Temocillin pharmacokinetics in healthy volunteers

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Introduction and purpose

Facing the increasing prevalence of Gram-negative multidrug resistance, the penicillin antibiotic temocillin (TMO) has recently been re-evaluated as a therapeutic option. Among the current and future indications of this compound are wound infections and soft tissue infections. To date, pharmacokinetics (PK) of TMO in soft tissues have not been investigated. This microdialysis study was designed to describe PK of TMO in plasma, muscle and subcutis of healthy volunteers. Given that the subcutaneous route of administration might be of interest in selected populations, healthy volunteers were randomized to receive TMO both intravenously (iv) and subcutaneously (sc) in a crossover fashion.

Methods

Eight (8) male healthy volunteers (mean ± SD age and body mass index, 32.9 ± 12.1 years and 24.4 ± 12.9 kg/m², respectively) underwent two study periods separated by a wash-out phase of at least three days in a crossover fashion. In the first study period, healthy volunteers received 2 g of TMO both intravenously (iv) and subcutaneously (sc) over 40 minutes. In both study periods, total TMO concentrations in plasma were measured up to 12 hours post-dose. In addition, only after iv administration, unbound TMO concentrations were directly measured in plasma, muscle and subcutaneous adipose tissue of healthy volunteers by means of microdialysis (figure 1) at defined time points up to 10 hours after dosing. TMO concentrations were assayed by a validated HPLC-MS/MS method (Clin Biochem, 2015 May;48(7-8):542-5).

Results

TMO was well tolerated after iv dosing. During sc infusion, pain (25%), burning sensation (50%) and heat sensation (7,2%) at the infusion site were reported, all of mild intensity and strictly limited to the time of sc infusion. Also, one case of circumscript hypaesthesia (mild, duration 5 months) and one case of tenderness (mild, duration 3 months) at the infusion site occurred after sc dosing. Concentration-time profiles of TMO in different compartments after iv and sc dosing are shown in figure 2. Compared to iv infusion, sc dosing produced a slower and less pronounced increase in total TMO in plasma. The AUC0-12h of TMO after sc dosing amounted to 818.1 ± 90.3 mg·h/L corresponding to 86.6 ± 10.0 % (range 70.1 - 100.9 %) of the value after iv administration (959.2 ± 185.0 mg·h/L). As for soft tissues, subcutaneous concentrations were generally higher than the expected unbound drug level over time. The AUC0-12h of TMO in plasma after iv dosing amounted to 818.1 ± 90.3 mg·h/L in muscle (11.5 ± 3.4 % of total drug in plasma). Key PK parameters of TMO in the investigated compartments are summarized in table 1.

Conclusion

This study is the first describing plasma and soft tissue PK of TMO after iv and sc administration. In spite of mild local discomfort mostly limited to the time of infusion, sc infusion might represent a valid treatment option. Unbound soft tissue concentrations measured by microdialysis were only slightly below (muscle) or even higher (subcutis) than the expected unbound fraction in plasma (13% according to SmPC).

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