**Introduction**

- Ivabradine, a selective inhibitor of the pacemaker current (If), is used for heart failure and coronary heart disease, and mainly metabolized by cytochrome P450 3A enzyme to S1898, an active metabolite.
- The purpose of this study was to explore the plasma and urine pharmacokinetics (PK) of ivabradine and S18982 by nonlinear mixed effect modeling in healthy Korean volunteers.

**Method**

- PK data from a phase I clinical trial for ivabradine where 35 healthy, Korean, adult males participated were used for this modeling analysis.
- The subjects received single and then multiple oral doses of Ivabradine at 2.5 (n=17), 5 (n=9), and 10 mg (n=9), and blood and urine were collected serially for PK.
- Plasma and urine concentrations of ivabradine and S18982 were measured using validated LC/MS-MS.
- Plasma and urine PK of ivabradine and S18982 were analyzed by nonlinear mixed effect modeling implemented in NONMEM (version 7.3).

**Result**

- The plasma PK of ivabradine was best described by a two-compartment model with mixed zero- and first-order absorption, linked to a two-compartment model for S18982.
- The final PK model described plasma concentration and cumulative amount excreted urine of ivabradine and S18982, reasonably well.
- The introduction of inter-occasional variabilities and period as covariate into absorption related parameters improved the model fit.

**Conclusion**

- We developed a population PK model describing the plasma and urine PK of ivabradine and S18982 in healthy Korean adult males.
- This model might be useful for predicting the plasma and urine PK of ivabradine, potentially helping to identify the optimal dosing regimens in various clinical situations.

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