Sulpiride Pharmacokinetics in Humans After Intramuscular Administration at Three Dose Levels

FRANÇOISE BRESSOLLE *x, JANINE BRES *, MARIE DOMINIQUE BLANCHIN *, and ROBERTO GOMENI ‡

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Abstract □ Pharmacokinetics of the disinhibitory psychotropic agent sulpiride was investigated in 9 healthy male subjects after intramuscular administrations of 50, 100, and 200 mg in a 3 × 3 Latin square design. Plasma and urine concentrations were measured by HPLC for 36 and 48 h, respectively. The lowest detectable concentration was 10 ng/mL. Plasma concentration *versus* time and urinary excretion rate *versus* time curves were consistent with an open two-compartment body model, where mean ±*SD* apparent half-lives of the absorption from muscle, λ_1 distribution, and λ_2 elimination phases were 6.96 ± 2.64 min, 0.220 ± 0.120 h, and 6.74 ± 2.67 h, respectively. The initial volume of distribution was 0.145 ± 0.063 L/kg, the steady-state volume of distribution was 0.639 ± 0.184 L/kg, and the total clearance was 89.8 ± 22.3 mL/min. The microscopic rate constants were $k_{12} = 2.53 \pm 1.13\ h^{-1}$, $k_{21} = 0.674 \pm 0.197\ h^{-1}$, and $k_{10} = 0.635 \pm 0.298\ h^{-1}$. Comparison of total clearance (89.8 mL/min), renal clearance (83.0 mL/min), and renal clearance of unbound drug (97.6 mL/min, $f = 0.15$) indicated that sulpiride is mainly excreted unchanged by the renal route, 93.1 ± 6.6% of the administered dose being recovered unchanged in urine. Statistical evaluation of all the above parameters, determined at the three dosage levels, did not show any variations related to dose; the pharmacokinetics of sulpiride, over the dose range tested, was therefore linear and independent of dose. The two-compartment body model proposed was validated by digital computer simulation on a small digital computer (32K).

Keyphrases □ Sulpiride—intramuscular administration, pharmacokinetics, humans □ Pharmacokinetics—intramuscular sulpiride, humans, HPLC

Sulpiride, 5-(aminosulfonyl)-*N*-[(1-ethyl-2-pyrrolidinyl)-methyl]-2-methoxybenzamide, a disinhibitory psychotropic drug belonging to the *o*-anisamide or substituted benzamide class of antipsychotic agents, is rapidly becoming an important psychotherapeutic agent in many parts of the world. Sulpiride is indicated mainly for the treatment of psychiatric disorders, peptic ulcers, and vertigo. At high dosage levels, it is a major nonsedative neuroleptic for use in acute psychosis, obsessional neurosis, and behavioral disorders. Sulpiride is characterized by its low incidence of extrapyramidal side effects, although it can induce endocrine effects, amenorrhea, or galactorrhea, probably as a result of direct interaction with prolactin cells. Benakis *et al.* (1) and Stefan *et al.* (2) demonstrated that the drug is specifically distributed into the pituitary.

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 adjustment of the dosage regimen and individualization of therapy.

The model which best describes the pharmacokinetics of a drug is that determined after intravenous administration or, when this is not possible, after administration by another route if absorption by this route is known to be rapid and total. Only then will the pharmacokinetic parameters determined be relevant. Sulpiride pharmacokinetics was investigated in humans after intravenous administration by Wiesel *et al.* (3, 4) and after intramuscular administration by Bres *et al.* (5–7) in order to choose the most appropriate model to describe the fate of sulpiride in humans and to determine the absolute bioavailability of several sulpiride preparations for oral administration. In bioavailability studies (5, 6), the intramuscular route was selected as the reference, following demonstration by the authors of bioequivalence between the intravenous and the intramuscular routes in the dog (8). All of these studies were conducted at one dose level only [1.5 mg/kg (3, 4), 6 mg/kg (5, 6), or 2.6 mg/kg (6)] and the linearity of the kinetics in humans was never truly demonstrated, as it had been in the dog (8). In the study presented here, the pharmacokinetics of intramuscularly administered sulpiride was evaluated at three dose levels (50, 100, and 200 mg) in nine healthy volunteers to determine the relationships between plasma levels, areas under the curve, rate constants, volumes of distribution, clearances, amounts of sulpiride recovered unchanged in urine, and the administered doses, and to ascertain whether all data deduced from sulpiride plasma levels and urinary excretion rate data were consistent with the two-compartment model with first-order transfer among compartments and first-order elimination.

Plasma and urine concentrations of sulpiride were determined by an original HPLC technique (7), since it has been shown that HPLC is a valid method for assay of benzamides in biological fluids (3, 4, 9–11). This technique has an increase in specificity compared with the spectrofluorometric determination of Kleimola *et al.* (12–14) and an increase in sensitivity compared with the quantitative TLC method developed for our earlier studies (5, 6, 8, 15–17).

EXPERIMENTAL SECTION

Drug Products and Materials—Sulpiride[1], sulpiride ampules[2] for intramuscular injection (100 mg/2 mL) were furnished. Nicotinamide[3] (used as an internal standard) was purchased. All chemicals and solvents were of analytical grade. Methanol and chloroform were twice-distilled in an all-glass apparatus before use. These solvents and distilled water were filtered through a 0.45-μm filter[4] before use.

Subjects—The study was conducted with nine male Caucasian subjects (25.6 ± 3.2 years) in good health as determined by screening, laboratory tests including hematology, urinalysis, blood chemistry (SMA-12), electrocardiogram, history, physical examination, and creatinine clearance. They were within the normal range for height (179 ± 6 cm) and weight (68.7 ± 5.0 kg) and 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 study design and were given all available data on sulpiride clinical and toxicological studies.

Study Design—Each subject received three different treatments, randomly allocated according to three series of 3 × 3 Latin squares (Table I); at least 7 d were allowed between treatments. Each person received no medication for at least 48 h before the drug administration. They fasted for 12 h prior to and 4 h after each drug administration. Food and water were then taken as usual. Water (300 mL) was taken before each dosage administration.

Each subject received a single dose of 50, 100, or 200 mg im of sulpiride into the upper outer quadrant of the gluteus muscle. A catheter was placed in a forearm vein and a continuous drip was maintained for the first 6 h after

[1] Delagrange, Paris, France.
[2] Dogmatil; Delagrange, Paris, France.
[3] Nicotinamide, Niacinamide; Sigma Chemical Co., St. Louis, Mo.
[4] Millipore Corp., Bedford, Mass.

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Table I—Subject Data and Treatment Schedule

Subject	Age, years	Weight, kg	Height, m	Creatinine Clearance, mL/min	Order of Administered Doses[a] 50 mg	100 mg	200 mg
1	26	74.0	1.87	104	1	2	3
2	24	71.0	1.80	110	2	3	1
3	28	64.5	1.74	223	2	3	1
4	23	72.0	1.81	113	3	1	2
5	29	63.5	1.85	145	1	2	3
6	31	69.0	1.76	143	3	1	2
7	21	60.0	1.68	128	3	1	2
8	24	74.5	1.80	115	1	2	3
9	24	69.5	1.83	292	2	3	1

[a] Randomized with a 3 × 3 Latin square design.

drug administration, during which time the subjects were nonambulatory.

Blood samples were obtained by venipuncture immediately before and 5, 10, 15, 20, 25, 30, 35, 40, 45, 60, 90 min, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30 and 36 h after each injection. Urine specimens were collected before drug administration and for the following intervals after the 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 immediately centrifuged; the plasma was removed and immediately frozen. The voided urine was collected, the total volume recorded, and an aliquot was placed in vials and stored frozen until analysis.

Assay Method—*Instrumentation*—The chromatograph[5] was connected to a 10-μL automatic loop injection system, a multiple-wavelength detector[6], and a computing integrator[7]. Chromatography was performed on a reverse-phase column[8] (filled in-house) with a precolumn[9], to extend column life.

The mobile phase contained 30 parts of methanol and 70 parts of 0.1 M ammonium acetate. The temperature was ambient, and the flow rate was 1.0 mL/min. The detector was set at 0.002 AUFS (197 nm), and the chart speed was 0.25 cm/min.

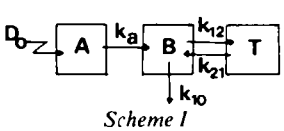
Sample Preparation—Plasma or urine (1-4 mL) was treated with 0.5 M NaOH (0.2 mL) and the pH was adjusted to 10. After extraction with 15 mL of chloroform for 20 min and centrifugation, a 15-mL aliquot of the organic phase was retained. After further extraction with 5 mL of chloroform, an additional 5 mL of the organic phase was retained. An internal standard was added (0.4 mL of nicotinamide at 1 mg/L in methanol for plasma and 1.0 mL of nicotinamide at 10 mg/L in methanol for urine) to the combined organic phases, and the extracts were evaporated to dryness. Before HPLC analysis, 0.3 mL of the mobile phase was added. After ultrasonic mixing[10], 10 μL of this solution was injected into the column by the automatic loop injection system.

The peak area ratio of sulpiride to nicotinamide (internal standard) was used as the assay parameter. Calibrations curves in control plasma (4 mL) were prepared for each two experiments from spiked pooled plasma samples of two subjects at concentrations of 20, 40, 50, 100, and 150 ng/mL. Calibration curves in control urine (2 mL) were prepared for each experiment from spiked urine samples of each subject at the concentrations of 0.5, 1.25, 6.25, 12.5, and 25 μg/mL. They were processed in the same manner as the *in vivo* samples.

Data Analysis—The plasma concentration of sulpiride for each subject was modeled using a two-compartment open model (Scheme I) with first-order absorption after intramuscular administration. The structural model describing the serum concentration C_p at time t is given by (18, 19):

$$C_p = \frac{k_a F D}{Vd_1}\left[\frac{(k_{21}-\lambda_1)e^{-\lambda_1 t}}{(k_a-\lambda_1)(\lambda_2-\lambda_1)} + \frac{(k_{21}-\lambda_2)e^{-\lambda_2 t}}{(k_a-\lambda_2)(\lambda_1-\lambda_2)} + \frac{(k_{21}-k_a)e^{-k_a t}}{(\lambda_1-k_a)(\lambda_2-k_a)}\right] \quad \text{(Eq. 1)}$$

where Vd_1 is volume of distribution in the central compartment, F is fraction



Scheme I

of dose D absorbed, λ_1 and λ_2 are first-order disposition rate constants in the distribution and elimination phases, k_{21} is the first-order transfer rate constant from the tissue compartment to the central compartment, and k_a is the first-order absorption rate constant from the muscle. Equation 1 is equivalent to:

$$C_p = -C_1' e^{-k_a t} + C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} \quad \text{(Eq. 2)}$$

The coefficients and exponents of the exponential terms were determined by an extended least-squares method..

The dispersion error on the measured concentrations was not known, so we decided to estimate the structural model parameters minimizing the log-likelihood function:

$$L = \sum_{i=1}^{N} \frac{(y_i - C_{pi})^2}{V_i} + \ln V_i \quad \text{(Eq. 3)}$$

where V_i is the error variance of the ith observation C_{pi}. Note that usually weighted least squares are appropriately used when it is assumed that the error variance is known up to a proportional factor. In our case the error variance is not known, so according to Sheiner (20) the following variance model was assumed:

$$V_i = a \times C_{pi}^b \quad \text{(Eq. 4)}$$

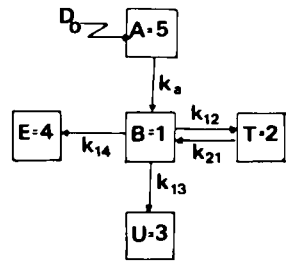
where a and b are variance model parameters. This is a reasonable model because it generalizes the usual weighting scheme applied to the weighted regression analysis, *e.g.*, for $a = 1$ and $b = 1$ the variance model becomes $V_i = C_{pi}^2$ and the weight is $1/y^2$. The exponential parameters as well as the error model parameters were estimated using the AUTOMOD II program (21-23) using a computer[11].

The microscopic rate constants k_{12} (first-order transfer rate constant from the central compartment to the tissue compartment), k_{21} (as previously determined), and k_{10} (first-order elimination rate constant from the central compartment) were determined from the coefficients and exponents of Eq. 2 (20). The total area under the plasma drug concentration-time curve (AUC_∞) was calculated from $AUC_{36\,h} + C_{36\,h}/\lambda_2$; $AUC_{36\,h}$ was calculated by the trapezoidal rule. Total body clearance, CL_{tot}, of sulpiride was calculated from the ratio of the dose of sulpiride and AUC_∞. The renal clearance, CL_r, of sulpiride was estimated either from the ratio of the amount of sulpiride eliminated unchanged in urine and the total area under the curve or from the slope of the plot of excretion rate *versus* plasma drug concentration at the midpoint of the drug excretion intervals.

The volume of distribution in the central compartment was evaluated by $Vd_1 = D \times k_a/[C_2 \times (k_a - \lambda_2)] + [C_1 \times (k_a - \lambda_1)]$; the volume of distribution in equilibrated tissues was evaluated by $Vd = CL_{tot}/\lambda_2$, and the steady-state volume of distribution was evaluated by $Vd_{ss} = Vd_1 \times (1 + k_{12}/k_{21})$. A pharmacokinetic analysis of the urinary excretion rate of sulpiride *versus* time curves (rate plot) and of amount of sulpiride remaining to be excreted *versus* time curves (σ^- plot) was undertaken for each subject using the GPHARM (24) computer program[12]. In some subjects three rate constants could then be determined for the absorption from muscle (phase 1), distribution (phase 2), and elimination (phase 3) processes, but in most of the subjects only the two latter phases could be measured with accuracy.

Digital Computer Simulations—Multicompartmental simulations on a small digital computer (32K)[12] was performed employing the GPHARM computer program (18, 24). The dose is introduced into an absorption compartment ($A = 5$). It then reaches the central compartment ($B = 1$), is distributed between the central and tissue compartments ($T = 2$), and is eliminated in urine ($U = 3$) or by another route of elimination ($E = 4$) (Scheme II).

The experimentally obtained sulpiride concentrations (in μg/mL) in plasma were expressed as percent of administered dose per milliliter of plasma and multiplied, for the three doses studied, by the mean initial volume of distri-



Scheme II

[5] Liquid chromatograph SP 8000; Spectra Physics, Orsay, France.
[6] Spectroflow monitor SF 770; Schoeffel Instruments, Cunow, Clichy, France.
[7] Computing integrator SP 4000; Spectra Physics, Orsay, France.
[8] Column Hypersil ODS 5 μm, 2.50 × 4.6 mm i.d.
[9] Precolumn Hypersil ODS 5μm, 50 × 1.5 mm i.d.
[10] Bandelin Snorex TK 52, Chrompack, Orsay, France.
[11] Model HP 1000; Hewlett-Packard, Orsay, France.
[12] Computing graphic system model 4051 with interactive digital plotter model 4662; Tektronix, Orsay, France.

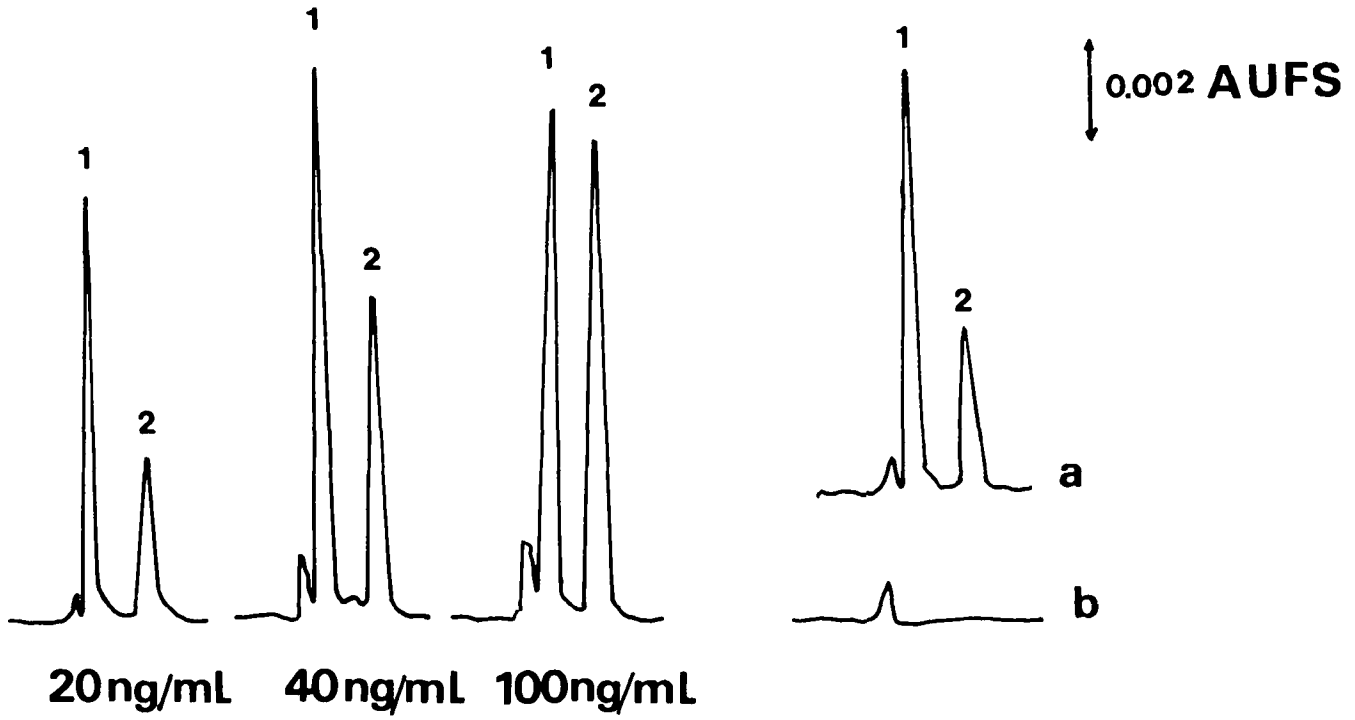


Figure 1—*Typical chromatograms obtained after injection on a Hypersil ODS column of 10-μL aliquots of the chloroform extracts of 4 mL of plasma spiked with sulpiride (20, 40, and 100 ng/mL) or taken from subject 3 before (b) and after (a) intramuscular administration of 96 mg of sulpiride.*

bution Vd_1 in order to obtain sulpiride amounts in the central compartment in terms of percent of administered dose (with the assumption that $F = 1$). For each subject, and for the three doses studied, these values and the experimentally obtained amounts of sulpiride excreted in urine as percent of administered dose were plotted against time. To account for the elimination of the remaining dose, another route of elimination from the central compartment was introduced into the model, so that at all times the mass balance was 100% of the dose.

For each subject, the mean microscopic rate constants obtained after pharmacokinetic analyses at the three dosage levels were taken as a first estimate for the simulations. They were then slightly modified to obtain the best fit between the curves generated with these values for plasma and urine and the experimentally obtained sulpiride amounts in plasma and urine at all times for the three doses.

Statistical Analysis—An analysis of variance on a randomized 3 × 3 Latin square design was performed on all the pharmacokinetic parameters determined to test variability between sequence of administrations, between doses, and between subjects.

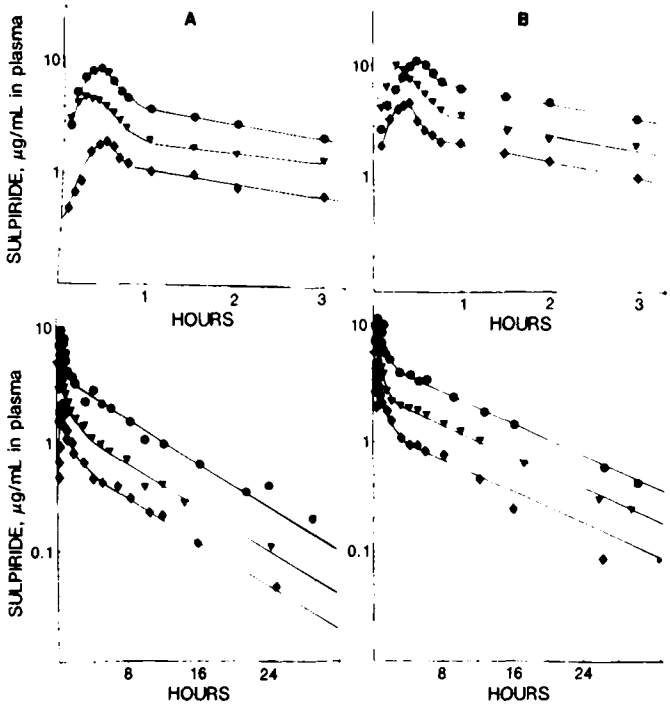


Figure 2—*Sulpiride plasma levels in two subjects following intramuscular administration of 50, 100, and 200 mg of sulpiride. The lines were obtained when the experimental data were fitted to a two-compartment model. Key: (A) subject 6: (♦) 52.24 mg; (▼) 94.53 mg; (●) 195.60 mg; (B) subject 5: (♦) 52.00 mg; (▼) 94.55 mg; (●) 196.15 mg.*

RESULTS

Sensitivity and Reliability of the Analytical Method—Retention times were 12 min for sulpiride and 6.8 min for the internal standard nicotinamide. There were no major interfering peaks in control plasma and urine samples at the retention times of the aforementioned compounds (Fig. 1). To improve the reliability of the assay, each sample was injected in triplicate. Detection limits, evaluated by the amounts of samples yielding a detector response equal to twice the detector noise, was 10 ng/mL. Recovery after extraction from the plasma and urine was 98%. A five-point calibration curve was run with every set of 50 samples, and the method was validated with spiked samples every 10 samples throughout the duration.

In plasma, the peak area ratio (R) of sulpiride over the internal standard varied linearly with concentration over the range used. These calibration curves passed through the origin with a slope $\pm SD$ of $146.4 \pm 0.54 \times 10^{-4}$ ng^{-1} mL and a coefficient of the linear regression analysis of 0.9998 ± 0.0001 ($n = 10$) (Fig. 1). The intercept was not significantly different from zero ($13.8 \pm 4.48 \times 10^{-3}$). For the urine samples the reliability of the assay was of the same magnitude, with a slope of $579 \pm 1.9 \times 10^{-3}$ ng^{-1} mL, an intercept of $12.7 \pm 10.1 \times 10^{-3}$, and a correlation coefficient of 0.999979 ± 0.000013 ($n = 10$).

A stability study of plasma and urine samples stored at −20°C showed that sulpiride was stable over 3 months. Storage of samples during the present studies did not exceed 3 months.

Pharmacokinetic Analysis—After the maximum, sulpiride plasma concentration follows a biexponential decay. For each subject, the three curves obtained after 50-, 100-, and 200-mg im administrations were parallel when concentration units were μg/mL (Fig. 2), and superimposable when concentrations are expressed as percent of administered dose per milliliter of plasma (Fig. 3). These results are consistent with a two-compartment body model with first-order transfers among compartments and first-order elimination (Scheme I). All the pharmacokinetic parameters included in this model were first evaluated by the residual method or "exponential stripping" using the GPHARM program (24), and their values have been reported by Blanchin

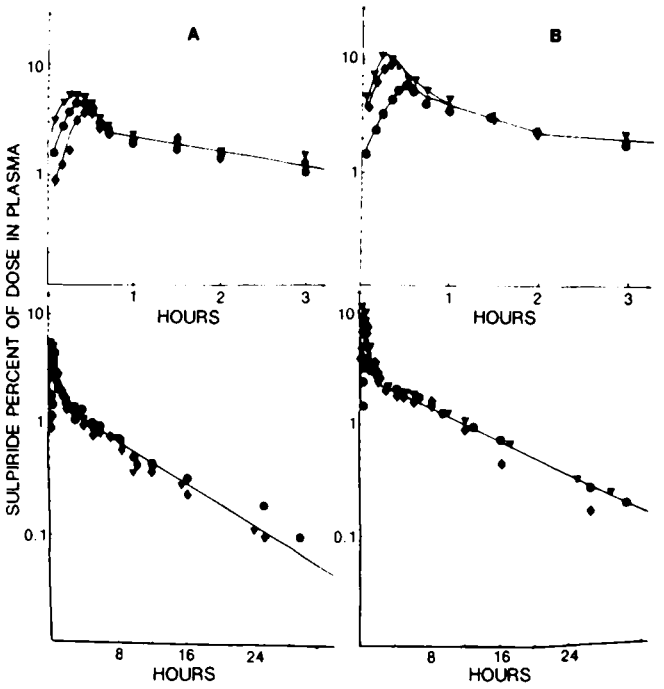


Figure 3—*Sulpiride plasma levels expressed as percent of the administered dose per milliliter in plasma, in two subjects, following intramuscular administrations of 50, 100, and 200 mg of sulpiride. Key as in Fig. 2.*

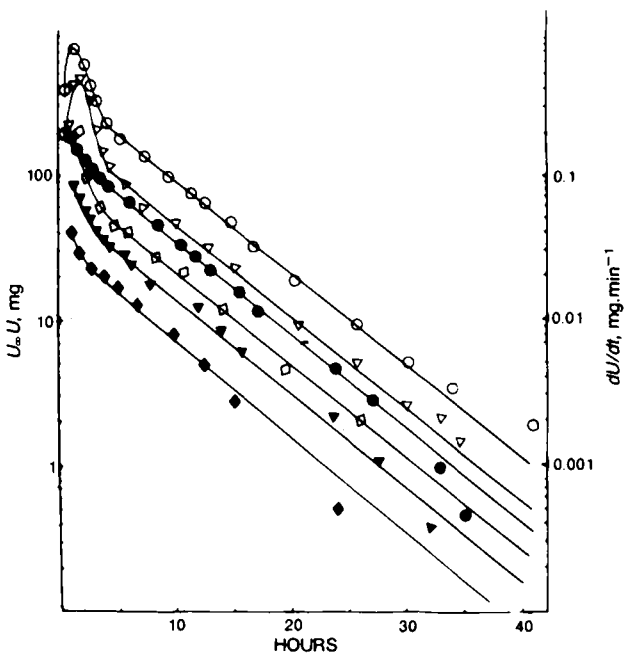


Figure 4—*Sulpiride urinary excretion rate (open symbols) and amount remaining to be excreted in form of unchanged sulpiride (closed symbols) following intramuscular administrations of 50, 100, and 200 mg of sulpiride to subject 6. Key: (◇, ◆) 52.24 mg; (▽, ▼) 94.53 mg; (○, ●) 195.60 mg.*

(7). The parameters so estimated were used as starting values for the more refined extended least-squares maximum-likelihood method to obtain the best possible evaluation (20-23) (Table II).

Absorption from muscle is fast and complete, but an important inter- and intrasubject variability was observed. The lag time determined in each case with the program used was always negligible. The mean half-lives of the λ_1 distribution and λ_2 disposition phases were 0.220 ± 0.120 and 6.74 ± 2.67 h, respectively; these values are in good agreement with those reported by Imondi *et al.* (25) and Wiesel *et al.* (3), but they differ from those we reported previously (5, 6).

Distribution in peripheral tissues was rapid (k_{12} = 2.53 ± 1.13 h^{-1}), with a rate of transfer from tissue to plasma of the same order of magnitude (k_{21} = 0.674 ± 0.197 h^{-1}) as the elimination rate constant (k_{10} = 0.635 ± 0.298 h^{-1}). The apparent volume of distribution of the central compartment, Vd_1 = 0.145 ± 0.063 L/kg, was very close to the extracellular water volume (from 0.15 to 0.20 L/kg in humans), while the apparent volume of distribution at steady state, Vd_{ss} = 0.639 ± 0.184 L/kg, seemed to correspond to total water, which varies in humans from 0.45 to 0.65 L/kg. Total plasma clearance was 89.8 ± 22.3 mL/min. For each subject the cumulative urinary excretion curves as percent of administered dose were superimposable; the rate and extent of sulpiride elimination in urine in the form of unchanged drug does not, therefore, seem to depend on the dose administered (Table II).

Elimination of sulpiride after intramuscular administration was mainly *via* the renal route, since 93.1 ± 6.6% was recovered unchanged in the urine. Renal clearance, evaluated from total amount of sulpiride eliminated unchanged in urine divided by AUC_∞, was 83.0 ± 19.8 mL/min, while the renal clearance evaluated from the slope of the plot of urinary excretion rate *versus* plasma concentration at the midpoint of the drug excretion interval was 62.3 ± 22.3 mL/min. Sulpiride renal clearance was 83.0 mL/min when total sulpiride (free and bound) was assayed in plasma. If the fraction bound to plasma protein was f = 0.15 (26), free sulpiride clearance would be 97.6 mL/min.

The apparent rate contants of the absorption, distribution, and elimination phases, determined from the variations with time of the urinary excretion rate (rate method) or from the variations with time of the amount remaining to be excreted (σ^- method), were close to those determined from plasma data (Fig. 4, Table II). Mean elimination half-lives determined by these two methods were 5.58 ± 1.41 and 5.68 ± 1.52 h, respectively.

Linearity—To test the linearity of sulpiride pharmacokinetics all the individual data were normalized by the dose administered and fitted to the full model of data (structural and error model). Using 3 × 3 Latin-square analysis of variance, the following parameters were then compared: time to peak and peak plasma levels, area under the time concentration curve, amount of drug excreted unchanged in the urine, λ_1, λ_2, k_a, k_{12}, k_{10}, total clearance, and renal clearance. The analyses did not show any sequence nor dose effects. While the interindividual variations with dose of all parameters are small, large variations are observed between subjects (Table III). Of all the parameters tested, clearance was the most variable within subjects and for a same subject within administration (Fig. 5). The system is linear and time invariant, because all the pharmacokinetic parameters are independent of drug concentration and time. It would appear that distribution and elimination kinetics of sulpiride in humans are linear over the dose range tested.

Validation of the Proposed Model by Digital Simulation—The two-compartment model was validated by digital simulation employing the mean microscopic rate constants determined for each subject after intramuscular administration at the three dosage levels. The good fit obtained between the simulated curves (percent of dose in the central compartment) and the experimental points after the maximum, at the three dosage levels, allowed a single value for each parameter to be given for each subject.

These values were for all subjects in the study (Table IV): k_a = 9.36 ± 1.84 h^{-1}, k_{12} = 1.36 ± 0.47 h^{-1}, k_{21} = 0.61 ± 0.15 h^{-1}, k_{10} = 0.53 ± 0.13 h^{-1}, Vd_1 = 0.18 ± 0.02 L/kg, and Vd_{ss} = 0.57 ± 0.08 L/kg. Simulated curves for the peripheral compartment showed that marked distribution in tissues did not occur. At the maximum tissue level, 40-60% of the administered dose was present in tissues (Fig. 6); after this maximum and up to 10 h, the total amount of sulpiride in the tissues was ~1.5-2 times higher than that in the central

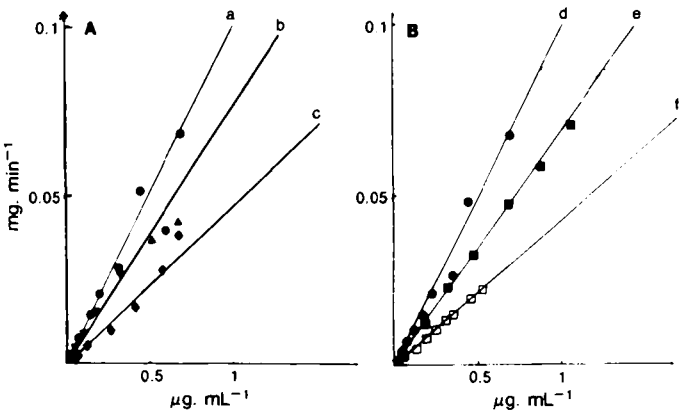


Figure 5—*Renal clearance of sulpiride in one subject for different administered doses (A) and for a same dose and for three different subjects (B), illustrating the large variations. Key: (A) subject 1: (◆) 47.55 mg; (▼) 97.90 mg; (●) 182.95 mg; (B) (●) subject 1; (■) subject 3; (□) subject 5. Rates: (a) 99 mL/min; (b) 77 mL/min; (c) 47 mL/min; (d) 99 mL/min; (e) 69.5 mL/min; (f) 43 mL/min.*

Table II—Pharmacokinetic Parameters After Intramuscular Administration of Sulpiride at 50, 100, and 200 mg

	Subject 1			Subject 2			Subject 3			Subject 4			Subject 5		
D_0[a]															
mg	47.55	95.90	182.95	52.17	97.32	193.88	50.00	96.00	172.42	47.71	95.33	149.90	52.00	94.55	196.15
mg/kg	0.643	1.296	2.472	0.709	1.333	2.810	0.769	1.488	2.673	0.673	1.288	2.026	0.813	1.501	3.114
k_a, h^{-1}	6.70	5.68	6.90	10.2	3.64	4.50	7.87	7.87	7.90	9.51	7.36	9.61	8.67	11.7	11.7
λ_1, h^{-1}	4.69	4.41	5.15	2.48	2.62	3.57	6.07	5.87	6.82	5.37	5.00	4.84	2.83	2.60	2.98
λ_2, h^{-1}	0.104	0.109	0.101	0.0702	0.044	0.0476	0.115	0.137	0.139	0.138	0.135	0.142	0.120	0.0845	0.0893
$t_{1/2}$, h Absorption	0.104	0.122	0.100	0.0681	0.190	0.154	0.0881	0.0881	0.0877	0.0728	0.0942	0.0721	0.0799	0.059	0.0595
$t_{1/2}$, h Distribution	0.148	0.157	0.135	0.279	0.264	0.194	0.114	0.118	0.102	0.129	0.139	0.143	0.245	0.267	0.233
$t_{1/2}$, h Elimination	6.66	6.34	6.89	9.87	15.6	14.6	6.00	5.08	4.98	5.03	5.12	4.90	5.78	8.20	7.76
k_{12}, h^{-1}	3.40	3.11	3.81	1.69	2.01	2.70	4.36	3.94	5.01	3.77	3.45	3.33	1.76	1.76	1.98
k_{21}, h^{-1}	0.575	0.602	0.678	0.527	0.337	0.280	0.587	0.538	0.978	0.829	0.952	0.768	0.718	0.503	0.720
k_{10}, h^{-1}	0.815	0.806	0.756	0.329	0.311	0.637	1.24	1.53	0.977	0.907	0.735	0.882	0.473	0.413	0.373
Vd_1, L/kg	0.0744	0.0892	0.0900	0.209	0.160	0.0976	0.075	0.0704	0.117	0.0941	0.117	0.0946	0.108	0.0973	0.125
Vd, L/kg	0.600	0.650	0.822	0.962	1.22	1.18	0.777	0.755	0.795	0.585	0.604	0.568	0.410	0.491	0.509
Vd_{ss}, L/kg	0.514	0.551	0.773	0.881	1.11	1.04	0.632	0.586	0.713	0.523	0.543	0.505	0.370	0.439	0.469
AUC, mg · h/L															
Observed	9.57	17.5	28.9	8.86	18.1	41.6	8.12	14.0	23.8	7.88	15.5	24.8	15.8	33.2	65.2
To infinity	10.3	18.3	29.8	10.5	24.9	50.0	8.61	14.4	24.2	8.33	15.8	25.1	16.5	36.2	68.5
$AUC_{(1\ mg/kg)}$; h/L/kg	16.1	14.1	12.1	14.8	18.7	17.8	11.2	9.69	9.07	12.4	12.3	12.4	20.3	24.1	22.0
CL, mL/min															
Total	76.9	87.3	102	82.8	65.1	64.6	96.8	111	119	95.5	100	99.5	52.5	43.5	47.7
Renal[b]	64.2	71.5	90.8	81.5	65.2	47.7	95.9	96.4	112	83.2	91.3	90.3	59.9	45.1	46.3
	(47.0)	(77.0)	(99.0)	(77.0)	(40.0)	(22.0)	(50.0)	(65.0)	(70.0)	(49.0)	(46.5)	(92.0)	(55.0)	(39.5)	(43.0)
Cumulative amount															
in urine (U_∞), %	83.4	81.9	88.7	98.4	100	73.8	99.1	86.8	94.0	87.1	90.8	90.7	96.8	97.9	97.0
Rate constant from rate plot, h^{-1}															
Absorption (phase 1)	—	—	—	—	5.72	—	—	2.09	—	—	—	3.19	—	—	—
Distribution (phase 2)	0.512	1.17	0.423	0.667	1.68	1.44	0.825	1.81	0.595	1.69	0.694	2.73	0.786	0.750	0.386
Elimination (phase 3)	0.126	0.0811	0.0898	0.120	0.0790	0.096	0.149	0.119	0.116	0.125	0.135	0.137	0.105	0.0916	0.0912
Rate constant from σ^- plot, h^{-1}															
Absorption (phase 1)	—	—	—	—	—	—	—	—	—	—	—	2.01	—	—	3.59
Distribution (phase 2)	0.742	1.56	0.282	0.574	0.666	1.14	0.652	0.793	0.634	1.99	0.786	0.635	0.819	0.860	2.19
Elimination (phase 3)	0.109	0.0816	0.0813	0.114	0.0833	0.084	0.106	0.116	0.118	0.119	0.135	0.129	0.0990	0.0956	0.103

Table II—*Continued*

	Subject 6			Subject 7			Subject 8			Subject 9		
D_0[a]												
mg	52.24	94.53	195.60	53.11	98.03	194.70	59.90	94.37	198.29	62.33	88.70	193.36
mg/kg	0.757	1.370	2.835	0.885	1.634	3.245	0.719	1.258	2.680	0.897	12.76	2.782
k_a, h^{-1}	4.19	5.57	4.30	4.97	4.18	4.50	6.82	4.70	2.91	6.76	6.18	9.35
λ_1, h^{-1}	3.62	4.20	3.41	3.81	3.34	3.11	4.35	1.26	1.19	1.84	3.15	2.03
λ_2, h^{-1}	0.121	0.138	0.0952	0.137	0.125	0.122	0.125	0.116	0.118	0.113	0.124	0.119
$t_{1/2}$, h Absorption	0.165	0.125	0.161	0.139	0.166	0.154	0.102	0.148	0.239	0.103	0.112	0.0741
$t_{1/2}$, h Distribution	0.191	0.165	0.203	0.182	0.207	0.223	0.159	0.550	0.585	0.378	0.220	0.342
$t_{1/2}$, h Elimination	5.71	5.02	7.28	5.05	5.53	5.68	5.54	5.97	5.89	6.14	5.57	5.83
k_{12}, h^{-1}	2.36	2.80	2.34	2.46	2.03	1.98	2.97	0.602	0.554	1.00	1.98	1.10
k_{21}, h^{-1}	0.903	0.809	0.624	0.889	1.01	0.746	0.718	0.384	0.382	0.619	0.833	0.696
k_{10}, h^{-1}	0.481	0.726	0.547	0.600	0.430	0.500	0.787	0.394	0.374	0.327	0.453	0.350
Vd_1, L/kg	0.206	0.121	0.144	0.211	0.213	0.162	0.123	0.155	0.164	0.315	0.200	0.276
Vd, L/kg	0.786	0.587	0.803	0.907	0.703	0.667	0.716	0.502	0.505	0.934	0.813	0.795
Vd_{ss}, L/kg	0.742	0.543	0.692	0.798	0.643	0.593	0.570	0.398	0.403	0.828	0.672	0.710
AUC, mg · h/L												
Observed	7.53	16.4	35.0	6.93	18.4	39.1	8.39	20.9	43.5	8.07	13.6	29.0
To infinity	7.96	16.9	37.1	7.13	18.6	39.9	8.92	21.6	45.0	8.50	13.9	29.4
$AUC_{(1\ mg/kg)}$, h/L/kg	10.52	12.3	13.1	8.06	11.4	12.3	12.4	17.2	16.8	9.48	10.9	10.6
CL, mL/min												
Total	109	93.2	87.9	124	87.8	81.3	112	72.8	73.4	122	106	110
Renal[b]	109	94.4	87.3	103	84.4	76.9	86.5	69.3	69.5	115	102	103
	(80.0)	(56.0)	(37.0)	(105)	(68.0)	(49.5)	(80.0)	(63.5)	(18.0)	(74.0)	(71.0)	(97.0)
Cumulative amount												
in urine (U_∞), %	100	101	93.3	83.2	96.0	94.5	85.9	95.2	94.6	91.6	95.5	93.6
Rate constant from rate plot, h^{-1}												
Absorption (phase 1)	—	2.55	—	—	—	—	—	—	—	—	—	—
Distribution (phase 2)	1.49	1.42	0.706	—	4.67	0.719	—	0.860	1.04	—	0.683	0.785
Elimination (phase 3)	0.150	0.133	0.149	0.180	0.158	0.167	0.182	0.139	0.135	0.140	0.159	0.153
Rate constant from σ^- plot, h^{-1}												
Absorption (phase 1)	—	—	—	—	—	—	—	—	—	—	—	—
Distribution (phase 2)	1.51	1.04	0.923	—	0.825	0.527	—	0.983	0.811	—	0.420	0.885
Elimination (phase 3)	0.151	0.153	0.150	0.195	0.153	0.168	0.227	0.148	0.137	0.135	0.149	0.146

[a] The administered dose was determined by weighing the syringe before and after the injection. [b] Renal clearance estimated from slope of the plot of excretion rate *versus* plasma drug concentration at midpoint of the drug excretion intervals is indicated in parentheses.

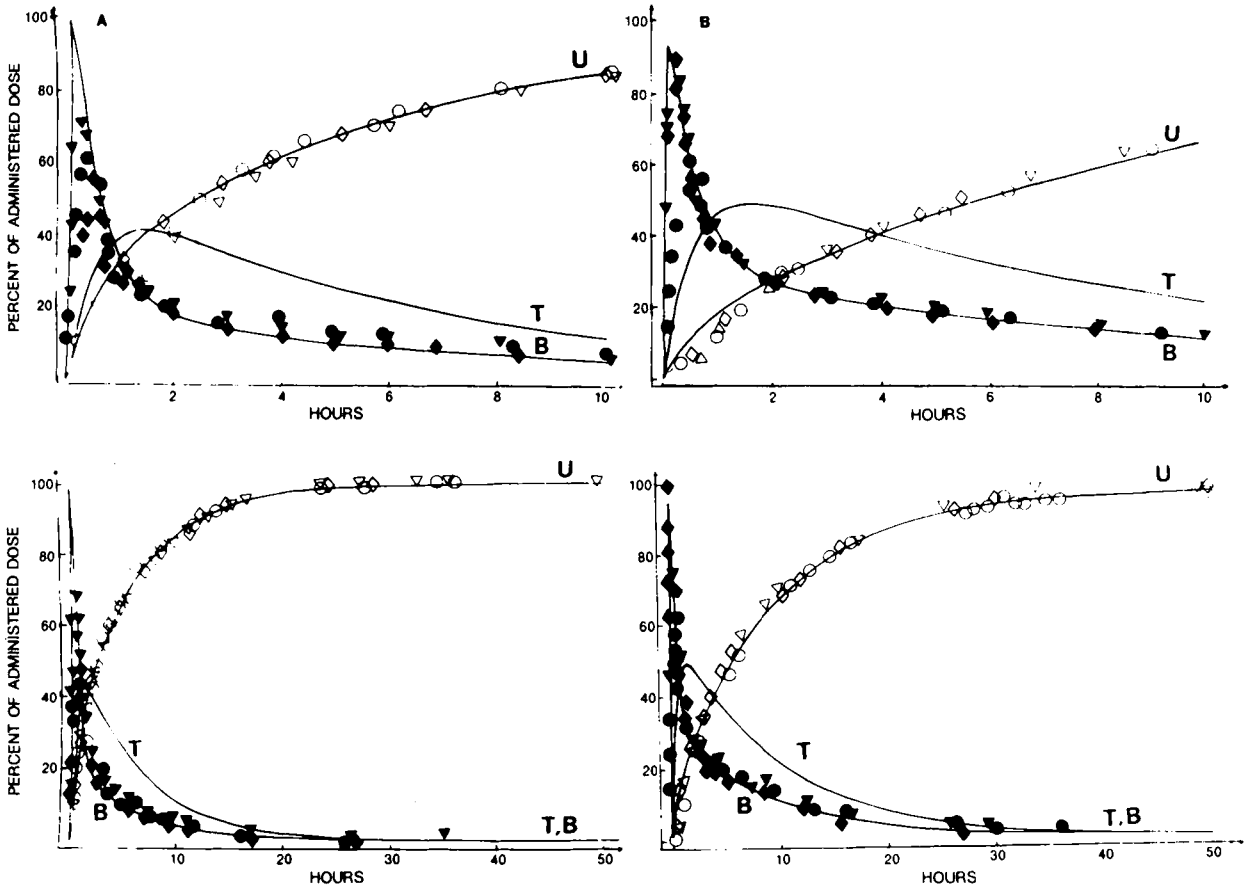


Figure 6—*Digital computer-fitting of sulpiride plasma (B) and urine (U) data following intramuscular administration of sulpiride, 50 (♦, ◇), 100 (▼, ▽), 200 mg (●, ○), to subjects 6 (A) and 5 (B). The curves labeled T are computer-generated amounts of sulpiride in the tissues in accordance with an open two-compartment model with first-order rates of transfer and elimination.*

compartment. The good fit obtained between the experimental points for urine and the curves generated from plasma data, at the three dosage levels, validates the proposed model.

DISCUSSION

Distribution in Peripheral Tissues—Distribution in the peripheral tissues can be estimated from the pharmacokinetic model consistent with sulpiride fate in humans. After intravenous (3) or intramuscular administration (5–7), plasma sulpiride levels follow a biexponential decay in most of the subjects. Two apparent rate constants can be determined for the λ_1 distribution and λ_2 elimination phases (Table V), since after intramuscular administration, absorption from the muscle is rapid and total. These results are consistent with a two-compartment open model with first-order transfer between compartments and first-order elimination from the central compartment. In four subjects (one male and three female), Bres *et al.* (5, 6) reported that only one phase of elimination was apparent since the distribution was too rapid to be detectable and the data were consistent with a one-compartment body model. Wiesel *et al.* (3) reported for two subjects, after intravenous administration, a triexponential decay consistent with a three-compartment body model. The terminal log-linear phase had half-lives of 11 and 13.9 h for the two subjects, respectively. The deep compartment added to fit the data in these cases did not modify the distribution rate constants between the central compartment and the shallow compartment (k_{12} and k_{21}).

Table III—Results of Statistical Analyses using a Replicated Latin Square Design [a]

Parameter	Period	Subjects	Dose
C_{max}/D_0, mg/L/kg	$F = 1.575$ (NS)	$F = 5.282$ ($p < 0.01$)	$F = 1.077$ (NS)
t_{max}, h	$F = 2.284$ (NS)	$F = 4.208$ ($p < 0.01$)	$F = 1.706$ (NS)
$t_{1/2,\lambda_1}$, h	$F = 1.842$ (NS)	$F = 5.369$ ($p < 0.01$)	$F = 0.776$ (NS)
$t_{1/2,\lambda_2}$, h	$F = 0.232$ (NS)	$F = 13.080$ ($p < 0.001$)	$F = 1.350$ (NS)
k_{12}, h^{-1}	$F = 1.945$ (NS)	$F = 9.236$ ($p < 0.001$)	$F = 0.793$ (NS)
k_{21}, h^{-1}	$F = 2.872$ (NS)	$F = 4.270$ ($p < 0.01$)	$F = 0.413$ (NS)
k_{10}, h^{-1}	$F = 0.070$ (NS)	$F = 5.111$ ($p < 0.01$)	$F = 1.218$ (NS)
AUC/D_0, h/L/kg	$F = 0.689$ (NS)	$F = 17.747$ ($p < 0.001$	$F = 2.636$ (NS)
CL, mL/min	$F = 0.253$ (NS)	$F = 8.203$ ($p < 0.001$)	$F = 1.788$ (NS)
Renal			
Total	$F = 0.696$ (NS)	$F = 6.942$ ($p < 0.01$)	$F = 1.958$ (NS)
U_∞, %	$F = 0.700$ (NS)	$F = 1.387$ (NS)	$F = 0.363$ (NS)

[a] NS = not significant.

Rate Constants of Transfer Between Compartments—The microscopic rate constant of transfer from the central compartment to the peripheral tissues (k_{12}), which regulates the amount going to tissues, had a values of 2.19 h^{-1} (5, 6), 2.29 h^{-1} (3), and 2.53 h^{-1} (Table V). The rates of transfer from tissues to plasma (k_{21}), which regulates output from tissues, were 1.24 h^{-1} (5, 6), 0.703 h^{-1} (3), and 0.674 h^{-1} (in this study). These values were of the same magnitude as the elimination microscopic rate constant, k_{10}. The values found in this study were consistent with those found in our earlier study and the values reported by Wiesel *et al.* (3) with different routes of administration and final sampling times.

In our earlier studies (5, 6), the large number of samples taken up to 10 h allowed good determination of k_{10}, even if the value of λ_2 was overestimated. The differences for k_{10} reported in these three studies, 0.73, 0.686, or 0.635 (mean) h^{-1}, were smaller than the differences reported for λ_2 (0.22, 0.103, or 0.103 (mean) h^{-1}; Table V).

Table IV—Individual Pharmacokinetic Parameters Obtained from Digital Computer Simulations and Fitting of Plasma and Urine Data When Sulpiride was Administered at Three Dose Levels

Parameter	Subject 1	2	3	4	5	6	7	8	9	Mean ± *SD*
Weight, kg	74.0	69.0	61.0	71.0	62.0	69.5	60.0	75.0	69.5	67.89 ± 5.57
Vd_1, L/kg	0.17	0.17	0.16	0.16	0.16	0.19	0.20	0.16	0.23	0.18 ± 0.024
Vd_{ss}, L/kg	0.66	0.64	0.65	0.58	0.43	0.53	0.61	0.48	0.54	0.57 ± 0.08
k_{12}, h^{-1}	1.61	1.20	1.63	2.36	1.00	0.90	1.50	1.00	1.00	1.36 ± 0.47
k_{21}, h^{-1}	0.56	0.43	0.53	0.90	0.60	0.50	0.73	0.50	0.74	0.61 ± 0.15
k_{10}, h^{-1}	0.45	0.60	0.59	0.73	0.30	0.58	0.64	0.47	0.41	0.53 ± 0.13
k_a, h^{-1}	10.9	6.0	11.0	10.5	9.3	10.0	6.5	10.0	10.0	9.36 ± 1.84
U_∞, %	89.7	90.8	93.3	89.6	97.0	100.0	92.7	92.0	93.6	93.18 ± 3.42

Table V—Sulpiride Distribution

Route of Administration	Dose, mg	Dose, mg/kg	$t_{1/2,\lambda_1}$, h	$t_{1/2,\lambda_2}$, h	λ_2, h^{-1}	*CL*, mL/min, Total	*CL*, mL/min, Renal	Vd_1, L/kg	Vd_{ss}, L/kg	k_{12}, h^{-1}	k_{21}, h^{-1}	k_{10} h^{-1}
Intramuscular[a]	300-500	6-7	0.17 (0.05)	3.11 (0.21)	0.223 (0.016)	220 (63)	190 (63)	0.30 (0.11)	1.06 (0.11)	2.19 (1.05)	1.24 (0.30)	0.73 (0.34)
Intravenous[b]	100	1.3-1.7		6.75 (1.78)		415 (84)	310 (91)	0.53 (0.10)	2.72 (0.66)	2.29 (0.91)	0.703 (0.213)	0.686 (0.197)
Intramuscular[c]	50	0.78	0.158 (0.063)	6.20 (1.47)	0.116 (0.0203)	96.8 (23.2)	88.7 (19.0)	0.157 (0.0822)	0.651 (0.171)	2.64 (1.08)	0.707 (0.141)	0.662 (0.302)
	100	1.38	0.232 (0.130)	6.94 (3.39)	0.113 (0.0307)	85.2 (21.5)	80.0 (18.5)	0.136 (0.0494)	0.609 (0.207)	2.41 (1.02)	0.663 (0.246)	0.644 (0.377)
	200	2.74	0.240 (0.147)	7.09 (2.98)	0.108 (0.0290)	87.3 (22.9)	80.4 (22.7)	0.141 (0.0577)	0.655 (0.192)	2.53 (1.37)	0.652 (0.209)	0.600 (0.231)
Mean			0.220 (0.120)	6.74 (2.67)	0.112 (0.0262)	89.8 (22.3)	83.0 (19.8)	0.145 (0.063)	0.639 (0.184)	2.53 (1.13)	0.674 (0.197)	0.635 (0.298)

[a] Blood (0-10 h) and urine (0-24 h) were collected from 1 male and 11 female subjects; the amount of drug was determined by quantitative TLC with UV detection (plasma). The data were fit to a one- or two-compartment model (5, 6). [b] Blood and urine were collected for 0-36 h from three male and three female subjects; the amount of drug was determined by HPLC with fluorometric detection (serum). The data were fit to a two- or three-compartment model (3). [c] Blood (0-30 h) and urine (0-48 h) were collected from nine male subjects; the amount of drug was determined by HPLC with UV detection (plasma). The data were fit to a two-compartment model (this research).

Volumes of Distribution—Large variations were apparent in the values reported by the authors for the volume of distribution of the central compartment and for the volume of distribution at steady state (Table V). The apparent volume of distribution of the central compartment (Vd_1) was very close to extracellular water (0.15 to 0.20 L/kg) in humans; the apparent volumes of distribution at steady state (Vd_{ss}) of 1.06 and 0.639 L/kg seemed to correspond with total body water, which ranges from 0.45 to 0.65 L/kg in humans. The slightly higher value reported by Imondi *et al.* (25), 1.8 L/kg, is overestimated. Since sulpiride was administered orally, the calculated volume of distribution (Vd/F), would give a value of 0.6 L/kg for Vd if the absorption coefficient F were 0.30.

These results are in accordance with the very low lipophilic properties of sulpiride, which should lead to a poor distribution in tissues and thus to a volume of distribution close to total body water volume. The high value of Vd_1 (0.53 L/kg) and Vd_{ss} (2.7 L/kg) found by Wiesel *et al.* (3) are related to the low plasma levels found either after oral or intravenous administration by these authors. It could be that within-subject variations of the distribution parameters gave rise to these differences between the populations studied. In our earlier study (5, 6), all the subjects but one were females and the volume of distribution was significantly higher than in the recent study conducted exclusively in male subjects. In three female and one male subject, the distribution phase was not apparent after intramuscular administration (5, 6). There could be sex-related variations in the distribution pattern of sulpiride in humans.

Total Elimination from Plasma—*Half-Life of Elimination*—The half-life of sulpiride elimination from the body was evaluated either from plasma data by the slope of the log-linear terminal part of the plasma concentration *versus* time curve (Table V), from the urinary excretion rate *versus* time curve plot (rate plot), and the amount remaining to be excreted *versus* time plot (σ^- plot) (Table VI). The mean values obtained by these three methods were very close and ranged from 6 to 8 h.

Wiesel *et al.* (3) obtained elimination half-lives of 6.75 h (λ_2) and 7.15 h (dU/dt) after intravenous administration. In this study, we report elimination half-lives after intramuscular administration of 6.87 h (λ_2), 5.58 h (dU/dt), and 5.68 h ($U_\infty - U$). These values, obtained either after intramuscular or intravenous administration, with a sample collection lasting up to 36 h, should be the closest values to the true ones. When plasma and urine samples were collected for a shorter period than in these studies, the terminal log-linear part of the curves was not reached and the half-life was underestimated (the rate constant was overestimated). Bres *et al.* (5, 6) reported elimination half-lives after intramuscular administration of 3.11 h (λ_2), 3.73 h (dU/dt), and 3.33 h ($U_\infty - U$), while after oral administration these values were 3.0, 3.6, and 3.0 h, respectively (Table VI).

Total Clearance—Total plasma clearances, estimated from the ratio of dose/AUC were 415 mL/min after intravenous administration (3) and 220 mL/min (5, 6) or 89.8 mL/min (this study) after intramuscular administration. The large differences observed in these three studies were related to variations in the volumes of distribution at steady state (Table V).

Excretion in Urine in the Form of Unchanged Sulpiride—*Extent of Sulpiride Elimination in Urine*—Sulpiride is mainly eliminated from plasma by the renal route. After intravenous administration of the drug, Wiesel *et al.* (3) found 72.3 ± 8.9% of the administered dose in urine over a 36-h period. After intramuscular administration, Bres *et al.* (5, 6) found 82.9 ± 7.4% of administered dose in urine (24-h collection). In this study, 93.1 ± 6.6% was found in urine, almost all the administered dose (48-h collection; Table VI).

Rate Constant of Elimination—The rate of elimination of sulpiride in urine was identical to the rate of disappearance of sulpiride from the plasma. The fraction of administered dose eliminated unchanged in urine is close to 1.0; nevertheless, another route of elimination had to be introduced for the simulations (Scheme II, with $k_{10} = k_{13} + k_{14}$).

Renal Clearance—The renal clearances of sulpiride were 310 mL/min after intravenous administration (3) and 190 mL/min (5, 6) or 83.0 mL/min (this study) after intramuscular administration. The large variations observed in these studies and the interindividual variations, estimated from the standard deviations, are mainly related to changes in the sulpiride apparent volume of distribution within subjects. The renal clearance of sulpiride, while slightly lower than the total clearance, is a good reflection of the sulpiride total

Table VI—Sulpiride Elimination[a]

Route of Administration	Dose, mg	Dose, mg/kg	k_e, h^{-1} $\frac{dU/dt}{U_\infty - U}$		$t_{1/2}$, h $\frac{dU/dt}{U_\infty - U}$		U_∞, %
Intramuscular	300-500	6 to 7	0.186	0.208	3.73	3.33	82.9 ± 7.4
Intravenous	100	1.3 for men 1.7 for women	0.097		7.15		72.3 ± 8.9
Intramuscular	50	0.78	0.144	0.143	4.95	5.21	92.3 ± 6.8
	100	1.38	0.122	0.124	6.09	5.95	94.1 ± 6.2
	200	2.74	0.111	0.124	5.77	5.92	91.8 ± 7.5
Mean			0.131	0.157	5.58	5.68	93.1 ± 6.6

[a] See Table V for collection procedures.

clearance from plasma. Since renal clearances of sulpiride and creatinine were simultaneously evaluated in all subjects in this study (Table I), we attempted to correlate these two values. With the large intraindividual variability (Table II, Fig. 5) in sulpiride renal clearance, it was not possible to find a positive correlation with creatinine clearance, but subjects 3 and 9 who had the highest sulpiride clearances also had the highest creatinine clearances.

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Pulmonary Absorption and Excretion of Compounds in the Gas Phase: Theoretical Pharmacokinetic and Toxicokinetic Analysis

PETER VENG-PEDERSEN

Received September 1, 1982, from *Division of Pharmacokinetics, School of Pharmacy, Purdue University, West Lafayette, IN 47907.* Accepted for publication July 29, 1983. Present address: College of Pharmacy, University of Iowa, Iowa City, IA 52242.

Abstract □ Kinetic equations were derived that describe the plasma concentration of an inhaled compound during and following single or repeated regular and irregular pulmonary exposures. The equations are based on a diffusional type of input function and assume a linear disposition with a biexponential unit-impulse response. The use of linear system analysis avoids the complexity of modeling the disposition processes; yet, the effect of these processes is still accounted for mathematically. The approach, therefore, appears to be more general and rational than approaches based on linear compartmental modeling. The ways in which the kinetic equations can be readily applied in pharmacokinetic or toxicokinetic analyses to obtain valuable parameters that enable kinetic predictions of the cumulation during prolonged exposure are discussed. The toxicokinetic problem of comparing the effect of different work schedules in occupational environments with air contaminants is discussed. Formulas derived from considerations of the blood plasma kinetics are presented for the calculation of an adjustment factor for the adjustment of the contaminant threshold limit value for abnormal work weeks. The use of these formulas appears to be more rational than that of similar formulas that have been proposed.

Keyphrases □ Absorption—pulmonary, excretion, theoretical pharmacokinetic and toxicokinetic analyses □ Pharmacokinetics—pulmonary absorption and excretion, toxicokinetics □ Toxicokinetics—pulmonary absorption and excretion, pharmacokinetics

Little attention has been given to the pharmacokinetic-toxicokinetic characterization of the pulmonary absorption and excretion of compounds in the gas phase. The kinetic investigations of the volatile drugs used in general anesthetics has been limited mainly to empirical quantitative analysis of uptake, metabolism, and pulmonary excretion (1–3), without a formal mathematical, pharmacokinetic analysis of the plasma level-time profile (4, 5).

The study of pulmonary absorption kinetics is also of particular interest in environmental toxicology (6–9). Special attention has been given to the risk assessment of work place exposures to vaporous air contaminants. Of particular concern

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