Trivalent lanthanum (La3+) Biodistribution Profiles from Intravenous and Oral Dosing of Two Lanthanum Complexes, La(dpp)3 and La(XT) and There Evaluation as Treatments for Bone Resorption Disorders

K. M. Wasan
University of Saskatchewan

Purpose
Two such chelators, 1,2-dimethyl-3-hydroxy-4-pyridinone (Hdpp) and bis-[[bis(carboxymethyl)amino]methyl]phosphinic acid (H5XT), have previously been the subjects of extensive physical, in vitro and in vivo testing as the tris- and mono-lanthanum(III) complexes La(dpp)3 and La(XT), respectively. In this study, we expand upon those studies to include 4-week intravenous (IV) and oral La3+ biodistribution profiles.

Methods
Rats were randomly placed in one of the following treatment groups (n=4): oral dosing of La(dpp)3 and of La(XT) at 50 mg/kg/day, IV dosing of either compounds at 1 mg/kg/week or a control group. Plasma samples from each time point were analysed for creatinine, alanine transaminase (ALT) and aspartate transaminase (AST) levels. Kidney and liver histology was performed and ICP-MS was used to determine lanthanum concentrations in tissue, plasma and bone samples.

Results
Of the two compounds, La(XT) demonstrates the more favourable in vivo characteristics, therefore dose-dependent oral biodistribution studies were carried out with this complex. These show drug saturation above a dose of 100 mg kg-1 day-1, so liver histology was performed in order to assess any potential toxicity. Finally, we improve upon the physical characterization of La(dpp)3 to include a single crystal X-ray structure, which exhibits an 8-coordinant La3+ centre with two bound water molecules, and a disordered exoclysterate-type hydrogen bonded network.

Conclusion
The present study has demonstrated that lanthanum, when administered as either La(dpp)3 or La(XT), accumulates in bone, the target organ, with overall uptake greater for La(XT). Biodistribution studies show that lanthanum accumulates mostly in the liver, spleen and intestine, with negligible amounts found in brain or heart tissue. Tissue levels were dose-dependent. Over the 4 weeks of chronic treatment, no significant kidney toxicity was found, and only minor abnormalities in the liver at the highest dose level. These results are encouraging to pursue La(XT) in studies of longer duration for ongoing investigations of its effect on bone. Acknowledgements: Funding from the Saskatchewan Health Research Foundation Establishment Grant Program to KMW, DC & CO.