Pharmacokinetics of Sulpiride in Humans after Intravenous and Intramuscular Administrations

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Abstract □ The pharmacokinetics of sulpiride in plasma, red blood cells (RBC), and urine were investigated after administration of 100 mg by the iv route to 15 subjects and by the im route to 12 subjects. The concentrations of sulpiride in plasma, RBC, and urine were measured by HPLC. All the data were consistent with a two-compartment, open-body model. After iv administration, the mean ± SD apparent elimination half-life of sulpiride was 6.47 ± 1.00 h, and the mean ± SD volume of distribution at steady state was 0.94 ± 0.23 L/kg. Renal clearance (119.5 ± 28.2 mL/min) was very close to total clearance (127.8 ± 26.2 mL/min). In urine, the mean ± SD recovery in form of the unchanged drug was 90.0 ± 9.68% of the administered dose, and the excretion rate versus time showed an elimination half-life similar to that found in plasma. The values of all these parameters were very close to those obtained after im administration. The sulpiride partition coefficient between RBC and plasma did not show any significant change as a function of time and concentration, with a mean value ± SD of 1.00 ± 0.043, indicating that sulpiride is evenly distributed between RBC and plasma. The pharmacokinetic parameters determined from the plasma and the RBC data were similar.

Sulpiride belongs to a special class of antipsychotic drugs, the substituted benzamides, and possesses a more specific pharmacological profile than the conventional neuroleptics. Sulpiride selectively blocks the so-called dopamine receptors and probably does not interact with noradrenergic or serotonergic receptor mechanisms.[1] Sulpiride is widely used as a behavior regulator to treat mental disorders, in the psychopathology of senescence, in depression, and in schizophrenia at a daily dose of 200 to 800 mg. Sulpiride is also used at doses of 50 to 150 mg in the treatment of gastric or duodenal ulcers, in the treatment of the irritable colon due to psychosomatic stress, and in various vertigo syndromes. Tolerance to sulpiride is very good, and extrapyramidal, neurovegetative, and endocrine side-effects are rare.[1-3]

Optimization of treatment with sulpiride requires knowledge of its bioavailability, pharmacokinetics, and metabolism in humans. The pharmacokinetic parameters determined after a single dose can then be used for dosage regimen adjustments and individualization of therapy. Sulpiride pharmacokinetics after iv or im administration of a single dose have been investigated by Bressolle et al.,[2] Wiesel et al.,[4,5] and Brès et al.[6] The apparent elimination half-life of sulpiride was ~7 h, and the volume of distribution at steady state was 1 L/kg.[2-5] Though several metabolites have been isolated and identified in different animal species, none of them was found in human urine.[7] Sulpiride is not bound to plasma proteins[8] and is predominantly excreted by the kidneys, mainly by glomerular filtration.[2] In patients with impaired renal function, the elimination half-life is prolonged, while the cumulative amount excreted in the urine, the total and the renal clearances, are significantly reduced.[3]

Several studies have been conducted in humans following oral administration of the two most commonly prescribed formulations, the 50-mg capsules and the 200-mg tablets.[6,9-13] These studies showed a relatively slow absorption rate and very large interindividual variations in the rate and extent of absorption; the mean value for oral bioavailability is ~35%, with values ranging from 10 to 70%.

The objective of the studies presented herein was to determine whether all data deduced from sulpiride plasma levels and the urinary excretion rate of the unchanged drug after iv administration were consistent with a two- or a three-compartment model, with first-order transfer rates among compartments, and a first-order elimination rate, and to determine the extent of interindividual variability. To this end, the pharmacokinetics of sulpiride administered iv was evaluated in 15 healthy volunteers (eight males and seven females). For both genders, two subjects received sulpiride on two separate occasions.

Another objective was to determine the absolute bioavailability of sulpiride after im administration to 12 of the 15 subjects. These studies were conducted at only one dosage level, 100 mg, since we have previously shown[2] that sulpiride pharmacokinetics are not dose dependent when the im dose is 50, 100, or 200 mg.

The last objective of our studies was to determine the extent of sulpiride uptake by red blood cells (RBC) and the concentration and time dependency of this uptake. Diffusion of drugs into RBC and the binding to intracellular components have almost as important clinical implications as plasma protein binding; that is, blood cells can be a vehicle for drug transport to its site of action or may serve a storage function, since in the RBC, the drug is neither metabolized nor filtered through the kidney.[14] It has been reported that many drugs tend to accumulate significantly in the RBC,[14-19] and the unbound fraction in the RBC is in rational agreement with the freely diffusible unbound fraction in the plasma.[14,18,19] For most of these drugs, the target site is the central nervous system, and drug concentration in RBC has been claimed to reflect the brain concentration and clinical responses.[14-17] For phenothiazine, the longer half-life observed in the RBC has been correlated with the clinical effect, namely, acute dystonic reactions.[17] For lithium, determination of the RBC-to-plasma ratio is a criteria of choice for drug monitoring during prolonged therapy,[20] since the level of lithium in brain tissues correlates more closely with the RBC than with the plasma concentration of the ion. We determined sulpiride concentration in the RBC in all samples taken after iv administration of the drug to eight subjects. The sulpiride RBC-to-plasma concentration ratio could thus be evaluated over the entire therapeutic range.

Experimental Section

Drugs—Sulpiride [5-(aminosulfonyl)-*N*[(1-ethyl-2-pyrrolidinyl) methyl]-2-methoxybenzamide] ampules for iv or im injection were obtained from the Laboratoire Delagrange (Paris, France). The 2-mL ampules contained an amount of sulpiride sulfate equivalent to 100 mg of sulpiride free base for every 2 mL.

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Subjects—Two studies were conducted in 15 Caucasoid subjects of both sexes, (19–30 years), who weighed no more than ± 10% of the ideal weight for height, as defined by the Life Insurance Companies Statistical Bulletin. All subjects were in good health as determined by screening, laboratory tests (including hematology, urine analysis, SMA-12, electrocardiogram), history and physical examination, and creatinine clearance. The demographic data and creatinine clearance for each subject are given Table I. The subjects had no history of recent drug intake or allergy. All laboratory parameters were monitored before and once during the study. The subjects were fully informed of the study design and were given all available data on sulpiride clinical and toxicological studies. They were enrolled in the study after having given written informed consent. The protocols were approved by the local Ethics Committee. The subjects were hospitalized for 24 h after each drug administration.

Study design—*Study I*—Twelve subjects (six males and six females; subjects 1 to 12) received the following two treatments according to a randomly assigned sequence: Treatment 1, 100 mg of sulpiride administered iv; and Treatment 2, 100 mg of sulpiride administered im. Subjects 1, 3, 4, 7, 9, and 10 received Treatment 1 followed by Treatment 2. Subjects 2, 5, 6, 8, 11, and 12 received Treatment 2 followed by Treatment 1. At least 7 days were allowed between treatments.

Study II—Seven subjects (four males: subjects 1, 4, 13, and 14; and three females: subjects 7, 11, and 15) received only Treatment 1.

For both studies, the subjects fasted 12 h prior and 4 h after each drug administration, and they received no medication 48 h prior to sulpiride administration. They were not allowed to take theophylline or common dietary xanthines, caffeine, or theobromine 48 h prior to the study and during sample collection. 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 maintained for 6 h, after which time blood samples were collected by venous puncture. No more than 200 mL or sterile isotonic saline (0.9%, w/v) was infused.

The iv administration was made in the forearm vein opposite to the catheter. The im administration was made in the upper quadrant of the gluteus muscle. Blood samples (8 mL) were obtained immediately before and 5, 10, 15, 20, 25, 30, 35, 40, 45, 60, and 90 min, and 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, and 36 h after each injection. Urine was collected before drug administration and at the following intervals after injection: 0–1, 1–2, 2–3, 3–4, 4–5, 5–6, 6–8, 8–10, 10–12, 12–16, 16–24, 24–28, 28–32, 32–36, and 36–48 h.

Sample Collection—Blood samples were collected in heparinized tubes and centrifuged immediately to separate the plasma and the RBC. Plasma (Studies I and II) and RBC samples (subject 12 in Study I and all subjects in Study II) were immediately frozen (−20 °C) since sulpiride is not very stable in biological fluids at room temperature.[21,22] The voided urine was collected, the total volume was recorded, and three 20-mL aliquots were placed in three vials and frozen until analysis.

Table I—Demographic Characteristics and Renal Function for the Fifteen Test Subjects

Subject	Sex	Age, years	Weight, kg[a,b]	Height, cm[c]	Creatinine Clearance, mL/min[b]
1	M	24	69; 70.3	181	113; 114
2	M	21	61	168	90
3	M	25	67	180	160
4	M	30	69; 68	177	120; 80
5	M	26	89	189	160
6	M	24	76	180	160
7	F	29	66; 65	175	120; 130
8	F	25	52	156	103
9	F	22	70	165	103
10	F	21	51	163	120
11	F	26	49.5; 51.5	162	110; 90
12	F	28	70	165	61
13	M	25	70	175	80
14	M	24	75	184	134
15	F	19	68	163	118

[a] Mean values (±SD) for males is 72.0 ± 8.3 kg, and for females is 60.9 ± 9.6 kg. [b] Subjects 1, 4, 7, and 11 received sulpiride iv on two separate occasions, with a 1-year interval between the two administrations. [c] Mean values (±SD) are 179.3 ± 6.2 cm for males and 164.1 ± 5.7 cm for females.

Assay Method—The plasma, RBC, and urine samples were adjusted to pH 10 and then sulpiride was extracted with chloroform. The internal standard used was 5-ethylsulfonyl-*N*[(1-ethyl-2-pyrrolidinyl)methyl]-2-methoxy-4-aminobenzamide (Laboratoires Delagrange, Paris, France). Sulpiride was assayed using a selective and sensitive HPLC method with minor modifications.[2,11,21,22]

The HPLC was carried out using a Spectra-physics apparatus (SP 8100 - 8110). The column was a Lichrosorb-CN 5 μm (25 × 4.6 mm i.d.) at 50 °C. The mobile phase contained methanol and 0.1 M ammonium acetate (7:93) at a flow rate of 1.2 mL/min. The detection of the drug was monitored at 220 nm, using a Schoeffel UV detector. Samples were introduced into the column with a Valco valve loop injector (50 μL). This assay procedure was validated according to GLP guidelines. The inter- and intraday reproducibility of the HPLC assay, as well as its within-run precision (recovery of spiked samples) were determined; the coefficient of variation was < 5% for a concentration range from 25 to 2000 ng/mL; the detection limit was 5 ng/mL.

Data Analysis—The plasma and RBC concentration of sulpiride for each subject was modeled using the PHARM program[23] on a SIRUS microcomputer by the extended least-squares method.[24,25] The exponential parameters, as well as the error model parameters, were estimated. All the results were evaluated according to a two- and a three-compartment model with respect to the following criteria in order to assess the goodness of fit of models to experimental data: correlation coefficient between observed and theoretical values; coefficient of variation of each parameter, defined by the formula CV = 100 × SD/P, where SD is the standard deviation and P the parameter value (SD was computed using the variance-covariance matrix); scatter of the plot of the residuals and of the standardized residuals (normalized to the variance model) against time and against computed values; and correlation matrix. The value of CV may give an indication of the accuracy of the estimate. If CV is > 20–30%, the lack of accuracy may be considered too large to be accepted.

Comparison between competing models was made by using the 2 Log Likelihood, the Akaike test, the Leonard test, and the Schwartz test.[23] The model which minimizes all these statistical tests was the two-compartment model; the pharmacokinetic parameters were determined for this model.

The microscopic rate constants k_{12} (first-order transfer rate constant from the central compartment to the tissue compartment), k_{21} (first-order transfer rate constant from the tissue compartment to the central compartment), and k_{10} (first-order elimination rate constant from the central compartment) were determined from the coefficients and exponents of the biexponential equation of the curve $C = C_1e^{-\lambda 1t} + C_2e^{-\lambda 2t}$. The total area under the plasma concentration versus time curve (AUC) was calculated from $AUC_{36\ h} + C_{36\ h} / \lambda_2$, and $AUC_{36\ h}$ was calculated by the linear trapezoidal rule. The parameter AUC_n is AUC normalized to the 1-mg/kg dose and has a dimension of mg*h/L/(mg/kg). Total body clearance (CL_{tot}) of sulpiride was calculated from the ratio of the dose of sulpiride to AUC. The mean residence time (MRT), a model-independent parameter, was determined by the ratio of AUMC to AUC. The AUMC is defined as the area under the first moment curve; its value can be obtained by the linear trapezoidal rule from the AUC of a plot of the product of drug concentration and time, versus time, with extrapolation to infinity. The renal clearance (CL_r) of sulpiride was estimated by the ratio of the total amount of unchanged sulpiride eliminated in urine (U_∞) to the total area under the curve. The volume of distribution in the central compartment Vd_1 and the steady-state volume of distribution Vd_{ss} were also evaluated.[2,12] A pharmacokinetic analysis of the urinary excretion rate of sulpiride versus time curves (rate plot) was undertaken for each subject using the same computer program.

The ratios of AUC_n [or U_∞ %] after im and iv administration were used to calculate the fraction of the administered dose which was absorbed or the absorption coefficient F_{AUC} (F_U).

Statistical Analysis—For all the results, individual parameters and mean (±SD) were determined; the CV (%) are also given.

An analysis of variance on a randomized 2 × 2 Latin Square design with six replicates was performed to test the equivalence of the im and iv routes. The following parameters were compared: half-life of elimination, microscopic rate constants, steady-state volume of distribution, area under the concentration–time curve, clearances, and

Table II—Pharmacokinetic Parameters Determined from Plasma Levels after Intravenous Administration of Sulpiride

Parameter	Subject 1		Subject 2	Subject 3	Subject 4		Subject 5	Subject 6		Subject 7		Subject 8	Subject 9	Subject 10	Subject 11		Subject 12	Subject 13	Subject 14		Subject 15
	I	II	I	I	I	II	I	I	II	I	II	I	I	I	I	II	I	I	II	II	II
Dose, mg/kg[a]	1.408	1.404	1.611	1.454	1.390	1.442	1.105	1.292	1.463	1.693		1.847	1.393	1.935	2.049	1.917	1.332	1.396	1.385		1.430
Cumulative amount in urine (U_∞), %	89.46	101.6	78.40	96.51	100.8	86.3	97.34	91.04	92.71	80.8		99.73	80.68	101.20	106.90	79.5	65.25	88.9	97.7		84.10
Mean urine flow, mL/min	1.202	1.087	1.337	1.115	1.347	0.757	1.992	1.112	0.809	0.736		0.428	1.480	0.995	0.719	1.055	1.070	0.413	0.758		1.449
AUC, mg · h/L																					
Observed	13.2	13.4	17.3	10.8	11.7	20.4	10.2	8.39	10.9	14.6		14.5	9.24	12.9	11.9	18.5	12.5	15.0	14.8		12.8
To infinity	13.9	13.7	17.7	11.5	12.1	20.7	10.5	8.74	11.0	14.8		15.8	9.41	13.8	12.4	18.7	13.2	15.4	15.1		13.0
Normalized	9.87	9.76	11.0	7.91	8.71	14.4	9.50	6.76	7.52	8.74		8.12	6.76	7.13	6.05	9.75	9.91	11.0	10.9		9.09
CL_{tot}, mL/min	116.5	121.1	92.3	140.9	132.9	79.0	155.4	187.2	146.1	124.3		106.9	172.6	119.2	136.1	88.0	117.5	110.1	119.2		123.6
CL_r, mL/min	109.4	123.2	74.7	141.9	137.6	68.2	156.5	171.6	142.5	100.1		109.4	162.9	125.3	151.4	70.0	81.0	98.0	116.4		104.1
MRT, h	7.62	7.77	7.83	7.76	8.84	7.18	8.14	7.08	6.98	7.81		10.3	4.36	10.3	8.90	7.53	9.86	8.62	6.81		7.80
Dist. $t_{1/2}$, h	0.105	0.124	0.219	0.151	0.131	0.114	0.154	0.291	0.102	0.0905		0.151	0.0713	0.0896	0.144	0.151	0.114	0.189	0.499		0.200
Elim. $t_{1/2}$, h[b]	6.12	6.43	6.14	6.38	6.94	5.83	6.72	5.70	5.71	5.74		7.66	4.54	8.00	7.39	5.99	8.20	7.24	5.33		6.10
Elim. $t_{1/2}$, h[c]	6.27	4.95	6.26	6.31	5.55	5.73	5.08	5.40	7.53	5.50		7.13	8.00	5.73	7.29	7.31	6.00	5.75	6.81		5.85
Vd_1, L/kg	0.105	0.106	0.192	0.154	0.163	0.0861	0.138	0.347	0.114	0.216		0.299	0.0434	0.151	0.185	0.149	0.0939	0.142	0.445		0.216
Vd_{ss}, L/kg	0.816	0.837	0.725	0.987	1.04	0.507	0.929	1.11	0.926	0.965		1.29	0.645	1.46	1.46	0.793	1.01	0.813	0.629		0.885
k_{12}, h^{-1}	4.97	4.10	2.06	3.28	3.93	3.41	3.21	1.41	5.07	5.56		3.27	6.04	6.17	3.50	3.26	4.59	2.58	0.606		2.30
k_{21}, h^{-1}	0.734	0.594	0.742	0.604	0.728	0.697	0.562	0.639	0.712	1.66		0.989	0.436	0.710	0.507	0.756	0.470	0.547	0.624		0.778
k_{10}, h^{-1}	1.02	1.02	0.483	0.827	0.723	0.821	0.825	0.453	1.16	0.557		0.419	3.40	0.944	0.889	0.705	1.09	0.644	0.290		0.508

[a] The administered dose was determined by weighing the syringe before and after the injection. [b] Half-life evaluated from plasma data. [c] Half-life evaluated from urinary excretion rate.

Figure 1—Sulpiride plasma levels in three subjects following iv administration of 100 mg of sulpiride. The lines were obtained when the experimental data were fitted to a two-compartment model. Key: (▲) subject 4; (■) subject 7; (●) subject 14.

total amount of unchanged sulpiride eliminated in urine. Subjects, sequence, and route of drug administration were used as the grouping variables. A p value of < 0.05 was considered significant. In order to ascertain the equivalence of the im and iv routes, these statistical analyses were completed for AUC_n and U_∞% by the construction of a symmetrical 90% confidence interval for the difference of two means according to Westlake,[26] and by two one-sided t tests.

A two-way analysis of variance was performed to test the difference of pharmacokinetic parameters obtained from sulpiride concentration either in RBC or in plasma. The following parameters were

Table III—Statistical Analyses of All Parameters Evaluated in Fifteen Subjects after Intravenous Administration of Sulpiride

Parameter	Mean Values					
	Males (n = 8)	CV, %	Females (n = 7)	CV, %	All Subjects (n = 15)	CV, %
U_∞, %	92.4	6.97	87.3	14.2	90.0	10.8
AUC_n, mg · h/L	9.81	17.2	8.15	13.3	9.03	18.1
CL_{tot}, mL/min	128.7	24.0	126.7	17.5	127.8	20.5
CL_r, mL/min	122.3	26.4	116.4	21.5	119.5	23.6
MRT, h	7.74	7.43	8.32	25.6	8.01	18.5
Distribution $t_{1/2}$, h	0.218	58.3	0.124	36.0	0.174	60.9
Elimination $t_{1/2}$, h[a]	6.27	9.33	6.70	20.0	6.47	15.4
Elimination $t_{1/2}$, h[b]	5.86	9.58	6.65	12.9	6.23	12.8
Vd_1, L/kg	0.206	59.7	0.162	50.7	0.185	56.8
Vd_{ss}, L/kg	0.849	18.0	1.05	25.6	0.944	24.6
k_{12}, h^{-1}	2.67	47.9	4.44	33.8	3.50	46.1
k_{21}, h^{-1}	0.637	10.7	0.744	36.6	0.687	28.0
k_{10}, h^{-1}	0.664	36.4	1.15	88.7	0.889	82.6

[a] Half-life evaluated from plasma data. [b] Half-life evaluated from urinary excretion rate.

compared: half-lives of distribution and elimination, mean residence time, microscopic rate constants, area under the concentration–time curve, steady-state volume of distribution, and clearances. Subject and biological fluids were used as the grouping variables in the two-way ANOVA. A p value of < 0.05 was considered significant.

Results

Pharmacokinetic Parameters from Plasma Data after Intravenous Administration of Sulpiride—After iv administration, all concentration versus time curves were analyzed systematically by the extended least-squares regression analysis, according to a two- or a three-compartment body model with first-order transfers among compartments and first-order elimination. Analysis according to a three-compartment model was not possible in seven cases out of the 19. In all the other cases, statistical analysis of the fit of model to the curves indicated that the data were consistent with a two-compartment body model (Figure 1). Individual pharmacokinetic parameters are given in Table II.

Total AUC was 13.52 mg · h/L for the 100-mg dose and the total AUC per dose, which is also the AUC for a 1-mg/kg dose or AUC_n, was 9.03 mg · h/L. The mean values and the corresponding CV (%) are given in Table III. When a subject received a treatment more than once, data were averaged and treated as one single observation before calculating the population mean. The mean half-lives of the λ_1 distribution and λ_2 disposition phases were 0.174 ± 0.106 and 6.47 ± 0.997 h, respectively. Distribution in peripheral tissues was rapid (k_{12} = 3.50 ± 1.61 h^{-1}), with a transfer rate constant from tissue to plasma of the same order of magnitude (k_{21} = 0.687 ± 0.192 h^{-1}) as the elimination rate constant (k_{10} = 0.889 ± 0.734 h^{-1}). Distribution appears to be slightly faster in the female group. The mean residence time was 8.01 ± 1.48 h. The apparent volume of distribution of the central compartment was very close to the extracellular water volume (inuline space), whereas, the apparent volume of distribution at steady state (Vd_{ss} = 0.944 ± 0.232 L/kg) seemed to correspond to total body water (antipyrine space). Total plasma clearance was 127.8 ± 26.2 mL/min; this value was always very close to plasma renal clearance.

Interindividual Variability—The interindividual variability was not very high, with a coefficient of variation for all subjects between 15 and 25% for most of the parameters and 40 to 50% for the distribution half-life and the microscopic rate constants (Table II and III).

Sex variations of all the pharmacokinetic parameters were evaluated by a one-way analysis of variance in seven female subjects and in eight male subjects. The apparent rate constant of the distribution phase (λ_1) was significantly higher ($F = 5.57$; $p < 0.05$) for women (6.21 h^{-1}) than for men (3.92 h^{-1}). The rate constant of transfer from the central compartment to the tissues was higher in women ($F = 6.12$; $p < 0.05$). The area under the curve normalized by the administered dose was significantly higher ($F = 4.92$; $p < 0.05$) for men than for women, whereas the other pharmacokinetic parameters did not show statistically significant differences.

Intraindividual Variability—For subjects 1 and 7, intrasubject variability was low, with a CV of <15% for most pharmacokinetic parameters (Table II). For the subjects 4 and 11, there was a greater variation of AUC, total clearance, renal clearance, U_∞ (%), and volume of distribution, but the elimination half-life did not change. For each parameter, the average intrasubject CV value is given in Table IV.

Pharmacokinetic Parameters from Plasma Data after Intramuscular Administration of Sulpiride—The results obtained in Study I after im administration to 12 subjects were modeled using a two-compartment open model with first-order absorption rate. The pharmacokinetic parameters were compared with those obtained after iv administration; they showed that except for the microscopic rate constants, k_{12} ($p < 0.01$) and k_{10} ($p < 0.01$), there was no significant difference between the two routes of administration (Table VI).

Absolute bioavailability of sulpiride administered im was 0.996 ± 0.397 when determined from plasma data (F_{AUC}), and 1.04 ± 0.185 when determined from urinary data (F_U).

For the amount recovered unchanged in urine and the AUC_n, the Westlake 90% confidence intervals were 10.2 and

Table IV—Intrasubject Variability

Parameter	Coefficient of Variation		
	Average	Minimal	Maximal
U_∞	16.6	12.8	25.6
AUC_n	36.0	1.11	65.3
CL_{tot}	23.7	3.95	40.6
CL_r	36.7	12.6	53.8
MRT	12.0	1.97	18.8
Distribution $t_{1/2}$	11.8	4.86	18.1
Elimination $t_{1/2}$[a]	10.1	0.525	18.9
Elimination $t_{1/2}$[b]	12.9	0.274	27.0
Vd_1	39.3	0.952	89.5
Vd_{ss}	25.9	2.57	51.2
k_{12}	11.8	6.86	17.5
k_{21}	51.4	4.26	49.1
k_{10}	21.6	0.00	52.0

[a] Half-life evaluated from plasma data. [b]Half-life evaluated from urinary excretion rate.

Table V—Pharmacokinetic Parameters after Intramuscular Administration of 100 mg of Sulpiride to Twelve Subjects (Study I)

Parameter	Mean	CV, %
U_∞, %	94.0	10.9
AUC_n, mg · h/L	7.81	37.9
CL_{tot}, mL/min	158.0	36.6
CL_r, mL/min	147.0	36.5
MRT, h	9.76	15.7
Absorption $t_{1/2}$, min	6.96	37.9
Distribution $t_{1/2}$, h	0.225	44.0
Elimination $t_{1/2}$, h[a]	7.17	15.2
Elimination $t_{1/2}$, h[b]	6.19	24.2
Vd_{ss}, L/kg	1.47	43.0
k_{12}, h^{-1}	2.53	59.7
k_{21}, h^{-1}	0.996	50.1
k_{10}, h^{-1}	0.389	26.0

[a] Half-life evaluated from plasma data. [b] Half-life evaluated from urinary excretion rate.

Table VI—Statistical Analyses of Parameters Evaluated in Twelve Subjects (Study I) after Either Intramuscular or Intravenous Administration

Parameter	Source of Variation[a]			90% Symmetrical Confidence Interval, %[c]
	Route	Period	Subject	
U_∞, %	F = 0.240 NS[b]	F = 0.519 NS	F = 0.868 NS	10.20
AUC_n	F = 0.284 NS	F = 1.177 NS	F = 1.488 NS	20.90

[a] Statistical analyses were performed using a replicated Latin Square design. [b] NS = not significant. [c] This confidence interval was constructed for the difference of two means for route of administration.

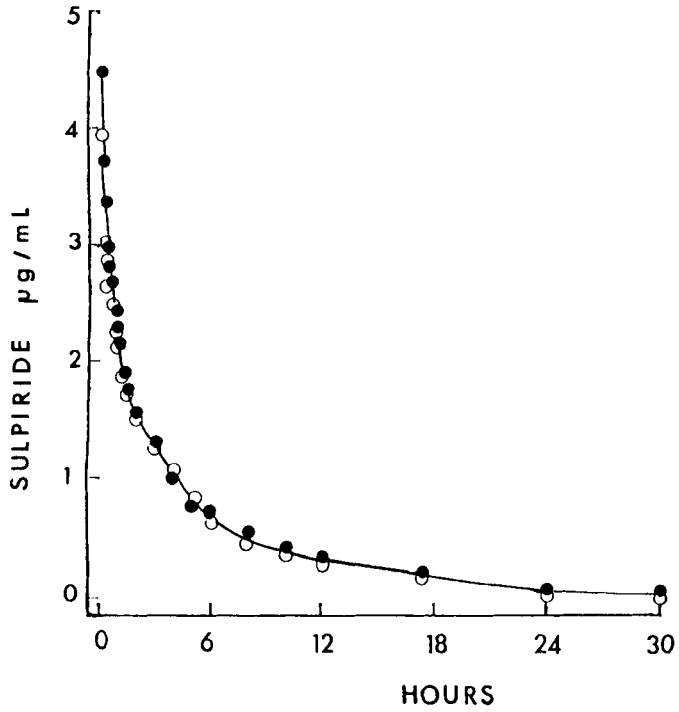

Figure 2—Plasma and RBC concentrations versus time in subject 14 following iv administration of 100 mg of sulpiride. Key: (●) plasma data; (○) RBC data.

20.9%, respectively (i.e., less than or equal to 20%; Table VI). The two one-sided *t* tests showed that both the upper and the lower bounds of the 90% confidence interval are within 20% of the mean for the reference. On the basis of these results, it can be concluded that the im and iv routes were bioequivalent in term of the intensity of absorption.

Distribution of Sulpiride between Red Blood Cells and Plasma after Intravenous Administration—The sulpiride RBC concentration versus time curves showed a biphasic decay. Sulpiride reached the same concentrations in RBC as in plasma. In Figure 2, typical drug concentration curves in plasma and RBC are given. The pharmacokinetic parameters determined from RBC levels for eight subjects with the mean values and coefficient of variation are given in Table VII. These parameters were always very close to those determined from the plasma data.

For the concentration range reached after iv administration of sulpiride, the RBC:plasma ratio of sulpiride concentrations (D) was determined at each sampling time. The mean values are shown in Table VIII; they were very close to 1. Sulpiride appeared to be distributed evenly between RBC and plasma, the distribution in the two "defined compartments" (plasma and RBC) was not concentration dependent.

Sulpiride Excretion in Urine and Renal Clearance after Intravenous Administration—Elimination of sulpiride after iv administration was mainly via the renal route, since 90.0 ± 9.68% was recovered unchanged in urine. The mean apparent elimination rate constant was 6.23 ± 0.799 h. This value was of the same order of magnitude as the one determined from the plasma data (Tables II and III). Renal clearance was 119.5 ± 28.2 mL/min when total sulpiride (free and unbound) was assayed in plasma. This value was close to the total clearance.

At each time of urine sampling, the urinary flow was calculated. The mean value was 1 mL/min, with large variations during the 48 h after dosing (Table II). Renal clearance for each urine collection period was calculated by the ratio of sulpiride excretion rate to plasma concentration at the midpoint of the drug excretion interval. Variations in sulpiride renal clearance were not correlated to urine flow and indicate that renal clearance did not depend on urine flow (0.3–9 mL/min). Our results also showed that it did not depend on the urine pH (5.3–7.2).

Discussion

Pharmacokinetic Parameters from Plasma Data after Intravenous Administration—The data were consistent with a two-compartment model ($t_{1/2}$ = 6.47 ± 0.997 h; n = 15), whereas Wiesel et al.[4] showed that for two subjects, a better fit was obtained when the data were analyzed according to a three-compartment body model. (The terminal half-life was longer for these two subjects than for the four other subjects they studied: 11 and 13.9 h instead of 5.33 ± 1.16 h[2,4].)

Since renal clearance of sulpiride (CL_{SUL}) and creatinine (CL_{CR}) were simultaneously evaluated in all subjects in our study (Table I and Table II), we attempted to correlate these two values. There was a positive correlation and CL_{SUL} = 19.17 ± 0.882CL_{CR}. The correlation coefficient (r = 0.732; df = 14) was not very high since all the values were within the normal range of creatinine clearance (60–160 mL/min).

Equivalence of the Intramuscular and Intravenous Routes—All the pharmacokinetic parameters determined in this study after iv administration are very close to those

Table VII—Pharmacokinetic Parameters Determined from Red Blood Cell Levels after Intravenous Administration of Sulpiride

Parameter	Subject									
	1	4	7	11	12	13	14	15	Mean	CV, %
Dose, mg/kg[a]	1.404	1.442	1.693	1.917	1.332	1.396	1.385	1.430	—	—
AUC, mg h/L										
Observed	14.0	19.6	14.4	16.7	10.2	13.6	13.8	12.8	14.39	19.25
To infinity	14.5	19.9	14.6	17.1	11.2	14.1	14.1	13.1	14.83	17.73
Normalized	10.3	13.8	8.62	8.92	9.25	10.1	10.2	9.16	10.04	16.33
CL, mL/min	114.7	82.3	125.4	96.4	126.2	120.3	128.0	122.8	114.5	14.41
MRT, h	7.28	7.49	10.28	6.62	9.85	9.28	6.66	7.77	8.15	17.79
Distribution $t_{1/2}$, h	0.124	0.183	0.128	0.199	0.110	0.264	0.722	0.790	0.315	87.94
Elimination $t_{1/2}$, h	6.07	6.23	7.52	5.44	8.28	7.47	5.29	6.35	6.58	16.26
Vd_1, L/kg	0.0942	0.100	0.275	0.164	0.0916	0.218	0.481	0.157	0.198	66.16
Vd_{ss}, L/kg	0.755	0.555	1.06	0.728	1.06	0.927	0.659	0.853	0.825	22.30
k_{12}, h^{-1}	4.04	2.58	3.81	2.27	4.75	1.73	0.342	2.69	2.78	50.72
k_{21}, h^{-1}	0.606	0.568	1.32	0.660	0.448	0.533	0.497	0.607	0.655	42.29
k_{10}, h^{-1}	1.05	0.741	0.377	0.671	1.18	0.457	0.253	0.699	0.678	47.20

[a] The administered dose was determined by weighing the syringe before and after the injection.

Table VIII—Distribution of Sulpiride between Plasma and Red Blood Cells after Intravenous Administration

Subject	Study	Distribution Coefficient (Mean ± SD)	n[a]
1	II	1.07 ± 0.098	24
4	II	0.980 ± 0.122	24
7	II	1.00 ± 0.0645	23
11	II	1.01 ± 0.243	23
12	I	0.987 ± 0.09	23
13	II	0.967 ± 0.142	24
14	II	0.927 ± 0.0704	23
15	II	1.02 ± 0.156	23

[a] The number of blood samples withdrawn after sulpiride administration.

reported by Wiesel et al.[4] after iv administration and by Bressolle et al.[2] following im administration of sulpiride.

We observed also in this study that the im and iv routes of administration were bioequivalent in terms of the extent of absorption, but not in terms of rate of absorption. As a consequence, the bioavailability of oral forms could be determined with reference to either one of these routes.

Distribution of Sulpiride between Red Blood Cells and Plasma—Sulpiride, like sultopride,[27] another substituted benzamide, is not bound to plasma proteins.[8] The rate of drug exchange between plasma and RBC is very fast and, as such, this has no impact on the pharmacokinetic of the drug. The distribution coefficient between RBC and plasma is close to 1.0. The value for sultopride is very similar (0.964 ± 0.348), yet this latter drug is more lipophilic with a volume of distribution of 3 L/kg compared with a volume of 1.0 L/kg for sulpiride.[2,11,27]

Distribution of sulpiride in RBC is not concentration dependent and does not indicate any saturation within the therapeutic range. Sulpiride is equally distributed between RBC and plasma, probably by passive diffusion through the RBC membrane, suggesting no specific binding either in RBC or plasma. On the basis of these results, sulpiride can be assayed in whole blood, as well as in plasma, for drug monitoring or for dosage regimen adjustment in patients.

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