51.2
III	200	—	—	—	—	8	32.7	17.6	8.3–57.2

[a] For several subjects, two sequential zero-order processes were observed: the first one for some subjects only, with a rate (k_{o_1}) up to 1–1.5 h, and the second one with a higher rate (k_{o_2}) between 1.5 and 4 h.

apparent, with a rate of 32.6 ± 13.6 mg/h during a period of 4 h (Table V).

References and Notes

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