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Pharmacokinetics of Chlorimipramine, Chlorpromazine and their *N*-Dealkylated Metabolites in Plasma of Healthy Volunteers After a Single Oral Dose of the Parent Compounds

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Abstract—A single oral dose of 0·7 mg kg^{-1} chlorimipramine (n = 18) and chlorpromazine (n = 16) was given to each subject 45 days apart and plasma concentrations of parent drugs and their monodesmethyl and didesmethyl metabolites were measured by GC. Ingestion of chlorimipramine resulted in an area under the plasma concentration-time curve (AUC_{0-24}) for parent drug plus metabolites 5-fold higher than that observed in the same subjects following chlorpromazine intake (600 ± 87 and 124 ± 14 ng mL^{-1}, respectively). Plasma chlorimipramine levels reached a mean peak value of 43·8 ng mL^{-1}, an average of 3·4 h after dosage, whereas the mean peak chlorpromazine level was 15·1 ng mL^{-1}, which occurred 2 h after administration. Desmethyl metabolite kinetics of chlorimipramine appeared to be elimination rate-limited and those of chlorpromazine appeared to be formation-rate-limited. The response to single doses of these two drugs in healthy subjects highlights the two distinct dispositional processes involved, thus offering pharmacokinetic explanation of the hitherto empirical discrepancy in dosage levels in chronic treatment.

Both chlorpromazine and chlorimipramine have a long established history as psychoactive agents in clinical practice. While chlorpromazine is a major tranquillizer and chlorimipramine an antidepressant, they have several pharmacological aspects in common. Moreover, they are structurally similar (Fig. 1).

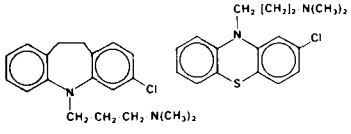

FIG. 1. Structure of chlorimipramine and chlorpromazine.

In spite of this similarity, however, their clinical usage calls for remarkably different oral daily dosages, up to 200 mg for chlorimipramine and 2000 mg for chlorpromazine. This is surprising since in man, oral bioavailability (Dahl & Strandjord 1977; Nagy & Johansson 1977; Evans et al 1980), lipophilicity (Westenberg et al 1977; Gigon et al 1983) and plasma protein binding capacity (Curry 1970; Campbell & Todrick 1970) are similar.

However, the effective oral dosage levels are reversed in rat (Jewett & Norton 1963; Delini-Stula 1980). Studies on the pharmacodynamics at known cellular target sites in the rat brain have provided evidence that chlorpromazine is effective at much lower concentrations than those required for the action of chlorimipramine (Iversen et al 1976 a, b; Koe 1976; Dahl et al 1986).

We felt that the difference in the clinical dosages could be related to a difference in disposition rates and pharmacokinetic behaviour. Results from different studies in the literature seem to support this hypothesis (Sakurai et al 1975; Jones & Luscombe 1976; Allen et al 1977; Evans et al 1980; Yeung et al 1983). The present investigation was carried out to minimize interindividual variations, in particular those related to genetic differences in the metabolic processing of these drugs. We therefore compared the kinetic behaviour of chlorimipramine and chlorpromazine in the same healthy subjects treated on two separate occasions with both drugs at the same dose.

Preliminary results of this study have been presented to the British Pharmacological Society (Sgaragli et al 1988).

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Materials and Methods

Materials

The hydrochloride salts of chlorimipramine and the monodesmethyl and bisdesmethyl derivatives were a generous gift from Ciba-Geigy, Milano, Italy. Amitriptyline was kindly supplied by Lepetit S.p.A., Milano, Italy. Chlorpromazine hydrochloride was supplied by S. Maria Nuova Hospital, Firenze, Italy. The hydrochloride salts of the desmethyl derivatives were gifts from Dr A. A. Manian, National Institute of Mental Health, Rockville, MD, USA. *n*-Heptane and *n*-hexane (analytical grade, distilled before use) were purchased from E. Merck, Darmstadt, Germany. Methanol (Aristar grade) was purchased from BDH Chemicals Ltd, Poole, UK. All other compounds used were of analytical grade.

Subjects

Eighteen volunteers, 9 females (age range 21–36 years and body weight 48–63 kg) and 9 males (age range 25–40 years

and body weight 60–73 kg), participated in the investigation after having given informed consent. The volunteers were considered healthy after a physical examination and ECG. The subjects had been drug-free for at least 3 weeks before the study and had taken no medication during the previous year. None had prior experience with either drug.

Drug was administered as enteric-coated capsules containing 0·7 mg kg^{-1} of the drug at 0900 h, 2 h after a light meal. Administration of chlorimipramine was followed 45 days later by administration of chlorpromazine. Two subjects (1 male and 1 female), underwent chlorimipramine treatment alone. At various intervals over 24 h after ingestion (0, 0·5, 1·0, 2·0, 4·0, 8·0 and 24 h) 6–10 mL of blood was withdrawn from a cubital vein by Vacutainers, avoiding blood contact with the caps. Following centrifugation within 30 min, plasma was collected and kept frozen at −20°C until assay. Subjects recorded the onset and duration of any side-effects experienced up to 48 h following drug administration.

Analysis

Drugs and metabolites were analysed by a GC method using a nitrogen-phosphorous selective detector as previously described (Ninci et al 1986). Following a three-step extraction into organic solvent from plasma which excluded the most polar metabolites, derivatization of the desmethyl metabolites with trifluoroacetic anhydride (Pierce Eurochemie, Rotterdam, The Netherlands) allowed the chromatographic separation and quantification of the parent drugs, their dehalogenated metabolites and both monodesmethyl and bisdesmethyl metabolites at the nanogram level. Concentrations in the 1–0·1 ng mL^{-1} range, although less precisely determined, were still quantifiable.

Pharmacokinetic analysis

The area under the experimental concentration curve (AUC) was calculated by a combined linear logarithmic trapezoidal method (Shumaker 1986). Pharmacokinetic parameters were determined by a model-dependent, curve fitting method. An acceptable fit of plasma drug concentrations vs time was obtained using a one compartment model with zero order input, using MKMODEL program (Holford 1988) for extended least-squares nonlinear regression (Peck et al 1984) on an IBM PC computer.

Absorption lag time (t_{lag}), zero input duration (t_{k0}), and apparent disposition half-life ($t_{\frac{1}{2}}$) were estimated.

Individual parameters were reported as mean values ± s.e. whereas group means, where feasible, were reported with their CV%. Given the low individual concentration levels of desmethyl metabolites, these were expressed as a group mean.

Statistical analysis

Group mean values for pharmacokinetic parameters were compared by the non-parametric Mann-Whitney test, and by the Wilcoxon signed rank test when paired observations were compared. Estimates of $AUC_{0\text{-}24}$ ratios of desmethyl metabolites and parent drug and their confidence intervals were obtained by Fieller's theorem, using two-tail 5% probability, according to Goldstein (1964). Data in contingency tables were analysed by the Chi-square test (Goldstein 1964).

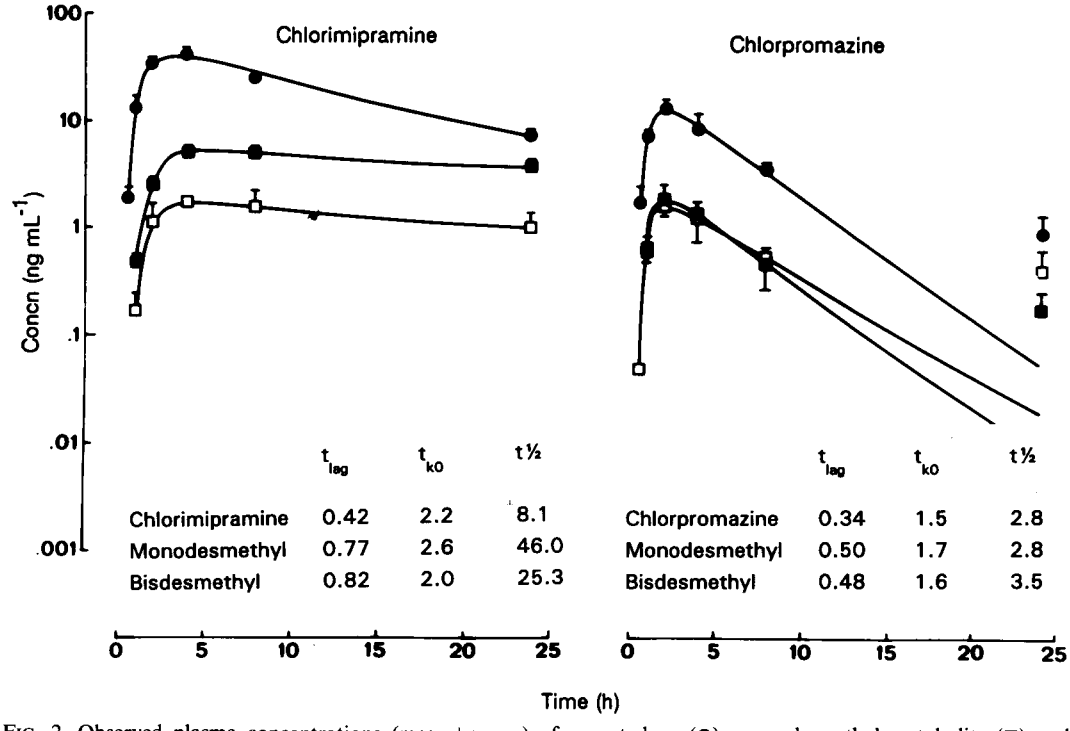

FIG. 2. Observed plasma concentrations (mean ± s.e.m.) of parent drug (●), monodesmethyl metabolite (■) and bisdesmethyl metabolite (□) in 18 healthy volunteers receiving chlorpromazine and in 16 healthy volunteers receiving chlorimipramine as a single oral dose (0·7 mg kg^{-1}). Lines represent the plasma concentration-time curves computed by fitting mean values to the one compartment model with zero absorption.

Table 1. Mean ± s.e.m. of plasma c_{max}, t_{max} and AUC_{0-24} values for drugs and metabolites in healthy volunteers following a single oral dose of the parent compounds (0·7 mg kg^{-1}).

		Chlorimipramine (n = 18)	Chlorpromazine (n = 16)
C_{max} (ng mL^{-1})	Parent	43·8 ± 7·6	15·1 ± 2·0**
	Monodesmethyl	5·7 ± 0·5	5·0 ± 2·6*
	Bisdesmethyl	1·8 ± 0·7	3·7 ± 1·5
t_{max} (h)	Parent	3·4 ± 0·2 (4)	2·0 ± 0·0 (2)**
	Monodesmethyl	8·2 ± 1·4 (8)	3·5 ± 0·5 (2)**
	Bisdesmethyl	14·5 ± 2·1 (8)	2·6 ± 0·4 (2)**
AUC_{0-24h} (ng mL^{-1} h)	Total	599·9 ± 87·4	124·2 ± 13·6***
	Parent	474·4 ± 80·8	90·3 ± 13·3***
	Monodesmethyl	92·7 ± 8·9	17·4 ± 4·8***
	Bisdesmethyl	28·3 ± 12·4	16·4 ± 4·1
Ratio	0·265	(0·182–0·406)	0·375 (0·149–726)

Values in parentheses are the median, for t_{max}, and the 95% confidence intervals, for the ratio (total area under the metabolite curves divided by the AUC for the parent compound). *$P < 0·05$, **$P < 0·01$ and ***$P < 0·001$, compared with chlorimipramine in the 16 subjects who underwent both drug treatments.

Results

Subjects characteristics

Males and females differed significantly in body weight (68·1 ± 1·6 and 54·7 ± 2 kg, respectively) but were comparable in age (28·0 ± 1·6 and 27·9 ± 1·6 years, respectively).

Plasma concentrations of chlorimipramine, chlorpromazine, N-demethylated and dechlorinated metabolites

Mean plasma concentrations of drugs and metabolites in subjects who received a single oral dose of the parent compounds are shown in Fig. 2 while C_{max} and t_{max}, together with the calculated AUC_{0-24} values are reported in Table 1. As a general trend, chlorimipramine reached higher, but later, peak plasma levels, than chlorpromazine. Chlorimipramine was still detectable in all the subjects 24 h post-ingestion in amounts ranging between 10 and 35% of peak levels. For chlorpromazine, however, the 24 h post-dose levels were almost undetectable (below 0·1 ng mL^{-1}) in eight of the subjects.

Taking the ratio AUC_{0-24} of desmethyl metabolites to the AUC_{0-24} of their parent compound (Table 1) as an indication of the relative plasma accumulation of both the primary and the secondary *N*-demethylated metabolites, no significant difference was observed between the two drugs.

Dehalogenation products (imipramine and promazine) were not detectable in any of the plasma samples examined.

Pharmacokinetics

Pharmacokinetic parameters were determined by a model-dependent curve fitting method according to a one-compartment zero-order input model, and are presented in Fig. 2 and Table 2.

Plasma concentration comparisons show that in the case of chlorpromazine, mean parent and metabolite levels measured at 24 h were much higher than those predicted by the model, possibly due to a bimodal distribution of subject response. As may be seen from Fig. 3 this dishomogeneity was exhibited only for chlorpromazine and was not found for chlorimipramine.

Table 2. Estimates of pharmacokinetic parameters of chorimipramine and chlorpromazine, according to the one-compartment zero-order input model, in the same population of healthy subjects, following a single oral dose of each compound.

	Chlorimipramine (n = 17)	Chlorpromazine (n = 14)
t_{lag} (h)	0·47 ± 0·04 (0·16 – 0·83)	0·39 ± 0·05 (0·14–0·91)
t_{k0} (h)	2·50 ± 2·20 (1·2 – 4·1)	1·50 ± 0·10*** (1·0 – 2·3)
$t_{\frac{1}{2}}$ (h)	8·60 ± 0·40 (5·8 – 11·1)	3·20 ± 0·40*** (1·3 – 6·4)

Parameter estimates were obtained by fitting data from individuals. Values are mean ± s.e.m., ranges are shown in parentheses. ***$P < 0·001$ compared with corresponding chlorimipramine values, using the Mann-Whitney test. The mean $t_{\frac{1}{2}}$ of chlorpromazine obtained including the 24 h time point was 6·4 ± 1·8 h.

Adverse effects

The incidence of various adverse effects experienced by the subjects up to 48 h after treatment is shown in Table 3. Onset times varied from 2 to 5 h and seemed unrelated to the sex of the individuals, with the exception of nausea which was reported significantly more frequently by females ($P < 0·05$, Chi-square test). Incidence, as well as the duration of adverse effects was always higher after chlorimipramine.

Discussion

The aim of this study was to elucidate the pharmacokinetic bases underlying the empirical divergence in dosage levels prescribed for two structurally similar compounds.

Though limited to a single dose and to a healthy population, our findings point to the remarkably different manner in which the same population processes the two drugs.

At the same dosage, chlorimipramine ingestion resulted in total plasma AUC_{0-24} values fivefold those following chlorpromazine intake despite a slower apparent absorption rate with peak plasma levels being reached 1·5 h later.

Various dynamic factors may affect both rate and extent of

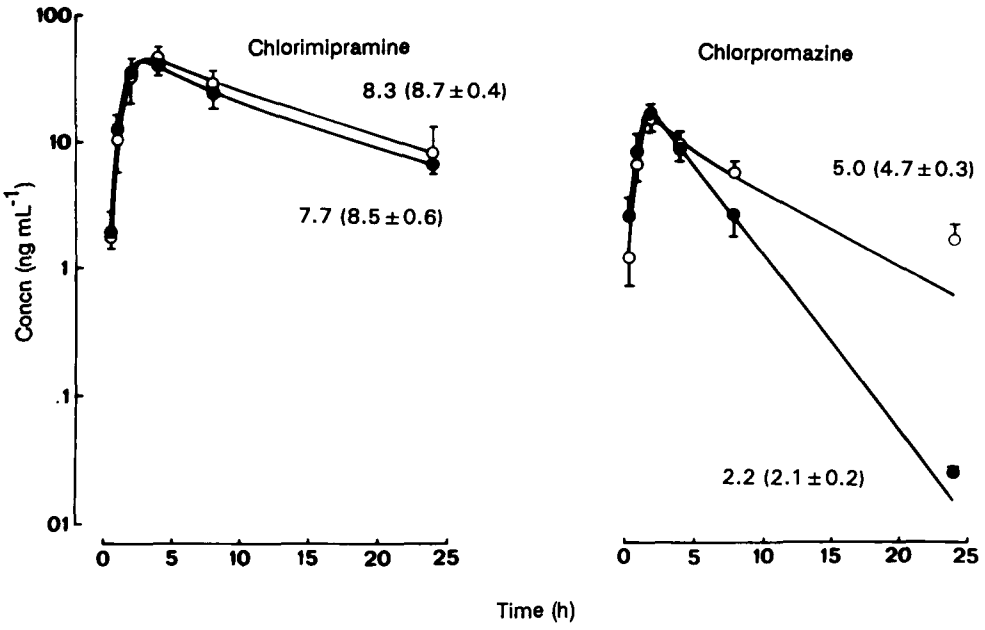

FIG. 3. Observed plasma concentrations (mean ± s.e.m.) of chlorimipramine and chlorpromazine obtained by grouping the subjects according to their chlorpromazine $t_{\frac{1}{2}}$ values: < 3 h (n = 9; open circles); > 4 h (n = 7; closed circles). Lines represent the plasma concentration-time curves computed by fitting mean concentration values to the one-compartment model with zero-order absorption, estimated $t_{\frac{1}{2}}$ values are shown; $t_{\frac{1}{2}}$ values (mean ± s.e.m.) obtained by computer fitting of concentration-time curves from individual subjects are also shown.

absorption. The gastrointestinal resistant capsules and the hydrochloride formulation of the two drugs should have ensured their bioequivalence. Previous studies on the relative bioavailability of orally delivered chlorimipramine and chlorpromazine (Dahl & Strandjord 1977; Evans et al 1980) proved them to be comparable.

An explanation for this kinetic difference might be found in the antimuscarinic effect which lowers the plasma concentration of concomitantly administered drugs. Indeed the cholinolytic property of chlorpromazine has been invoked to explain the low plasma levels in heavily medicated chronic schizophrenics (Rivera-Calimlin & Hershey 1984). However, this line of reasoning fails to account for the fact that chlorimipramine is an even greater anti-muscarinic agent than is chlorpromazine, as the present study and others have shown (Weinstock & Cohen 1976; Snyder & Yamamura 1977; Shein & Smith 1978; Dahl et al 1986). Thus, although anticholinergic factors may contribute to the lower apparent absorption rate of chlorimipramine, it does not explain its higher plasma concentrations.

A hypothesis that accounts for this discrepancy in concentration might be the rapid overall disposition rate of chlorpromazine as seen by its shorter half-life and by the plasma concentration profiles of its metabolites.

The chlorpromazine metabolite profiles parallel the behaviour of the parent compound, suggesting that their elimination occurs very rapidly, their concentrations being limited by the rate of production.

Table 3. Frequency and onset time (mean ± s.e.m.) of various effects experienced by healthy volunteers up to 48 h following a single oral dose of chlorpromazine and chlorimipramine (0·7 mg kg^{-1}) given 45 days apart.

	Chlorpromazine			Chlorimipramine		
	Male	Female	Onset time (h)	Male	Female	Onset time (h)
Xerostomia*	3/8	5/8	2·4 ± 1·2	4/8	7/9	2·3 ± 1·4
Increased heart rate	3/8	1/8	—	1/8	4/9	
Dystonia	0/8	0/8	—	3/8	5/9	5·0 ± 3·2
Tremor	0/8	0/8	—	2/8	2/9	3·3 ± 0·2
Vertigo	0/8	0/8	—	1/8	6/9	3·1 ± 0·1
Nausea	0/8	0/8	—	1/8	4/9	3·2 ± 2·0
Loss of appetite	0/8	0/8	—	2/8	6/9	—
Drowsiness	5/8	4/8	3·5 ± 1·1	4/8	4/9	4·1 ± 2·6
Insomnia	0/8	0/8	—	5/8	5/9	—
Impaired perception	0/8	0/8	—	3/8	6/9	—
Anxiety	0/8	0/8	—	2/8	2/9	—

Values represent mean ± s.e.m. * Lasting up to 24 and 48 h after chlorpromazine and chlorimipramine treatment, respectively.

For chlorimipramine, the desmethyl metabolites appeared to be eliminated at a much slower rate than the parent drug, their concentrations being elimination rate limited.

It was also observed that chlorpromazine and its metabolites reached peak plasma concentrations simultaneously, suggesting that a significant portion of the drug is *N*-demethylated during pre-systemic absorption.

Chlorimipramine too has been reported to undergo extensive demethylation before it reaches the systemic circulation (Nagy & Johansson 1977; Della Corte et al 1979; Evans et al 1980). However, the observed delayed time to reach peak levels of its metabolites may indicate that some demethylation also occurs systemically. Although the sample size prevents any firm conclusions, a further difference in the bioprocessing of the two drugs is exhibited by the bimodal distribution in the half-life rapid elimination phase of chlorpromazine. Irrespective of gender, individual subjects evenly fell into two clearly defined half-life categories, one with a $t_{\frac{1}{2}}$ of 2·2 h, the other with a $t_{\frac{1}{2}}$ of 5 h. No such bimodularity was observed in the half-life of chlorimipramine.

The extrapolation of this single dose study to clinical application must, however, be qualified by the fact that steady-state conditions may substantially affect the pharmacokinetic profile. Thus the present authors have previously shown (Sgaragli et al 1986; Valoti et al 1992) that whereas chlorpromazine leads to promazine formation when administered chronically, a single dose is not apparently metabolized by dechlorination.

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References

Allen, J. J., Vaddadi, K. S., Rack, D. H. (1977) Differences in the effects of clomipramine on English and Asian volunteers. Preliminary report on a pilot study. Postgrad. Med. J. 53 (Suppl. 4): 79–86

Campbell, I. C., Todrick, A. (1970) Plasma protein binding of tricyclic antidepressive drugs. J. Pharm. Pharmacol. 22: 226–227

Curry, S. H. (1970) Plasma protein binding of chlorpromazine. J. Pharm. Pharmacol. 22: 193–197

Dahl, S. G., Strandjord, R. E. (1977) Pharmacokinetics of chlorpromazine after single and chronic dosage. Clin. Pharmacol. Ther. 21: 437–448

Dahl, S. G., Hough, E., Hals, P. A. (1986) Phenothiazine drugs and metabolites: molecular conformation and dopaminergic, alpha adrenergic and muscarinic cholinergic receptor binding. Biochem. Pharmacol. 35: 1263–1269

Delini-Stula, A. (1980) Drug-induced alterations in animal behaviour as a tool for the evaluation of antidepressants, correlation with biochemical effects. In: Hoffmeister, F., Stille, G. (eds) Handbook of Experimental Pharmacology. Vol. 55. Springer-Verlag, Berlin, Heidelberg, New York, pp 505–526

Della Corte, L., Heeley, A. F., Broadhurst, A. D., James, H. D., Sgaragli, G. P., Faravelli, C., Filippini, S., Pazzagli, A. (1979) Clinical response and tricylcic plasma level during treatment with clomipramine. Br. J. Psychiatry 134: 390–400

Evans, L. E. J., Bett, J. H. N., Cox, J. R., Dubois, J. P., Van Hees, T. (1980) The bioavailability of oral and parenteral chlorimipramine (Anafranil). Prog. Neuropsychopharmacol. 4: 293–302

Gigon, P. L., Van Hees, H., Bickel, M. H. (1983) A technique for the comparison of biological distribution and solvent partition of drugs. Experientia 39: 801–804

Goldstein, A. (1964) Biostatistics: An Introductory Text. Collier MacMillan, London

Holford, N. (1988) MK Model. An Extended Least Squares Modeling Program. Biosoft, Cambridge, UK

Iversen, L. L., Horn, A. S., Miller, R. J. (1976a) Structure-activity relationship for interactions of agonist and antagonist drugs with dopamine-stimulated adenylate cyclase of rat brain—a model for CNS dopamine receptors? In: Sedvall, G., Uvnas, B., Zotterman, Y. (eds) Antipsychotic Drugs. Pergamon Press, Oxford, New York, pp 285–303

Iversen, L. L., Horn, A. S., Miller, R. J. (1976b) Comparison of the effects of neuroleptic drugs on pre- and post-synaptic dopaminergic mechanism in the rat striatum. Mol. Pharmacol. 12: 251–262

Jewett, R., Norton, S. (1963) Drug effects on behaviour of rat under chronic isolation. Pharmacologist 5: 240

Jones, R. B., Luscombe, D. K. (1976) Single dose studies with clomipramine in normal subjects. Postgrad. Med. J. 52 (Suppl. 3): 62–67

Koe, K. G. (1976) Molecular geometry of inhibitors of the uptake of catecholamines and serotonin in synaptosomal preparations of rat brain. J. Pharmacol. Exp. Ther. 199: 649–661

Nagy, A., Johansson, R. (1977) The demethylation of imipramine and chlorimipramine as apparent from their plasma kinetics. Psychopharmacology 54: 125–131

Ninci, R., Giovannini, M. G., Della Corte, L., Sgaragli, G. P. (1986) Isothermal gas chromatographic determination of nanogram amounts of chlorimipramine, chlorpromazine and their *N*-desmethyl metabolites in plasma using nitrogen-selective detection. J. Chromatogr. 381: 315–322

Peck, C. C., Beal, S. L., Sheiner, L. B., Nichols, A. I. (1984) A possible solution to the choice of weights problem in analysis of individual pharmacokinetic data. J. Pharmacokinet. Biopharm. 12: 545–558

Rivera-Calimlin, L., Hershey, L. (1984) Neuroleptic concentrations and clinical response. Ann. Rev. Pharmacol. Toxicol. 24: 361–386

Sakurai, Y., Nakahara, T., Takahastri, R. (1975) Prediction of response to CPZ treatment in schizophrenics. Psychopharmacology 44: 195–203

Sgaragli, G. P., Ninci, R., Della Corte, L., Valoti, M., Nardini, M., Andreoli, V., Moneti, G. (1986) Promazine: a major plasma metabolite of chlorpromazine in a population of chronic schizophrenics. Drug Metab. Dispos. 14: 263–266

Sgaragli, G. P., Ninci, R., Della Corte, L., Valoti, M., Palmi, M. (1988) Pharmacokinetics of chlorpromazine (CPZ) and chlorimipramine (CI) in healthy volunteers. Br. J. Clin. Pharmacol. 25: 134–135P

Shein, K., Smith, S. E. (1978) Structure activity relationship for the anticholinoceptor action of tricyclic antidepressants. Br. J. Pharmacol. 62: 567–571

Shumaker, R. C. (1986) PKCALC: a BASIC interactive computer program for statistical and pharmacokinetic analysis of data. Drug Metab. Rev. 17: 331–348

Snyder, S. H., Yamamura, H. I. (1977) Antidepressants and the muscarinic acetylcholine receptor. Arch. Psychiat. 34: 236–239

Valoti, M., Palmi, M., Della Corte, L., Nardini, M., Corti, P., Sgaragli, G. P. (1992) Dehalogenation and *N*-dealkylation of chlorpromazine as revealed by plasma concentrations of metabolites in a population of chronically medicated schizophrenics. Meth. Find. Exp. Clin. Pharmacol. 14: 445–450

Weinstock, M., Cohen, D. (1976) Tricyclic antidepressant drugs as antagonists of muscarinic receptors in sympathetic ganglia. Eur. J. Pharmacol. 40: 321–328

Westenberg, H. G., De Zeeue, R. A., Decuyper, H., Van Praag, H. M., Korf, J. (1977) Bioanalysis and pharmacokinetics of clomipramine and desmethylclomipramine in man by means of liquid chromatography. Postgrad. Med. J. 53 (Suppl. 4): 124–130

Yeung, P. K., Hubbard, J. W., Cooper, J. K., Midha, K. K. (1983) A study of the kinetics of chlorpromazine sulfoxide by a specific radioimmunoassay after a single oral dose of chlorpromazine in healthy volunteers. J. Pharmacol. Exp. Ther. 226: 833–838