Clinical Effects of a Randomized Switch of Patients From Clozaril to Generic Clozapine

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Introduction: Clozapine was discovered in 1959 but withheld from the United States market after several deaths due to agranulocytosis. The medication was approved in the United States in 1989 on a compassionate-use basis and was first marketed in 1990 as Clozaril. In 1999, following approval by the U.S. Food and Drug Administration, Zenith Goldline Pharmaceuticals (ZGP) introduced a generic form of clozapine. ***Method:*** After 5 weeks of data collection (phase I), 24 patients were randomly assigned to group A and 21 patients to group B. Patients had DSM-IV diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder with psychosis, or atypical psychosis with mood disorder. In phase II, group A received a mean daily dose of 630 mg of generic clozapine, and group B continued to receive Clozaril at a mean daily dose of 610 mg, each for 8 weeks. In phase III, group A was reassigned to Clozaril, and group B was switched to generic clozapine, each for 8 weeks. At the end of phase III, group B resumed Clozaril. Efficacy was measured with the Clinical Global Impressions-Improvement (CGI-I) scale, the Brief Psychiatric Rating Scale (BPRS), and the Beck Depression Inventory (BDI). ***Results:*** Five patients experienced relapse when they were switched from Clozaril to generic clozapine. Eleven patients worsened short of full relapse, 9 while receiving ZGP generic clozapine and 2 while receiving Clozaril. CGI-I scores and BPRS scores favored patients receiving Clozaril significantly. Only BDI scores favored patients receiving generic clozapine significantly. ***Conclusion:*** Until more studies have been performed, clinicians and administrators should carefully monitor stable Clozaril-treated patients who are being switched to generic clozapine.

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Clozapine was discovered in 1959 but withheld from the United States market because of several deaths in Europe due to agranulocytosis. Because of the demonstrated clinical superiority of clozapine in treatment-resistant schizophrenia, in 1989, Sandoz Pharmaceuticals sought and received U.S. Food and Drug Administration (FDA) approval to introduce clozapine in the United States on a compassionate-use basis; Clozaril was first distributed in this country in 1990. Currently, it is marketed by Novartis Pharmaceuticals Corporation. In 1999, following FDA approval, Zenith Goldline Pharmaceuticals (ZGP) introduced a generic form of clozapine.

In 1998, Bellnier et al.[1] reported a comparison of Clozaril with ZGP clozapine in 41 state hospital patients with diagnoses of schizophrenia or schizoaffective disorder. They found no significant differences between Clozaril and ZGP clozapine on Positive and Negative Syndrome Scale scores or in serum clozapine concentrations. They concluded that the 2 drugs were clinically equivalent.

In 2000, there were 2 reports of significant pharmacokinetic differences between the 2 drugs in a single study group of 21 patients suffering from chronic psychotic disorders who were stabilized on Clozaril treatment and then switched to ZGP clozapine. Ereshefsky et al.[2] found a significantly lower maximum plasma concentration (C_{max}), a small numeric difference in mean area under the curve (AUC), and a systematic bias toward lower plasma concentrations for ZGP clozapine than for Clozaril. Their findings suggested a significant difference in the amount of drug absorbed. They also reported that significant differences found in their K_a and time to maximum concentration (T_{max}) compartmental pharmacokinetic analysis indicated a difference in the rate of absorption between the 2 formulations. Toney et al.[3] reported a post hoc analysis of the data collected in the same group of patients. They pointed out that the usual bioavailability criteria for a generic medication are met when 90% confidence intervals for AUC and C_{max} are in a range of 0.8 and 1.2. They found

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that C_{max} was significantly lower for ZGP clozapine for groups both inside and outside the 80% to 120% AUC. In vitro studies indicate that, for drugs like clozapine with loose D_2 binding, D_2 receptor occupancy above 60% might occur only above a certain threshold plasma concentration.[4] Toney et al.[3] offered this explanation for reports about clinical worsening.

ZGP generic clozapine is substantially less expensive than Clozaril. For example, at Saint Peter Regional Treatment Center (St. Peter, Minn.), Clozaril costs $2.47 per 100-mg tablet and $0.96 per 25-mg tablet. ZGP clozapine, by contrast, costs $1.04 per 100-mg tablet and $0.40 per 25-mg tablet. Given the potential for large cost savings, Minnesota state hospital facilities were eager to substitute generic clozapine for Clozaril. However, because of concerns at the Minnesota Security Hospital about clinical equivalence, and because at that time, there were no published clinical studies in patients, our team did a comparison study of the 2 compounds. We report here the results of our comparison study of Clozaril and ZGP clozapine in 45 patients with schizophrenia, schizoaffective disorder, bipolar disorder with psychosis, or atypical psychosis with mood disorder. We assessed clinical effectiveness and serum clozapine and norclozapine concentrations.

METHOD

Setting

The study was done at the Minnesota Security Hospital, which has approximately 170 patients, about 14 of whom are women. There are no patients under the age of 18 years. The majority are committed as mentally ill and dangerous.

Length of stay typically extends over a number of years. The hospital is secure, and the entry of contraband, including alcohol and illicit drugs, is nonexistent, or nearly so. The patients' daily routine is regular and occupied by therapy, including therapeutic work assignments for which patients are paid. They are assured of adequate nutrition, and their general health and personal safety are carefully monitored.

Study Design

The 21-week study was divided into 3 phases. Phase I consisted of 5 weeks of baseline data collection, and phases II and III consisted of 8-week medication change phases. The patients were randomly assigned to group A (24 patients) or group B (21 patients). During phase II, group A received ZGP clozapine, while group B continued to receive Clozaril. During phase III, group A again received Clozaril, and group B received ZGP clozapine. At the completion of phase III, group B stopped taking ZGP clozapine and resumed Clozaril therapy.

The nurses who dispensed the medication could distinguish Clozaril from ZGP clozapine by a small mark on otherwise identical tablets. Prior to the start of the study, the nurses were instructed not to reveal the identity of the drug being taken by a patient. The treatment staff knew that a study was being conducted, but would not have known which patients were receiving which medication unless one of the nurses revealed this information. A careful examination of the tablets would have been necessary to determine generic clozapine from Clozaril. There were no reports that any patient noticed any difference between tablets. The hospital pharmacy was specifically informed about which patients were to receive which drug. Individual medication setups were prepared in the pharmacy and transported across the treatment center's campus to the Security Hospital. The psychiatrists and psychologists completing the rating scales were not involved in the medication administration.

The treating psychiatrist was free to change the dosage or to discontinue treatment with clozapine on the basis of clinical indications.

Patient Selection

All 49 patients receiving clozapine in May 1999 were entered into the study. Four patients were subsequently dropped from the study: 3 were discharged from hospital, and a fourth chose to discontinue clozapine to stop the required regular venipuncture. The study group contained 1 woman. The median duration of clozapine therapy at the start of the study was 38 months, with a range between 2 and 41 months. DSM-IV diagnoses included schizophrenia, schizoaffective disorder, bipolar disorder with psychosis, or atypical psychosis with mood disorder.

Outcome Measures

Psychopathology was assessed by the Clinical Global Impressions-Improvement (CGI-I) scale administered by a psychiatrist, the 18-item Brief Psychiatric Rating Scale (BPRS) administered by a psychologist, and the 21-item, patient-rated Beck Depression Inventory (BDI). The BPRS and CGI-I both use a scale of 1 to 7; higher scores reflect greater pathology. The BDI has a possible total response range from 0 to 63, and higher scores indicate greater depression. Each instrument was given every 4 weeks as follows: phase I at weeks 1 and 5; phase II at weeks 9 and 13; and phase III at weeks 17 and 21.

Serum clozapine and norclozapine levels were measured every 2 weeks during the 21 weeks of the study. Blood was drawn at least 12 hours after the last dose. The values reported are the mean for each phase. The analyses were made by comparing the data from the phase immediately preceding the switch from Clozaril to ZGP clozapine with the data obtained in the phase after the switch. Serum levels were measured 2 to 3 times during each phase; these measures were averaged and compared to the average from the phase when the other formulation of the drug was administered.

Table 1. Mean CGI-I, BDI, and BPRS Scores in Patients Taking Clozaril vs. Generic ZGP Clozapine[a]

Scale	N	Mean Score During Treatment: Clozaril	Mean Score During Treatment: ZGP Clozapine	p Value
CGI-I[b]	45	3.94	4.32	.008
BDI[c]	35[d]	12.97	10.83	.027
BPRS mean score of items[e]	45	2.59	2.88	.001

[a]Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, BDI = Beck Depression Inventory, BPRS = Brief Psychiatric Rating Scale, ZGP = Zenith Goldline Pharmaceuticals.
[b]CGI-I scores significantly worsened during treatment with ZGP clozapine. There was also a significant interaction between drug and group (group A received generic in phase II, and group B received generic in phase III).
[c]BDI scores improved significantly during treatment with ZGP clozapine.
[d]Number of patients completing BDI during both study phases.
[e]Significant difference between drug and group (group A received generic in phase II, and group B received generic in phase III).

Table 2. Mean Dosage and Serum Levels in 45 Patients Taking Clozaril vs. Generic ZGP Clozapine[a]

Measure	Clozaril	ZGP Clozapine	p Value
Dose, mg/d	610.17	629.50	.027
Serum clozapine, ng/mL[b]	400.43	362.52	.085
Serum norclozapine, ng/mL[b]	238.42	215.71	.001

[a]Abbreviation: ZGP = Zenith Goldline Pharmaceuticals.
[b]Significant interaction between drug and group (group A received generic in phase II, and group B received generic in phase III).

Statistical Analysis

The scores analyzed were the mean of all scores obtained on each measure during each separate phase, by repeat measures analysis. The means of drug dose and serum concentrations were most often based on 3 or 4 assessments during each phase. The mean CGI-I, BPRS, and BDI scores were most often based upon 2 rating scale scores within a phase. Statistical analysis was done using the Statistical Package for the Social Sciences, Release 5.0.

RESULTS

Patient Characteristics

Between-group comparisons revealed no statistically significant differences in dependent measures between the 2 groups during any of the 3 study phases. This indicates both that the random assignment was effective in producing equivalent groups at phase I and that any effects of drug manufacture were too small relative to between-subject variation to yield a significant between-group contrast during phases II and III.

Psychotic Relapse

During the course of the study, 5 patients relapsed when their drug was changed from Clozaril to generic clozapine. No patient relapsed while receiving Clozaril. All 5 relapsing patients had been resistant to previous neuroleptics, all had a superior response to Clozaril, and some had maintained that response without exacerbations or relapse for years. Two patients had had complete remission of symptoms that was sustained for more than 1 year.

The relapsed condition was marked by insomnia, increased anxiety, and the return of marked exacerbation of positive psychotic symptoms. Three patients have not fully regained their prerelapse functional level. The exact probability of this distribution of relapses is significant ($p = .0079$). After the resumption of Clozaril after week 21, the patients' medical records were reviewed and treatment staff interviewed. Eleven additional patients were found to have worsened short of full relapse, with notable increases in irritability, insomnia, anger, and anxiety. Nine of the 11 were receiving generic clozapine at the time.

Rating Scales

Within-group (repeated measures) analysis revealed that scores on the average of all BPRS items were significantly worse when patients were receiving ZGP clozapine than while they were taking Clozaril ($p = .001$). Individual items assessing somatic concern ($p = .042$) and depressive mood ($p = .047$) also reflected a worsening of these symptoms. Ratings of motor retardation reflected an improvement following the switch from Clozaril to ZGP clozapine ($p = .031$).

Repeated measures analysis reflected a significant worsening of CGI-I scores when patients were switched to ZGP clozapine ($p = .008$). However, BDI scores were significantly improved ($p = .027$) after the switch to ZGP clozapine group. The mean BDI score of patients on Clozaril was 12.97 as opposed to 10.83 on ZGP clozapine (Table 1).

Dosage and Serum Concentration

The mean serum clozapine level was 400.43 ng/mL while patients were receiving Clozaril compared to 362.52 ng/mL while taking generic ZGP clozapine (Table 2). This difference is not statistically significant. Mean serum norclozapine levels showed a significant decrease ($p = .001$) after patients were switched from Clozaril to ZGP clozapine with values of 238.42 ng/mL and 215.71 ng/mL, respectively. There was a significant increase ($p = .027$) in the dose of medication prescribed following the switch to ZGP clozapine (mean dose of 610.17 mg/day on Clozaril and 629.50 mg/day on ZGP clozapine).

DISCUSSION

In this study, ZGP clozapine was not clinically interchangeable with Clozaril. Scores on the BPRS and CGI-I were significantly worse during the time when patients were taking ZGP clozapine. Norclozapine levels were significantly lower with generic ZGP clozapine versus Clozaril, but there were no statistical differences in serum cloza-

pine concentrations. Generally, clozapine levels, and not norclozapine levels, are associated with clinical response. Only the BDI scores were significantly improved in patients receiving the generic ZGP clozapine.

Most importantly, we saw clinically significant worsening in 16 patients, 14 of whom were receiving generic ZGP clozapine at the time. Five of these 16 patients relapsed with an incapacitating recurrence or exacerbation of psychotic symptoms to the extent that they were set back in their treatment programs. In 2 patients, there has not yet been a full return to previous function. In 1 patient, discharge has been delayed by at least a year. In all 5 instances, the patients who relapsed were receiving generic ZGP clozapine.

One explanation for worsening in patients taking generic clozapine may be that the generic and branded formulations do not have the same rate of absorption. Ereshefsky et al.[2] stated that the significant differences in K_a and T_{max} revealed by compartmental pharmacokinetic analysis indicate a difference in the rate of absorption between formulations. Toney et al.[3] reported that in vitro dissolution comparisons between ZGP clozapine and Novartis Clozaril were not the same; this finding also raised questions about whether the generic product is absorbed at a rate and amount adequate to produce the same clinical result at the same dose.

Zenith Goldline Pharmaceuticals compared generic ZGP clozapine with Novartis Clozaril by using a single 12.5 mg dose (1/2 of a 25-mg tablet) in 19 normal healthy subjects.[4] Mean plasma clozapine profiles for the 2 products were comparable with mean plasma levels at 1.5 hours of 21.5 ng/mL for ZGP clozapine and 23.2 ng/mL for Clozaril. They found no difference in AUC or C_{max} between the 2 formulations.

The rate of absorption may be crucial to the action of clozapine. Toney et al.[3] cited the findings of Seeman and Tallerico,[5] who suggested that D_2 receptor occupancy above 60% might occur only above a threshold serum drug concentration. If the generic is absorbed too slowly, the AUC might not change, but the level of peak concentration might never rise above a threshold needed for sufficient D_2 receptor saturation, thereby blunting or eliminating clinical response.

Another explanation for the lack of a difference in those who had no change is that the rate of clinical decline is between 6% and 10% when clozapine is discontinued altogether. There was not sufficient time in the 8-week crossover phases to show this effect at its fullest.

A 12.5-mg dose of clozapine might be insufficient to make a comparison for the purpose of establishing bioequivalence since our patients receive, on average, approximately 600 mg/day of Clozaril and have been taking it for months or years. The difference in dosing in this example is almost 50-fold. Some individual patients receive more than 1000 mg/day of Clozaril.

Cost Savings

Our system of state hospitals was very interested in the savings that would have been realized by adopting a lower cost, therapeutically equivalent generic clozapine. For our facility alone, using generic clozapine would have meant savings of $100,000 per year. Our cost of hospitalization per year is over $100,000. If, because of lack of therapeutic equivalence, we add 1 patient-year to the budget, the cost advantage of generic clozapine is lost. During the course of this 21-week study, we had at least one such case.

CONCLUSION

The results of this study and of other initial studies suggest that Clozaril and generic ZGP clozapine may not be bioequivalent. Although generic clozapine offers considerable cost savings to medical institutions when compared with Clozaril, such savings are easily offset by the costs of rehospitalization for just 1 relapsing patient per year. Further studies are indicated, but for the present, clinicians should be cautious in switching stable treatment-resistant patients with schizophrenia and other psychotic disorders from Clozaril to generic clozapine.

Drug name: clozapine (Clozaril and others).

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