Population Pharmacokinetics of Didanosine in Patients with Human Immunodeficiency Virus Infection

To the Editor—We read with interest the results of Grasela et al. [1], who discussed the potential clinical utility of monitoring didanosine (ddI) serum levels during therapy in order to optimize efficacy and prevent life-threatening pancreatic toxicity [1]. Of particular interest was the considerable degree of interindividual and intraindividual variability in ddI pharmacokinetics they noted. Previous studies have suggested that changes in bioavailability over time may account for much of the intraindividual variability [2].

We have evaluated the pharmacokinetics of ddI in patients with advanced AIDS. In brief, eligible patients had human immunodeficiency virus (HIV) disease and were receiving ddI in accord with one of two expanded access protocols at the University of California San Francisco AIDS Clinical Research Center between March 1990 and November 1991 [3, 4]. Patients with HIV disease were eligible for the expanded access protocols if they had received ≥500 mg of zidovudine per day for ≥6 months and had objective evidence of clinical deterioration or zidovudine intolerance. Patients were excluded if they were receiving antiretroviral therapy other than zidovudine, had a malignancy necessitating systemic chemotherapy within the coming 3 months, had a history of acute pancreatitis, required concomitant phenytoin, had a poorly controlled seizure disorder, had peripheral neuropathy, or were pregnant or breast-feeding.

All patients received 250 or 375 mg of ddI orally every 12 h in a sachet formulation. This formulation was provided as a sterile powder containing a phosphate-citrate buffer and was reconstituted by the patients before ingestion. Blood samples were obtained during the regularly scheduled clinic visits for drug level measurements. Serum drug concentrations were measured by high-performance liquid chromatography [5]. Pharmacokinetic analysis was done with the NONMEM computer program developed for population analysis [6]. The plasma concentrations of ddI were fitted by a one-compartment model with first-order absorption and elimination.

A total of 66 serum drug concentrations from 30 enrolled patients were available for pharmacokinetic analysis. The period between successive concentration measurements for a patient was long (7–212 days). The means ± SEs of the oral clearance (CL), volume of distribution (VD), and absorption rate constant were 238 ± 15 L/h, 438 ± 65 L, and 1.21 ± 0.50/h, respectively. The plasma half-life was 1.3 h. We observed large (50%) residual CL variability, which is a combination of intraindividual and measurement variability. This variability was significantly larger than the 12% interindividual CL variability we observed. Of particular interest was the larger VD we found compared with that reported by others [5, 7–9]. None of the covariates, including age, weight, height, CD4 lymphocyte count, serum creatinine, serum uric acid, dosage, and time since enrollment significantly influenced the pharmacokinetic parameters. The large intraindividual variability observed was not likely to be secondary to assay variability (<10%) but was most likely due to between-occasion variability within 1 individual. The individual pharmacokinetics may have changed considerably over the long periods in this study because of ongoing changes in disease severity and numerous changes in concomitant drug therapy. This observation along with the finding of a larger VD makes the prediction of ddI pharmacokinetics in an individual patient very difficult. We agree with Grasela et al. [1] that more pharmacokinetic work needs to be done on ddI to determine whether monitoring of plasma levels might be a useful adjunct to optimize use of the drug.

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References

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