A2-029

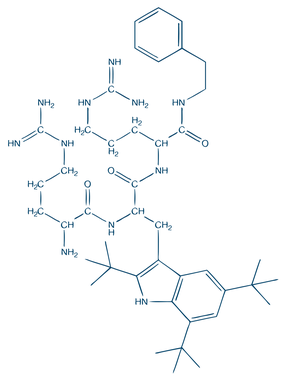
Evaluation of the *In Vitro* ADME Profile of LTX-109 – A Novel Antimicrobial Drug

B. MORTENSEN, A. FUGELLI AND W.M. OLSEN
Lytix Biopharma, Norway

Lytix Biopharma

LTX-109

- A synthetic protein fragment - a peptidomimetic
- High stability against degradation
- Prooduced synthetically in large scale
- Low cost of synthesis



Chemical structure of LTX-109.

Background

LTX-109 is a novel antimicrobial drug in clinical development for skin infections and nasal decolonisation of MRSA. The drug mimics the effects of natural antimicrobial peptides in a synthetic small molecule. LTX-109 has demonstrated a broad activity against several Gram (+) and Gram (-) bacteria *in vitro*, as well activity against a range of yeast and fungal species. The compound is equally effective against antibiotic-resistant species such as methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *Enterococci* (VRE) and multi-resistant Pseudomonas isolates. The ultra-rapid membrane lysing mode of action may result in a lower propensity to resistant development and a rapid bactericidal mechanism of action, as shown in *in vitro* studies. To date LTX-109 demonstrates no *in vitro* cross-resistance with other classes of antibiotics.

This study was designed to investigate potential tissue, species and gender differences in the metabolism of [^{14}C] LTX-109 in rat, mini-pig and human hepatocytes, skin discs and blood. Furthermore, the protein binding of [^{14}C] LTX-109 was investigated.

Methods

The metabolic profile of [^{14}C] LTX-109 was examined *in vitro* in whole blood, skin discs and hepatocytes from Sprague Dawley rats, Göttingen minipigs and humans. The hepatocytes were shown to be metabolically active producing metabolites of [^{14}C]-7-ethoxycoumarin. The skin discs used in this study were shown to be enzymatically active by the measurement of phenyl acetate hydrolysis. [^{14}C] LTX-109 and metabolites present in the resultant incubation supernatants were resolved by HPLC with on-line radio detection.

The *in vitro* plasma protein binding and blood cell partitioning of [^{14}C] LTX-109 in rat, dog, and human was determined by equilibrium dialysis at ca 37°C for 3 h. Various concentrations were used, 700, 2500, 10000 ng/mL, far in excess of the plasma concentrations anticipated following dosing via the intended clinical route. Samples prepared in scintillation fluid were subjected to liquid scintillation counting using liquid scintillation analyser.

Results

Protein binding was similar and high for each species and was ranked: rat < dog = human (table 1). Plasma protein binding does not appear to be concentration dependant. Blood cell association was low in all species, again not appearing to be dependant on concentration. The plasma: whole blood ratio was >1 in all species, indicating that [^{14}C] LTX-109 was predominantly distributed in the plasma.

In skin, there was some evidence of metabolism of [^{14}C] LTX-109 (fig. 1). No time-related increase in metabolites was observed in heaptocytes (fig. 2) or whole blood (not displayed) for all species tested.

Species	Protein binding	Blood Cell association
Rat	97.3 - 97.4	0.9-6.1
Dog	98.3 - 99.2	0-0.1
Human	99.1	0-3.4

Table 1. Protein binding and blood cell association

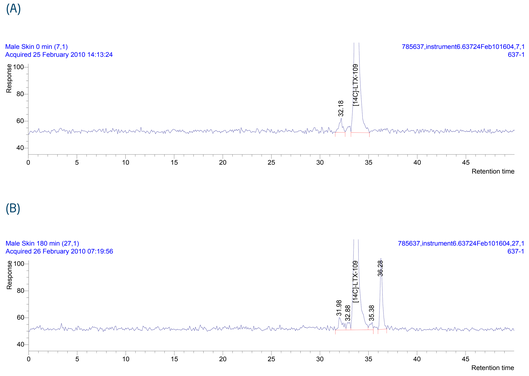


Figure 1. Incubation with [^{14}C] LTX-109 and Male Human Skin Discs for 0 min (A) and 180 min (B)

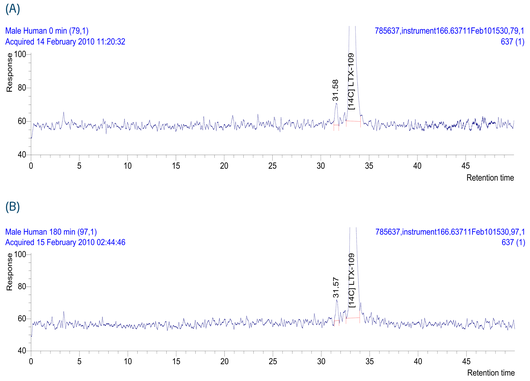


Figure 2. Incubation with [^{14}C] LTX-109 and Male Human Cryopreserved Hepatocytes for 0 min (A) and 180 min (B)

Conclusions

- LTX-109 has a well-characterised ADME profile
- The drug has minimal metabolism by hepatocytes, skin discs and blood and a high degree of protein binding
- Tested in Phase I and two Phase I/IIa trials with good tolerance, minimal systemic bioavailability
- Demonstrated Proof-of-Concept in decolonisation of nasal MRSA / MSSA. Further Phase II studies are planned to demonstrate efficacy in larger patient populations

LTX-109

- Novel mechanism of action
- Broad spectrum of activity
- Low propensity for resistance development and active against drug-resistant strains
- Effective against fungal and bacterial biofilms
- Superior efficacy compared to market leaders (Bactroban®, Fucidin®, Altabax®/Altargo®)

Lytix Biopharma AS | P.O. Box 6447 | NO-9294 Tromsø, Norway | E-mail: post@lytixbiopharma.com | Phone: +47 77 67 55 00 | Fax: +47 77 67 55 01