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HALOPERIDOL VERSUS THIORIDAZINE FOR HOSPITALIZED PSYCHOGERIATRIC PATIENTS: DOUBLE-BLIND STUDY*

MIN-MIN TSUANG, M.D., LEIGH MIN LU, M.D., BERNARD A. STOTSKY, Ph.D., M.D. AND JONATHAN O. COLE, M.D.**

Boston State Hospital, Boston, Massachusetts

ABSTRACT: **A 12-week double-blind study was started with 60 actively psychotic geriatric patients residing in Boston State Hospital, to compare the psychopharmacological efficacy of haloperidol with that of thioridazine. The dosage was flexible—an initial low dosage followed by gradual increments until a satisfactory therapeutic response was obtained. Average maintenance dosages were about 2 mg a day for haloperidol and 100–125 mg a day for thioridazine. The rating instruments used were the Brief Psychiatric Rating Scale (BPRS), Stotsky Mental Status, Clinical Global Impression, NOSIE-30 (Nurse's Observation Scale), and Activities of Daily Living. At the end of the study, 50 patients were available for analysis. Our results indicated significant decreases in many areas of psychotic psychopathology for both drug groups, without significant differences between the actions of the two drugs. For both haloperidol and thioridazine, significant (P .05) improvement occurred in the following variables on the BPRS and the NOSIE-30: anxiety, excitement, irritability, hostility, suspiciousness, hallucinatory behavior, mannerisms, tension, unusual thoughts, blunted affect, neatness, and manifest psychosis.**

Side effects, with the low dosages used, were not common, and were surprisingly similar for the two drugs. Haloperidol appeared essentially equivalent to thioridazine in both efficacy and in the frequency and type of side effects observed.

There have been relatively few controlled double-blind evaluations of the comparative efficacy of antipsychotic drugs in the treatment of psychotic symptoms in elderly psychiatric patients. Even thioridazine, often considered the neuroleptic of choice in such patients, has been the subject of only one published controlled clinical study in which oral medication was used (1).

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** *Correspondence to be addressed to:* Jonathan O. Cole, M.D., Boston State Hospital, 591 Morton Street, Boston, Massachusetts 02124.

The apparent popularity of thioridazine (2, 3) has two logical bases. First, it causes fewer neurological side effects (4) than do most available antipsychotic drugs, and this presumably is an advantage in elderly patients. Second, it is believed to have a more sedative action than the piperazine phenothiazines or haloperidol. Conversely, thioridazine's tendency to produce autonomic side effects and drowsiness may be a disadvantage in the treatment of geriatric patients, since they are liable to be disturbed by autonomic side effects, may have cardiovascular disorders, and are often unsteady on their feet. A low dosage of a more potent neuroleptic drug might be better tolerated by some patients despite occasional, mild neurological side effects.

Several years ago, Cole (5) mentioned that haloperidol might well be useful for geriatric psychotic patients if it proved to have as few autonomic side effects as claimed by Janssen (6). One earlier controlled study by Sugarman et al. (7) had shown haloperidol to be significantly more effective than placebo in an elderly psychotic population.

The present study, in which thioridazine is compared with haloperidol in disturbed psychotic geriatric patients, grew from the foregoing considerations. It was designed to test whether or not:

1. Thioridazine and haloperidol might differ in clinical efficacy in psychotic geriatric patients.
2. The side effects associated with each might differ in frequency or kind.

Although potent antipsychotic drugs generally had not shown clear differences in clinical efficacy in younger adult schizophrenic patients, it did not necessarily follow that important clinical differences would not be observable in elderly patients.

MATERIAL AND METHODS

Subjects

A 12-week double-blind controlled study was undertaken on 60 hospitalized psychotic patients, 63 years of age or older, who were selected from short-term and long-term geriatric wards. All patients manifesting psychotic symptoms such as agitation, excitement, delusions or hallucinations, were screened with regard to suitability for the study. Patients with the following disorders were excluded: acute myocardial disease, severe renal disease, Parkinson's disease, an active convulsive disorder, clouded sensorium, organic brain syndrome with marked dementia, and inability to communicate during interviews. All patients pronounced suitable for the study on psychopathological and medical grounds were included, irrespective of the recorded psychiatric diagnosis.

The 60 patients meeting these criteria were randomly assigned to one of the two drug study groups, after initial evaluation. [Later, the group was reduced to 50 patients for completion of the study (v. infra)].

Methods

Patients admitted to this study were kept on the original geriatric wards from which they were selected and were exposed to virtually similar ward milieus. They were followed by the same psychiatrist and the same nurse throughout the study period.

Drugs. Both haloperidol and thioridazine were prepared in identical capsules and were dispensed in double-blind fashion. Each capsule contained either haloperidol (0.5 mg) or thioridazine (25 mg). The initial dosage for either drug was 1 capsule twice daily (a total daily dose of 1.0 mg for haloperidol and 50 mg for thioridazine). This dosage schedule was maintained for three to five days, depending upon patient's response, and was increased as required by 1 capsule every three to five days until a satisfactory therapeutic effect was obtained, or side effects intervened. The treating psychiatrist was satisfied with modest levels of clinical improvement and did not systematically explore high levels of drug dosage, which could cause definite side effects, before he established a suitable maintenance dosage. Dosage adjustment was recorded in detail. Each patient received active medication for twelve weeks without interruption. The minimal and maximal daily doses of haloperidol were 1.0 mg and 4.0 mg for thioridazine they were 50 mg and 500 mg. Mean dosages per day were 2.0 mg of haloperidol and 113 mg of thioridazine; thus any patient receiving 500 mg of thioridazine was the exception rather than the rule. Antiparkinsonian agents were used only when necessary.

No other tranquilizers were administered during the study period. For patients already in the hospital for more than one month, no other tranquilizers were used for at least one month before administration of the study drug.

Clinical and psychiatric evaluations. Before the study began, all patients were evaluated physically and mentally, including baseline vital signs, hemogram, blood sugar, serum creatinine, serum transaminase (SGOT), alkaline phosphatase, electrocardiogram (ECG), and urinalysis. Vital signs (blood pressure, temperature, and pulse) were recorded again after four, eight and twelve weeks of medication. The hemogram, ECG, and serum SGOT level were re-examined at the end of the study.

The following 5 tests were given (by the same psychiatrist and the same nurse) before medication was started and again after four, eight and twelve weeks of medication:

(A) Brief Psychiatric Rating Scale (BPRS) (8).

(B) Mental Status (MS) (9). This consists of 20 items in simple question form, and is specifically designed to assess the degree of impairment in memory, orientation, and alertness in geriatric patients.

(C) Clinical Global Impression (CGI). This is one of the forms prepared by the National Institute of Mental Health (NIMH) for use in drug-research programs.

(D) Nurse's Observation Scale for In-patient Evaluation (NOSIE 30) (9).

(E) Activities of Daily Living (ADL) (10). This form was developed to differentiate the degrees of social and physical impairment in performing activities of daily living on the part of geriatric patients.

Of these rating scales, BPRS, MS, CGI were completed by a psychiatrist. NOSIE-30 and ADL were completed by the head nurses on the wards.

Adverse reactions were clearly recorded on each case-report form and on the TES (Treatment Emergent Symptoms) form prepared for the NIMH's Early Clinical Drug Evaluation Unit (ECDEU) program.

These forms, including the ECDEU TES, drug résumé, and dosage record forms, were also completed by the research psychiatrist.

Analysis of covariance of the data was conducted by the Biometric Laboratory of the George Washington University.

RESULTS

General data

Ten of the 60 patients were dropped during the study period for reasons judged unrelated to the toxicity of either drug. Of these 10 patients, 3 were dropped because of administrative difficulties such as "elopement" or refusal of medication; in the other 7, intercurrent medical and surgical problems developed. One patient had a seizure two days after the start of haloperidol therapy; so it was terminated. This recently admitted patient was subsequently found to have a past history of a cerebrovascular accident and of status epilepticus. The seizure was considered unrelated to the drug. Another patient receiving haloperidol died of bleeding esophageal varices. He had a long history of alcoholism with previous bleeding episodes. The study medication was not considered to have contributed to his death. Five other patients were dropped from the study and transferred to the Medical Surgical Building for reasons such as congestive heart failure, pneumonia, or fever of unknown etiology.

Fifty patients were available for analysis. Of these, 26 (11 males and 15 females) received haloperidol and 24 (10 males and 14 females) received thioridazine. The age range was 63–85 years for the haloperidol group (mean age, 71.5) and 66–99 years for the thioridazine group (mean age, 73.7). There were no significant differences between groups with regard to age, sex, socio-economic status, chronicity, treatment, and family history of psychiatric illness, or course of psychiatric illness before and during the present hospital admission. Table 1 shows the classification of the patients

TABLE 1
Classification of the 50 Patients According to Diagnosis

Diagnosis	Haloperidol		Thioridazine	
	males	females	males	females
Organic brain syndrome: senile dementia or cerebral arteriosclerosis	4	5	0	5
Psychotic depression	0	4	3	3
Chronic schizophrenia	5	5	6	6
Undefined psychosis	1	1	1	0
Mental deficiency	1	0	0	0
Total	11	15	10	14

TABLE 2
Age of Patients and Hospitalization Data

	Haloperidol (N = 26)	Thioridazine (N = 24)
Age (range and mean)	63–85 (71.5)	66–99 (73.7)
More than one hospital admission	17 (65%)	18 (75%)
Duration of present hospitalization beyond 1 year	17 (65%)	14 (58%)
Rapid onset of present episode	5 (19%)	5 (21%)

according to diagnosis, and Table 2 shows some characteristics with regard to age range, number of hospital admissions, duration of hospital stay, and type of onset of the psychotic episode.

Clinical evaluation

Analysis of covariance for the 50 subjects showed significant clinical improvement during both drug treatments, and no clear discrimination between the two conditions. Both the psychiatrist and the nurses rated approximately similar proportions of patients as improved or unimproved.

All statistical significances cited are at the .05 level or lower, except when otherwise noted. Significant group differences between drug treatments were not obtained for any of the variables of the CGI, the BPRS, the ADL, or the MS scales.

Table 3 shows the results of analysis of covariance on the NOSIE-30 scale, indicating significant improvement in both drug groups regarding irritability, manifest psychosis, total assets, and neatness. However, there were indications that the haloperidol group was slightly slower than the

TABLE 3
Significant Variables in the Analysis of NOSIE-30

Variables	Level	Type	Direction
Neatness	.01	P	Both groups improved over time.
	.05	G × P	Haloperidol group improved only at the 2nd and 3rd month.
			Thioridazine group improved at all periods.
Irritability	.01	P	Both improved over time.
Manifest psychosis	.01	P	Both improved over time.
Total assets	.05	P	Both improved over time.
	.10–.20	G × P	Haloperidol group showed greater improvement in late period.
			Thioridazine group showed greater improvement in early period.

thioridazine group in achieving change on two measures—neatness and total assets.

On the BPRS, 7 of the 18 items showed significant improvement over time at the level of $P < .01$, and 3 additional variables at the level of $P < .05$ in both drug groups. Drug effects were demonstrated for the following variables: excitement, hostility, hallucinatory behavior, suspiciousness, grandiosity, mannerisms, and anxiety at the level of $P < .01$; and tension, unusual thoughts and blunted affect at the level of $P < .05$.

Figure 1 indicates the percentage of change on each BPRS item for each drug group. Improvement in the CGI score was also significant at the level of .05 in both drug groups. MS and ADL ratings revealed minimal improvement for approximately half of the patients in both drug groups, but neither drug differences nor before-and-after differences were statistically significant.

Toxicity

TES and other individual records indicated 26 symptoms occurring 48 times in 15 patients across three rating periods in the haloperidol group. Eleven patients were asymptomatic throughout the study period. In the

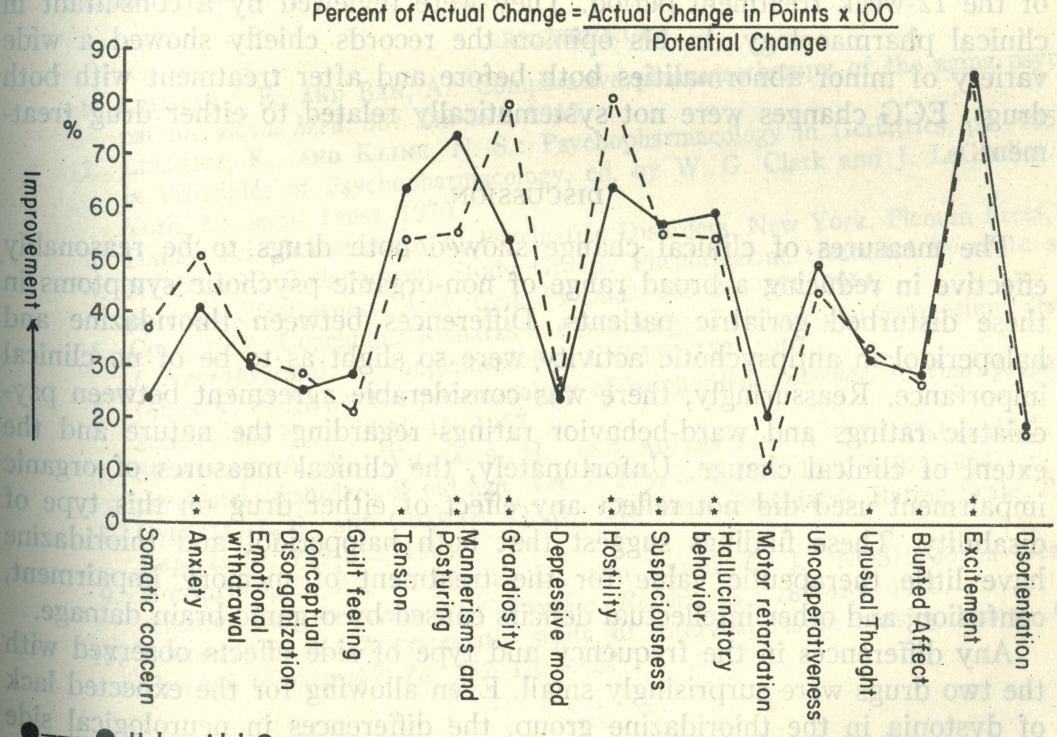

FIG. 1. Percentage of change observed for each variable of the Brief Psychiatric Rating Scale, in both drug groups.

thioridazine group 20 symptoms were reported as occurring 30 times in 12 subjects across three rating periods. Twelve patients remained asymptomatic. In the haloperidol group the most frequently reported or observed symptoms were tremor, drowsiness, dystonia, blurred vision, and weight loss. Among the thioridazine group the most frequent symptoms were drowsiness, tremor, depression, blurred vision, and tachycardia. Most of the side effects were considered mild, and none of the patients completing the study required even temporary discontinuance of medication in either drug group. Antiparkinson medication was required in only 7 patients of the haloperidol group and in 6 of the thioridazine group.

Laboratory data and vital signs

No significant changes in blood pressure were observed throughout the study period. There were sporadic reports of tachycardia in the group treated with thioridazine, and some observations of weight loss in the haloperidol group. Hemograms and SGOT determinations made before the study and at the time of termination, indicated no significant changes except in 1 thioridazine patient whose SGOT level was elevated from 10 to 40 units for no observable clinical reason.

Electrocardiograms were obtained just before the study and at the end of the 12-week treatment period. They were reviewed by a consultant in clinical pharmacology. In his opinion the records chiefly showed a wide variety of minor abnormalities both before and after treatment with both drugs. ECG changes were not systematically related to either drug treatment.

DISCUSSION

The measures of clinical change showed both drugs to be reasonably effective in reducing a broad range of non-organic psychotic symptoms in these disturbed geriatric patients. Differences between thioridazine and haloperidol in antipsychotic activity were so slight as to be of no clinical importance. Reassuringly, there was considerable agreement between psychiatric ratings and ward-behavior ratings regarding the nature and the extent of clinical change. Unfortunately, the clinical measures of organic impairment used did not reflect any effect of either drug on this type of disability. These findings suggest that both haloperidol and thioridazine have little therapeutic value for the treatment of memory impairment, confusion, and other intellectual deficits caused by organic brain damage.

Any differences in the frequency and type of side effects observed with the two drugs were surprisingly small. Even allowing for the expected lack of dystonia in the thioridazine group, the differences in neurological side effects were quite modest. Both drugs caused drowsiness and blurred vision to similar extents. Tachycardia and depression in a few thioridazine patients and weight loss and dystonia in a few haloperidol patients were the only observable differences in toxicity.

The low dosages used may account both for the relative infrequency of side effects and the lack of clear differences in the side effects during treatment. The use of a more aggressive dosage regimen might have made these possible differences clearer, but such an approach seemed contraindicated in most of these elderly patients.

It is always unsatisfying, in one sense, not to find clinically significant differences between drugs, since it can be argued that better assessment measures or a different design might have shown some major dissimilarity. However, except in the area of side effects, we know of no testable hypotheses concerning differences in clinical efficacy between the two drugs, though there is a vague clinical belief that thioridazine is the preferred antipsychotic agent for use in elderly psychiatric patients. Our data provide no support for this assumption. In our somewhat heterogeneous group of elderly psychotic patients, there was no clear basis for preference of one drug over the other.

In the absence of a placebo group, it cannot be proved that either drug was clinically effective. However, the changes were sufficiently striking to constitute real antipsychotic effects. In a separate controlled study carried out in the same setting on a less disturbed but more demented group of chronically ill geriatric patients, the placebo response was found to be virtually nil.

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