Simultaneous Determination of Haloperidol and Its Reduced Metabolite in Serum and Plasma by Isocratic Liquid Chromatography with Electrochemical Detection

Esa R. Korpi, Bruce H. Phelps, Hugh Granger, Wen-Ho Chang, Markku Linnola, James L. Meek, and Richard J. Wyatt

We describe a liquid-chromatographic method for simultaneous quantification of haloperidol and its reduced metabolite in plasma and serum. Haloperidol and reduced haloperidol are concentrated from blood samples by liquid/liquid extraction into a hexane/isoamyl alcohol mixture, with chlorohaloperidol as the internal standard. For chromatographic separation we used a reversed-phase cyano-bonded column and a mobile phase of pH 6.8 phosphate buffer/acetonitrile (55/45 by vol). Haloperidol and its reduced metabolite are detected electrochemically at +0.90 V potential between the working and reference electrodes. As little as 0.5 ng per injection is detectable. Within- and between-day CVs for determinations of haloperidol and reduced haloperidol ranged from 4 to 7% each at a concentration of 10 μg/L. Haloperidol concentrations measured by this method correlated well with those by gas-chromatography with nitrogen-sensitive detector and by radioimmunoassay. The present method can be used to study the effects of haloperidol on the central nervous system. It is simple enough for use in clinical laboratories that are monitoring haloperidol concentrations in the blood of psychiatric patients.

Additional Keyphrases: psychotropic drugs · drug metabolism

Haloperidol, 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone, a potent and commonly used neuroleptic of the butyrophenone series, is considered to have no psychoactive metabolites (1), being cleaved at the hydrocarbon chain in an initial catabolic step (Figure 1). Forsman and Larsson (2), however, have shown that in humans haloperidol can also be reduced to a slightly more hydrophilic alcohol metabolite (reduced haloperidol, Figure 1), structurally very similar to haloperidol, which also may influence brain function. Hence there is a need for convenient and sensitive methods for simultaneously measuring the concentrations of haloperidol and reduced haloperidol in serum. Although most of the present methods—either gas chromatography (GC) (3–5), "high-performance" liquid chromatography (HPLC) (6, 7), RIA (8, 9), or radioreceptor assays (10, 11)—have been designed to give accurate estimates of only haloperidol, one RIA (involving a two-step subtraction technique) allows for determination of both haloperidol and reduced haloperidol (12). This method, however, cannot easily be adapted for use in clinical laboratories.

The method we present here, based on organic extraction and subsequent isocratic reversed-phase HPLC with electrochemical detection of haloperidol and its reduced metabolite, provides enough sensitivity and precision for clinical drug monitoring and pharmacokinetic studies. We also compare the results of this method with haloperidol measurements by GC with nitrogen–phosphorus detection and by RIA.

Materials and Methods

Reagents

Haloperidol, reduced haloperidol (4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone), and chlorohaloperidol (4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-chlorophenyl)-1-butanone) were kindly donated.

6 Nonstandard abbreviations: HPLC, “high-performance” liquid chromatography; GC, gas-chromatography; BSA, bovine serum albumin.
by McNeil Pharmaceutical, Spring House, PA 19477. Flura-
zepam was from Roche Laboratories, Nutley, NJ 07110. 

[3H]Haloperidol (specific activity 19 kCi/mol) was purchased
from Damon Diagnostics, Needham Heights, MA 02194; "Aquassure" liquid-scintillation counting fluid from New
England Nuclear, Boston, MA 02118; RIA-grade charcoal
from Becton Dickinson Immunodiagnostics, Baltimore, MD
21201; Dextran-70 from Pharmacia, Inc., Piscataway, NJ
08854; fatty-acid-free bovine serum albumin (BSA) from
Miles Laboratories, Inc., Elkhart, IN 46514; hexane from
Waters Associates, Milford, MA 01757; and isoamyl alcohol
from J. T. Baker Chemical Co., Phillipsburg, NJ 08865. 

Rabbit antiserum raised against BSA-linked haloperidol
was generously donated by Dr. Russell Poland (Harbor
UCLA Medical Center, Torrance, CA 90509).

HPLC Assay

Extraction of serum or plasma. Pipet 2 mL of patient's or
control serum or heparinized plasma into disposable borosi-
licate culture tubes (16 × 125 mm) with Teflon-lined screw
caps, already containing 20 μL of standard haloperidol and
reduced haloperidol (both at a final concentration ranging
from 1.0 to 40 μg/L) and (or) the internal standard, chloro-
haloperidol.

Prepare combined haloperidol and reduced haloperidol
standards freshly each day by diluting a methanolic 1 g/L
stock solution with the mobile phase to give final concen-
trations from 0.1 to 4.0 μg/L.

Mix the samples, let them stand for 5 min, then add 250
μL of NaOH, 2 mol/L, followed by 4 mL of the extraction
solution: hexane/isoamyl alcohol (98.5/1.5, by vol). Vortex-
mix the tubes' contents three times for 1 min each with a
multi-tube vortex-type mixer and then centrifuge for 5 min
at 1000 × g. Transfer the clear (top) organic phases into a
new set of tubes containing 1 mL of HCl, 0.2 mol/L. Repeat
the extraction step on the aqueous (lower) phase once, then
pool the organic phases of each sample by simply decant-
ing them after freezing the aqueous phase on solid CO2.
Vortexmix the pooled samples, centrifuge, and remove and discard
the organic layers by gentle aspiration through Pasteur
pipettes. Wash the remaining acid layers briefly with 2 mL
of extraction solvent and alkalize by adding 200 μL of
NaOH, 2 mol/L. Then re-extract the drugs into 2 mL of
extraction solvent. Repeat this extraction step again, pool
the resulting organic extracts in 10 × 75 mm borosilicate
glass tubes, and evaporate the extracts under a gentle
stream of dry nitrogen at 45 °C. Seal the tubes and store
overnight in the dark at −10 °C. On the following day
reconstitute the samples with 150 μL of mobile phase and
inject into the chromatograph. Samples are fully stable
under these storage conditions for at least three days, with
no interconversion of the drugs observed during the extract-
ion or storage steps. Parallel measurements of haloperidol
and reduced haloperidol concentrations in serum and plasma
samples taken simultaneously from five patients gave
respectively identical results. The same extraction pro-
dure can also be used for urine and brain samples (brain
tissue is homogenized in water before the extraction).

Chromatographic apparatus. The HPLC system consisted of
a Waters 6000A pump (Waters Associates, Milford, MA
01757), a manual Valco injection valve equipped with a 100-
μL sample loop, and a LC-4A amperometric detector with a
glassy carbon TL-5 flow cell (Bioanalytical Systems Inc.,
West Lafayette, IN 47906). The detector was operated at
+0.90 V potential between the working electrode and the
Ag/AgCl reference electrode at a sensitivity of 10 nA full-
scale deflection. The column (μBondapak CN, 3.9 × 30 cm,
10-μm particle size, Waters Associates) was kept at a
temperature of 30 °C with an aluminum column jacket and
a water circulator. Chromatograms were recorded with a
Kipp and Zonen BD9 two-channel recorder operated at 1-
and 10-V full scale.

Mobile phase and conditioning of the column. Mobile
phase is prepared freshly every day. It consists of prefiltered
(through 0.45-μm HA-filters; Millipore, Bedford, MA 01730)
potassium phosphate buffer, 40 mmol/L (adjusted to pH 6.8
with 5 mol/L KOH) and HPLC-grade acetoniitrile, 55/45 (by
vol). The mobile phase is constantly bubbled with helium
gas to stabilize the baseline by decreasing the amount of
dissolved air (13).

The nitrile-bonded μBondapak CN columns are initially
washed (50–100 mL each wash) with doubly distilled water,
then with sodium acetate buffer (50 mmol/L, pH 4.8),
followed by acetonitrile in the acetate buffer (40/60, by vol).
Potassium phosphate is then introduced to the column at a
low concentration (5 mmol/L, pH 4.8) and then finally
equilibrated with the mobile phase described above.

Calculation of results. Peak heights in the chromatograms
were measured manually. Concentrations of haloperidol
and reduced haloperidol were assessed by using the slope
of the standard curve for peak-height ratios for the analytes
and the internal standard.

Comparison Methods

Gas-chromatography of haloperidol. The GC method for
haloperidol was modified from Forsman et al. (3), Bianchetti
and Morselli (4), and Franklin (5). In brief, serum samples (2
to 4 mL) were extracted according to the same procedure as
described in the HPLC assay, except that flurazepam served
as an internal standard (40 ng per assay tube); the extrac-
tion solvent was hexane/isoamyl alcohol (98/2, by vol), and
all solutions were transferred by Pasteur pipettes without
freezing the tubes. Evaporated residues were reconstituted
with the extraction solution, and 10 μL was injected into the
GC system. A Hewlett-Packard 5880A gas chromatograph
equipped with a nitrogen–phosphorus detector and a glass
column (2 m × 2 mm, i.d.) packed with 3% OV-17 on Gas-
Chrom-Q 100/120 mesh (Alltech Associates, Inc., Deerfield,
IL 60015) were used. The instrument was operated with the
following temperature program: initial temperature 220 °C
at 0 min, rate 20 °C/min up to 3.5 min, final temperature
290 °C maintained for 10 min. Helium was used as a carrier
gas (flow rate, 30 mL/min) with hydrogen (3 mL/min) and
air (60 mL/min) as detector gases. The retention times of
haloperidol and flurazepam were 5.5 and 4.4 min, respecti-
vely. The detection limit of the assay (peak height 3 ×
noise) was 1 ng of haloperidol per injection.

Radioimmunoassay of haloperidol. The RIA procedure for
haloperidol was modified from Poland and Rubin (9). Hal-
operidol was extracted from 0.5-mL aliquots of serum or
plasma, after addition of [3H]haloperidol (2000 dpm in 5 μL)
as an internal standard for the extraction step and 100 μL of
2 mol/L NaOH, with 5 mL of the HPLC extraction solvent.
The organic phase, separated from the aqueous phase by
freezing the aqueous phase on solid CO2, was decanted and
evaporated under a gentle stream of nitrogen. The residue
was reconstituted in aqueous methanol (300 mL/L) to its
original volume. Analytical recovery of the extraction step,
80 ± 13% (mean ± SD, n = 41), was assessed by comparing
[3H]haloperidol radioactivity before and after the extrac-
tion.

In general, duplicate 50-μL aliquots of the extract were
diluted first with 0.5 mL of pH 7.5 buffer containing, per
liter, 0.2 mol of phosphate, 0.3 g of sodium azide, and 20 g of
fatty-acid-free BSA. Rabbit antiserum raised against BSA-
conjugated haloperidol (9) was diluted 300-fold in this

CLINICAL CHEMISTRY, Vol. 29, No. 4, 1983 625
phosphate buffer and a 0.1-mL aliquot was added to each tube. Finally, we added 50 μL of [3H]haloperidol (30 000 dpm) in aqueous methanol, 300 mL/L. To construct the standard curve we used 50-μL aliquots of standard haloperidol solutions (0.05 to 4 ng/50 μL) in the aqueous methanol. All tubes were tightly capped, vortex-mixed, and incubated in the dark at 25 °C with shaking overnight. The next day, all tubes were cooled at 4 °C for 30 to 40 min. To each tube 0.2 mL of a charcoal–dextran suspension in the phosphate buffer (20 g of charcoal and 2 g of dextran per liter) was added. The contents of the tubes were vortex-mixed, left to stand at 4 °C for 30 min, and finally centrifuged at 900 x g at 4 °C for 10 min. After decanting the supernates into glass liquid scintillation vials and mixing with 1 mL of water and 10 mL of Aquasure, we counted their radioactivity in a Model LS-9000 liquid scintillation counter (Beckman Instruments, Fullerton, CA 92634), correcting the counts for quenching by external standardization. To measure total radioactivity we prepared duplicate tubes containing only 0.8 mL of buffer, 50 μL of the aqueous methanol, and 50 μL of [3H]haloperidol (no charcoal–dextran). Zero-time binding was measured with tubes containing 0.5 mL of buffer, 0.1 mL of diluted antibody, 50 μL of the aqueous methanol, and 50 μL of [3H]haloperidol; nonspecific binding tubes contained 0.8 mL of buffer, 50 μL of the aqueous methanol, and 50 μL of [3H]haloperidol.

The sensitivity of the assay (i.e., the amount of haloperidol that decreased the initial binding ability by at least 10%) was 0.05 ng per assay tube. The mean interassay and intra-assay CVs for repeated measurements of a serum pool containing 40 ng of haloperidol per milliliter were about 9 and 7%, respectively. Of the major metabolites of haloperidol, only the reduced haloperidol produced a minimal but measurable interference at high concentrations. The ratio of reduced haloperidol concentration to haloperidol concentration that displaced [3H]haloperidol binding to antibody by 50% was 300; no interference by reduced haloperidol was detected at 50 ng/mL.

Results and Discussion

Chromatographic Conditions

Figure 2 shows the separation of haloperidol, reduced haloperidol, and chlorohaloperidol. Although the drugs were separated on either nitrile-bonded (μBondapak CN) or C18-bonded (μBondapak C18) columns, the lesser polarity of the C18-bonded columns caused each of the drugs to be more strongly retained; in addition, some late-eluting impurities were obtained with C18-bonded columns. For these reasons, we used nitrile-bonded columns routinely for the separations.

Detector sensitivity decreased as the pH of the mobile phase was decreased from neutrality to about 4.5. The CN-columns retained butyrophenones less efficiently and lost selectivity at low mobile-phase pH values; in addition, unknown peaks from extracted sera interfered with the separation of the drugs under these conditions. It is also known that nitrile-bonded phases degrade at pH values higher than neutrality. For these reasons, a mobile-phase pH value of 6.8 was chosen for further development of the method. Unknown substances in drug-free sera were eluted before the butyrophenones at pH 6.8, if the acetonitrile concentration in the mobile phase was at least 400 mL/L. No other substances co-eluted with the butyrophenones in drug-free samples.

Voltage profiles of haloperidol, reduced haloperidol, and chlorohaloperidol obtained with the system are shown in Figure 3. An electrode potential of +0.90 V provided maxi-

![Figure 2](https://via.placeholder.com/150)

Fig. 2. Representative chromatograms of standard and patients' samples

A. Chromatogram of extracted 2-mL sample of standard serum: 5 ng of haloperidol and reduced haloperidol and 20 ng of chlorohaloperidol (internal standard) per milliliter. The residue was reconstituted with 150 mL of mobile phase, and 100 mL was injected into the HPLC system. 1, reduced haloperidol; 2, haloperidol; 3, chlorohaloperidol. B. Chromatogram of extracted serum at patient's drug-free period. C. Chromatogram of patient's extracted serum after haloperidol treatment.

![Figure 3](https://via.placeholder.com/150)

Fig. 3. Electrochemical profiles of haloperidol, reduced haloperidol, and chlorohaloperidol

Haloperidol, reduced haloperidol, and chlorohaloperidol, each 300 μg/L, in mobile phase. Each point represents the mean of two injections (100 μL). Chromatographic conditions are as described in Materials and Methods except that the voltage between the working and the reference electrodes was varied.
Table 1. Precision of Haloperidol and Reduced Haloperidol Determination by HPLC Assay

<table>
<thead>
<tr>
<th></th>
<th>Haloperidol</th>
<th>Reduced haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean, µg/L</td>
<td>CV, %</td>
</tr>
<tr>
<td>Within-day precision</td>
<td>2.04</td>
<td>12.2</td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Between-day precision</td>
<td>2.06</td>
<td>7.8</td>
</tr>
<tr>
<td>n</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Assay Characteristics

**Precision.** Reproducibility of the method was assessed by analyzing four to five replicate samples taken on each of six different days from two serum pools. Equal concentrations of haloperidol and reduced haloperidol (about 2 or 10 µg/L) were added to the serum pools. Chlorohaloperidol served as an internal standard at a concentration of 15 µg/L. As shown in Table 1, when the drug concentrations were 2 µg/L (i.e., a concentration slightly higher than the detection limit of the assay), the coefficients of variation (CVs) are doubled. Reproducibilities were comparable for haloperidol and reduced haloperidol. The CVs calculated at the higher drug concentration agree well with the CVs obtained by other methods, including GC and HPLC with ultraviolet detection (3–7). Maximum intra- and interassay CVs obtained in RIA exceed the CV observed with this method at the lower haloperidol concentration (9).

**Accuracy.** The absolute recoveries of haloperidol (10 µg/L), reduced haloperidol (10 µg/L), and chlorohaloperidol (15 µg/L) were 92 ± 3, 98 ± 3, and 81 ± 2% (mean ± SD, n = 14), respectively. The standard curve was linear with butyrophenone concentrations up to 120 µg/L (Figure 4).

Table 2 compares results of haloperidol determinations by HPLC, GC, and RIA in patients' samples. In general, the mean values obtained with each method are comparable. The value of Pearson's correlation coefficient for the HPLC and the GC results was 0.78 (p < 0.02) and for the HPLC and the RIA results 0.76 (p < 0.02).

**Sensitivity.** Haloperidol and reduced haloperidol could be detected by the HPLC assay with equal sensitivity. The detection limit (i.e., peak height equal to 3 × baseline noise) was 0.5 ng, allowing routine measurements of 1–2 µg/L in a 2-mL serum or plasma sample and 0.25 to 0.5 µg/L in a 4-mL sample volume. Thus, the sensitivity of the HPLC method was lower than that of RIAs, but about the same as that of GC and GC/mass spectrometric methods (14).

Interference from Other Drugs

The retention times of several psychotropic compounds (100 ng each) injected into the HPLC system are compared in Table 3. Interferences can be expected in samples from patients who are treated with a combination of haloperidol and other neuroleptics or antidepressants. Anticholinergics, however, which are most commonly used in combination with haloperidol, do not interfere with the assay. Although other drugs may not co-elute with haloperidol, the sensitive electrochemical detector can be overloaded if several drugs are present in the sample. This is a genuine concern, because the concentrations of haloperidol in blood are quite low as compared with those of other psychotropic drugs currently in use.

As can be seen from Table 3, the HPLC method described here has the potential of being used to determine the concentrations of other neuroleptic and antidepressant drugs, if they can be quantitatively extracted from the blood.

Table 2. Comparison of Analytical Methods for Haloperidol Determination

<table>
<thead>
<tr>
<th>Drug treatment, mg/day*</th>
<th>GC</th>
<th>RIA</th>
<th>HPLC</th>
<th>HPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>80/4</td>
<td>35.4</td>
<td>28.9</td>
<td>31.3</td>
<td>43.6</td>
</tr>
<tr>
<td>45/2</td>
<td>30.4</td>
<td>13.7</td>
<td>16.2</td>
<td>4.0</td>
</tr>
<tr>
<td>45/2</td>
<td>20.9</td>
<td>11.3</td>
<td>11.6</td>
<td>4.5</td>
</tr>
<tr>
<td>30/2</td>
<td>23.0</td>
<td>22.7</td>
<td>24.3</td>
<td>8.0</td>
</tr>
<tr>
<td>22/2</td>
<td>6.6</td>
<td>24.7</td>
<td>10.8</td>
<td>2.4</td>
</tr>
<tr>
<td>21/2</td>
<td>12.6</td>
<td>8.9</td>
<td>12.4</td>
<td>12.8</td>
</tr>
<tr>
<td>64/4</td>
<td>28.9</td>
<td>27.3</td>
<td>26.1</td>
<td>29.0</td>
</tr>
<tr>
<td>50/2</td>
<td>23.5</td>
<td>21.4</td>
<td>24.3</td>
<td>6.0</td>
</tr>
<tr>
<td>24/2</td>
<td>16.0</td>
<td>11.7</td>
<td>11.0</td>
<td>28.5</td>
</tr>
</tbody>
</table>

*Haloperidol (free base)/benztropine (mesylate salt).

*Mean of two determinations.

*Mean of three determinations.
Table 3. Chromatographic Mobility of Some Psychotropic and Antiparkinsonian Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Retardation factor, K'</th>
<th>K', relative to haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced haloperidol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorohaloperidol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meponone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trifluperidol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bromperidol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pimozide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoridazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulpiride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butaclamol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluphenazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-OH-Desipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-OH-Imipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorimipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iprindole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mianserin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zimelidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortripsyline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benztpine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biperiden</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimepyridyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atropine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scopolamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamylcholine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acoline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caffeine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = no response in electrochemical detector in 30 min following the injection.

We have described an HPLC method with the sensitivity, precision, and accuracy necessary for clinical monitoring of haloperidol concentrations and for pharmacological investigations of haloperidol metabolism. In addition, the method allows for the simultaneous quantitation of reduced haloperidol, a potentially psychoactive metabolite of haloperidol. The basic and clinical pharmacology of reduced haloperidol is still poorly understood, even though this compound seems to be a major metabolite of haloperidol in man. For example, although haloperidol steady-state concentrations in serum correlated with the daily dose (r = 0.80, p < 0.02), a similar correlation with reduced haloperidol was much weaker (r = 0.58, p > 0.09) (Table 2). In addition, using the same HPLC method, we have observed about equally high concentrations of haloperidol and reduced haloperidol in human postmortem brain tissue obtained from patients who had a history of haloperidol treatment (Korpi, Costakos, and Kleinman, unpublished). These observations underscore the need to measure reduced haloperidol concentrations in clinical research studies of haloperidol metabolism.

The present HPLC method for haloperidol is equivalent in sensitivity and precision to GC methods. RIAs are more sensitive, but they appear to be less precise than the HPLC assay. In addition, HPLC (and GC) analyses can be automated after the extraction step. Hence, haloperidol concentrations in blood of psychiatric patients can be conveniently measured by high-performance liquid chromatography with electrochemical detection, but lower haloperidol concentrations such as those present in cerebrospinal fluid may necessitate the use of an RIA procedure. The main advantage of the HPLC method is that it allows for the simultaneous determination of haloperidol and reduced haloperidol concentrations.

We thank Miss Denise Ondrias for her expert secretarial assistance.

References