Nano-mupirocin: A 2-Week Repeat Dose Intravenous Toxicity and Toxicokinetic Study Followed by a 7-Day Recovery Period in Rats

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Background

Nano-mupirocin is a PEGylated nano-liposomal formulation of mupirocin. Mupirocin has a unique mode of action: inhibition of isoleucyl tRNA synthase, not shared by other antibiotics. Yet, due to rapid metabolism and high protein binding, its current use is limited to topical administration. Nano-mupirocin overcomes these limitations and enables efficacy of mupirocin by the parenteral route as demonstrated in animal models (necrotizing fasciitis, osteomyelitis, endocarditis and pneumonia). Here we present a 2-week repeated dose toxicity and toxicokinetic (TK) study in rats performed at ITR laboratories Canada Inc.

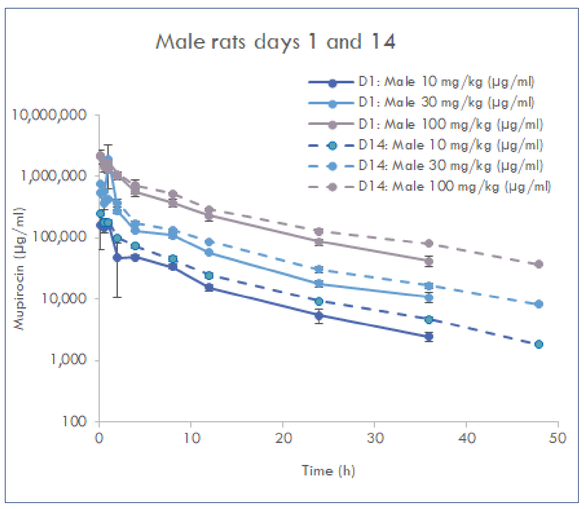
Study design

Nano-mupirocin and control buffer were administered to rats by slow IV (10, 30 and 100 mg/kg) or IM injection (10.5 mg/kg) on Days 1, 4, 7, 9, 11 and 14. Monitored parameters included; mortality, clinical signs, food consumption and body weight. Blood samples were collected for TK on Days 1 and 14. Some animals were left to recover for additional 7 days. At necropsy, blood samples were collected for hematology, clinical chemistry and coagulation analysis and organs were subjected to gross pathology and histopathological evaluation. TK samples were analyzed for mupirocin levels by an LCMS method.

TK analysis

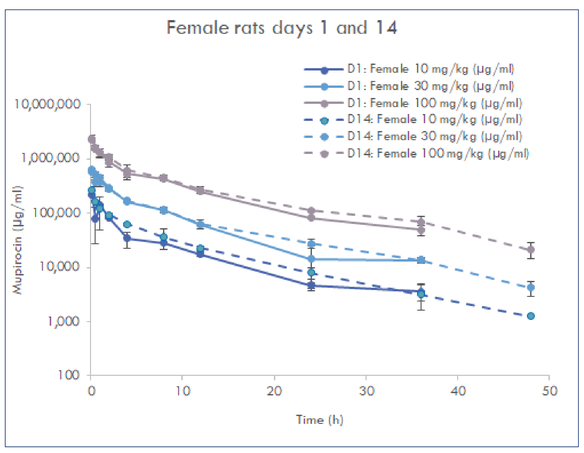
IV administration

Male



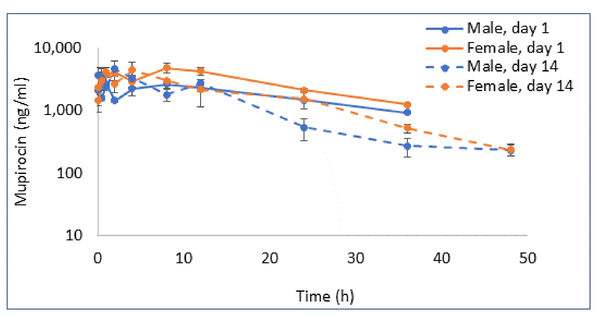
	$T_{1/2}$	C0	AUC_{INF}
	(hr)	(µg/mL)	(hr*µg/mL)
Day 1			
10 mg/kg	9.06	160	820
30 mg/kg	8.33	596	2,745
100 mg/kg	9.78	2,246	10,596
Day 14			
10 mg/kg	9.87	266	1,234
30 mg/kg	12.59	787	3,863
100 mg/kg	12.41	2,381	14,213

Female



	$T_{1/2}$	C0	AUC_{INF}
	(hr)	(µg/mL)	(hr*µg/mL)
Day 1			
10 mg/kg	9.04	265	808
30 mg/kg	6.76	639	2,917
100 mg/kg	8.89	2,610	10,848
Day 14			
10 mg/kg	9.13	288	1,053
30 mg/kg	8.72	664	3,143
100 mg/kg	9.54	2,401	12,273

IM administration



	$T_{1/2}$	C_{max}	AUC_{INF}
	(hr)	(µg/mL)	(hr*µg/mL)
Day 1			
Male	18.5	2.6	89
Female	13.5	4.8	130
Day 14			
Male	10.7	4.6	65
Female	9.0	4.4	80

- **Half-life of mupirocin after Nano-mupirocin administration was 7-19 h.**
- **The exposure in terms of Cmax and AUC was high above the MIC range of mupirocin (≤ 1 µg/ml, depending on bacteria) at all doses.**
- **Nano-mupirocin showed dose proportionality increase in exposure to mupirocin with the increase in doses.**
- **No accumulation was observed following 3 times/ week dosing.**

Toxicity results

- No mortalities or clinical signs noted during the study.
- No effect on body weight, food consumption or hematology and coagulation parameters that could be attributed to treatment.
- No macroscopic changes noted at necropsy.
- An increase in cholesterol values for all IV treated animals was obtained. This increase was due to the cholesterol found in the liposomal formulation. At the end of the recovery period partial or full reversal was observed.

Conclusions

- **The No Observable Adverse Effect Level (NOAEL) was determined to be the highest dose assessed (100 mg/kg).**
- **The NOAEL results in exposure that is much higher than the MIC range of mupirocin over the tested period and is much higher than the therapeutic dose showed in mice models.**

The present study demonstrated a safe profile for Nano-mupirocin and a good systemic exposure. These pre-clinical observations further support the potential of Nano-mupirocin to be safely used in humans at doses high enough to eradicate bacterial infections.

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