Pharmacokinetic Evaluation of Novel Amino-Spectinomycin Antibiotics

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Purpose
To evaluate the drug metabolism and pharmacokinetic properties of novel amino–spectinomycin (amSPC) antibiotics for the treatment of respiratory tract and sexually transmitted bacterial infections.

Methods
Novel amSPC antibiotics have shown excellent potency against common respiratory tract pathogens, particularly against Streptococcus pneumoniae and Haemophilus influenza, and sexually transmitted bacteria Neisseria gonorrhoea and Chlamydia trachomatis. To evaluate the pharmacokinetic profile and phase-I metabolism of these active amSPC compounds (1946, 1948, 1950, 1980, 2106, 2324 and 2533) in–vivo pharmacokinetic studies were conducted in rats by intravenous administration (10 mg/kg), and phase–I metabolic stability was assessed using rat hepatic microsomal preparations. Metabolic half-life and intrinsic clearance (CLint) were calculated and interpreted with CLint classification bands based on the well-stirred model. The chemical stability of amSPC compounds were examined in comparison to spectinomycin at pH 9, 7 & 2. Plasma protein binding was analyzed by equilibrium dialysis. LC–MS/MS assays were developed to quantify concentrations in test samples.

Results
Amino-spectinomycin compounds exhibited low to moderate plasma protein binding (32.0±5.49–62.6±3.26 %) and were found to be metabolically stable. Based on the CLint classification system all the amSPC antibiotics were found to be low cleared compounds (CLint: 0.40–1.70 µL/min/mg protein). While the percentage of spectinomycin continuously declined over time at pH 9 and 7, amSPC compound 1950 was highly stable at pH 9, 7 and 2 (more than 99% of parent compound remained intact after 96 h of incubation). Following intravenous administration, all amSPC compounds showed a similar and predictable systemic exposure with peak plasma concentrations of 17.1±2.74–21.5±4.51 mg/L and an area under the curve of 15.6±2.97-19.6±3.11 mg*h/L. The compounds exhibited biexponential plasma concentration–time profiles with a half-life of 0.94±0.17–1.99±0.24 h at therapeutically relevant concentrations above the MIC. Compounds 1950 and 1980 had low distribution volumes (0.64±0.25 and 0.66±0.29 L/Kg), whereas 1946, 1948, 2106, 2324 and 2533 exhibited higher distribution volumes than spectinomycin (1.24±0.29–1.55±0.83 L/Kg). Renal excretion is the major elimination pathways for amSPC compounds with 43–82% excreted unchanged in urine, except for compound 2106 with a lower value of 22%.

Conclusion
The DMPK studies indicate amSPC compounds possess favorable pharmacokinetic properties for further development as novel antibacterial agents.