How to Obtain Robust Dose-Response Relationships in Clinical Trials with Dose-Titration Design: Barnidipine Trial in Patients with Renal Parenchymal Hypertension

KS Yu, KS Bae, W Huh[1], IJ Jang, SG Shin,
CW Park, JS Han[1], S Kim[1], DS Han[2], JS Park[3]

Dept. of Pharmacol. and Clin. Pharmacol. Unit, and Dept. of Internal Med., Seoul Nat'l Univ.[1], Yonsei Univ.[2], and Univ. of Ulsan College of Medicine

Barnidipine is a potent and long-acting dihydropyridine calcium channel blocker. The effectiveness and safety of barnidipine for the treatment of renal parenchymal hypertension were evaluated in 70 patients. The study was done as placebo run-in (2 weeks) and dose titration manner. Treatment period started with barnidipine 5 mg q.d. for 2 weeks. If the treatment goal (decrease in systolic BP>20 mmHg or diastolic BP>10 mmHg) or normalization of BP was not attained, the dose of barnidipine was escalated to 10 or 15mg at 2 week intervals. Dose-response data was analyzed with NONMEM using linear and E_{max} PD model. GAM (generalized additive modeling) was used for finding significant covariates. The bootstrap method was used for validation of standard errors of parameters. Monte Carlo simulation using SAS was done to set confidence intervals for response (BP) from estimated parameters.

Among the 52 subjects who completed the study, 18 patients were maintained at 5 mg, 22 patients were escalated to 10 mg, and 12 patients to 15 mg of barnidipine. There were no significant changes in HR, renal function, daily urinary protein/sodium excretion, serum renin, aldosterone, electrolyte, uric acid and LFT. Blood pressure was effectively reduced in 84% of the patients. GAM results showed sCr (serum creatinine) and history of previous treatment to be significant, but only sCr was shown to be significant during model building with NONMEM. Dose-response modeling for diastolic BP revealed a linear model with slope value of 1.68 - 0.131 $\times$sCr mmHg/mg (interindividual variance of 0.174) and E_0 of 101 mmHg (interindividual variance 39.9). Diastolic BP was also explainable by an E_{max} model with E_{max} value of 33.3 - 2.46$\times$sCr, E_0 of 101 mmHg (interindividual variance 39.4), and ED_{50} of 11.5. Bootstrap resampling procedure was used to create 200 synthetic data sets, and NONMEM runs were done for each data set. Standard errors of the parameters were almost the same with those of the original NONMEM output, validating the parameter estimates.

Overall, the dose-response relationship could be reasonably explained by both linear and E_{max} models; the linear model was better regarding parameter SEs; the E_{max} model was better regarding MVO (minimum value of objective function).