Letter to the Editor

Normal Volunteers Should Not Be Used for Bioavailability or Bioequivalence Studies of Clozapine

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As a general rule, normal volunteers given dopamine-blocking antipsychotic agents experience significant adverse events at dose levels that are tolerated by the majority of patients with schizophrenia. This is true as well for clozapine.

In a bioequivalence study we observed cardiac arrest in 2 of 17 normal young male volunteers (12%) after a single 25 mg oral dose of clozapine. In contrast, syncope accompanied by cardiac and/or respiratory arrest after an initial (or second) dose of 25 mg of clozaril ('first dose phenomenon') has been reported in only 1 per 300 patients with treatment-resistant (i.e., resistant to standard neuroleptics) schizophrenia (0.3%), an incidence probably very close to the actual incidence because of the monitoring system under which patients receive clozapine.[1]

The clozapine bioequivalence study in normal subjects involved 8 who had been pretreated with 1 gram per day of vitamin C for 13 days and 9 who had not. A single 25 mg dose of clozapine was given in the fasted state on day 14. Orthostatic hypotension (lowest value 60/29 mmHg) occurred in 10 subjects (5 on vitamin C and 5 without), and severe bradycardia (below 40 beats per minute) in 8 (5 on clozapine and 3 on clozapine plus vitamin C). The cardiac arrest seen in two subjects (one on vitamin C and one without vitamin C) lasted 10 and 60 seconds, respectively. In the former case restoration of normal sinus rhythm occurred spontaneously; in the latter it followed a chest thump. The orthostatic hypotension and bradycardia were observed between approximately 1 and 4 hours after administration of clozapine. Blood pressure and pulse rates recovered within 5 minutes after placing the subjects in the Trendelenburg position. The cardiac arrests occurred approximately 2 hours after drug administration. Because of the adverse events the study was terminated before subjects could be crossed over to the opposite regimen. Nevertheless, it can be concluded that vitamin C had no apparent effect on the bioavailability of clozapine. Furthermore, the adverse events did not correlate with C_{max} of clozapine or weight of the subjects.

Clozapine is commonly associated with tachycardia but bradycardia has been reported only very rarely in patients and it has not previously been reported in normal volunteers. Hypotension is seen in about 9% of patients (compared with 59% in our normal volunteers).

We are aware of only two other bioavailability studies with clozapine conducted in normal volunteers. One involved 6 subjects who received 50 mg clozapine-^{14}C as an oral solution.[2] Although lightheadedness occurred, none of the subjects experienced the severe events reported above. Despite the higher dose, plasma AUC and C_{max} levels were similar to those noted in the aforementioned study. The other study by Salt *et al.* consisted of a pharmacodynamic comparison between another neuroleptic and clozapine as a reference compound.[3] No serious adverse events were described. Although blood levels of the other neuroleptic were reported elsewhere, blood levels of clozapine were not determined. This was a double blind study and it is possible that the bioavailability may have been altered in preparing the blinded medication.

Because of the potential for serious adverse events in normal volunteers given clozapine, we recommend that bioavailability and bioequivalence studies be performed in patients with treatment-resistant schizophrenia. We have specified treatment-resistant schizophrenia because we have no data on whether patients responsive to standard neuroleptics would experience the cardiovascular effects noted in normal volunteers.

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