Poster

[P25-1] P25-1: Anti-infective drugs (1): Aminoglycosides and beta-lactams

Chair: Andrew McLachlan, Australia

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[P25-1-8] Highly variable absorption of clavulanic acid during the day: a population pharmacokinetic analysis

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Background

Clavulanic acid is a beta-lactamase inhibitor used in combination with beta-lactam antibiotics to target beta-lactamase-producing strains. Several non-compartmental PK studies showed highly variable pharmacokinetics for oral clavulanic acid, but a population PK model is not available in literature. We developed a population PK model to explore the variability of clavulanic acid exposure after oral administration of amoxicillin/clavulanic acid and determined target attainment using Monte Carlo simulations for both fAUC and %fT>Ct (% of dosing interval that the unbound concentration exceeds a threshold concentration), because the PD target is still unknown.

Methods

Two groups of healthy male volunteers received amoxicillin/clavulanic acid tablets at the start of a standard meal on two separate days one week apart. One group (n=14) received 875/125 mg BID and 500/125 mg TID; the other group (n=15) 500/125 mg BID and 250/125 mg TID. 1479 blood samples were collected until 8-12 h after administration. Concentrations were analysed using non-compartmental (WinNonLin) and population pharmacokinetic methods (NONMEM 7.2).

Results

Median C_{max} and AUC_{0-8} were 2.21 mg/L (0.21-4.35) and 4.99 mg*h/L (0.44-8.31), respectively. In 40/58 daily concentration-time profiles, C_{max} and AUC_{0-8} of the morning dose were higher than later doses. Population pharmacokinetics was best described by the following parameters, between-subject variability (BSV, %CV), between-occasion variability (BOV, %CV): lag time (0.447 h), first-order absorption (3.99 h^{-1} at 8:00h, BSV 52.8%, BOV 48.5%), one distribution compartment (33.0 L, BSV 23.9%) and first-order elimination (24.6 L/h, BSV 26.7%). Compared to dosing at 8:00h, the absorption rate decreased by 9.70% (16:00h), 39.0% (20:00h) and 36.4% (24:00h). Bioavailability (BOV 28.2%) was fixed to 1 at 8:00h and decreased to 0.873 (16:00h), 0.799 (20:00h) and 0.801 (24:00h). Target attainment for 97.5% of the population after 125 mg BID or TID was %fT>Ct at 0.5 mg/L 12.5% (BID) and 19.6% (TID), at 1 mg/L 2.2% (TID), $fAUC_{0-24}$ 4.07 (BID) and 6.15 (TID) mg*h/L.

Conclusions

Clavulanic acid pharmacokinetics in healthy volunteers is highly variable. Bioavailability and absorption rate decreases over the day. The model developed may serve to suggest dosing regimens of clavulanic acid to optimize efficacy and prevent underdosing.

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