**INTRODUCTION**

Idiosyncratic drug reactions (IDR's)
- Occur in small subset of patients.
- Unrelated to the pharmacological action of drugs.
- Unpredictable and rare, but with a fatal outcome.
- IDR's with hepatic origin are a major health concern.

Idiosyncratic toxicities
- Rarely observed before marketing.
- Not only driven by drug exposure but other depend on several drug- and patient-related risk factors.

Well known immunological contribution to IDR's
- BUT
- A metabolic role is suspected, although no undeniable evidence provided so far.

**AIMS**

- Develop an animal model to assess the metabolite contribution of IDR's.
- Investigate the metabolic mechanisms of IDR's using a metabonomic approach.
- Evaluate in rats several drugs known to induce IDR's.

**MATERIALS & METHODS**

**Immunologic Models**
- Felbamate (TALOXA *) 800 mg/kg
- Nevirapine (VIRAMUNE *) 100 mg/kg

**Drugs**
- Ranitidine (ZANTAC *) 30 mg/kg

**Metabolic Models**
- Lipopolysaccharide (LPS)

**Samples Preparation**
- 40 µl of urine + 200 µl of phosphate buffer
- 13,000 rpm to min

**NMR Analysis**
- 9.4 T

**DISCUSSION & CONCLUSION**

- Immunological model:
  - Changes observed for Felbamate and Nevirapine, not for Ranitidine (fig.2).
  - Increase in citrate, alpha-ketoglutarate and succinate.
  - Reduction in Krebs cycle intermediates concentrations.
  - Increase in hippurate = indicator of the hepatic function.

- Metabolic model:
  - Increase creatine/creatinine and decrease hippurate, alpha-ketoglutarate and citrate (fig.3).
  - Markers of hepatic toxicity.
  - Analysis of the metabolic trajectories (fig.4).
  - Revealing of various levels of intensity following the treatment (Veh/Veh < Veh/Drug < LPS/Veh < LPS/Drug).

In conclusion, using one biomarker may not be the best approach.
- Instead, consider the full metabolic signature and temporal changes to diagnose early IDR's.

**Figures**

- Fig. 1: NMR PCA scores plots of 00 to 816 h posttreatment urine samples means and metabolic trajectories. Rats were treated with vehicle only (black) or vehicle and drug (red) or with 2.5 x 10^6 EU/kg LPS and vehicle (blue) or 2.5 x 10^6 EU/kg LPS and drug (green). Drugs: 100 mg/kg Felbamate (a), 600 mg/kg Nevirapine (b), 70 mg/kg Ranitidine (c).

- Fig. 3: ‘H NMR spectra (400 MHz) of urine for ‘metabolic model’. Rats were pretreated with vehicle and after 30 mg/kg Ranitidine (1) or pretreated 2.5 x 10^6 EU/kg LPS and after 30 mg/kg Ranitidine (2) or pretreated with LPS 2.5 x 10^6 EU/kg LPS and after vehicle (3). Peaks showing major differences and the components identified: (a) alpha-ketoglutarate, (b) creatine/creatinine, (c) citrate, (d) trimethylamine-N-oxide (TMAO), (e) hippurate.

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**References**

- University of Mons, Department of Human Biology and Toxicology, Université de Mons, Belgium **CMFA, Université catholique de Louvain, Belgium**.
- For further information: raphael.conotte@umh.ac.be.
- Mouse model: male C57BL/6J mice; Lipopolysaccharide (LPS) 500 µg/kg i.p.
- Human subjects: A total of 24 healthy volunteers; Drug treatment: 25 mg/kg Nevirapine.