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Letter to the Editor

Simplified measurement of haloperidol by gas chromatography with nitrogen–phosphorus detection

Sir,

Quantitation of haloperidol by gas chromatography (GC) with nitrogen–phosphorus detection (NPD) has been previously described [1]. Here we report a simplification of this method, whereby sensitivity and specificity are maintained but sample preparation time is greatly reduced.

EXPERIMENTAL

A Hewlett-Packard Model 5840A gas chromatograph equipped with a nitrogen–phosphorus detector was used. The column was coiled glass, 1.22 m × 2 mm I.D., packed with 3% SP-2250 on 80–100 mesh Supelcoport (Supelco, Bellefonte, PA, U.S.A.). The carrier gas was ultra-high-purity helium at a flow-rate of 30 ml/min. The detector purge was ultra-high-purity hydrogen at 3 ml/min mixed with dry air at 50 ml/min. Operating temperatures were: injection port, 310°C; column, 280°C; detector, 300°C. Before being connected to the detector, a new column was conditioned at 290°C for 24–48 h with a carrier gas flow-rate of 15–20 ml/min. At the start of each work day, the column was primed with 2–4 μg of asolectin (phospholipid) in benzene.

The following reagents were used as received from commercial sources: *n*-hexane, isoamyl alcohol, toluene, sodium hydroxide and methanol.

Pure haloperidol and chlorohaloperidol (McN-JR-1854) were kindly provided by McNeil Labs. (Fort Washington, PA, U.S.A.). Stock solutions of each were prepared by dissolving 100 mg in 100 ml of methanol. Working solutions of 1 and 0.1 μg/ml were prepared by sequential dilutions. The solutions were stored in the dark in glass-stoppered bottles at 4°C and were stable for at least three years.

A 100-μl volume of chlorohaloperidol working solution (1 μg/ml), containing 100 ng chlorohaloperidol (internal standard), was added to a series of 15-ml round-bottom glass culture tubes with PTFE-lined screw-top caps. Calibration standards for haloperidol were prepared by adding 1, 2.5, 5, 10, 20, 35 and 50 ng of drug to consecutive tubes. The organic layer was evaporated to dryness at 40°C

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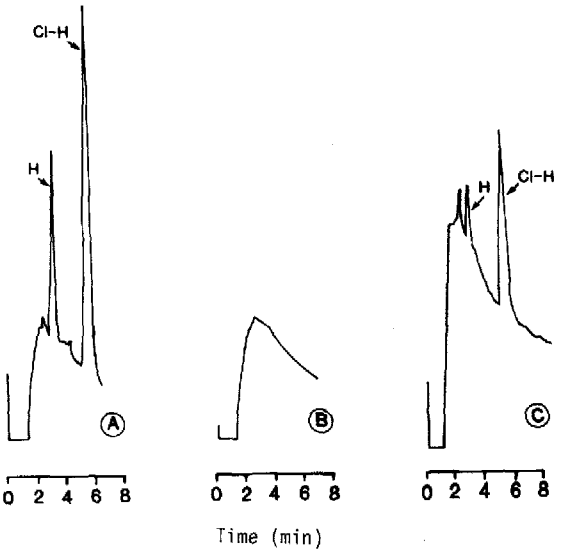

Fig. 1. (A) Calibration standard containing 25 ng/ml haloperidol (H) and 100 ng/ml chlorohaloperidol (Cl-H), the internal standard. (B) Chromatogram of a drug-free blank plasma sample. (C) Chromatogram of a sample from a patient receiving maintenance therapy with haloperidol. The measured haloperidol plasma concentration was 14 ng/ml.

under moderately reduced pressure. A 1-ml sample of drug-free control serum or plasma was added to each of the calibration tubes; unknown serum or plasma was added to the tubes containing internal standard only.

A 0.25-ml volume of 1.0 *M* sodium hydroxide and 2.0 ml of hexane–isoamyl alcohol (98:2) were added to each tube, and the tube was vortex-mixed in the upright position for 1 min. The samples were then centrifuged at room temperature for 5 min at 400 *g*. The organic layer was then transferred to 13-ml conical-bottom glass tubes and evaporated to dryness as described above. The samples were reconstituted with 10–25 μl to toluene–isoamyl alcohol (85:15), of which 6–10 μl were manually injected into the chromatograph.

RESULTS AND DISCUSSION

Under the described conditions the retention times for haloperidol and chlorohaloperidol were approximately 3.2 and 5.5 min, respectively (Fig. 1); these values will vary depending on the characteristics of the specific column as well as the age of the column. Extracts of blank plasma or serum contained no interfering peaks. The relation between haloperidol plasma concentrations and peak-height ratio (versus internal standard) is linear at least to 50 ng/ml. Analysis of twenty-two standard curves over four months showed that the correlation coefficient was always greater than 0.98; the day-to-day coefficient of variation in the slopes was 10.7%.

The limit of detection was 1 ng/ml for a 1-ml sample. Within-day coefficients of variation for identical samples were: at 1 ng/ml, 17.5%; at 2.5 ng/ml, 7.0%; and at 5 ng/ml, 5.4%.

This paper describes a reliable, selective method for the quantitation of haloperidol in serum or plasma using GC–NPD. The method consistently produces blank plasma samples that are free of interfering peaks in the area corresponding to the retention times for haloperidol and the internal standard. The method features a straightforward extraction into hexane–isoamyl alcohol, without back-extraction or clean-up. Therefore sample preparation is rapid. This method is sufficiently sensitive to permit monitoring of steady-state concentrations of haloperidol during chronic therapy.

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