[S3-1] [4/18/2003(Fri) 09:30-10:10/Grand Hall]

# Population Pharmacokinetic Characteristics of Levosulpiride and Terbinafine in Healthy Male Korean Volunteers

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The purposes of this study were to evaluate the population pharmacokinetics of levosulpiride and terbinafine according to several pharmacokinetic models and to investigate the influence of characteristics of subjects such as age, body weight, height and serum creatinine concentration on the pharmacokinetic parameters of levosulpiride and terbinafine, respectively.

Serum levosulpiride and terbinafine data from 192 and 73 healthy male Korean subjects were used for this analysis, respectively. After overnight fast, each subject received a single 25 mg oral dose of levosulpiride or a single 125 mg oral dose of terbinafine. Serum concentrations of levosulpiride and terbinafine were measured using HPLC with fluorescence detector and UV detector, respectively. Several pharmacokinetic models were fitted to the levosulpiride and terbinafine data using WinNonlin and NONMEM.

One-compartment model with lag time was fitted well to the levosulpiride data using WinNonlin. In STS method, population mean of Vc/F, $K_a$, $K_{el}$, and $T_{lag}$ were $5.03\times10^5$ ml, .0963 $hr^{-1}$, 0.0768 $hr^{-1}$ and 0.43 hr, respectively. And there were significant relationships between body weight and Cl/F ($r=0.294$, $p<0.01$), body weight and Vc/F ($r=0.276$, $p<0.01$), height and $K_{el}$ ($r=0.161$, $p<0.05$). In one-compartment covariate model as built by NONMEM, population mean of Vc/F, $K_a$, $K_{el}$, and $T_{lag}$ could be obtained (Table 1 and Figure 1).

Two-compartment model with lag time was fitted to the terbinafine data using NONMEM. Population mean Cl/F, $V_c$/F, $K_a$, $V_p$/F, Q/F and $T_{lag}$ were $5.20\times10^4$ ml/hr, $1.22\times10^4$ ml, 0.50 $hr^{-1}$, $4.39\times10^5$ ml, $2.55\times10^4$ ml/hr and 0.43 hr, respectively. Intersubject coefficient of variation (CV) ranged from 13.25 to 41.37% and residual intrasubject CV was 34.43%. A two-compartment

model with lag time was well fitted to the terbinafine data, and there were no influences of age, body weight, height and serum creatinine concentration on fitting (Table 2 and Figure 2).

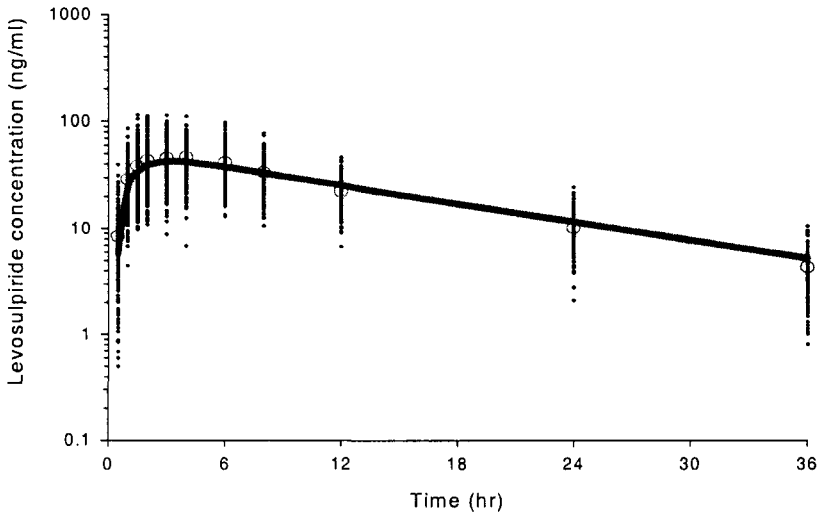


**Figure 1.** The plot showing the comparison of predictied levosulpiride concentrations between STS method and NONMEM.
Keys: +; individual levosulpiride observations, —; predicted concentration obtained by NONMEM, 0 ; predicted mean concentration at each time by STS method.

**Table 1.** Population pharmacokinetic parameter estimates of levosulpiride using NONMEM.

| Population parameter | Estimate | Intersubject variability (CV%) | Intrasubject variability (CV%) |
|---|---|---|---|
| Cl/F (㎖/hr) | 32100 | 27.60 | 24.31 |
| $V_c$/F (㎖) | 7290×weight | 35.07 | |
| $K_a$ ($hr^{-1}$) | 1.05 | 67.01 | |
| $T_{lag}$ (hr) | 0.39 | 35.78 | |

**Table 2.** Population pharmacokinetic parameter estimates of terbinafine using NONMEM.

| Population parameter | estimate | Intersubject variability (CV%) | Intrasubject variability (CV%) |
|---|---|---|---|
| CL/F (ml /hr) | 52000 | 21.43 | |
| $V_c$/F (ml) | 12200 | - | |
| $K_a$ ($hr^{-1}$) | 0.50 | 24.00 | 34.43 |
| $V_p$/F (ml) | 439000 | 41.37 | |
| Q/F (ml /hr) | 25500 | - | |
| $T_{lag}$ (hr) | 0.43 | 13.25 | |

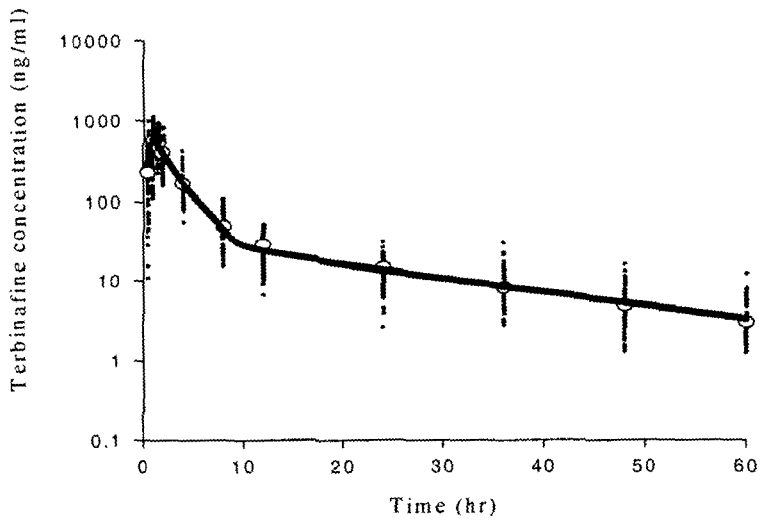


**Figure 2.** The plot showing the comparison of predictied terbinafine concentrations between STS method and NONMEM.
*Keys:* +; *individual terbinafine* observations, —; predicted concentration obtained by NONMEM, 0 ; predicted mean concentration at each time by STS method.

## References


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2. Pharsight Corp. WinNonlin Users Guide Ver. 3.0, 1998-1999.

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## Acknowledgments

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