HPLC DETERMINATION AND PHARMACOKINETICS OF PIPOTHIAZINE AFTER DEPOT INJECTION

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Pipothiazine is a phenothiazine with increasing use in the treatment of schizophrenia. It is administered as the palmitate in a depot injection every 4 weeks. Plasma concentrations of pipothiazine after oral administration of the hydrochloride are low (Le Roux et al 1982) but those after depot injection have not been reported.

We have developed a reverse-phase HPLC method with fluorescence detection for measurement of pipothiazine in plasma. To 2.0 ml of plasma are added 200 µl of a freshly prepared solution of internal standard (IRS) (promethazine hydrochloride, 6.25 µg/ml), 500 µl methanol, 100 µl 7M sodium hydroxide solution and 8 ml of freshly prepared hexane: dichloromethane (50:50 v/v) mixture. After extraction and evaporation of the organic solvent the dry sample was reconstituted in 100 µl of eluent and injected on to the column. Analysis was on a 250 x 4.6 mm stainless steel column of SAS-Hypersil 5 µm maintained at 45°C. The eluent was acetonitrile:ammonium carbonate 0.05M 50:50 (v/v) at a flow-rate of 1.4 ml/min. Detection was with a Kratos FS970 fluorimeter set at 263 nm excitation and 470 nm emission wavelengths. Peak height ratios (pipothiazine/IRS) were rectilinearly related to pipothiazine concentration ($r = 0.999$) in the range 1.25 - 12.5 ng/ml. The coefficient of variation was 3.1% (at a concentration of 5 ng/ml: $n = 8$) and the limit of detection was 0.25 ng/ml.

Three possible metabolites of pipothiazine, pipothiazine-N-oxide, pipothiazine sulphoxide and 7-hydroxy-pipothiazine as reference standards, were adequately resolved and the first two were efficiently extracted (Table).

Table. Phase capacity ratios and extraction efficiencies of pipothiazine and possible metabolites.

Compound	Phase capacity ratio k'	Extraction efficiency
Pipothiazine	1.97	84%
Pipothiazine-N-oxide	0.45	71%
Pipothiazine sulphoxide	0.74	86%
7-hydroxy-pipothiazine	1.04	<1%
Promethazine	3.89	77%

Many drugs commonly used in psychiatric patients did not interfere with the assay and amongst 19 phenothiazines tested, 12 caused no interference. However, plasma samples from patients receiving several oral phenothiazines contained metabolites that co-eluted with pipothiazine or promethazine.

The favourable fluorescence of pipothiazine allowed quantitation in plasma from patients receiving pipothiazine palmitate in depot injection. Preliminary studies in 3 patients gave apparent peak concentrations at 7-14 days that were related to dose: 8.4 ng/ml after 250 mg, 2.0 ng/ml after 37.5 mg and 1.0 ng/ml after 20 mg. No accumulation was observed in these patients during three dose intervals.

Y. Le Roux et al (1982) J. Chromatogr. 230: 401-404.

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