

Use of Metabonomics and Contrast-Enhanced Relaxometry in pre-clinical evaluation of drug toxicity.

J.M. Colet¹ and R.N. Muller²

¹ *Service de Biologie Humaine et Toxicologie, Faculté de Médecine et Pharmacie, Université de Mons-Hainaut.*

² *Service de Chimie Générale, Organique, et Biomédicale, Faculté de Médecine et Pharmacie, Université de Mons-Hainaut.*

Introduction: Despite the precautions taken during the pre-clinical development of new drugs, toxicities may still be identified later on in clinical trials or even during marketing. New tools allowing a better prediction of such toxicities are thus needed. Here, we report some results obtained by metabonomics and contrast-enhanced relaxometry in the evaluation of the acute effects of some well-known liver and renal toxicants in rats.

Materials & Methods: Fischer rats received single doses of either liver or renal toxins.

Metabonomics protocol: urine samples were collected daily before and after treatment and proton NMR spectra were acquired on a Bruker instrument at either 300 or 600 MHz¹.

Relaxometry protocol: After treatment with the toxins, animals received 0.1 mmol/kg of either a non-specific (Magnevist[®]) or a liver specific (Primovist[®]) contrast agent. Longitudinal relaxation time measurements of plasma and urine samples were performed at 37°C on a spin analyser Minispec (Bruker) for the determination of the plasma and urine concentrations of the contrast agent over time.

Results: The metabonomics approach identified timely toxin-specific metabolic changes. For instance, ANIT induced reductions in citrate and α -ketoglutarate together with a dramatic release of bile acids, while glucosuria, amino aciduria, organic aciduria, and a complete disappearance of hippurate were indicative of the damage caused to the renal proximal tubules by gentamycin. In the relaxometric approach, the biliary excretion of Primovist was dramatically reduced by ANIT which is known to damage the bile ducts. In the same way, renal toxins altered the renal excretion of the non-specific contrast agent Magnevist.

Conclusions: NMR-based protocols were successfully applied to evaluate the effect of liver and renal toxins in rats after a single exposure. Metabonomics allowed the identification of toxin-specific metabolic trajectories and potential urine markers of the lesions. The relaxometric protocol indicated functional impairment of the biliary and/or urinary excretion routes. Although extensive work is needed to validate the methods, the combination of both approaches could represent a robust tool for the screening of liver and renal toxicities in pre-clinical drug development. In addition, such non-invasive techniques could also be easily transposed to human clinical studies.

¹ This work was done in collaboration with Eli Lilly & company.