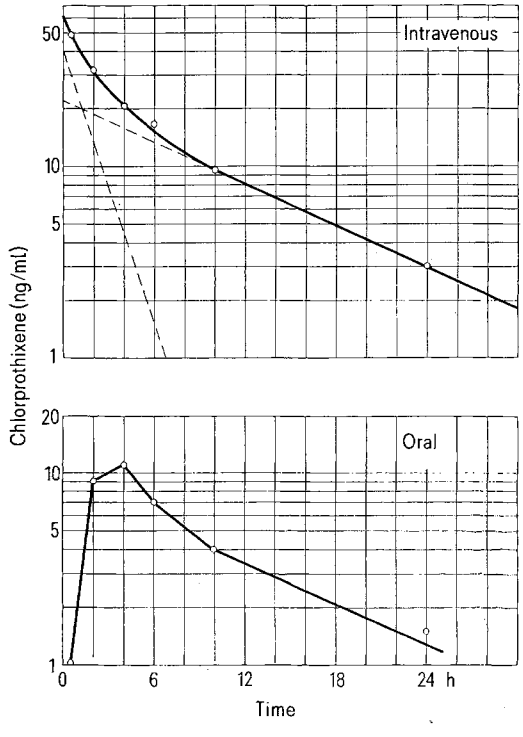
On the Pharmacokinetics of Chlorprothixene in Man

Since its introduction into human therapy, chlorprothixene[1] has been widely used as a major tranquillizer in psychiatry, anesthesiology, pediatrics and in general medical practice. The elimination of the drug from the blood occurs through biotransformation in the liver. Three of the main metabolites formed and excreted in urine have been isolated and identified, namely chlorprothixene-sulfoxide, N-desmethyl-chlorprothixene-sulfoxide and chlorprothixene-sulfoxide-N-oxide[2,3]. Little is known of the pharmacokinetics of the drug[4]. This is mainly due to the difficulties in evaluating the minute amounts of chlorprothixene in the blood after intake of average doses. Having recently had the opportunity of measuring the chlorprothixene blood levels after a single dose of 30 mg given both by the oral and the i.v. route in 3 subjects by an improved method, we wish to give a brief account of the results obtained.

Methods. Three healthy adult volunteers served as test subjects. For the i.v. experiment an ampoule of Taractan® Roche (2.0 ml containing 30 mg chlorprothixene) was slowly injected into a vein of the forearm. For the oral experiment, 8 days later each subject received 2 dragées of Taractan® Roche (containing 15 mg chlorprothixene each) on an empty stomach together with a cup of tea. 30 min later a small breakfast was allowed.

Blood sampling. Venous blood samples were taken in oxalated tubes 0.5, 2.0, 4.0, 6.0, 10.0 and 24.0 h after intake or injection of the drug. The samples were stored at 0 °C until analyzed.

Analytical method. 2.0 ml of whole blood are made alkaline with 0.4 ml of 0.5 *N* NaOH and extracted with 10.0 ml *n*-Heptane (containing 1% (v/v) isopentylalcohol). 8.0 ml of the extract are equilibrated with 1.6 ml of 40% (w/v) analytical grade sulfuric acid. The acid phase is removed and analyzed fluorimetrically by means of an Aminco-Bowman-Spectrophotofluorometer (excitation wavelength 386 nm, emission wavelength 550 nm). Sensitivity: approx. 1 ng/ml of blood. Specificity: judged satisfactory, as 100 ng/ml of chlorprothixene-sulfoxide, the main metabolite of the drug, gives no measurable fluorescence. Desmethylchlorprothixene, which fluoresces in sulfuric acid and therefore could weaken the specificity of the assay, most probably does not interfere, since in analogous experiments with rats the unchanged drug, chlorprothixene-sulfoxide and desmethyl-chlorprothixene-sulfoxide but no desmethyl-chlorprothixene could be detected by TLC of the blood extracts[5].



Chlorprothixene blood levels in subject C.N. following i.v. and oral administration of 30 mg chlorprothixene.

Results and interpretation. The log c in blood against time curve after i.v. injection of chlorprothixene, as exemplified in the Figure for the subject C.N., shows that the drug behaves according to the rules of a two compartment open model. The main results and pharmacokinetic constants derived from the experimental data of the 3 subjects tested are listed in the Table. Several points are to be noted. The half-life $t_{\frac{1}{2}}$ during the β-phase of chlorprothixene elimination is of medium magnitude (8–12 h). The total volume of distribution $(V_d)_\beta$ is very large, indicating a high dispersion of the drug into the tissues. Remarkably high are also the values of the total clearance. From these, a considerable first pass effect can be presumed to occur. According to the data at the bottom of the Table, a rather poor oral availability was indeed found in all 3 subjects. Furthermore, the agreement of the average availability[6] found, and the availability predicted according to Gibaldi[7], permits one to say that the absorbability of chlorprothixene from the gut, as governed by the solubility, dissolution rate and permeability characteristics of the drug molecule were apparently good. Also, the solubility of chlorprothixene in neutral to slightly acid solution is fairly good and the partition coefficients in biphasic systems are known to be high[3]. It may be mentioned further that in a recent cross-over study with 4 subjects the oral availability of dragées and solution of chlorprothixene were found to be similar[5]. All these items, then, corroborate the smooth enteral absorption of the drug.

Surveying the current literature on the pharmacokinetics of tricyclic psychotropics, it appears that pertinent data are available for desipramine[8,9] and nortriptyline[9,10], while data on the corresponding

[1] Active compound of Taractan®, Truxal® and other brand specialities.

[2] L. G. Allgen, B. Jönsson, B. Nauckkoff, M. L. Andersen, I. Huus and I. Moller-Nielsen, Experientia *16*, 325 (1960).

[3] J. Raaflaub, Arzneimittel-Forsch. *17*, 1393 (1967).

[4] J. A. F. De Silva and L. D'Arconte, J. forens. Sci. *14*, 184 (1969).

[5] J. Raaflaub, unpublished data.

[6] The individual values of availability found and availability predicted, on the other hand, show rather large discrepancies. The main reason probably is that in the calculation of availability according to Gibaldi a mean value of the liver blood flow (taken as 1.7 l/min) is used, while the true individual value may and actually frequently does differ considerably from this mean value.

[7] M. Gibaldi, R. N. Noyes and S. Feldman, J. pharm. Sci. *60*, 1338 (1971).

[8] W. M. Hammer and B. B. Brodie, J. Pharmac. exp. Ther. *157*, 503 (1967).

[9] W. M. Hammer and F. Sjöqvist, Life Sci. *6*, 1895 (1967).

[10] B. Alexanderson and F. Sjöqvist, Ann. N.Y. Acad. Sci. *179*, 739 (1971).

Pharmacokinetic profile and bioavailability of chlorprothixene in 3 human subjects

Subjects tested		C.N. (♀, 23 y, 48 kg)	B.E. (♂, 31 y, 72 kg)	M.M. (♂, 26 y, 74 kg)
i.v. administration (30 mg)				
General equation: $C_b = A\,e^{-\alpha t} + B\,e^{-\beta t}$				
A	(ng/ml)	38	24	48
B	(ng/ml)	22	36	24.5
α	(h^{-1})	0.55	0.58	0.48
β	(h^{-1})	0.082	0.087	0.059
$(t_{1/2})\beta$	(h)	8.4	8.0	11.8
Area u.c.	(h × ng/ml)	337	455	515
$(V_d)\beta$	(l)	1088	758	987
	(l/kg)	22.7	10.5	13.3
Total clearance	(l/min)	1.48	1.10	0.97
Oral administration (30 mg)				
Area u.c.	(h × ng/ml)	124	106	330
Availability found (%)		37	23	64
Availability predicted (%)		13	35	43
Means of availability of the 3 subjects				
Found (%)			41	
Predicted (%)			30	

tertiary amines imipramine and amitriptyline are scarce. As may be anticipated from the chemical structure and physicochemical properties of the tricyclic compounds, their pharmacokinetic profiles are similar. All have a rather long half-life, a very large volume of distribution and are eliminated from the blood by biotransformation in the liver. Recently it has been reported that nortriptyline is subject to a marked liver first pass effect and therefore has a low oral availability[11]. The results of the present study show an analogous effect with chlorprothixene. This again, seems to be a typical feature of the whole group.

As regards the therapeutical implications of the results, the following may be said. Like most psychotropic drugs, chlorprothixene is frequently used in long term treatment. However, steady state levels in such cases have not been measured up to now. The most thoroughly studied parent drug in this respect is again nortriptyline, and it is interesting to note that wide inter-individual variations extending from low and practically ineffective to very high, subtoxic blood concentrations have been observed[10]. Among the factors responsible for this phenomenon, the inter-individual variation of the drug clearance (comprizing the variation in the elimination constant β and of the distribution volume $(V_d)_\beta$, since the clearance is equal to the product of these parameters) and of the oral availability as governed by the liver first pass effect, are the most important. Most likely then, with further experimental data accumulating, it will become apparent that, for the very reasons just outlined, most if not all tricyclic psychotropic drugs are prone to give widely varying steady state levels in different subjects.

Appendix. Formula used in the evaluation of experimental data. For details see M. GIBALDI et al., J. pharm. Sci. *58*, 193 (1969).

i.v. Experiment:

$$\text{Area u.c.} = \frac{A}{\alpha} + \frac{B}{\beta}$$

$$(V_d)_\beta = (V_d)_{\text{area}} = \frac{\text{Dose}}{\beta \times \text{Area u.c.}}$$

$$\text{Clearance} = \frac{\text{Dose}}{\text{Area u.c.}}$$

Oral experiment:

$$\text{Area u.c.} = \int_0^T C \cdot dt + C_T \frac{1}{\beta}$$

The term $\int_0^T C \cdot dt$ was calculated by means of the trapezoid rule.

$$\%\ \text{Availability found} = \frac{(\text{Area u.c.})\ \text{oral}}{(\text{Area u.c.})\ \text{i.v.}} \times 100$$

$$\%\ \text{Availability predicted} = \left(1 - \frac{\text{Clearance}}{\text{LBF}}\right) \times 100$$

(using eq. 11 of GIBALDI[7])

For the liver blood flow (LBF) an average value of 1.7 l/min was assumed.

Zusammenfassung. Die Pharmakokinetik von Chlorprothixen nach oraler und intravenöser Gabe bei 3 erwachsenen Probanden wird beschrieben. Die Hauptcharakteristika sind: eine Eliminationshalbwertzeit (β-Phase) von 8–12 h, ein grosses Verteilungsvolumen $(V_d)_\beta$ von 11–23 l/kg und eine hohe totale Clearance (0,97–1,48 l/min). Die orale Verfügbarkeit des Arzneimittels beträgt infolge des Effekts der ersten Leberpassage (liver first pass effect) 23–64 %der verabreichten Dosis.

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Department of Experimental Medicine, F. Hoffmann-La Roche & Co. Ltd., CH-4002 Basel (Switzerland), 16 January 1975.

[11] B. ALEXANDERSON, O. BORGA and G. ALVAN, Eur. J. clin. Pharmacol. *5*, 181 (1973).