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The Pharmacokinetics of BC-3781 in Muscle and Adipose Tissue in Healthy Subjects

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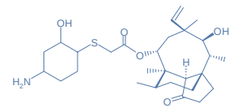
BC-3781



nabriva THERAPEUTICS

ABSTRACT

Background: BC−3781 is an investigational semi-synthetic pleuromutilin derivative inhibiting ribosomal protein synthesis currently in Phase II clinical development. Pharmacokinetics (PK) at the site of action is a crucial part in modern development of antibiotics. Thus in the present study the PK of BC−3781 in the interstitium of muscle and subcutaneous adipose tissue, i.e. the relevant compartment for skin and skin structure infections was determined.

Methods: A single dose of 150 mg BC−3781 was administered intravenously over 1 hour to 12 healthy male subjects. Pharmacokinetics of BC−3781 was determined by LC−MS/MS in microdialysate from muscle and adipose tissue as well as in plasma over 24 hours.

Results: Mean area under the concentration−time curves (AUCs) from 0 to 24 hours were 6872 ± 1582 ng·h/ml for the total concentration in plasma; 893 ± 206 ng·h/ml for the calculated unbound fraction in plasma (~87 % protein binding) and 852 ± 324 ng·h/ml and 825 ± 243 ng·h/ml for the measured free fraction in skeletal muscle and adipose tissue, respectively. Ratios of free AUCs in skeletal muscle and adipose tissue versus plasma were 0.98 ± 0.36 and 1.01 ± 35, respectively.

Conclusions: For BC−3781 fast and total equilibration between both investigated tissues and plasma was observed immediately after the end of the infusion until the end of the observation period. These data are in support of a recently concluded successful Phase II study with BC−3781 on patients with acute bacterial skin and skin structure infections.

INTRODUCTION

BC-3781 is an investigational semi-synthetic pleuromutilin derivative. Pleuromutilin antimicrobial agents inhibit protein synthesis through interaction with the 50S ribosomal subunit and cross resistance with other antimicrobial classes is uncommon. BC-3781 has demonstrated potent antimicrobial activity against Gram-positive cocci and Gram-negative pathogens relevant for bacterial skin and skin structure infections and for community-acquired bacterial pneumonia.

BC-3781 is being developed for the treatment of serious skin infections and bacterial pneumonia caused by *Staphylococcus aureus*, β-hemolitic streptococci, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarhhalis*, *Mycoplasma* spp., *Clamidophila pneumoniae*, *Legionella pneumophila* and other bacteria, including drug resistant strains such as MRSA and vancomycin resistant *Enteroccocus faecium*.

INTRODUCTION (cont.)

BC-3781 is under development for treatment of acute bacterial skin and skin structure infections (ABSSSI) and hospital treated community-acquired pneumonia (HCAP) with intravenous and oral dosing formulations.

BC-3781 concentrations were determined in blood plasma, interstitial space fluid of subcutaneous and skeletal muscle tissue in the course of a clinical study (NAB-BC-3781-1005) aimed to support the development for ABSSSI.

MATERIALS & METHODS

Male volunteers were screened in order to identify 12 eligible healthy subjects for this pharmacokinetic study. Subjects were admitted to the Department of Clinical Pharmacology on the evening before the study day.

On the study day each subject received 150 mg of BC-3781 as infusion into an antecubital vein over 1 hour. In the morning of the study day two microdialysis probes (CMA63 microdialysis probe, cut-off 20000 Dalton, CMA, Solna, Sweden) were inserted into muscle and subcutaneous adipose tissue of the thigh. The probes then were constantly perfused with a physiological solution at a flow-rate of 2 µl/min by a microinfusion-pump. Microdialysis samples were taken at baseline and at predefined time points up to 24 hours after drug administration. Microdialysis is based on sampling of analytes from the extracellular space by means of a semi-permeable membrane at the tip of a microdialysis probe[1]. To obtain interstitial concentrations of BC-3781 from dialysate concentrations microdialysis probe calibration was assessed according to the retrodialysis method. The principle of this method relies on the fact that the diffusion process is quantitatively equal in both directions through the semi-permeable membrane. *In vivo* calibration by retrodialysis was performed at the end of the sampling period by perfusing the system with a calibration solution containing BC-3781 at a known concentration. The *in vivo* recovery value was thus calculated as:

Recovery [%] = 100 - (100·analyte concentration$_{out}$ / analyte concentration$_{in}$)

Interstitial concentrations was calculated according to the following equation:

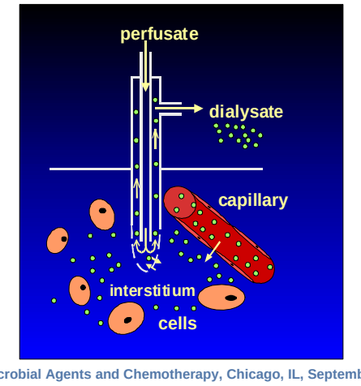
Interstitial concentration [%] = 100 · (sample concentration / *in vivo* recovery)

In addition to microdialysis samples blood samples were collected from a vein in the opposite arm from the arm in which the infusion of BC-3781 was given at baseline and up to 24 hours after dosing. Plasma was immediately separated by centrifugation at 2,000*g* for 10 minutes at approximately +4° C and plasma specimens were stored at –20° C or cooler until analysis.

Plasma and MD samples were analyzed for the concentration of BC-3781 using validated liquid chromatography-tandem mass spectrometry method. Non-compartmental pharmacokinetic analysis was performed using Kinetica 2000 (Version 3.0, Innaphase, PA).

Figure 1. Microdialysis probe

Figure 2. Schematic diagram of microdialysis



RESULTS & DISCUSSIONS

All subjects concluded the study according to the protocol. Overall tolerability of BC-3781 was good, no serious adverse events occurred and all observed adverse events fully resolved spontaneously.

Mean PK parameters are presented in Table 1. As shown in Figure 1 after an intravenous dose of 150 mg of BC-3781 total equilibration between the unbound fraction in plasma and tissue concentrations occurred uncommonly fast (i.e. within 15 minutes after end of the infusion). Thereafter free concentration time profiles in tissue and plasma closely resemble each other, indicating very fast exchange of BC-3781 within central compartment and interstitium. This observation is supported by the finding that the drug activity maintains retained in the presence of serum and the binding affinity of BC-3781 to the two major drug binding human plasma proteins (HAS and AGP) is low. This was further supported with the results from a QWBA study in rats where the concentrations measured in the majority of tissues, including skin and skin structure tissues were higher compared to the amounts measured in the circulating blood.

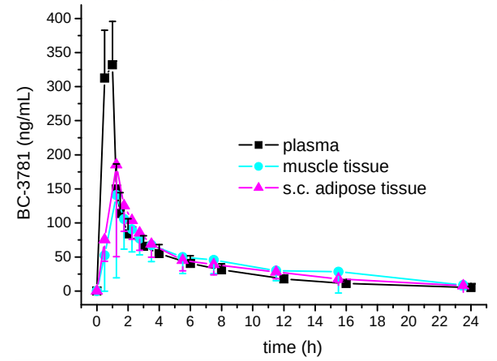
In the present study after a single dose of 150 mg BC-3781 free AUC_{0-24} values of 852 ± 324 ng·h/ml and 825 ± 243 ng·h/ml were observed for skeletal muscle and adipose tissue, respectively. However, clinically investigated dosing regimens employ twice daily administration of BC-3871, so free AUC_{0-24} approximating 2µg·h/ml can be expected in clinical practice. The exposures in blood plasma are in accordance with recent data from a Phase II study in ABSSSI which showed high clinical success rate comparable to vancomycin, (L-966 "A Phase II Study Comparing the Safety and Efficacy of Two Doses of BC-3781 versus vancomycin in Acute Bacterial Skin and Skin Structure Infections (ABSSSI))

Table 1. Mean pharmacokinetic parameters of BC−3781 following a single oral dose of 150 mg. For plasma a free fraction of 13 % was used in the calculations.

	AUC_{0-24} [ng·h/ml]	C_{max} [ng/ml]	t_{max} [h]	$t_{1/2}$[1] [h]	AUC_{tissue} / $AUC_{free\ plasma}$
Plasma $_{total}$	6872 ± 1582	2576 ± 492	0.88 ± 0.23	6.11 ± 0.67	ND
Plasma $_{free}$	893 ± 206	335 ± 64	0.88 ± 0.23	6.11 ± 0.67	ND
Muscle tissue	852 ± 324	151 ± 105	1.92 ± 0.70	6.97 ± 1.91	0.98 ± 0.36
Adipose tissue	825 ± 243	183 ± 125	1.75 ± 0.40	7.04 ± 3.13	1.01± 0.35

[1] Mean pharmacokinetic parameters were calculated using PK sampling up to 24 hours

Figure 3. Unbound concentration – time profiles of BC−3781 in plasma, muscle tissue and subcutaneous adipose tissue. For plasma a free fraction of 13 % was used for calculations.



CONCLUSIONS

- BC−3781 showed rapid penetration into sub−cutaneous adipose tissues, skeletal muscle after a single 150 mg one hour intravenous infusion.
- Therapeutic exposure levels of BC−3781 in target tissues are expected to be reached within the first day of treatment and are similar to the levels reached in blood plasma.
- For the distribution into ABSSSI relevant target tissues, the AUC_{plasma} was shown to be an appropriate marker for PK/PD.
- These data are in support of a recently successfully concluded Phase II study with BC−3781 in patients with acute bacterial skin and skin structure infections .

REFERENCES

1. Muller M. Microdialysis in clinical drug delivery studies. Adv Drug Deliv Rev 2000; **45**: 255-69.

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