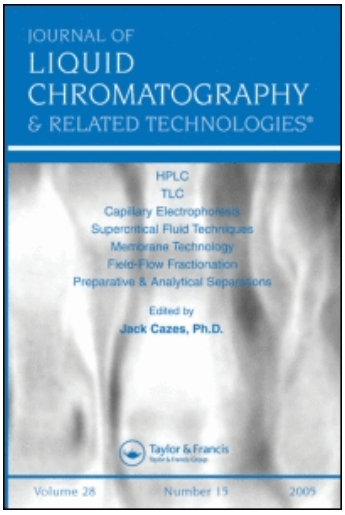

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A Simple HPLC Method for the Quantitation of Molindone in Human Plasma or Serum

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A SIMPLE HPLC METHOD FOR THE QUANTITATION OF MOLINDONE IN HUMAN PLASMA OR SERUM

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ABSTRACT

A simple HPLC method is described for the quantitation of molindone in human serum or plasma using trazadone as an internal standard and UV detection (247 nm). The method was successfully used to determine the steady state levels of molindone in 15 patients receiving the drug. The HPLC results were confirmed by identifying the HPLC peak using LC thermospray mass spectrometry.

INTRODUCTION

Molindone (Moban), a dihydroindolone class of neuroleptic agent, has been in use as an antipsychotic agent for two decades (1). It is sometimes described as an "atypical" neuroleptic (2) and is as effective as conventional antipsychotics (3) (Abuzzahab, 1973). There is no data on plasma levels and therapeutic range in human beings, possibly due to lack of a well defined assay method. We have now developed a simple High Pressure Liquid Chromatography with ultra violet detection (HPLC-

UV) for measuring plasma or serum levels of molindone and report the range of levels consistent with clinical treatment in 14 subjects.

MATERIALS AND METHODS

Trazodone and molindone samples were obtained from Merrell Dow and Dupont respectively. Stock solutions were prepared in methanol to contain 1 mg/ml as base. Diluted standards of 10 ug/ml were prepared from the stock solution by adding 10 ul of the stock to 1 ml of deionized distilled water. Serum standards of molindone containing 50, 100, and 200 ng/ml were prepared using drug free control serum samples from the Blood Bank. Sodium carbonate solution was prepared by dissolving 5 g in 100 ml of deionized distilled water. Extraction solvent consisted of ethylacetate, hexane, isoamyl alcohol (50:49.5:0.5).

HPLC System: A BioRad HPLC system with a Rheodyne injection valve with 50 ul injection loop and a variable UV detector set at 247 nm was used in this study. The other conditions were: column:Supelco cyano 5 um., 15 cm x 0.4 I.D., mobile phase phosphate buffer pH 7.1 (0.01 M), acetonitrile, methanol (65:26:9), flow rate 1.5 ml/min.

Extraction of Serum Samples: A mixture of 0.5 ml of serum, 250 ng (25 ul) trazadone (Internal Standard) and 0.5 ml of sodium carbonate was extracted with 5 ml of the solvent mixture by vortexing for 30 seconds. After centrifugation for 10 minutes, the top layer was transferred into 5 ml centrifuge tube or culture tube and the solvent evaporated under nitrogen at 40° C. The residue was dissolved in 100 ul of mobile phase, centrifuged and 25 ul of the clear supernate injected into HPLC system. A standard calibration curve was obtained by the same procedure using serum standards containing 0, 50, 100 and 200 ng/ml of molindone. From the peak height ratios of the sample and internal standards, the molindone level in the serum sample is calculated.

Subjects: These were patients seeking treatment at the Medical College of Virginia Hospitals for psychoses and for whom the attending psychiatrist had chosen molindone as the antipsychotic agent. They had been diagnosed to have Schizophrenia (n=8) or Schizoaffective disorder (n=6) using Research Diagnostic Criteria (4). Blood was drawn in a red-topped tube when the patients had been on their highest dose of molindone for at least 5 days and a steady state had been reached.

RESULTS

Molindone and trazadone are well separated in this HPLC system, and the retention times are 4.3 and 6.0 minutes respectively. In the standard calibration curve, the r value was 0.998 and the intercept -5.0. With the UV detector at 247 nm, the method is sensitive with a detection limit of 10 ng/ml. In replicate analysis, the coefficient of variation (n=5) was 3.5%. Blank control serum samples (n-10) did not show any interfering compounds under the experimental conditions used. The recovery of molindone by this extraction procedure was over 95% and of trazadone almost 100%. The chromatogram of standards and serum samples is shown in Fig. 1. The values for serum levels in subjects treated with varying doses of molindone are shown in Table I. With the mobile phase used here, other antidepressant and antipsychotic drugs have longer retention times and therefore do not interfere with the assay.

The identity of the molindone peak in HPLC was confirmed using Thermospray Liquid Chromatography-Mass Spectrometry (LCMS) and Gas Chromatography Mass Spectrometry (GCMS). The LCMS and GCMS mass spectra for molindone are shown in Figures II and III.

DISCUSSION

We have described a simple and rapid method for the quantitation of molindone in serum samples using HPLC technique and trazadone as an internal standard. We have determined serum levels in the steady state in fourteen psychiatric patients. The

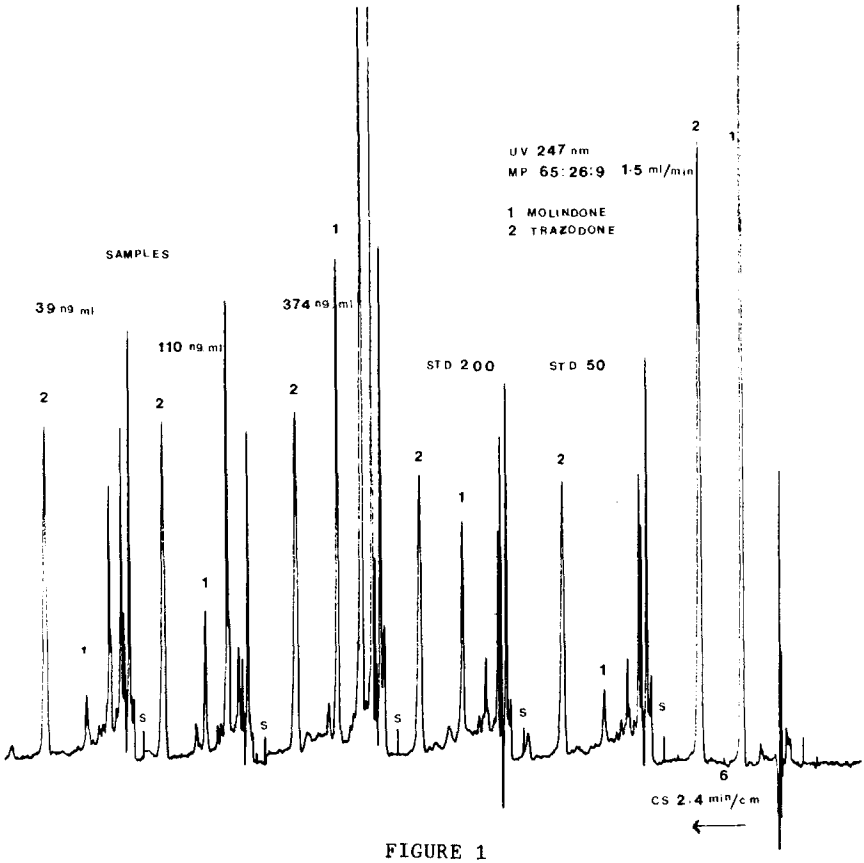


FIGURE 1

levels in these patients ranged between 39 ng/ml to 374 ng/ml. Thus this is the first report of the range of molindone levels in a clinical population. We are separately reporting the correlation between therapeutic response and serum levels of molindone and prolactin levels induced by molindone (5). The manufacturer recommends a maximum dose of 225 mg/day (6) for this agent. In this study patients received up to 400 mg/day and one patient

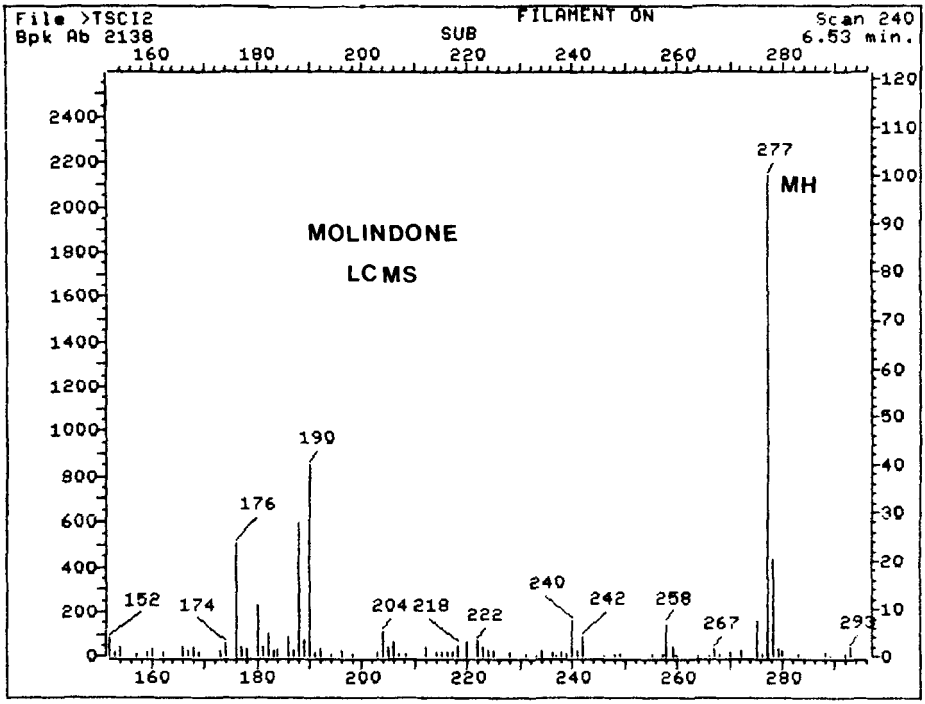
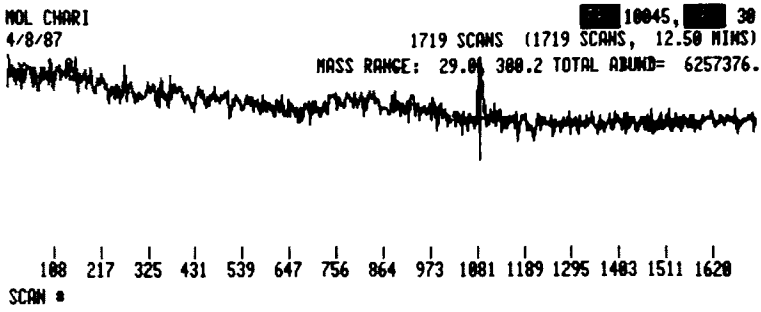


FIGURE 2

Table I

Dosage of Molindone Used and Serum Molindone Levels

Subject #	Molindone Dosage in mg/day	Molindone Level in mg/ml
1	100	64
2	100	258
3	200	84
4	100	172
5	100	187
6	225	66
7	400	130
8	400	44
9	600	320
10	100	39
11	300	374
12	400	203
13	250	147
14	200	47



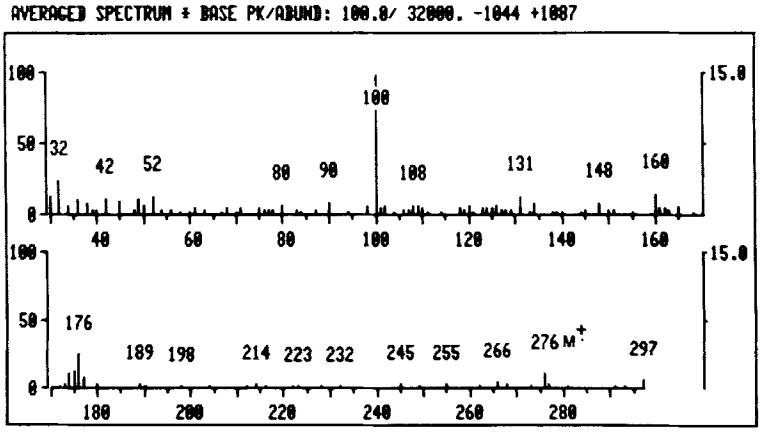


FIGURE 3

received 600 mg/day. Thus, the upper end of the range of levels reported here might be an exaggerated one. The wide variation of serum levels with similar doses of the drug suggests varying metabolism of the drug in the patients. Work on the identification of a likely metabolite is currently in progress.

REFERENCES

1. Sugerman, A. A., and Herman, J.: Molindone, An indole derivative with antipsychotic action. Clin. Pharmacol. Therap., 8, 261 (1967).

2. Ayd, F. J., Jr., A critical evaluation of Molindone (Moban): A new indole derivative neuroleptic. Dis. Nerv. Sys., 35 (10) 447 (1974).
3. Abuzzahab, F. S., Treatment of acute schizophrenia with molindone., J. Clin. Pharm., 13, 226 (1973).
4. Spitzer, R. L., Endicott, J., and Robins, E.: Research Diagnostic Criteria for a Selected Group of Functional Disorders, 3rd Edition. Biometrics Research, New York State Psychiatric Institute: New York, 1977.
5. Pandurangi, A. K., and Narasimhachari, N. In Press.
6. Physician's Desk Reference 1987. Moban product information. Medical Economics Company: Oradell, NJ, p. 901.