Pharmacokinetic Studies of Antipsychotics in Healthy Volunteers Versus Patients

Neal R. Cutler, M.D.

In clinical trials of dopamine-blocking antipsychotics, significant adverse events may occur in healthy volunteers at dose levels that are well tolerated by schizophrenic patients. Because of these differences in tolerability, bioequivalence and pharmacokinetic studies of antipsychotics should be performed in schizophrenic patients rather than in healthy volunteers. When clozapine is the drug being investigated, pharmacokinetic and bioequivalence studies should be carried out in real-life dosage conditions because the half-life of clozapine increases with multiple doses. Under real-life conditions, the evaluation of multiple doses of clozapine in a population of schizophrenic patients can provide direct therapeutic relevance to bioavailability findings. This article discusses patient recruitment and informed consent in pharmacokinetic trials of schizophrenia, issues in studying antipsychotic agents in healthy volunteers versus schizophrenic patients, and a bioequivalency study of Clozaril (Novartis Pharmaceuticals) and generic clozapine (Creighton [Sandoz]) in schizophrenic patients.

(J Clin Psychiatry 2001;62[suppl 5]:10–13)

Because of differences in tolerability, bioequivalence and pharmacokinetic studies of antipsychotics should be performed in schizophrenic patients rather than in healthy volunteers. This article will discuss patient recruitment and informed consent in clinical trials of schizophrenia, issues in studying antipsychotic agents in healthy volunteers and schizophrenic patients, and a bioequivalency study of Clozaril (Novartis Pharmaceuticals) and generic clozapine (Creighton, generic house for Sandoz, which is now Novartis Pharmaceuticals) in schizophrenic patients.

PATIENT RECRUITMENT AND INFORMED CONSENT

The symptoms of schizophrenia often affect patient recruitment, and many potential participants decline to take part in clinical trials. Patients with predominantly positive symptoms tend to be suspicious of researchers' motives while patients with predominantly negative symptoms lack the motivation to enroll.[1] Some schizophrenic patients are simply unable to participate in clinical trials because they cannot tolerate discontinuing maintenance medications; in such cases, the cohort will ultimately consist of stable patients or those who have responded poorly to other agents. Many persons with a diagnosis of schizophrenia may be challenged by the cognitive demands of the informed consent process for participation in research.[2] In many cases, the patients' reduced capacity for understanding the informed consent process can be compensated by a more intensive educational intervention by the researchers. Efforts to identify the basis for the observed impairments and devise means of attempted remediation are needed. This conclusion is supported by a report[3] of the good performance of schizophrenic subjects on informed consent material after several learning and practice sessions.

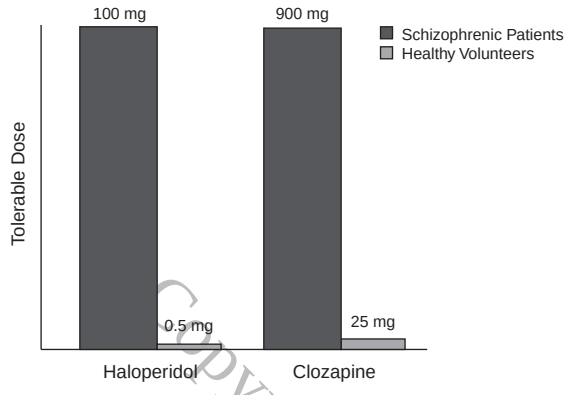
It is vital that patients understand the known risks and benefits of participation in a clinical trial. Patients should also be reassured that they can leave the study at any time for any reason. The language of the consent form should be clear, simple, and at an eighth-grade level of understanding. The print should be large and easy to read because blurred vision is a common side effect of antipsychotic medications. In severe cases, the caretaker can give the consent. I always try to obtain the written consent of the next of kin or any responsible party in addition to that of the patient so that close relatives and friends have an understanding of the trial objectives.

ANTIPSYCHOTIC STUDIES IN HEALTHY VOLUNTEERS AND SCHIZOPHRENIC PATIENTS

The effects and side effects of psychotropic drugs are determined by many variables, and the host factor is one

From California Clinical Trials, Beverly Hills, Calif.
Presented at the symposium "Comparison of Bioequivalence of Generic vs. Branded Clozapine," which was held July 29, 2000, in New York, N.Y., and supported by an unrestricted educational grant from Novartis Pharmaceuticals Corporation.
Reprint requests to: Neal R. Cutler, M.D., 8500 Wilshire Blvd., Beverly Hills, CA 90211.

Figure 1. Examples of Antipsychotic Drug Tolerance: Schizophrenic Patients vs. Healthy Volunteers



of the most important. Schizophrenic patients with mild, moderate, or severe illness can experience differences in tolerance to antipsychotics. Furthermore, dopamine-blocking antipsychotic agents may produce significant adverse events in healthy volunteers at dose levels that are well tolerated by schizophrenic patients.[4] Administration of haloperidol (0.2 mg/kg) to healthy volunteers and patients in the acute stages of schizophrenia produced a higher incidence of side effects and a greater need for anticholinergic drugs in the volunteers than in unmedicated schizophrenic patients.[5] At equivalent chlorpromazine doses, healthy volunteers showed greater sedative effects than schizophrenic patients.[6] Additionally, postmortem studies report higher dopamine-2 (D_2) receptor densities in postmortem brain tissue from schizophrenic patients than those in control brains.[7] Differences in tolerability between patients and healthy volunteers have also been observed in individuals taking benzodiazepines,[8] tricyclic antidepressants,[9] and medications for the treatment of Alzheimer's disease.[10]

Examples of antipsychotic drug tolerance in schizophrenic patients versus healthy volunteers are shown in Figure 1. In a patient population, haloperidol can be given up to a recommended dose of 100 mg/day,[11] whereas the tolerance level in healthy volunteers has been as small as 0.5 mg/day. In a bioequivalence study[12] in which 17 healthy male volunteers received a single 25-mg dose of Clozaril, 8 of 17 subjects experienced severe bradycardia (< 40 beats/min), and 2 subjects had a cardiac arrest, with cardiac pauses lasting 10 and 60 seconds, respectively. The researchers reported the adverse events and recommended that future clozapine bioequivalence/bioavailability studies be performed only in schizophrenic patients. The Center for Drug Evaluation and Research arm of the U.S. Food and Drug Administration subsequently released a statement[13] that said, "Until conditions are defined in which clozapine can be safely administered to clozapine-naive normal subjects, it may be prudent to conduct clozapine in vivo bioequivalence studies in patients."

CLOZAPINE DOSE-RESPONSE RELATIONSHIPS

Clozapine pharmacokinetics demonstrate considerable variability among individuals and are influenced by factors such as smoking, gender, and age.[14] The metabolism of clozapine appears to be controlled by the 1A2 subfamily of hepatic cytochrome P450 enzymes and may be affected by compounds that induce (e.g., tobacco) or inhibit (e.g., caffeine) the activity of that system.[4] The primary metabolite of clinical significance is *N*-desmethylclozapine (norclozapine), which has demonstrated affinity for D_2, serotonin-1C (5-HT_{1C}), and 5-HT_2 receptors.

Dose-response relationships are difficult to determine in the overall clinical pharmacology of antipsychotics. Multiple receptor targets are involved, and downstream effects must be taken into account. Furthermore, there are few pharmacodynamic measures of outcome in schizophrenic patients. In a 12-week study[15] of steady-state blood clozapine concentrations in 58 schizophrenic patients, discriminant function analysis determined that a plasma clozapine concentration of 420 µg/L optimally distinguished responders from nonresponders. Schizophrenic patients who had plasma clozapine concentrations greater than 420 µg/L had a 60% response rate after 4 weeks of treatment compared with an 8% response rate for patients with plasma clozapine levels less than 420 µg/L. In a study[16] of 29 treatment-resistant schizophrenic inpatients, a receiver operator curve demonstrated that the threshold plasma clozapine concentration for therapeutic response was 350 µg/L. A total of 64% of the treatment-refractory schizophrenic patients who had plasma clozapine concentrations greater than 350 µg/L responded, whereas only 22% of patients with levels less than 350 µg/L responded. To determine the relationship between serum clozapine levels and therapeutic response, VanderZwaag et al.[17] studied 56 schizophrenic inpatients who were randomly assigned to 12 weeks of double-blind treatment at 3 different serum clozapine ranges. Psychopathology was rated using the Brief Psychiatric Rating Scale and the Scale for the Assessment of Negative Symptoms. The analyses of the results of treatment supported the superior efficacy of the 200 to 300 µg/L and the 350 to 450 µg/L serum clozapine ranges over the 50 to 150 µg/L ranges. Since there is increasing evidence of a significant relationship between blood clozapine concentrations and clinical response, it is crucial to establish the bioequivalence of generic versus brand clozapine.

Bioequivalence of Clozaril vs. Generic Clozapine (Creighton)

Bioequivalence is the scientific basis on which generic and brand-name drugs are compared.[18] Bioavailability is

Table 1. Possible Treatment Sequences in Pharmacokinetic Study of Clozaril (Novartis) and Generic Clozapine (Creighton [Sandoz])[a]

Sequence	Period 1 Day 6–12	Period 2 Day 13–19	Period 3 Day 20–26
1	A	B	C
2	B	C	A
3	C	A	B
4	B	A	C
5	A	C	B
6	C	B	A

[a]From Sramek et al.,[4] with permission. After a 3-day washout, all patients received Clozaril for 5 days, titrated upward from 12.5 mg b.i.d. to 75 mg b.i.d.
A = Clozaril one 100-mg tab b.i.d., B = clozapine four 25-mg tabs b.i.d., C = clozapine one 100-mg tab b.i.d.

Table 2. Pharmacokinetic Results in 22 Patients Taking Clozaril (Novartis) and Generic Clozapine (Creighton [Sandoz])[a]

	Clozaril 1 (100 mg)		Clozapine 4 (25 mg)		Clozapine 1 (100 mg)	
Measure[b]	Mean	SD	Mean	SD	Mean	SD
AUC (μg/L/h)	2547	1429	2683	1613	2781	1775
C_{max} (mg/L)	317	163	351	167	358	184
C_0 (mg/L)	149	95	155	106	160	128
C_{12} (mg/L)	141	149	140	106	153	130
T_{max} (h)	2.50	1.09	2.02	0.832	1.93	0.758

[a]Data from Sramek et al.[4]
[b]p = not significant.
Abbreviations: AUC = area under the concentration-time curve, C_{max} = peak plasma concentration, C_0 = plasma concentration prior to drug administration, C_{12} = plasma concentration 12 hours after administration, T_{max} = time to peak plasma concentration.

the rate and extent to which a drug is absorbed or is otherwise available to the treatment site in the body. For 2 products to be considered bioequivalent, their bioavailability must not differ significantly when they are given in studies at the same dosage under similar conditions. Because the half-life of clozapine (7.9 hours) increases after a single oral dose to 14.2 hours after multiple doses,[19] bioequivalence and pharmacokinetic studies of clozapine should be performed under clinical real-life conditions. Using multiple doses of drugs, Sramek et al.[4] conducted a bioequivalence study to evaluate the steady-state pharmacokinetics and safety of Clozaril and generic clozapine (Creighton) in schizophrenic patients. The rationale for performing the study in schizophrenic patients was based primarily on tolerability concerns, including the high risk of serious cardiovascular events associated with the use of clozapine in healthy individuals.[12] For ease of recruitment and study conduct, 30 stable DSM-III-R schizophrenic outpatients who were receiving typical antipsychotics as maintenance treatment were entered into the study in 3 sequential cohorts.

After a 3-day washout period, patients received Clozaril titrated upward from 12.5 mg b.i.d to 75 mg b.i.d. over a period of 5 days. Patients were then randomly assigned to receive 1 of 6 different sequences of 1-week treatment periods during which 100 mg b.i.d. of Clozaril or clozapine (Creighton) was given (Table 1).[4] On the last 4 days of each 1-week treatment period (period 1, 2, and 3), blood samples were taken just prior to administration of the morning dose to measure trough plasma clozapine concentrations. Additionally, blood samples for measurement of plasma concentrations and pharmacokinetic determinations were taken at 0.5, 1, 2, 2.5, 3, 4, 6, 9, and 12 hours after the morning dose on the last day of each period. On the last day of period 3, blood samples were collected at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 24, 36, 48, and 72 hours after the final morning dose. It was hoped that the subjects who had mild-to-moderate schizophrenia could tolerate the initial clozapine dose of 12.5 mg b.i.d. However, 6 patients of the first cohort (N = 10) experienced clinically significant orthostatic hypotension after the first 12.5-mg dose of clozapine. Five of the 6 patients who experienced orthostatic hypotension also exhibited dizziness, light-headedness, pallor, and diaphoresis. The sixth patient experienced a syncopal episode. Because of the adverse events, the protocol was altered to include hospitalization during the initial titration period, and vital signs were monitored closely during the entire inpatient period. Although there were no significant differences in safety parameters between groups, a high (6 of 30 patients, 20%) incidence of symptomatic orthostatic hypotension was found in the initial titration of Clozaril, which emphasized the need for careful monitoring even in the target population. It is possible that the stable outpatients were more susceptible to the cardiovascular side effects of clozapine than treatment-refractory patients would have been.

A total of 22 patients were included in the statistical analysis, and the pharmacokinetic results showed no significant statistical differences between Clozaril and generic clozapine (Creighton). The areas under the drug concentration–time curve were comparable between products and both tablet strengths (four 25-mg tablets and one 100-mg tablet) of generic clozapine were bioequivalent to Clozaril, 100 mg, justifying their interchangeable use (Table 2).[4] Demonstrations of comparable maximum plasma drug levels and tolerability profiles between Clozaril and clozapine (Creighton) provided additional support for the efficacy, as well as the tolerability, of either drug product in clinical use.

CONCLUSION

Because of differences in tolerability, bioequivalence and pharmacokinetic studies of antipsychotics should be performed in schizophrenic patients rather than in healthy volunteers. The half-life of clozapine increases with multiple doses; thus, bioequivalence and pharmacokinetic studies of clozapine should be carried out in real-life dosage conditions, and subjects should be carefully monitored. In the bioequivalence study[4] of Clozaril versus ge-

neric clozapine (Creighton), the evaluation of multiple doses of clozapine in the schizophrenic population provided direct therapeutic relevance to bioavailability findings. Both tablet strengths (four 25-mg tablets and one 100-mg tablet) of generic clozapine were bioequivalent to Clozaril, 100 mg, justifying their interchangeable use.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others).

REFERENCES

1. Lester H, Wilson S. Practical problems in recruiting patients with schizophrenia into randomized controlled trials [letter]. BMJ 1999;318:1075
2. Carpenter WT Jr, Gold JM, Lahti AC, et al. Decisional capacity for informed consent in schizophrenia research. Arch Gen Psychiatry 2000;57:533–538
3. Wirshing DA, Wirshing WC, Marder SR, et al. Informed consent: assessment of comprehension. Am J Psychiatry 1998;155:1508–1511
4. Sramek JJ, Anand R, Hartman RD, et al. A bioequivalence study of brand and generic clozapine in patients with schizophrenia. Clin Drug Invest 1999;17:51–58
5. Miller AL, Maas JW, Contreras A, et al. Acute effects of neuroleptics on unmedicated schizophrenic patients and controls. Biol Psychiatry 1993;34:178–187
6. Okuma T. Differential sensitivity to the effects of psychotropic drugs: psychotics vs normals; Asian vs Western populations. Folia Psychiatr Neurol 1981;35:79–87
7. Farde L, Wiesel FA, Hall H, et al. No D_2 receptor increase in PET study of schizophrenia. Arch Gen Psychiatry 1987;44:671–672
8. Sramek JJ, Fresquet A, Marion-Landais G, et al. Establishing the maximum tolerated dose of lesopitron in patients with generalized anxiety disorder: a bridging study. J Clin Psychopharmacol 1996;16:454–458
9. Grof P, Akhter MI, Campbell M, et al, eds. Clinical Evaluation of Psychotropic Drugs for Psychiatric Disorders: Principles and Proposed Guidelines. Seattle, Wash: Hogrefe & Huber; 1993
10. Sramek JJ, Hurley DJ, Wardle TS, et al. The safety and tolerance of xanomeline tartrate in patients with Alzheimer's disease. J Clin Pharmacol 1995;35:800–806
11. Haldol (haloperidol). Physicians' Desk Reference. Montvale, NJ: Medical Economics. 2000:2153–2155
12. Pokorny R, Finkel MJ, Robinson WT. Normal volunteers should not be used for bioavailability or bioequivalence studies of clozapine [letter]. Pharm Res 1994;11:1221
13. Food and Drug Administration. FDA Update on Clozapine Guidelines. Rockville, Md: 1996
14. Haring C, Meise U, Humpel A, et al. Dose-related plasma levels of clozapine: influence of smoking behavior, sex, and age. Psychopharmacology (Berl) 1989;99(suppl):S38–S40
15. Potkin SG, Bera R, Gulasekaram B, et al. Plasma clozapine concentrations predict clinical response in treatment-resistant schizophrenia. J Clin Psychiatry 1994;55(9, suppl B):133–136
16. Perry PJ, Miller DD, Arndt SV, et al. Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenic patients. Am J Psychiatry 1991;48:231–235
17. VanderZwaag C, McGee M, McEvoy JP, et al. Response of patients with treatment-refractory schizophrenia to clozapine within three serum level ranges. Am J Psychiatry 1996;153:1579–1584
18. A Drug Review Glossary. US Food and Drug Administration Web site. Available at: http://www.fda.gov/fdac/special/newdrug/bengloss.html. Accessed August 15, 2000
19. Choc MG, Hsuan F, Honigfeld G, et al. Single- vs multiple-dose pharmacokinetics of clozapine in psychiatric patients. Pharm Res 1990;7:347–351