Evaluation of Bayesian Estimation in Comparison to NONMEM for Population Pharmacokinetic Data Analysis: Application to Pefloxacin in Intensive Care Unit Patients

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The pharmacokinetics of pefloxacin (PF) were investigated in a population of 74 intensive care unit patients receiving 400 mg bid as 1-hr infusion using (i) Bayesian estimation (BE) of individual patient parameters followed by multiple linear regression (MLR) analysis and (ii) NONMEM analysis. The data consisted of 3 to 9 PF plasma levels per patient measured over 1 to 3 dosage intervals (total 113) according to four different limited (suboptimal) sampling 3-point protocols. Twenty-nine covariates (including 15 comedication) were considered to explain the interpatient variability. Predicted PF CL for a patient with median covariate values was similar in both BE/MLR and NONMEM analysis (4.02 and 3.92 L/hr, respectively). Bilirubin level and age were identified as the major determinants of PF CL by both approaches with similar predicted magnitude.


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of effects (about 40 and 30% decrease of median CL, respectively). Confounding effects were observed between creatinine clearance (26% decrease of PF CL in the BE/MLR model), simplified acute physiology score (a global score based on 14 biological and clinical variables) (18% decrease of median CL in the NONMEM model) and age (entered in both models) which were highly correlated in our database. However, both models predicted similar PF CL for actual subpopulations by using actual covariate values. Finally, the NONMEM analysis allowed identification of an effect of weight on CL (decrease of CL for weight < 65 kg) whereas the BE/MLR analysis predicted an increase of CL in patients treated with phenobarbital. In conclusion, both approaches allowed identification of the major risk factors of PF pharmacokinetics in ICU patients. Their potential use at different stages of drug development is discussed.

KEY WORDS: pefloxacin; population pharmacokinetics; intensive care unit; Bayesian estimation; NONMEM.

INTRODUCTION

The use of observational data obtained in patients during premarketing clinical trials (pharmacokinetic screen) coupled with population pharmacokinetic/pharmacodynamic analysis (1-3) has been advocated by regulatory agency employees (4,5) to assess the pharmacokinetic/pharmacodynamic variability in the target patient population, identify subpopulations at risk, and therefore contribute to the design of optimal dosage regimens. However, the feasibility and the place of this population approach during drug development are still controversial (6-8). This subject is receiving a great deal of attention by the pharmaceutical industry as evidenced by a survey recently presented at the Manchester Conference (9). The main difficulties are related to the reliability of the individual data collected in clinical trials and the data analysis.

The current reference approach for population data analysis involves mixed-effect modeling as implemented in the NONMEM software (10). Other methods are currently being investigated including nonparametric maximum likelihood and Bayesian methods (11). In a previous retrospective study using experimental data on pefloxacin (12) we showed the ability of Bayesian estimation (BE) to estimate altered pharmacokinetics in subpopulations using fragmentary data and a priori information from healthy volunteers. In the present work we have further evaluated BE in processing population data issued from a prospective study of pefloxacin (PF), a broad-spectrum antibacterial agent of the quinolone group effective in severe systemic infections (13), administered to intensive care unit (ICU) patients. Population parameter estimates (and their relationship to physiological covariates) were obtained using two approaches: (i) BE of individual patient parameters associated with a subsequent second stage statistical analysis of their variability (principal component analysis and multiple linear regression) and (ii) NONMEM analysis. The results obtained are compared and the potential of BE with respect to NONMEM is discussed.