

# Branded Versus Generic Clozapine: Bioavailability Comparison and Interchangeability Issues

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Clozapine has been the treatment of choice for patients with refractory schizophrenia. Generic clozapine has recently become available, because of a waiver of the usual criteria for establishing bioequivalence. However, there are biopharmaceutical, bioavailability, and clinical concerns related to the generic formulation raised by both clinicians and academic researchers. We conducted a prospective, randomized, crossover study to evaluate steady-state pharmacokinetics, pharmacodynamics, and tolerability of generic clozapine (Zenith Goldline Pharmaceuticals) versus Clozaril (Novartis Pharmaceuticals) in schizophrenic patients. A preliminary report of the pertinent bioavailability results is presented here. Despite comparable mean plasma concentration-time curves, significant differences were found in the primary pharmacokinetic parameters of the 2 formulations in almost 40% of patients. Such intraindividual differences raise the issue of average bioequivalence versus individual bioequivalence and the implication for interchangeability of different clozapine formulations. The decision to switch a patient from branded to generic clozapine should be made on an individual basis with special emphasis on clinical outcome, and patients should be monitored closely during the transition.

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Clozapine remains the gold-standard treatment for patients with refractory schizophrenia who have had an inadequate or no response to other antipsychotic therapy.<sup>1,2</sup> The Expert Consensus Guideline<sup>1</sup> recommends the use of clozapine after 2 failed trials of other antipsychotics (at least 1 of which was an atypical drug) and considers it to be the treatment of choice after 3 or more failed drug trials. The American Psychiatric Association Practice Guideline<sup>2</sup> advises clozapine trials for patients whose symptoms have not responded to at least 1 other antipsychotic as well as for those who have had intolerable adverse effects from at least 2 antipsychotics from different classes.

Although it is common to conduct bioavailability studies in healthy volunteers to support generic drug approval, the use of clozapine has been shown to result in serious ad-

verse events in healthy subjects.<sup>3,4</sup> Therefore, special guidance was issued in 1996 for approval of generic clozapine formulations.<sup>5</sup> Based on the guidance, an *in vivo* study of branded and generic clozapine in 19 healthy subjects, using a 12.5-mg dose (half of a 25-mg tablet) of clozapine, was conducted. The results from the clinical study, together with *in vitro* dissolution data for the 100-mg tablet, were submitted as part of an abbreviated new drug application for approval of the generic formulation from Zenith Goldline Pharmaceuticals (ZGP).<sup>6</sup>

However, this substitution of *in vitro* results for the 100-mg tablet in lieu of actual study with the 100-mg tablet raises some biopharmaceutical and bioavailability concerns. For example, available comparative dissolution data of the Clozaril and ZGP clozapine 100-mg tablet formulations showed a different dissolution profile with a slower dissolution rate for the generic formulation.<sup>6</sup> Based on the dissolution data, the calculated Food and Drug Administration (FDA) Scale-Up and Post-Approval Changes (SUPAC) similarity factor<sup>7</sup> between the 2 formulations was reported to be in the low-to-mid 30s, below the recommended 50 to 100 range. This suggests that the rate and extent of drug absorption of the two 100-mg formulations might be different.

Furthermore, data also showed that the weight ratios for the 25-mg and 100-mg ZGP clozapine tablet formulations was 1:1.4, compared with 1:4 for the corresponding Clozaril tablet formulations (data on file, Novartis Pharmaceuticals, July 22, 1998). This means that the change in

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tablet weight for the ZGP clozapine formulation is not directly proportional to the change in dose, a finding that is likely related to the difference in the amount of inactive pharmaceutical excipients in the 2 tablet strengths. Therefore, it cannot be assumed that the 100-mg tablet of ZGP clozapine will be absorbed in the same way or at the same rate as the 25-mg tablet. However, the pharmacokinetic and bioavailability implications of this difference in excipient amount and tablet weight between the 2 tablet strengths of ZGP clozapine have not been explored. In addition, since patients receiving chronic clozapine as their antipsychotic agent are likely to receive multiple doses of the 100-mg tablet, the clinical implications of the excipient difference between the 2 strengths of ZGP clozapine, with respect to switching between branded and generic formulations, are unknown.

Another concern is the observation that the pharmacokinetic profile of clozapine is different after administration of a single dose versus multiple doses.<sup>8</sup> In the literature, the mean terminal elimination half-life ranged from 6 to 14 hours after a single dose versus 10 to 16 hours after multiple doses. The area under the concentration-time curve (AUC) for a single 75-mg dose of clozapine was reported to be 27% less than that for steady state (normalized to a 75-mg dose).<sup>8</sup> This pharmacokinetic difference related to single versus multiple dosing adds further complexity of extrapolating the bioavailability result with the 12.5-mg dose to the clinical environment.

After the generic drug became available for use, there were also anecdotal and isolated reports of relapse after patients previously stabilized on Clozaril treatment were switched to ZGP clozapine.<sup>9</sup> Since no literature data on bioavailability of the 100-mg tablet are available to show comparable concentrations, there is no pharmacokinetic explanation for these clinical reports of relapse.

On the basis of these biopharmaceutical and pharmacokinetic issues, clinical concerns, and the lack of human bioavailability data comparing the 100-mg tablet formulation, we designed and conducted a prospective, randomized, crossover study using the 100-mg tablet of both generic and branded clozapine dosed to steady state. Our objective was to determine the bioavailability of ZGP clozapine formulation relative to that of Clozaril. We also investigated individual differences in bioavailability to determine whether the 2 formulations are interchangeable.

## PATIENTS AND METHOD

Male and female schizophrenic patients between the age of 18 and 65 years old were eligible to enter the study. The study was approved by our University Institutional Review Board. Written informed consent was obtained from the patients and/or their guardians.

All patients had been stable for at least 3 months on Clozaril treatment and taking a stable dose of Clozaril for

at least 28 days prior to the study. They had to have received twice-daily dosing for at least 14 days prior to randomization. After a 2-week baseline run-in period on their respective stable doses of Clozaril, the patients were randomly assigned to receive the same dosage regimen of either ZGP clozapine or Clozaril for 2 weeks and then were crossed over to the other treatment for 2 more weeks. The naturalistic study design also allowed uneven morning and evening doses, as well as concomitant medications. However, no medication changes were allowed during the 28 days before or during the study.

Trough concentrations were obtained at the end of the baseline Clozaril run-in period and on days 7, 11, 12, 13, and 14 of each treatment period to determine achievement of steady state and to ensure compliance. On day 14 of each treatment period, a predose blood sample was obtained before administration of the morning dose. After drug administration, an additional 10 blood samples were obtained at different times over 12 hours. Aliquot plasma harvested from each sample was then frozen until analyzed for clozapine by high-performance liquid chromatography with UV detection and a lower detection limit of 20 ng/mL. The primary pharmacokinetic parameters determined were AUC, steady-state peak plasma concentration ( $C_{max,ss}$ ), and time to peak plasma concentration ( $T_{max}$ ). Secondary pharmacodynamic parameters were also determined. These included assessment of psychopathology by the Positive and Negative Syndrome Scale (PANSS)<sup>10</sup> and the Clinical Global Impressions scale.<sup>11</sup> Extrapyramidal symptoms were evaluated by the Extrapyramidal Symptom Rating Scale.<sup>12</sup> A cognitive battery of tests to assess cognitive performance was also performed at the end of the baseline run-in period as well as at 0, 1, and 4 hours relative to the morning dose on each AUC day. All personnel and raters for analytical, pharmacokinetic, and psychopathology measures were blinded to treatment arm.

Mixed effects analyses of variance were used to analyze differences in the mean logarithmic transformed pharmacokinetic parameters, using an alpha level of .05 for significance. The 90% confidence intervals (CI) for the log-transformed parameter ratios (generic to brand) were also determined. Based on the current FDA guideline, bioequivalence between the 2 products would be established if the CI of one falls within the range of 80% to 125% of the other.

## RESULTS

Twenty-one patients completed the study. A complete report, including detailed statistical treatment of data, presentation of results, and information on study subject dropout, will be the subject of another publication. On the basis of the criterion of less than 30% difference between adjacent trough clozapine concentrations in each treatment phase, steady-state conditions were achieved in all

Figure 1. Mean Clozapine Concentration After Dosing on the Day of Area Under the Curve Sampling

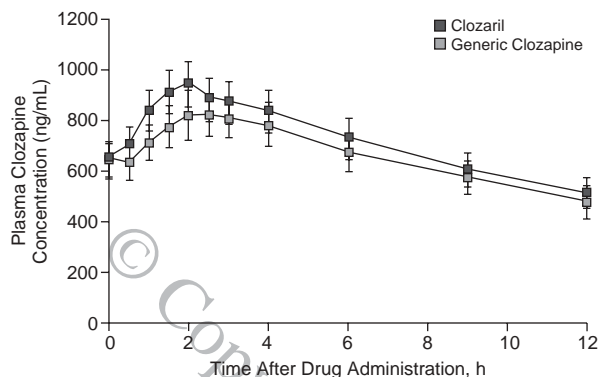


Table 1. Group Results for Steady-State Pharmacokinetic and Pharmacodynamic Parameters<sup>a</sup>

Parameters	Clozaril		Clozapine		p Value
	Mean	SD	Mean	SD	
Change in concentration ( $C_{max} - C_0$ ), ng/mL	363.80	164.84	260.80	189.03	.006
Overall cognitive score at 1 h	0.00	0.12	0.10	0.12	.042
$C_0$ , ng/mL	650	320	645	313	NS
Elimination half-life, ng/mL	11.6	6.5	14.1	11.8	NS

<sup>a</sup>Abbreviations:  $C_0$  = plasma concentration before drug administration,  $C_{max}$  = peak plasma concentration.

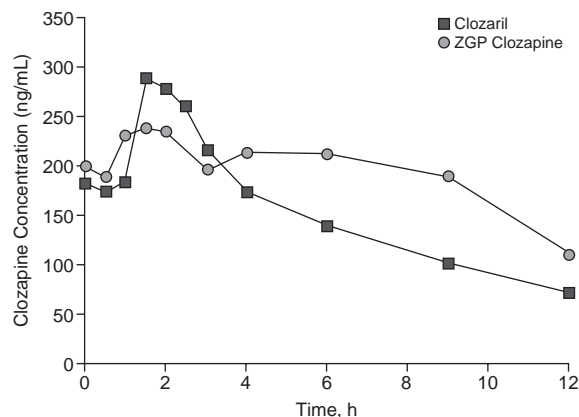
patients after receiving the Clozaril formulation and in 18 patients after receiving the ZGP clozapine formulation.

Although lower at each sampling timepoint, the mean ZGP clozapine concentration profile over the 12-hour AUC sampling period resembled that of Clozaril (Figure 1). Despite a 90% CI of log AUC ratio within 80% to 125%, statistical treatment of the observed small numeric difference in mean AUC suggests a systematic bias toward lower drug exposure for ZGP clozapine compared with Clozaril. On the other hand, a greater numeric difference was found in mean  $C_{max,ss}$  between the 2 formulations. A statistically significant difference was found between the mean log-transformed  $C_{max,ss}$  ratio ( $p = .002$ ), and the 90% CI of the log ratio fell outside the 80% to 125% range.

The bigger difference in the  $C_{max,ss}$  between the 2 formulations is further confirmed when one evaluates the change in clozapine concentration peak  $C_{max}$  to trough levels (Table 1). Of note is that the higher Clozaril  $C_{max,ss}$  was reflected in a difference between formulations on overall cognitive scores at 1 hour (see Table 1). The overall cognitive score was calculated on the basis of an equation using results from each test expressed as a z score. Results of the individual neurocognitive performance tests will be presented in a later publication.

Because one of our objectives was to assess the issue of interchangeability, we also calculated both the AUC and

Figure 2. Clozaril vs. Zenith Goldline Pharmaceuticals (ZGP) Clozapine: Subject 10<sup>a</sup>



<sup>a</sup>Patient is a 42-year-old white man receiving a daily dose of clozapine of 100 mg every morning and 300 mg at bedtime. Despite the higher AUC on ZGP clozapine vs. Clozaril (AUC ratio = 1.28), the differences in absorption characteristics are still demonstrated, e.g., lower  $C_{max}$ . The maintenance of patients on their clinically derived uneven daily dosing for this study maximized patient stability, but reduced the ability to detect differences since all bioavailability parameters were obtained during the smaller morning dosing interval.

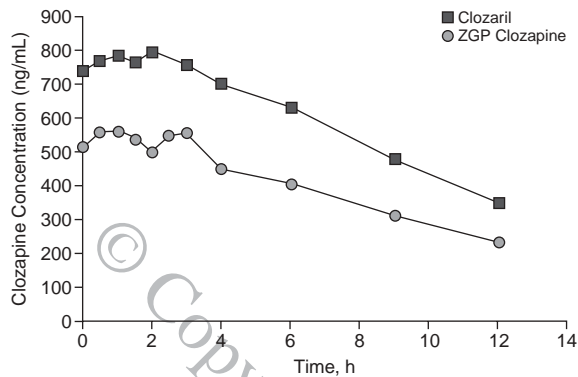
$C_{max,ss}$  ratios of ZGP clozapine to Clozaril for each patient. Five and 8 patients, respectively, had AUC and  $C_{max,ss}$  ratios outside the 80% to 120% (nontransformed) range. With the exception of 1 patient with an AUC ratio higher than the 120% upper limit, the remainder of these 5 patients' AUC ratios were all lower than the lower limit of 80%. Figures 2 and 3 portray 2 subjects' data from the bioavailability study. These patients were selected by the following rationale. Figure 2 portrays the only patient who had an AUC for generic greater than that for Clozaril. For Figure 3, rather than portray the most dramatic outlying patient in this study with an AUC for Clozaril greater than that for generic clozapine, we selected the patient who had the second most different AUC ratio.

## DISCUSSION

As a result of safety concerns regarding the use of the clozapine 100-mg tablet formulation in healthy, normal volunteers, establishing bioequivalence of generic clozapine formulations based on bioavailability comparison of the 100-mg dose was considered neither feasible nor safe. Approval of generic clozapine formulations, including that from ZGP, was therefore based on in vivo data using a much smaller dose (half of a 25-mg tablet), as well as in vitro dissolution profile for the 100-mg tablet.

However, as discussed in the introduction, biopharmaceutical differences exist between the 2 formulations, as well as between 2 tablet strengths of the generic clozapine formulations. Should in vitro data be substituted for bioavailability data in humans, and is an accepted population

Figure 3. Clozaril vs. Zenith Goldline Pharmaceuticals (ZGP) Clozapine: Subject 12<sup>a</sup>



<sup>a</sup>Patient is a 36-year-old white man receiving a daily dose of clozapine of 100 mg every morning and 500 mg at bedtime. The maintenance of patients on their clinically derived uneven daily dosing for this study, as described in Figure 2, is clearly demonstrated in this figure. The high concentrations from the preceding evening reduce the ability to cleanly define the peak concentrations for both products. Nonetheless, maximal concentrations, overall concentrations throughout the morning dosing interval, and the AUC are much less for generic clozapine than for Clozaril (AUC ratio = 0.68).

bioequivalence in a normal population adequate to predict individual patient bioequivalence? These questions prompted us to design a study to assess the bioavailability of the generic formulation relative to the branded product in the intended target population and to determine whether the 2 formulations are interchangeable.

Twenty-one schizophrenic patients completed this prospective, randomized, crossover bioavailability study using the 100-mg tablet of both formulations dosed to steady state. The mean plasma concentration profile was similar over the 12-hour AUC sampling time period, and the 90% CI for the mean log-transformed AUC ratio was within the 80% to 125% range. However, both the mean log-transformed AUC ratio and the 90% CI were less than 1.0, suggesting a lower drug exposure associated with the use of the generic formulation. The corresponding data for mean log-transformed  $C_{max,ss}$  ratio also showed a value less than 1.0 and, more importantly, a 90% CI that falls outside the 80% to 125% range. It is not the intention of our study to address whether the 2 products are bioequivalent. However, the FDA guideline of bioequivalence requires the CI for both mean log-transformed AUC and  $C_{max}$  ratios of generic to brand product to be within the 80% to 125% range.

According to recent reports,<sup>13</sup> clozapine binds loosely to the dopamine  $D_2$  receptor.  $D_2$  receptor occupancy above 60% is associated with good response<sup>14</sup> and may only occur above a certain threshold plasma clozapine concentration. Potkin et al.<sup>15</sup> found that trough plasma clozapine concentration above 420 ng/mL predicted clinical response in their group of treatment-resistant schizophrenic patients. Therefore, the observed differences in  $C_{max}$  in individual

patients during our study may have clinically important implications when considering switching between different clozapine formulations. Of note, the patient with the greatest pharmacokinetic parameter differences between the 2 formulations had a generic-to-brand AUC ratio less than 54% and generic-to-brand  $C_{max,ss}$  ratio less than 55%. Similar to those clinical cases reported by Kluznik et al.,<sup>9</sup> this patient's PANSS score increased by 29% compared with baseline during the ZGP clozapine treatment period. The patient continued to worsen (47% increase in PANSS score compared with baseline) after switching back to Clozaril. However, the change in PANSS score could be partially affected by the concomitant psychosocial stressors he experienced during the study. The further increase in PANSS score observed is not uncommon, since typically it will take months for a decompensated patient to be clinically restabilized. The results of an end-of-study urine alcohol screen were positive in this patient, probably reflective of his clinical worsening. It is interesting to note that the results of his beginning and midpoint study drug screens, including alcohol, were negative, and he is without a history of alcohol abuse or dependence. His clinical worsening and dramatically lower concentrations occurred during the first randomized treatment period with generic clozapine (after being switched from long-term, stable Clozaril treatment).

As indicated in Table 1, the mean trough concentration revealed in this study was similar to that of an internal study conducted in North Carolina,<sup>16</sup> e.g., no statistical difference in trough concentration. However, the North Carolina study did not evaluate potential differences in AUC and  $C_{max}$ , which in our study are different between the 2 formulations and more variable within individual patients.

The lower  $C_{max}$  trend toward lower AUC for ZGP clozapine, and differences in absorption characteristics suggest that 100-mg tablets of ZGP clozapine and Clozaril may not be interchangeable in some patients. The results are consistent with the in vitro dissolution findings and may provide a possible explanation for anecdotal reports of patient decompensation after switching from Clozaril to ZGP clozapine.<sup>9</sup> Considering data on file with the FDA, it is also of special note that the generic clozapine formulation manufactured by Mylan Pharmaceuticals has a faster in vitro dissolution profile compared with that of Clozaril. The potential changes in bioavailability and clinical effects when switching patients between 2 generic formulations have never been investigated and can only be speculated at this time.

Obviously, interchangeability, whether between branded and generic products or between 2 generic products, is not a simple black-and-white issue. We are not discouraging the use of generic products. Instead, our results suggest that while the bigger issue of bioequivalency and relative bioavailability can be addressed with population studies, the decision to switch or not must be made on a clinical and



individual basis. Available evidence suggests that most patients stabilized on Clozaril can be switched provided that adequate monitoring during the transition period occurs. In addition, switching of clozapine products by a health care system or pharmacy service should not be done without the knowledge of physicians and patients. When patients, especially outpatients, are switched between different clozapine formulations, they must be monitored carefully and more frequently to guard against changes in clinical status.

*Drug name:* clozapine (Clozaril and others).

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