

Mesoridazine and Thioridazine: Clinical Effects and Blood Levels in Refractory Schizophrenics

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Seven schizophrenic (according to DSM-III criteria) inpatients completed a two-phase study; each phase had a 1-week drug-free period followed by 6 weeks of a drug trial. The first phase uniformly involved treatment with chlorpromazine, and in the second phase patients received either mesoridazine (N=3) or thioridazine (N=4). Clinical ratings (Brief Psychiatric Rating Scale and Clinical Global Impressions) and neuroleptic blood levels were obtained weekly throughout the study. Whereas patients failed to respond to chlorpromazine 1800 mg/day, response to mesoridazine 400 mg/day and to thioridazine 800 mg/day was established on all Brief Psychiatric Rating Scale factors except for anxiety-depression. A higher neuroleptic blood level was achieved with mesoridazine or thioridazine at less than half the reference chlorpromazine dosage. Correlations between neuroleptic blood level and clinical response were positive for mesoridazine, negative for chlorpromazine, and nonsignificant for thioridazine. These findings are consistent with earlier research. We conclude that drug-resistant schizophrenics seem to improve clinically with mesoridazine or thioridazine, unlike with chlorpromazine, and that for mesoridazine this difference may be a function of selective dopamine receptor blockade

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Neuroleptics are the therapy of choice for acute schizophrenic disorders and for the prevention of relapse in chronic schizophrenia. Unfortunately, many patients continue to experience productive psychotic symptoms, even in the presence of standard neuroleptic therapy. These patients range from the "neuroleptic nonresponder," who receives no benefit at all, to the "neuroleptic partial responder," who receives only partial benefit.

Several studies¹⁻⁴ suggest that some refractory schizophrenics may respond better if their therapy is switched to mesoridazine, a major metabolite of thioridazine, in the piperidine group of phenothiazines. Thioridazine is converted, on the one hand, into two active metabolites, thioridazine side-chain sulfoxide (mesoridazine) and thioridazine side-chain sulfone or sulforidazine, and, on the other hand, into two inactive metabolites, thioridazine ring 5-sulfoxide and thioridazine 2-5 disulfoxide.^{1,2,4} Neuroleptic nonresponders treated with thioridazine had a higher concentration of the inactive ring 5-sulfoxide than of the active side-chain 2-sulfoxide and 2-sulfone. In these studies, although the levels of the parent compound did not differentiate responders from nonresponders, high plasma levels of mesoridazine were associated with a good clinical outcome.^{1,4} Furthermore, nonresponders treated with mesoridazine showed a significant improvement, and all had high mesoridazine blood levels.^{2,4} Greater clinical improvement was associated with a higher ratio of active drug to inactive metabolite.

The above-described studies seem to indicate that mesoridazine is probably the most important thioridazine metabolite and that its administration is likely to result in higher neuroleptic blood levels. Therefore, one would expect mesoridazine to be more efficacious for refractory schizophrenics if neuroleptic response is related to neuroleptic blood level.

Although the research on the clinical effects of mesoridazine and thioridazine has been of great heuristic importance, the findings and interpretations are limited because of methodologic difficulties, such as the use of a flexible dose schedule^{1,4} and diagnostic heterogeneity.^{1,4}

The present study evaluated mesoridazine and thioridazine in regard to clinical effects, differential response of target symptoms, and the correlation of therapeutic efficacy with total neuroleptic activity as monitored by dopamine-receptor blocking assay. We hypothesized that these drugs, particularly mesoridazine, would produce better clinical response than a standard neuroleptic, such as chlorpromazine, and that such changes would be associated with higher neuroleptic blood levels.

METHOD

The sample consisted of chronic schizophrenic inpatients who were refractory to neuroleptics. "Refractoriness" was defined as the persistence of productive psychotic symptoms (e.g., delusions, hallucinations, and thought disorders) after 6 months of treatment with what would usually be considered an adequate daily dosage of neuroleptic, such as chlorpromazine 1200 mg, haloperidol 100 mg, or thiothixene 100 mg. All patients had been ill for longer than 5 years and had never achieved a clinically significant response, even after extensive treatment with various neuroleptics at the dosages mentioned or at even higher dosages.

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Table 1. Planned Comparisons of Response During Neuroleptic Treatment Against Drug-Free Baseline

Clinical Rating	Drug														
	Chlorpromazine (week)						Combined Weeks	Thioridazine or Mesoridazine (week)							
	1	2	3	4	5	6		1	2	3	4	5	6	Combined Weeks	
CGI															
Severity of illness	<1	<1	<1	<1	<1	<1	<1	<1	<1	1.76	3.72 ^a	4.20 ^b	7.03 ^c	2.85 ^a	5.22 ^b
BPRS															
Total psychopathology	<1	1.03	<1	<1	<1	<1	<1	<1	<1	1.82	3.16 ^a	7.06 ^c	10.80 ^d	2.15	6.33 ^c
Anxiety-depression	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Anergia	<1	3.50 ^a	1.93	2.40	1.38	<1	2.48	<1	1.11	2.70	1.91	4.16 ^b	<1	<1	2.22
Thought disturbance	<1	<1	<1	2.22	1.45	<1	1.55	<1	2.34	1.36	3.50 ^a	5.54 ^c	<1	<1	3.47 ^a
Activation	<1	<1	<1	<1	<1	<1	<1	<1	<1	2.13	4.63 ^b	11.68 ^d	4.96 ^b	<1	5.29 ^b
Hostility-suspiciousness	<1	<1	<1	<1	<1	<1	3.21 ^c	<1	<1	1.65	2.44	5.08 ^b	<1	<1	2.50

^ap < .05.^bp < .02.^cp < .01.^dp < .001.^eChange in the direction of clinical worsening.

Immediately before their participation in the study, the patients were being treated on their respective wards with the following drugs: 1) fluphenazine decanoate 25 mg i.m. weekly plus chlorpromazine 100 mg/day, 2) fluphenazine decanoate 150 mg i.m. weekly, 3) chlorpromazine 400 mg plus lithium carbonate 1200 mg/day, 4) chlorpromazine 1000 mg/day, and 5) perphenazine 96 mg plus lithium carbonate 1500 mg (in three patients). All patients were first treated with chlorpromazine as a reference drug to further confirm the lack of response to neuroleptics.

Inclusion in the study required confirmation of the schizophrenic diagnosis by an independent psychiatrist, who applied DSM-III criteria⁵ after reviewing a patient's chart and performing a detailed clinical interview. The Present State Examination (PSE)⁶ also was conducted by the psychiatrist to establish the presence of at least two of the following positive psychotic symptoms: hallucinations, delusions, and thought disorder.

The prestudy workup included a medical history, physical examination, complete blood count, chemistry panel, urinalysis, serology, and electrocardiography. Patients with known medical illnesses, seizure disorder, hypersensitivity to phenothiazines, an organic mental syndrome, or a history of alcohol or drug abuse were specifically excluded from the sample. Written informed consent was obtained after the procedures had been fully explained.

From a total of 100 patients on 12 wards who had been screened, 11 fulfilled all criteria and entered the study, and 7 of these completed the full protocol. Of these 7 patients, 5 were male and 2 were female, 4 were white and 3 were black, and 2 were married and 5 had never been married. Their mean age at onset of the illness, as judged by the age at first hospitalization, was 18.29 years (range, 6–25; SD=6.50). At the time of this study their mean age was 31.71 years (range, 19–37; SD=6.34), and the mean duration of their illness since onset was 13.43 years (range, 5–25; SD=6.48). Of the 4 patients who did not complete the protocol, 1 became uncooperative and withdrew during the second week, 2 were dropped because of

a dermatologic reaction to chlorpromazine, and 1 left the hospital without consent.

Each patient underwent two 7-week phases of study: a drug-free baseline period followed by a 6-week trial with neuroleptic treatment. The first phase uniformly involved treatment with chlorpromazine under single-blind conditions; during the second phase (triple-blind), the patients received either thioridazine (4 patients) or mesoridazine (3 patients). Clinical measurements and blood assays were conducted weekly.

Drugs and Dosages

Patients initially were observed for 1 week under drug-free baseline conditions and were then treated for 6 weeks with chlorpromazine, beginning at a dosage of 400 mg/day. The dosages were increased every other day and were 1800 mg/day by the end of Week 2 for all patients. Thereafter, the patients were drug-free again for up to 7 days (this period was curtailed when clinically essential); for another 6 weeks, they then received, according to a random code, either thioridazine 800 mg/day or mesoridazine 400 mg/day, and the dosage was increased over a week. During chlorpromazine treatment, the drug was administered 4 times a day; during mesoridazine or thioridazine treatment, the drug was given twice a day. All drugs were taken orally in liquid form throughout the study.

Because of the customary 2:1 ratio between the dosages of thioridazine and mesoridazine, these drugs were provided by the pharmacist in such a way that the dose of thioridazine administered was twice that of mesoridazine on a milligram per milligram basis. Each patient had his or her own individualized unlabeled container, and the medication was prescribed by the physician on a milliliter basis as predetermined by the pharmacist (i.e., 1 ml equals 50 mg of thioridazine or 25 mg of mesoridazine). Trihexyphenidyl (2 to 5 mg b.i.d.) was administered to 3 patients who showed drug-induced extrapyramidal symptoms. In 2 of these patients the medication was present during both study phases, and in the third case it was introduced during the second phase in conjunction with me-

soridazine. None of the patients was receiving any other drugs known to interfere with the neuroleptic assay.

Measures

During the first drug-free baseline week of observation, a psychiatrist applied selected parts of the Present State Examination⁶ to evaluate the existence of thought disorder, hallucinations, delusions, and abnormalities of behavior, affect, and speech. The Brief Psychiatric Rating Scale (BPRS)⁷ and the Clinical Global Impressions Scale (CGI)⁷ were applied weekly throughout the study by a psychiatrist, after a half-hour psychiatric interview, to monitor clinical effects. The seven-point BPRS provided measures of five clinical factors and also total psychopathology, whereas the CGI enabled overall ratings of severity of illness and also drug side effects.

Neuroleptic Assay

Neuroleptics in serum were assayed in terms of chlorpromazine equivalents, expressed in nanograms per milliliter, by using the radioreceptor assay of Creese and Snyder.⁸ Venous blood samples were drawn weekly throughout the study and were obtained 4 hours after the morning dose during the active drug treatment.⁹ Samples of serum (50 μ l) were assayed in triplicate for determination of total serum levels of neuroleptics by displacement of 0.1 nM of tritiated spiroperidol from a rat striatal membrane preparation.^{8,9} The triplicate samples agreed with each other within 5%, and in a range of 50 to 1000 ng/ml of chlorpromazine equivalents the interassay coefficient of variation was 12%.

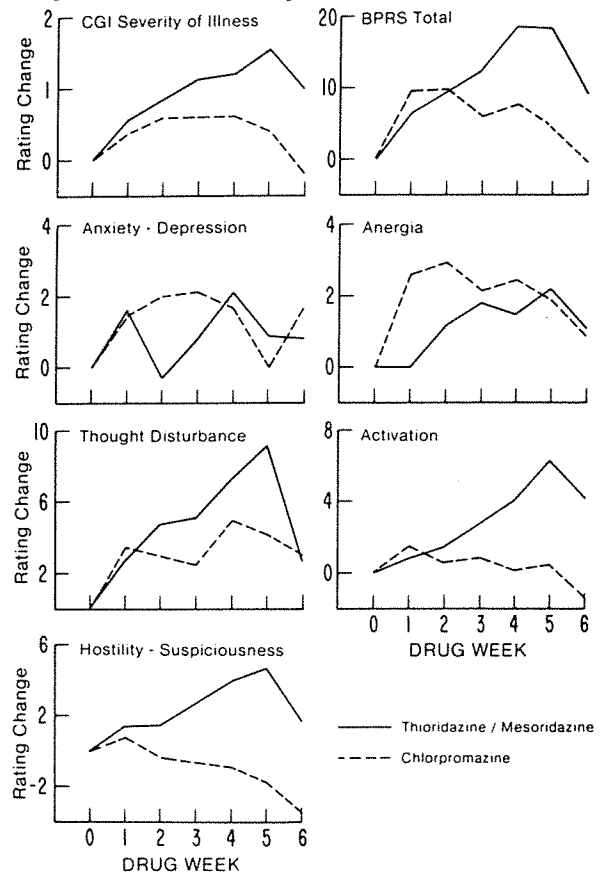
RESULTS

Comparison of Neuroleptic Effects

The therapeutic response of patients to chlorpromazine and to mesoridazine or thioridazine was evaluated by planned comparison of blind clinical ratings from the drug-free baseline against each of the 6 subsequent weeks of neuroleptic treatment and also against the combined neuroleptic period. This statistical approach was adopted in preference to the omnibus F test and post hoc comparisons because it was restricted to pertinent comparisons and thus enabled increased statistical power without proliferation of analyses. The planned comparisons were based on analysis of variance, treatment-by-subjects design, and employed directional tests because only clinical improvement, and not worsening, was hypothesized a priori and anticipated under neuroleptic conditions.

Table 1 summarizes the results of these analyses, and Figure 1 illustrates the clinical response in terms of the differences from the baseline ratings. In keeping with the patients' histories and selection criteria, the patients failed to benefit from chlorpromazine treatment. When compared with the drug-free period, none of the factors improved significantly across the combined 6 weeks of chlorpromazine treatment; in fact, the hostility-suspiciousness factor of the BPRS unexpectedly showed a non-significant ($p < .10 > .05$) exacerbation. In general, there were limited gains up to the second week of chlorpromazine

Figure 1. Changes From Drug-Free Baseline on the CGI and BPRS During Treatment With Thioridazine or Mesoridazine and During Treatment With Chlorpromazine*



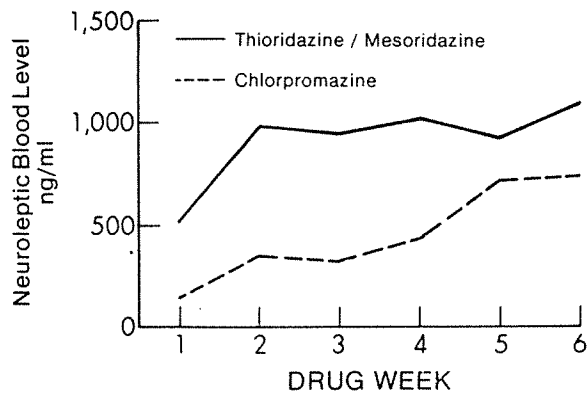
*Upward deflection represents clinical improvement and downward deflection, worsening.

zine therapy, followed by gradual erosion of progress. The only significant improvement during chlorpromazine treatment was in anergia during Week 2, but thereafter this factor, too, showed steady decline.

A response to mesoridazine or thioridazine, however, was established on most dimensions (Table 1). Overall, significantly better ratings were obtained for CGI severity of illness, BPRS total psychopathology, and the specific BPRS factors of thought disturbance and activation. These gains emerged early during treatment, generally achieved significance by Week 3 or 4, were most pervasive during Week 5, and abated during the final week. Although these factors were the primary areas of change, considerable improvement also occurred in anergia and hostility-suspiciousness during the fifth treatment week. The only factor that seemed entirely unaltered by the mesoridazine or thioridazine regimen was the anxiety-depression factor.

In view of the apparent opposition in therapeutic course observed between the two classes of phenothiazines for activation and hostility-suspiciousness (Figure 1), the directional differences from the baseline were statistically compared using tests of significance of difference between correlated proportions. Significant opposition of changes (i.e., improvement with mesoridazine or thioridazine and worsening with chlorpromazine) was

Figure 2. Median Neuroleptic Blood Levels During 6 Weeks of Treatment With Thioridazine or Mesoridazine Compared With Those During Treatment With Chlorpromazine



found for activation in Weeks 4 and 5 and through the combined neuroleptic phase (Weeks 1 through 6) and for hostility-suspiciousness in Week 5 ($p < .05$ in all cases).

Drug side effects, in contrast to the measures of psychopathology, were minimal and remarkably stable across the 6 weeks of treatment under both neuroleptic conditions. There were no significant differences between conditions, which uniformly yielded mean ratings that ranged between 0 and .20 on any given week and averaged identically at .07 across the 6 weeks on the 0-3 CGI scale.

Clinical Effects in Relation to Neuroleptic Blood Levels

Although the potency-adjusted neuroleptic dosage was more than twice as great for chlorpromazine as for mesoridazine or thioridazine, the median neuroleptic blood levels seemed considerably higher during the latter drug condition (Figure 2). A Wilcoxon matched-pairs signed-ranks test was used to analyze these differences instead of parametric statistics because the numerical values could be meaningfully ranked but lacked properties of an equal-interval scale.¹⁰ During the 6 weeks, the difference in blood levels for the two classes of phenothiazines approached significance ($z=1.75$, $p=.06$, two-tailed). When compared on a week-by-week basis, substantial differences were found during Week 2 ($z=1.75$, $p=.06$) and Week 4 ($z=2.02$, $p=.04$).

Correlations between neuroleptic dosages and blood levels were conducted across the 6 treatment weeks to determine the degree of association. Because of the numerous tied ranks for drug dosage, Pearson product-moment correlations were applied to these data in place of Spearman rho, as recommended by Ferguson.¹⁰ The results demonstrated that the variations in neuroleptic blood levels were a function of mesoridazine dosage, but they were less conclusive for thioridazine and chlorpromazine. The coefficient relating blood levels with neuroleptic dosage was significant ($p < .05$) with mesoridazine in two of three cases, with thioridazine in one of four, and with chlorpromazine in none.

The relationship between neuroleptic blood levels and global clinical response was examined for all three drugs by correlating the variations in these paired data across the 6 treatment weeks. The clinical progress was gauged by

Table 2. Neuroleptic Blood Levels in Relation to Changes in Global Psychopathology From Baseline During 6 Weeks of Treatment With Neuroleptics

Analysis	Measure of Global Psychopathology	
	CGI Severity of Illness	BPRS Total Psychopathology
Correlation (r) Between Neuroleptic Blood Level and Clinical Improvement		
Chlorpromazine	-.39	-.84 ^a
Thioridazine	-.16	-.06
Mesoridazine	.81 ^a	.59
Test of Differences (z) Between Two Correlation Coefficients		
Chlorpromazine versus mesoridazine	1.88 ^b	2.31 ^c

^a $p < .05$.

^b $p = .06$.

^c $p < .02$.

weekly change scores from the drug-free baseline on CGI severity of illness and BPRS total psychopathology; this procedure adjusted for any baseline differences in degree of illness and focused only on the clinical effects associated with the intervention of medication. Chlorpromazine blood level was inversely related to clinical improvement, an effect that reached significance for BPRS total psychopathology (Table 2). Conversely, mesoridazine blood level was directly related to clinical progress, and significantly so as measured by CGI severity ratings. Thioridazine blood level, however, showed no relationship to clinical status on either scale. A statistical comparison of the correlation coefficients obtained with chlorpromazine and mesoridazine indicated that the differences between drugs approached significance for the CGI and was clearly significant for the BPRS (Table 2). Other comparisons fell short of significance. Accordingly, higher neuroleptic blood levels corresponded to improved mental status with mesoridazine but clinical worsening with chlorpromazine.

DISCUSSION

The object of this study was to evaluate the hypothesis that mesoridazine and thioridazine would provide greater clinical benefit than chlorpromazine because of their achievement of higher neuroleptic blood levels. We thus compared these drugs in terms of clinical effects and blood levels by using a 7-week, fixed-dosage design in chronic refractory schizophrenics.

A principal limitation was our small sample size and the consequent necessity for combined analysis of mesoridazine and thioridazine data. This approach was possible, however, because of the pharmacologic similarities of the two drugs and the parallel trial of the reference drug, chlorpromazine, which served as a control condition. Other limitations in the design were the lack of balance for order of drug administration, the use of an antiparkinsonian agent in some cases, and the physically distinctive characteristics of the mesoridazine concentrate, although the drug was accessible only to the nurse in charge of medication. Despite these weaknesses, which

tend to increase the chance of type II (counter-hypothesis) error, the data support our hypothesis and are, furthermore, consistent with previous findings.¹⁴

Our results indicated that serum levels of mesoridazine and thioridazine were much higher than those of chlorpromazine, a finding that is in agreement with that of an earlier report.¹¹ Blood levels were directly related to clinical outcome in patients treated with mesoridazine, although this relationship was not apparent in the thioridazine group and was actually in the opposing direction for chlorpromazine.

All neuroleptics are postulated to exert their therapeutic and side effects via postsynaptic dopamine receptor blockade. If this assumption is correct, it would follow that therapeutic doses of all neuroleptics known to be clinically effective would result in similar brain levels, as expressed by dopamine receptor blocking activity. Although the issue of a relationship between serum levels and brain levels of neuroleptics remains open, such a relationship would conceivably depend on numerous pharmacokinetic variables. As such, these factors would be the same for the parent drug and the active metabolites.

On the basis of the finding of a ratio of serum to spinal fluid levels higher for thioridazine than for other neuroleptics, thioridazine may have less access to the brain than other neuroleptics.¹² One would tend to assume the same to be true for its metabolite, mesoridazine. However, high levels of thioridazine⁹ are associated in some cases with an exacerbation of psychomotor agitation, hallucinations, or the emergence of violence.

In our study, the inverse correlation between blood levels and clinical response and also the downward curve on the BPRS factors of hostility-suspiciousness and activation at high chlorpromazine serum levels may suggest a chlorpromazine-induced behavioral toxicity. With mesoridazine, however, there was no evidence of psychotoxicity despite very high serum levels.

Thus, neuroleptic-resistant schizophrenics seemed to improve clinically while receiving mesoridazine or thioridazine but not chlorpromazine, as reflected by all the BPRS factors except anxiety-depression. Blood levels were directly related to clinical outcome in patients treated with mesoridazine, whereas this relationship was not observed in the thioridazine group and was in the opposing direction for chlorpromazine. This finding suggests that mesoridazine in particular may be preferable for refractory schizophrenics. Indeed, 2 patients who were treated with thioridazine or chlorpromazine without response showed marked improvement when later treated openly with mesoridazine. Conversely, 2 patients who received chlorpromazine during both phases of the study (not included in the data analysis) clearly were unimproved despite alterations in dosages (1800 versus 800 mg).

Most factors showed apparent clinical deterioration during the last week of each phase of the study, when neuroleptic levels were highest. Similar results were obtained by other investigators using haloperidol, with a concomitant decrease of spinal fluid levels of homovanillic acid and gamma-aminobutyric acid by the fifth week.¹³

This finding suggests a "tolerance" phenomenon and deserves further investigation in this population.

In our study, the variations in blood levels were related primarily to mesoridazine. Two studies^{1,2} found that, among the thioridazine metabolites, only sulforidazine correlated strongly with dopamine receptor blockade. One may speculate that the active metabolites, mesoridazine and sulforidazine, may have a more selective site of action (mesolimbic versus nigrostriatal predominance), as proposed by Borison et al.¹⁴

These considerations require empirical verification with animal and large-scale clinical studies for more definitive conclusions to be reached. Particularly useful would be monitoring of thioridazine metabolites and total neuroleptic activity in correlation with erythrocyte drug levels, which have been shown to reflect neuroleptic activity more accurately at critical brain sites than do plasma levels.¹⁵

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