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Multiple-dose pharmacokinetics of telithromycin in peripheral soft tissues

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ABSTRACT

Based on clinicians' expectations of high concentrations of telithromycin (TEL) in tissues, combined with its excellent in vitro antimicrobial characteristics, TEL is casually considered as a potential therapeutic option for the therapy of minor cases of soft tissue or bite-wound infections. To clarify this clinically important issue, the present investigation was carried out to measure the pharmacokinetic profile of TEL in the interstitial space fluid (ISF) of skeletal muscle and subcutaneous adipose tissue by means of the microdialysis technique in 10 healthy subjects following repetitive daily doses of 800 mg TEL. These data were compared with free concentrations of TEL determined in plasma. External controls for the present examination were the use of historic, single-dose data collected by our study group utilising identical methods and the same trial subjects. Despite an increase in the median half-life from ca. 3 h after a single dose to ca. 10 h at steady-state conditions in all compartments, accumulation of TEL in ISF of soft tissues and plasma was clinically non-relevant. Median free peak concentrations in plasma, skeletal muscle and subcutis were 0.52, 0.13 and 0.19 mg/L, respectively. The median ratios of the tissue to plasma free areas under the concentration–time curves from 0 to 24 h ($fAUC_{0-24}$ tissue/$fAUC_{0-24}$ plasma) were 0.27 and 0.58 for muscle and subcutis, respectively ($P > 0.05$). The present multiple-dose investigation of TEL is in line with a previous single-dose study confirming that TEL 800 mg/day may not be optimally effective in the therapy of soft tissue infections.

1. Introduction

Telithromycin (TEL) is the first member of the ketolides, a class of semisynthetic antimicrobials that were developed and introduced into the market to overcome the problem of worldwide increasing macrolide resistance of Gram-positive cocci [1]. Owing to its favourable in vitro antimicrobial spectrum, TEL was suggested as a therapeutic option in minor cases of soft tissue and bite-wound infections, although double-blind trials have not proved this and no indication for treatment of skin infection was ever sought from the US Food and Drug Administration (FDA) or European regulatory agencies [2,3].

TEL has recently been subjected to heavy scrutiny because of serious safety concerns and, as a consequence, the FDA retracted two of three indications in February 2007 [3,4]. Thus, in the USA, TEL is now approved solely for the therapy of community-acquired pneumonia (CAP). Nevertheless, in the USA and elsewhere, off-label use of TEL is still significant despite all FDA concerns regarding hepatotoxicity and other safety risks [5].

In our initial study, we evaluated the pharmacokinetics (PKs) of TEL in soft tissues in a single oral dose study by use of the microdialysis technique in 10 healthy male volunteers [6]. However, in this experiment concentrations in the interstitial space fluid (ISF) of tissues were disappointingly low and hardly matched with clinical data reporting on excellent activity in patients presenting with CAP [7]. This discrepancy was expected to be due to histological differences in the lung compared with subcutaneous adipose tissue and skeletal muscle. In fact, the lung is composed of several key compartments, including epithelial fluid, different levels of bronchi and bronchioles, four vascular systems, an interstitial lymphatic system, and the alveolus consisting of pulmonary alveolar macrophages and type I and type II pneumonocytes. Skeletal muscle and subcutaneous adipose tissue, on the other hand, appear to be much less complex from a histological point of view.

Nevertheless, many clinicians are still speculating that clinically relevant concentrations may be reached in the ISF of soft tissues at steady-state conditions. Basically, this is related to PK considerations such as the observation of an increase of plasma half-life from

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ca. 3 h after single-dose administration to ca. 10 h at steady-state conditions [6,8], the biexponential elimination profile of TEL [6,8], its large volume of distribution [8] and a convincing link to data on its efficacy in the therapy of patients presenting with *Staphylococcus aureus* CAP [7].

2. Subjects and methods

The present study investigated the ability of TEL to penetrate into soft tissues following multiple doses in healthy male subjects. A previous investigation employing identical methods and inviting exactly the same subjects was used for comparison and the PK data are presented in Table 1(A).

2.1. Subjects

Ten healthy male volunteers (aged 18–40 years) who participated previously in a single-dose study [6] were invited to undergo the same procedure at steady-state conditions following repetitive oral doses of 800 mg/day TEL (Ketek™ 800 mg tablets; Sanofi-aventis Inc., Bridgewater, NJ) over 5 days. All volunteers received standardised meals on study days and were instructed to avoid caffeine and grapefruit juice during the entire study period.

2.2. Microdialysis

On study Day 5, microdialysis was performed as described previously [6]. In brief, a microdialysis probe with molecular mass cut-off of 20 000 (CMA12; CMA/Microdialysis AB, Solna, Sweden) was inserted into one thigh muscle and into the subcutaneous adipose tissue at the ventrolateral side of the thigh under aseptic conditions with a guidance cannula. The probe was constantly perfused with Ringer's solution (perfusate) at a flow rate of 1.5 μL/min by means of a precision pump (Precidor; Infors AG, Basel, Switzerland). After a 60-min equilibration period, 800 mg of TEL was administered orally to the fasting volunteers. Subsequently, sampling of microdialysates (dialysate) and venous blood was performed at 20-min intervals from 0 to 4 h and then at 30-min intervals for later sampling points. Individual recovery values of TEL were determined by use of the in vivo 'retrodialysis method' [10]. Accordingly, TEL was added at a concentration of 5 mg/L to the perfusion fluid and its rate of disappearance through the microdialysis membrane was determined in duplicate. The individual recovery was calculated using the equation: Recovery = $1 - (C_{dialysate}/C_{perfusate})$, where $C_{dialysate}$ and $C_{perfusate}$ are the concentrations of dialysate and perfusate, respectively. All samples were stored at minus 80 °C until analysis.

2.3. Sample analysis and calculations

TEL concentrations in plasma and microdialysates were analysed using a validated high-performance liquid chromatography (HPLC) method [11]. Dialysate concentrations were corrected by the individual in vivo recovery value of the respective microdialysis probe using the formula: Concentration (C) = $C_{measured}$/recovery. A value of 70% for plasma protein binding of TEL derived from the literature was used for the present PK calculations [12] (Fig. 1).

PK calculations were performed using commercially available computer software (Kinetica version 3.0; InnaPhase, Philadelphia, PA). The areas under the concentration–time curves from 0 to 8 h (AUC_{0-8}), 0–24 h (AUC_{0-24}) and 0 h to infinity ($AUC_{0-\infty}$) in plasma and interstitial fluid were calculated by the linear trapezoidal rule.

Wilcoxon's test was used for comparison of the AUCs in plasma, skeletal muscle and subcutis within subjects. A two-sided P-value of <0.05 was considered significant. Multiple testing for significance was adjusted using the Bonferroni method.

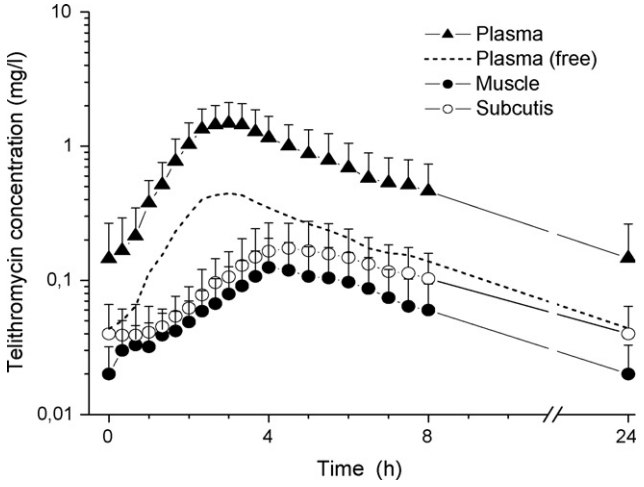

Fig. 1. Plasma and tissue pharmacokinetics of telithromycin at steady state following multiple doses of 800 mg/day (mean + standard deviation; $n = 10$).

3. Results

In vivo recoveries for TEL in microdialysates were 62.0 ± 4.3% and 63.4 ± 1.6% (mean ± standard deviation) for skeletal muscle and subcutaneous adipose tissue, respectively.

The main PK data observed previously by our study group after single-dose administration are shown in Table 1(A). Data collected in the present investigation following administration of five repetitive doses of TEL 800 mg/day are summarised in Table 1(B). The PK profiles in plasma, skeletal muscle and subcutaneous adipose tissue show that steady-state conditions were reached for all compartments investigated. As expected, the peak concentrations of free TEL are somewhat higher in plasma compared with soft tissues. Equilibration of TEL is incomplete between the free plasma compartment and the ISF of soft tissues. The plasma PK profile at steady state is in accordance with findings in the scientific literature [8], whilst no data on TEL tissue PKs are available for steady-state conditions. Maximum concentrations (C_{max}) and AUC_{0-24} of free TEL ($fAUC_{0-24}$) in the ISF of subcutaneous adipose tissue are comparable with corresponding values in skeletal muscle ($P > 0.05$). The median values for C_{max} are 0.52, 0.13 and 0.19 mg/L for free TEL in plasma, skeletal muscle and subcutaneous adipose tissue, respectively. The corresponding half-lives are 8.6, 9.8 and 11.7 h after multiple doses, respectively. The ratios of the $fAUC_{0-24}$ of TEL in tissues to the $fAUC_{0-24}$ in plasma show considerable variability between subjects, ranging from 0.16 to 1.43 for skeletal muscle and from 0.28 to 1.34 for subcutis. The respective median ratios were 0.27 and 0.58 (Table 1(B)). These findings were in line with single dose data (Table 1(A)) derived from historic controls [6].

4. Discussion

The present experiment set out to test the ability of TEL to penetrate and accumulate in the ISF of soft tissues. Microdialysis probes were implanted into subcutaneous adipose tissue and skeletal muscle in 10 healthy subjects after 5 consecutive days of oral intake of TEL. Performance of the present study in the same individuals used in a previous single-dose trial of TEL minimises interindividual variability in tissue and plasma PKs. This approach therefore increases the overall value of the present investigation in the given situation of a predefined relatively small sample size of 10 subjects.