MEDICAL UNIVERSITY OF VIENNA

Temocillin pharmacokinetics in healthy volunteers

P Matzneller[1], P Ngougni Pokem[2], A Capron[3], F Van Bambeke[2], M Zeitlinger[1]

[1]Department of Clinical Pharmacology, Medical University of Vienna, Austria
[2]Pharmacologie cellulaire et moléculaire, Université catholique de Louvain, Brussels, Belgium;
[3]Clinical Chemistry Department, Cliniques Universitaires St. Luc, Université catholique de Louvain, Brussels, Belgium

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/m^2, respectively) underwent two study periods separated by a wash-out phase of at least three days in a sequence determined by randomization. In the first study period, subjects received **2 g of TMO as iv infusion over 40 minutes**. In the second study period, **2 g of TMO** (together with 0.5% lidocaine, total infusion volume approximately 4.3 mL) were administered as **sc infusion over 20 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 **muscle** and **subcutis** 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).

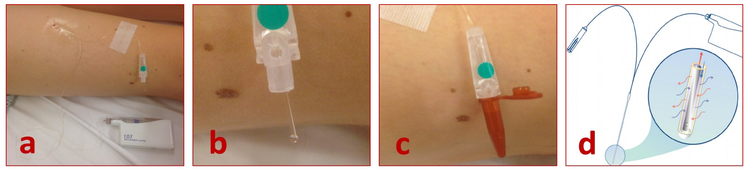

FIGURE 1 Microdialysis. **1a-c** are pictures of a microdialysis probe inserted into soft tissue of a healthy subject's thigh. The probe is continuously perfused by means of a portable precision pump connected to the inlet tubing (**a**). The fluid leaving the outlet tubing (**b**) is collected by means of sampling vials attached to the tubing (**c**). For the present study, two **63 Microdialysis Catheters** (M Dialysis, Sweden) with a molecular weight cut-off of **20 kDa** and a membrane length of **10 mm** were used. **1d** shows a schematic illustration of a microdialysis system.

Results

TMO was **well tolerated** after **iv** dosing. During **sc** infusion, **pain** (25%), **burning** sensation (50%) and **heat** sensation (12,5%) 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 of total TMO in plasma, compensated by sustained drug levels over time. The **$AUC_{0\text{-}12h}$** 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, **subcutis** showed a slightly **higher** exposure to unbound drug as denoted by a calculated $AUC_{0\text{-}12h}$ of 179.3 ± 55.2 mg·h/L (**18.9 ± 5.8 % of total TMO in plasma**) compared to 108.9 ± 30.5 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.

	After iv dosing						After sc dosing	
	PLASMA		MUSCLE		SUBCUTIS		PLASMA	
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
C_{max} (mg/L)	**233.5**	50.2	**20.6**	6.8	**34.1**	14.6	**100.0**	15.5
T_{max} (h)	**0.7**	0.0	**1.8**	0.5	**1.8**	0.5	**4.8**	2.0
$AUC_{0\text{-}12h}$ (mg·h/L)	**959.2**	185.0	**108.9***	30.5*	**179.3***	55.2*	**818.1**	90.3
t/2 (h)	**5.8**	1.2	**7.7**	5.1	**6.1**	3.0	**7.2**	1.9
Cl (L/h)	**1.1**	0.3					**2.1**	0.5
V_D (L/kg)	**0.11**	0.02					**0.25**	0.02

TABLE 1 Key pharmacokinetic parameters of temocillin in plasma, muscle and subcutaneous adipose tissue of healthy volunteers after intravenous (values in red) and subcutaneous (values in blue) administration of 2 g of temocillin. C_{max}, peak concentration. T_{max}, time to peak concentration. $AUC_{0\text{-}12h}$, area under the time-concentration curve from time point 0 to 12 hours post-dose. **t/2**, elimination half-life. **Cl**, Clearance. V_z, apparent volume of distribution. *In soft tissues, drug concentrations were measured only up to 10 hours post-dose. $AUC_{0\text{-}12h}$ was therefore calculated by extrapolating 12h concentrations in assumption of first-order elimination kinetics.

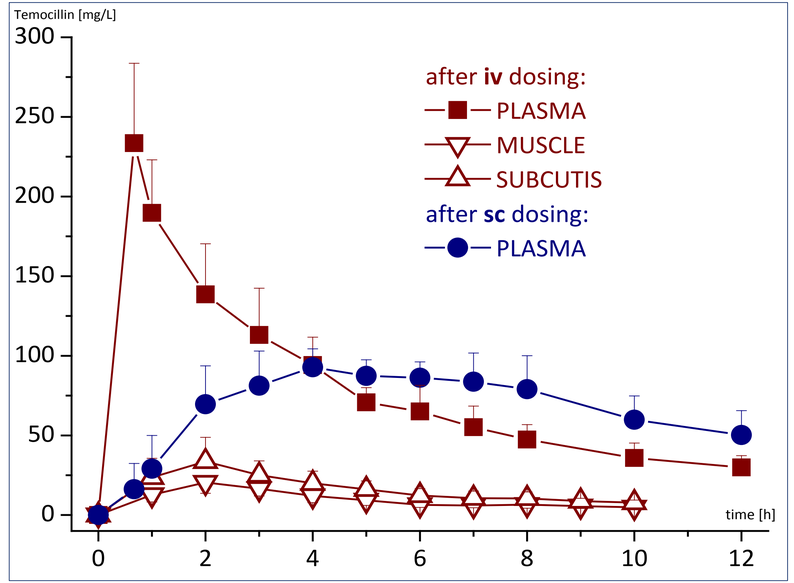

FIGURE 2 Concentration-time profiles of total (closed symbols) and unbound (open symbols) temocillin in plasma, muscle and subcutaneous adipose tissue of healthy volunteers after intravenous (iv, red) and subcutaneous (sc, blue) administration of 2 g of temocillin.

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 (15% according to SmPC).

Funding: the conduct of this study was in part supported by EUMEDICA S.A., Belgium.