Serum Haloperidol and Neuroleptic Receptor Levels in Chronic Psychosis*

DONALD J. CANNON, Ph.D.,†‡§ DONALD E. McMILLAN, Ph.D.,∥ JOSEPH E. O. NEWTON, M.D.,†∥ EDWARD P. FODY, M.D.,†∥ W. STEVEN METZER, M.D.,†∥ MARSHA CLAYBROOK, R.N.P.,† LETHA COUCH, B.S.,† and STEPHEN R. PAIGE, Ph.D.,∥

†John L. McClellan Memorial Veterans Hospital, and Departments of ‡Biochemistry, §Neurology, ¶Pathology, ∥Pharmacology, and ∥Psychiatry, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205

ABSTRACT

Serum haloperidol and serum dopamine blocking activity were measured, and steady state levels were compared in 22 chronic male schizophrenic patients. Haloperidol levels were measured by high pressure liquid chromatography (HPLC), and dopamine blocking activity was measured by a radioreceptor assay (NRRA). Clinical status was determined by the Brief Psychiatric Rating Scale (BPRS) and the Abnormal Involuntary Movement Scale (AIMS). Patients were stabilized on individual doses of haloperidol for at least three weeks and dosages ranged from five to 200 mg per day. All measures were determined on two occasions, one week apart.

All measures (AIMS, BPRS, HPLC, and NRRA) showed a high degree of repeated test reliability. The behavioral measures showed a high degree of interobserver reliability on both occasions. There were significant correlations at both time points among haloperidol dosage, serum haloperidol levels, and dopamine blocking activity. Although the correlations between serum levels measured by HPLC and NRRA were positive and significant on both occasions, they never accounted for more than 58 percent (coefficient of variation) of the total variance.

Introduction

Neuroleptic drugs are thought to alleviate symptoms of schizophrenia by blocking dopamine receptors in the brain.1,3,17 Despite the wide use of neuroleptics,5 there is mounting concern about their adverse effects, particularly neuroleptic-induced movement disorders with long-term effects such as tardive dyskinesia.2,8 Data on acute psychotic patients12 indicate the potential
utility of therapeutic drug monitoring in neuropsychiatry. For at least one neuroleptic, haloperidol, several studies indicate that, for acutely psychotic patients, there is a therapeutic window, such that maximal response to the drug occurs within a relatively narrow band of serum levels.9,13

Recent studies on the effects of drug holidays have suggested altered pharmacokinetics in the distribution and elimination of haloperidol in chronic schizophrenic patients.11,15 Therefore, the present study was designed to determine steady-state serum levels of haloperidol and dopamine receptor blocking activity in serum in the same samples from chronic schizophrenic inpatients. The Pearson product-moment correlation coefficients were determined between these levels and the following: the dosage of haloperidol, the degree of psychosis, and the severity of tardive dyskinesia in a sample of chronic patients.

Materials and Methods

Patients

This study included 22 male veterans who were being treated for chronic schizophrenia on one of the extended care inpatient psychiatric units of the John L. McClellan Veterans Administration Medical Center. Demographic data on the patients were as follows (Mean ± S.D.): age = 50.7 ± 11.9 years; weight = 80.9 ± 24.4 Kg; duration of psychosis = 22.6 ± 10.9 years; and duration of neuroleptic treatment = 18.8 ± 8.8 years. All patients were stabilized on haloperidol (Mean ± S.D. = 0.49 ± 0.39 mg per kg per day, Range = five to 200 mg per day) for at least three weeks prior to being placed in the study. Steady-state haloperidol serum levels are reported to be generally achieved within six days.6 Patients were excluded from the study if they had serious co-existing medical problems or if oral neuroleptics in addition to haloperidol were prescribed. A signed informed consent was obtained from each patient.

Mental status was measured by means of the Brief Psychiatric Rating Scale (BPRS),16 and tardive dyskinesia was assessed using the Abnormal Involuntary Movement Scale (AIMS).14 Measurements of both mental status and tardive dyskinesia were made by two observers independently on each patient on two occasions one week apart. The observers were blind to the dosage of haloperidol and to the biochemical data.

Biochemical Methods

Haloperidol levels were determined on a Beckman Altex Model 334 high pressure liquid chromatography (HPLC) system with an Altex ODS-C (5μ; 0.46 × 15 cm) column. Standard addition procedures7 were used resulting in 60 percent recovery with a sensitivity of two ng per ml. As a quality control, bilevel commercially obtained serum samples containing 20 ng per ml and 40 ng per ml haloperidol were included in each run. Mean quality control values (corrected for recovery) were 17.14 ng per ml ± 6.13 (S.D.) and 30.91 ng per m ± 10.93 (S.D.), respectively. Samples and controls were made basic with NaOH, extracted with cyclohexane, and then back extracted into perchloric acid. The resulting aqueous extract was chromatographed directly. The column was heated to 40°C and eluted with 50 mM potassium dihydrogen phosphate, pH 3.8, acetonitrile (65:35) at 1.25 ml per min. Detection was at 200 nm, and a standard curve was run daily. Linear regression analysis of standard curve peak height versus ng injected was calculated, and sample values were determined from this regression line and cor-
rected for recovery. Haloperidol was measured in serum samples drawn 10 to 12 hours after the last dose of the drug.

Aliquots of serum (100 μl) were assayed in duplicate for the dopamine receptor blocking activity of neuroleptics using a radioreceptor assay. Results are expressed as neuroleptic units/liter (NU per L), in which one unit of blocking activity is the amount of displacement in the assay of 3H-spiperone by 1 nmole of haloperidol. Non-specific binding averaged 8.4 percent, the zero standard percent counts per minute bound (corrected for nonspecific binding) averaged 17.6 percent, and the intercept value for the standard curve averaged 173.3 NU per L across all determinations. These values all fall well within the quality control parameters suggested by the manufacturer for a satisfactory assay. Statistical analysis of data was performed on a QT Systems computer, using customized software for mean/standard deviation and correlation matrices.4

Results

In table I are shown reliability data for the experiment in the form of Pearson product-moment correlation coefficients. Interobserver reliability was high for the AIMS, for both the initial observation and for the second observation one week later. Since interobserver reliability was high, the observer ratings were combined when computing repeated test reliability. The first and second observations on the AIMS were highly correlated. Interobserver reliability for the BPRS was slightly lower than for the AIMS, although the correlation between the independent observers was positive and significant. Observer ratings were also combined for computing repeated test reliability for the BPRS, and a significant positive correlation was found between the first and second observations on the BPRS.

In table I are also shown the correlations between the first and second determinations of serum haloperidol level by HPLC and dopamine receptor binding by NRRA. Both correlations were statistically significant and were of approximately equal magnitude. The correlations were higher than that obtained for repeated determinations of the BPRS but lower than that for the AIMS.

In table II are shown the intercorrelations among the biochemical assays, the behavioral tests, and haloperidol dosage. The measurements of haloperidol serum levels by HPLC and dopamine receptor binding by NRRA correlated significantly with each other on both occasions. In figure 1 this relationship is graphically depicted. Although the two assays were significantly correlated, the slope of the regression line of the logarithmically transformed values (0.509) differed from unity. The radioreceptor assay was not

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* Wellcome Diagnostics.
TABLE II
Correlations Between Biochemical Assays, Behavioral Tests and Haloperidol Dosage

<table>
<thead>
<tr>
<th>Variables</th>
<th>Observation 1</th>
<th>Observation 2</th>
</tr>
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<tbody>
<tr>
<td>HPLC &amp; NRRA</td>
<td>0.76†</td>
<td>0.49*</td>
</tr>
<tr>
<td>HPLC &amp; AIMS</td>
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<td>-0.16</td>
</tr>
<tr>
<td>HPLC &amp; BPRS</td>
<td>0.44*</td>
<td>0.33</td>
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<tr>
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<tr>
<td>NRRA &amp; BPRS</td>
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<td>0.25</td>
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<tr>
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<td>-0.03</td>
</tr>
<tr>
<td>DOSE &amp; NRRA</td>
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<td>DOSE &amp; HPLC</td>
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<td>DOSE &amp; AIMS</td>
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</tr>
<tr>
<td>DOSE &amp; BPRS</td>
<td>0.34</td>
<td>0.39</td>
</tr>
</tbody>
</table>

AIMS - Abnormal involuntary movement scale.
BPRS - Brief psychiatric rating scale.
HPLC - Haloperidol serum levels by high pressure liquid chromatography.
NRRA - Neuroleptic radioreceptor activity.
*p<0.05
†p<0.01

two equal groups based on the median serum haloperidol concentration and on the median dose level. Although a comparison of the high serum concentration patients with the low serum concentration patients failed to show a significant mean difference in BPRS scores, the high dosage group showed significantly higher (p = 0.034) mean BPRS scores than the low dosage group.

Discussion

The major finding of this study was that serum haloperidol levels, as measured by HPLC, were significantly correlated with dopamine receptor binding expressed as neuroleptic units per liter, as measured by the NRRA. Although the correlations were positive and significant, they accounted for only 24 percent (second observation) to 58 percent (first observation) of the total variance (coefficients of variation).

There are several factors that might explain the modest degree of correlation. Since the NRRA met the manufacturer’s criteria for quality control, and since repeated analyses of serum spiked with haloperidol showed moderate variability and serum levels that were directly proportional to the amount of haloperidol added, it seems unlikely that analytical errors limited the correlations. However, it does seem likely that the lack of

![Figure 1](image_url)

**Figure 1.** Regression line relating serum haloperidol levels to dopamine receptor binding assay. Abscissa: log serum haloperidol concentration in ng per ml measured by high pressure liquid chromatography. Ordinate: log serum neuroleptic units (NU per L) measured by radioreceptor assay. Each point represents a single observation on a different patient.
sensitivity of the NRRA contributed to this problem. There were 10 instances where the NRRA could not detect binding activity. In eight of these 10 instances, the HPLC analysis showed serum haloperidol levels of 11 ng per ml or less, while the remaining two values were 16.8 and 21.8 mg per ml. In calculating the correlations, the NRRA values were entered as zero in these instances. Had the sensitivity of the NRRA allowed for quantitative measurement of receptor binding activity at these low serum levels, a higher correlation might have been obtained. Other factors that might limit the degree of correlation are variations in the degree of nonspecific binding of haloperidol to plasma protein and differences that have been reported in the interaction of individual sera with membrane preparations. These problems account at least in part for the decreased use of the NRRA.

Serum haloperidol levels correlated significantly with BPRS scores on one occasion, and there was a positive but not statistically significant correlation on the other occasion (table II). Patients receiving higher doses of haloperidol also showed significantly higher BPRS scores than those receiving lower doses. The association of higher haloperidol dosage and higher serum levels with higher BPRS scores may reflect an attempt by the therapists to treat those patients with more severe symptoms with higher doses of antipsychotic drugs.

Interobserver reliability for the behavioral tests was high (table I), especially for the AIMS. The correlations between repeated behavioral measurements (week 1 versus week 2) were at least as high as those between the repeated measurements of serum haloperidol levels and repeated measurements of dopamine receptor binding, suggesting that under at least some conditions, carefully constructed scales for measuring behavior can be as reliable as those based on measuring the chemistry of biological systems.

Acknowledgments

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References

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