Table 1 Pharmacokinetics of i.v. propranolol (0.15 mg/kg) in patients with Crohn's disease (C) and rheumatoid arthritis (RA)

Patient	*Condition*	*Age (years)*	*ESR (mm/h)*	*Free fraction (%)*	*AUC (0–1 h)*	*AUC (0–∞) (μg ml⁻¹ min)*	*AUC (free) (0–∞)*	*V_d (l/kg)*	*$T_{½}$ (min)*
1	C	30	11	14.9	107	445	66.3	6.28	215
2	C	54	12	13.4	106	385	51.6	4.76	141
3	C	27	32	6.7	241	—	—	—	*
4	C	26	37	8.2	158	430	35.3	4.18	139
5	C	37	42	8.1	158	658	53.3	4.04	205
6	C	35	44	5.6	297	835	46.8	2.27	146
7	C	27	64	7.0	217	646	45.2	2.39	119
8	RA	78	51	3.9	359	914	35.6	1.80	127
9	RA	67	62	7.4	218	556	41.1	2.55	109
10 (a)	RA	42	100	4.1	289	798	32.7	2.34	144
10 (b)	RA	42	39	5.8	171	537	31.1	3.34	138
11	RA	71	112	7.0	241	734	51.4	2.23	126

* = insufficient data
AUC = Area under the total plasma concentration-time curve in $\mu g\ ml^{-1}$ min.
AUC (free) = Area under the free concentration-time curve in $\mu g\ ml^{-1}$ min.
V_d = dose divided by AUC × β.

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References

DE LEVE, L.D. & PIAFSKY, K.M. (1981). Pharmacokinetic consequences of variation in plasma propranolol binding due to rheumatoid arthritis. *Clin. Pharmac. Ther.*, **29**, 239–240.

McDEVITT, D.G., FRISK-HOLMBERG, M., HOLLIFIELD, J.W. & SHAND, D.G. (1976). Plasma binding and the affinity of propranolol for the beta receptor in man. *Clin. Pharmac. Ther.*, **20**, 152–157.

NATION, R.L., PENG, G.W. & CHIOU, W.L. (1978). High pressure liquid chromatographic method for the simultaneous quantitative analysis of propranolol and 4-hydroxy propranolol in plasma. *J. Chromatog.*, **145**, 429–436.

PARSONS, R.L., KAYE, C.M., RAYMOND, K., TROUNCE, J.R. & TURNER, P. (1976). Absorption of propranolol and practolol in coeliac disease. *Gut*, **17**, 139–143.

PIAFSKY, K.M., BORGA, O., ODAR-CEDERLOF, I., JOHANSSON, C. & SJOQVIST, F. (1978). Increased plasma protein binding of propranolol and chlorpromazine mediated by disease-induced elevations of plasma α_1-acid glycoprotein. *New Engl. J. Med.*, **299**, 1435–1439.

SCHNEIDER, R.E., BABB, J., BISHOP, H., MITCHARD, M., HOARE, A.M. & HAWKINS, C.F. (1976). Plasma levels of propranolol in treated patients with coeliac disease and patients with Crohn's disease. *Br. med. J.*, **2**, 794–795.

SCHNEIDER, R.E., BISHOP, H. & HAWKINS, C.F. (1979). Plasma propranolol concentrations and the erythrocyte sedimentation rate. *Br. J. clin. Pharmac.*, **8**, 43–47.

A SIMPLE AND SENSITIVE H.P.L.C. METHOD FOR THE ASSAY OF PROCHLORPERAZINE IN PLASMA

Prochlorperazine [2-chloro-10-(3,4′-methylpiperazin-1-pylpropyl)phenothiazine; Stemetil] is widely used for the treatment of nausea, vomiting, migraine, anxiety and schizophrenia. Hitherto, it has not been possible to monitor plasma levels of this drug during therapy because of the lack of adequately sensitive assay procedures, although for some other phenothiazines suitable methods, based on gas-liquid

chromatography (e.g. Laitem *et al.*, 1978; Cooper & Lapierre, 1981; Gillespie & Sipes, 1981) and high-performance liquid chromatography (h.p.l.c.) (e.g. Tjaden *et al.*, 1976; Curry *et al.*, 1981; Wallace *et al.*, 1981a, b) have been reported. The method described below utilises h.p.l.c., and achieves sufficient sensitivity by employing electrochemical detection. Another phenothiazine drug, methotrimeprazine [(−) 10-(3-dimethylamino-2-methylpropyl)-2-methoxyphenothiazine, the active constituent of Veractil and Nozinan], is used as the internal standard.

The experimental procedure was as follows: to the plasma sample (2 or 5 ml) was added the internal standard to yield a final concentration of 5 ng/ml, 1 M aqueous sodium hydroxide (1 ml) and a mixture (4:1 v/v) of diethyl ether/chloroform (8 ml). After shaking for 10 min and centrifuging, the upper organic layer was evaporated to dryness at 50°C under a stream of nitrogen (oxygen-free). The residue was dissolved in 50 μl of the mobile phase (see below), and suitable aliquots were injected on to the h.p.l.c. column. The analytical column (15 cm × 4.6 mm) contained Spherisorb nitrile-bounded silica (5 μm), and the mobile phase, saturated with nitrogen (oxygen-free) and then degassed under vacuum in an ultrasonic bath, consisted of 0.1 M aqueous dipotassium hydrogen phosphate (adjusted to pH 6.5 with orthophosphoric acid), acetonitrile and methanol, 7:6:4 v/v, respectively. The chromatographic process occurred at ambient temperature, and the compounds of interest were detected with an electrochemical detector (model LCA 15-EDT Research) by their oxidation at a glassy carbon electrode at +0.85 v. With this procedure the coefficients of variation for prochlorperazine at 1 and 5 ng/ml of plasma were found to be 8.9 and 6.5%, respectively, using 6 replicates for each. For concentrations of prochlorperazine less than 1 ng/ml, a plasma volume of 5 ml was used and the limit of detection was about 0.2 ng/ml. The calibration graph was linear up to at least 50 ng/ml. No interference from late-eluting peaks was noted, and the detector was suitably stable for routine use.

Illustrated in Figure 1 are typical h.p.l.c. traces obtained with extracts of blank human plasma (5 ml) (trace a), and blank human plasma (2 ml) to which had been added prochlorperazine at 1 ng/ml and the internal standard, methotrimeprazine, at 5 ng/ml (trace b).

As an example of its potential the present method was used to measure the level of prochlorperazine in plasma samples collected from a healthy male volunteer up to 12 h after a single oral dose of Stemetil (12.5 mg). The chromatogram obtained with an extract of the 6 h sample of plasma (5 ml), to which had been added methotrimeprazine at a final concentration of 5 ng/ml, is illustrated in Figure 1 (trace c). The plasma level/time profile of prochlorperazine in these samples is illustrated in Figure 2. As can be seen, the

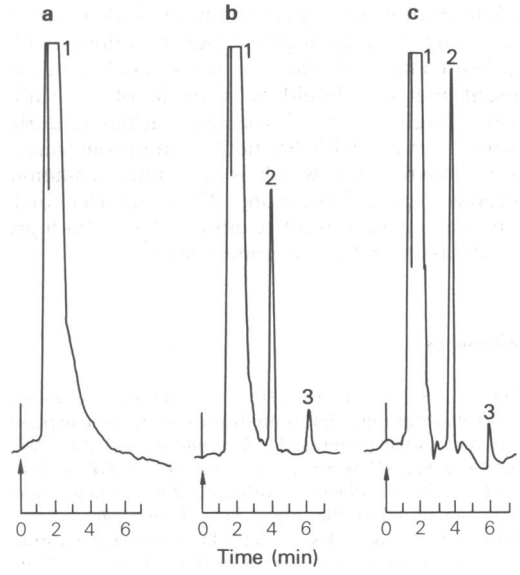

Figure 1 H.p.l.c. chromatograms of extracts of: (a) Blank human plasma (5 ml). (b) Blank human plasma (2 ml) to which have been added prochlorperazine at 1 ng/ml and the internal standard, methotrimeprazine, at 5 ng/ml. (c) Plasma (5 ml) obtained from a healthy volunteer 6 h after single oral dose of Stemetil (12.5 mg), and modified by the addition of methotrimeprazine at 5 ng/ml. Identification of peaks: 1 = solvent front; 2 = internal standard, methotrimeprazine; 3 = prochlorperazine.

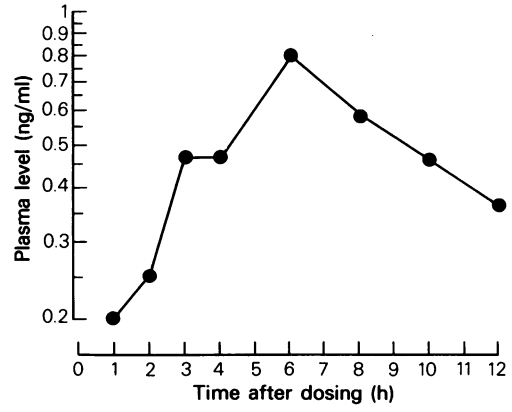

Figure 2 Levels of prochlorperazine in plasma samples obtained up to 12 h after the administration of a single oral dose of Stemetil (12.5 mg) to a healthy male volunteer.

peak level of prochlorperazine in this individual was below 1 ng/ml following the single oral dose of 12.5 mg. With a limit of detection of about 0.2 ng/ml, the present method should be capable of measuring plasma levels of prochlorperazine achieved during chronic therapy with Stemetil. Chlorpromazine, a phenothiazine drug which is sometimes co-administered with prochlorperazine, did not interfere in the assay, having a different retention time to both prochlorperazine and methotrimeprazine.

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References

COOPER, S.F. & LAPIERRE, Y.D. (1981). Gas-liquid chromatographic determination of pipotiazine in plasma of psychiatric patients. *J. Chromatogr.*, **222**, 291–296.

CURRY, S.H., STEWART, R.B., SPRINGER, P.K. & POPE, J.E. (1981). Plasma trifluoperazine concentrations during high dose therapy. *Lancet*, **i**, 395–396.

GILLESPIE, T.J. & SIPES, I.G. (1981). Sensitive gas chromatographic determination of trifluoperazine in human plasma. *J. Chromatogr.*, **223**, 95–102.

LAITEM, L., BELLO, I. & GASPAR, P. (1978). Gas chromatographic determination of tranquillizer residues in body fluids and in the meat of slaughtered animals. *J. Chromatogr.*, **156**, 327–329.

TJADEN, U.R., LANKELMA, J., POPPE, H. & MUUSZE, R.G. (1976). Anodic coulometric detection with a glassy carbon electrode in combination with reversed-phase high-performance liquid chromatography. *J. Chromatogr.*, **125**, 275–286.

WALLACE, J.E., SHIMEK, E.L. Jr., HARRIS, S.C. & STAVCHANSKY, S. (1981a). Determination of promethazine in serum by liquid chromatography. *Clin. Chem.*, **27**, 253–255.

WALLACE, J.E., SHIMEK, E.L. Jr., STAVCHANSKY, S. & HARRIS, S.C. (1981b). Determination of promethazine and other phenothiazine compounds by liquid chromatography with electrochemical detection. *Analyt. Chem.*, **53**, 960–962.