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 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
that $C_{\text{max}}$ 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 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.
The relapsed condition was marked by insomnia, incontinence, somatic agitation, mood, and the return of marked exacerbation of positive psychotic symptoms. Nine 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 revealed 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 bio-equivalence 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 names**: clozapine (Clozaril and others).

**REFERENCES**