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Note

Quantitative determination of oxcarbazepine

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Oxcarbazepine (10,11-dihydro-10-oxo-carbamazepine) (Ciba-Geigy, GP 47680) is a potential anticonvulsant drug. Studies suggest good efficacy and tolerability of the new compound, which is metabolized in humans to 10,11-dihydro-10-hydroxycarbamazepine (GP 47779) and 10,11-dihydro-10,11-*trans*-dihydroxy-carbamazepine (CGP 10.000). GP 47779 possesses an anticonvulsant activity of its own [1–4].

This note describes a simple high-performance liquid chromatographic assay for monitoring the plasma of patients when therapeutic doses are administered.

MATERIALS AND METHODS

Reagents

Ammonia (25% NH_3; UCB 4747), ammonium nitrate (Merck 1188), isopropanol (Merck 9634), ethyl acetate (Merck 863) and ethanol (UCB 1115) were from UCB and E. Merck.

10,11-Dihydro-10-oxo-carbamazepine (oxcarbazepine) (GP 47680), 10,11-dihydro-10-hydroxycarbamazepine (metabolite) (GP 47779), 10,11-dihydro-10,11-*trans*-dihydroxy-carbamazepine (metabolite) (GGP 10.000), and 9-hydroxymethyl-10-carbamyl-acridine (internal standard) (CGP 9955) were from Ciba-Geigy.

Carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone and valproic acid were from our collection.

Apparatus

A Pye-Unicam liquid chromatograph type LCXPD was used with a dual-piston reciprocating pump, a Rheodyne injection valve (Model 7120, capacity

0378-4347/83/$03.00

200 µl) and a variable-wavelength detector with a Philips PM 8251/02 recorder. A Macherey-Nagel column (200 × 6 mm O.D. × 4 mm I.D.) packed with reversed-phase C_{18} silica gel, particle size 7.5 µm (Polygosil® 60-7C_{18}) was used.

Sample preparation

To 1 ml of plasma or serum in a 20-ml glass centrifuge tube were added 1 ml of internal standard solution (2 mg/l CPG 9955) and 2 ml of water. This mixture was extracted with 6 ml of ethyl acetate by mechanical shaking. The tube was then centrifuged at 3000 *g* for 5 min. The organic phase was transferred to an evaporation tube and the ethyl acetate layer evaporated to dryness on a water-bath under a stream of dry nitrogen [4]. The residue was redissolved in 1 ml of mobile phase of which 200 µl were injected into the chromatographic column.

Chromatography

The mobile phase consisted of 56% of solution A and 44% of solution B. Solution A: 6‰ (w/v) of ammonium nitrate and 0.15‰ (v/v) of ammonia solution in deionized and distilled water. Solution B: 50% solution A and 50% isopropanol.

Instrumental conditions were as follows: flow-rate, 1.0 ml/min; temperature, 22–26°C; detection wavelength, 250 nm.

Quantitative estimation was by measurement of peak height, relative to the internal standard.

RESULTS

Under the experimental conditions used the following retention times were recorded (Figs. 1 and 2): CGP 10.000 (metabolite) 4.0 min, GP 4779 (metabolite) 6.1 min, oxcarbazepine 8.7 min, CGP 9955 (internal standard) 10.6 min.

Carbamazepine, ethosuximide, phenytoin, primidone and valproic acid

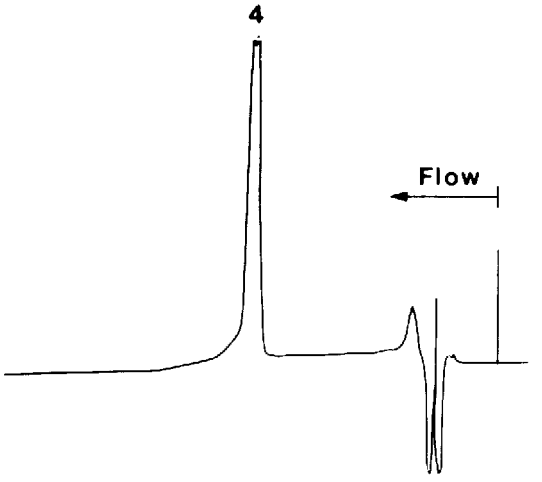

Fig. 1. Chromatogram of blank serum with internal standard (4). Sensitivity 0.32 a.u.f.s.

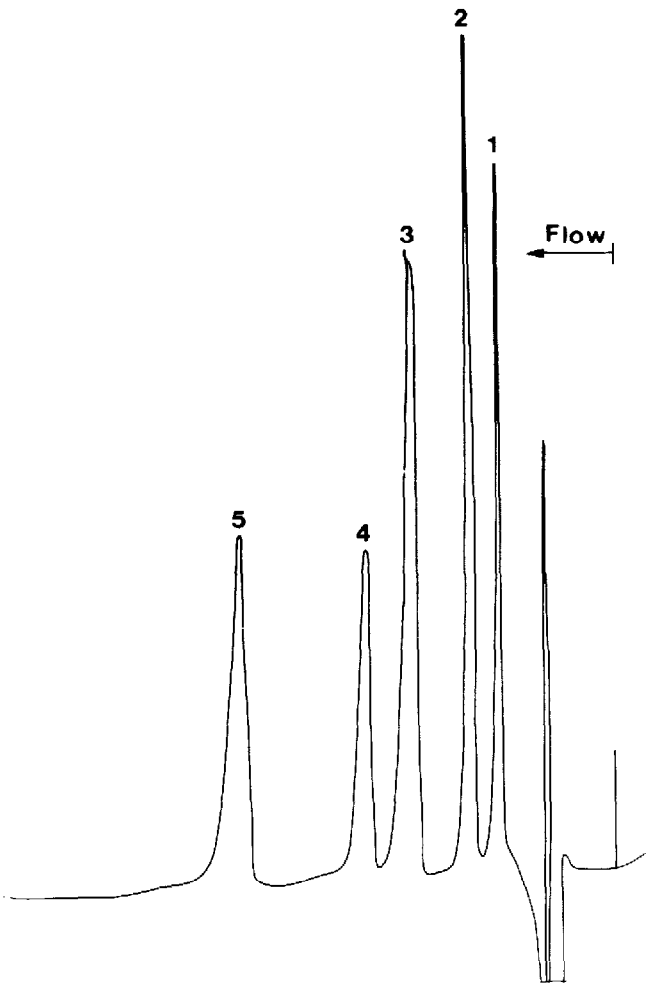

Fig. 2. Chromatogram of serum containing 4 mg/l of GCP 10.000 (1), GP 47779 (2), oxcarbazepine (3), internal standard (4) and carbamazepine (5). Sensitivity 0.16 a.u.f.s.

were found not to interfere in the analysis. For phenobarbital the retention time is 6.4 min.

The quantitative limits are about 150 ng/ml for oxcarbazepine and 1000 ng/ml for GP 47779 and CGP 10.000.

The recovery was found to be 99.99 + 4.75% for oxcarbazepine at a concentration of 4 mg/l. At 4 mg/l, the within-run variation is 101.60 ± 3.97% and over a long period (five months) 101.06 ± 5.34%.

The determination of serum levels of oxcarbazepine and its metabolites after administration of oxcarbazepine to patients is the objective of this study. These results will be published in due course, but at this stage it is apparent that the metabolite GP 47779 is the principal constituent present in serum and that the serum therapeutic level is probably the same as for carbamazepine (4—9 mg/l).

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