Discussion

Comparison of the Bioequivalence of Generic Versus Branded Clozapine

Dr. Meyer: How does the evidence presented today speak to the issues of bioavailability, bioequivalence, and interchangeability for clozapine? Are we convinced that there is no problem whatsoever with the 100-mg tablet of the generic product?

Dr. Lam: I think the reverse is true.

Dr. Glazer: The signal that is emerging from the available studies gives us reason for concern. In your study, Dr. Kluznik, the mean daily dosage for the generic was actually a little higher and the mean serum concentration was about 10% lower than that for Clozaril. This needs to be investigated.

Dr. Price: I supervise one extended care facility that has a high number of psychiatric patients. In July 1999, all the residents who were being treated with Clozaril (somewhere between 25 and 30) were switched to generic clozapine. Within 6 months, 8 patients had relapsed and required inpatient hospitalization totaling 100 patient days.

Anecdotally, I could describe several other facilities where the switch to the generic product was made by the pharmacy. For example, I was treating one refractory patient with severe schizophrenia who had been on multiple medications. Gradually, I tapered him off the regimen and he became stabilized on Clozaril alone. After he was switched to generic clozapine, he decompensated and remained so until he was returned to Clozaril.

Dr. Kluznik: What was the timing for relapse in your group of elderly patients?

Dr. Price: The first patient relapsed within a week. Some of the other relapses occurred months later. Most, but not all, of these patients were geriatric.

Dr. Mofsen: In one of the residential facilities that I attend, the pharmacist switched from branded to generic clozapine unbeknownst to me or the director of nursing. When I made my rounds, the director of nursing pointed out that 6 of the 23 clozapine-treated patients were decompensating (2 had to be hospitalized). Fortunately, I noticed that their tablets had been changed from Clozaril to generic clozapine. They resumed Clozaril treatment, and 6 of the 8 stabilized. Unfortunately, 2 patients never returned to their baseline status.

Dr. Meyer: As a specialist in biopharmaceutics, I am concerned about the lack of adherence to normal U.S. Food and Drug Administration (FDA) standards in the bioequivalence studies submitted as part of the Abbreviated New Drug Applications (ANDA) for clozapine. Generally, the FDA requires bioequivalence studies of the highest strength dose of a product, but, for generic clozapine, a waiver was granted to allow studies of a 12.5-mg dose, the smallest tablet cut in half. The waiver was granted on the basis of in vitro dissolution findings, but the strength of ingredients in the 25-mg and 100-mg dose may not be exactly proportional. Clinically, it appears as if the amount of anecdotal evidence of problems with interchangeability is growing.

Dr. Lam: Interchangeability can be an issue in a switch from Clozaril to generic clozapine, from one generic product to another, or from generic clozapine to Clozaril.

Dr. Meyer: We know that the 100-mg generic product was approved in an unconventional manner and we have seen preliminary results from a clinical study (Lam et al. in this supplement) that suggests there may be a difference in the absorption between Clozaril and generic clozapine. However, we are unable to conduct bioequivalence studies of the 100-mg formulation in healthy, young volunteers. Several clinicians here today have provided anecdotal evidence about symptomatology in patients who are switched from Clozaril to generic clozapine. We need a well-designed clinical study.

Dr. Cutler: We know, for certain, that a study using the 100-mg tablet should be performed and such a study could only be performed in patients.

Dr. Lam: Such a study will be difficult to conduct. It can take up to 6 months to see a statistical difference between the patient groups because it takes that long for a patient to relapse and restabilize. Area under the curve (AUC) data that are derived over such a long time period could be suspect. However, a brief study in institutionalized patients will not address the issues we are concerned about.

Dr. Meyer: A 2-way crossover study, similar to the one you just completed, would provide rate of absorption (C_{max}) and AUC data. If the AUC and C_{max} for the 2 formulations remain similar, my level of comfort would increase.

Dr. Lam: How would you differentiate between the pharmacokinetic data and the response data?

Dr. Meyer: I believe that response follows kinetics. If the kinetics are interchangeable, the response should be interchangeable. I would not worry about a 10% differ-

ence in the AUC data. If a patient is unstable, the clinician is generally going to change the dose by at least 12.5 mg (one half of a 25-mg tablet).

Dr. Glazer: What about comparing 2 groups of hospitalized patients who are treated with Clozaril or generic clozapine from day 1? After several weeks, they could be discharged to supervised settings (each subject would need a caregiver). They could receive follow-up assessments every 6 months. Patients with schizophrenia tend to decompensate at a certain rate, so this design would provide some comparative data.

Dr. Meyer: Of course, we are talking about a protocol that requires multiple dosings followed by long-term monitoring. There may already be data available that could be used to estimate the expected rate of relapse for patients stabilized on Clozaril. Such baseline data could be valuable in interpreting reports of patient failures after switching from Clozaril to a generic clozapine.

Dr. Kluznik: I have not found reports of spontaneous relapse in patients who have been maintained on Clozaril therapy for long periods of time.

Dr. Meyer: What don't we know about the bioequivalence of Clozaril and generic clozapine?

Dr. Glazer: We don't know why there is such a consistent and striking difference between tolerable doses of clozapine in healthy subjects versus patients with schizophrenia. I think this question is extremely important. Dr. Cutler's presentation questions the validity of bioequivalence studies of antipsychotics in healthy patients.

Dr. Meyer: We don't know if there is a physiologic difference between a patient with schizophrenia and a healthy volunteer.

Dr. Lam: Even though we do not understand the dynamic difference between the healthy subject and the patient with schizophrenia, Dr. Cutler's presentation emphasizes the point that bioequivalence investigations of antipsychotics should be multiple-dose, steady-state studies in patients with schizophrenia, but most of the research involves single-dose studies in healthy volunteers.

Dr. Meyer: On another subject, what have we learned about cost-effectiveness evaluations from the studies we have discussed today? Dr. Kluznik suggested the cost savings in switching 45 patients to generic clozapine was offset by the additional costs incurred in hospitalizing the single patient who relapsed.

Dr. Lam: We need additional data. The Zenith Goldline generic product is considerably less expensive than Clozaril, and the Mylan product is expected to cost about 10% less than the Zenith Goldline formulation.

Dr. Glazer: North Carolina made the switch to generic clozapine in a carefully planned, sequenced manner. Texas, on the other hand, has decided to continue Clozaril (brand) treatment in stable patients and to encourage clinicians not to switch their patients to generic forms.

Dr. Price: I think it comes down to the pay-me-now or pay-me-later phenomenon. When patients begin to decompensate, we start increasing the use of adjunct medications. Then, of course, the need for hospitalization adds to the expense. I don't think the cost savings will be large.

We also have to factor in the cost of human suffering. How many of these patient's lives have been irreparably damaged because of a switch from Clozaril to generic clozapine? One of my patients was ready for occupational training in computers when he relapsed during a switch.

Dr. Kluznik: According to my findings, the switch to generic clozapine is not cost effective in the short term. In my facility, the pharmacy would save $100,000 per year if every Clozaril-treated patient were switched to generic clozapine. But we lost that $100,000 savings last year when a single patient relapsed and had to be hospitalized for an additional year. We have 2 other relapsing patients who may or may not recover full capacity and be discharged.

Dr. Meyer: Once a patient with schizophrenia decompensates, he or she may not return to baseline, even after treatment is resumed. With other illnesses, patients generally respond to treatment.

Dr. Price: It may have taken 4 or 5 years of Clozaril treatment for some of these patients to reach a functional level. If they decompensate, it may take another 4 or 5 years to return them to baseline status.

Dr. Meyer: Here is where some historical data would be helpful. What percentage of Clozaril-treated patients decompensate per month? Our dilemma is to try to ferret out a failure of a drug product versus a failure of therapy in a particular patient, which is extremely difficult.

Dr. Glazer: The reports we have heard today indicate that 10% of the patients who are switched from Clozaril to generic clozapine will have problems. The take-home message today is procedures must be established for switching patients from Clozaril to generic clozapine. These procedures should include monitoring blood clozapine levels for 6 to 12 weeks after such a switch. It should not be acceptable for the pharmacy to switch formulations in the dispensary without informing the staff. The clinical staff should create a protocol for educating patients and staff. This is the approach that was used in North Carolina, where the switch to a generic product was made successfully.

Dr. Kluznik: Perhaps an extra neuroleptic is temporarily needed to bridge the transition, if the switch is abrupt.

Dr. Glazer: Abrupt switches should be avoided.

Dr. Meyer: We know numbers have power. We have heard several anecdotal reports here today as well as presentations from 2 clinical studies. Perhaps the data from different sites and investigators should be gathered and examined. Then the results could be published.