Long Term Metabolic Changes Induced in Idiosyncrasy-like Liver Toxicity

R. Conotte*, Z. Kahvecioglu*, N. Matuszak** and J-M. Colet*

* Departement of Human Biology and Toxicology, Université de Mons, Belgium ; ** CMFA, Université catholique de Louvain, Belgium

For futher information: raphael.conotte@umh.ac.be

Departement of Human Biology and Toxicology

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 ather depend on several drug- and patient-related risk factors.

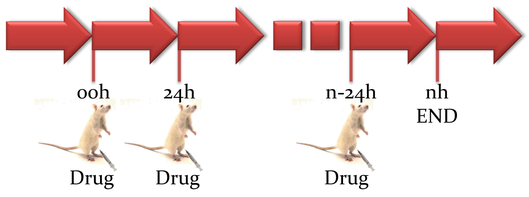
Well known immunological contribution to IDR's
BUT
A metabolic role is suspected,
although no undeniable evidence provided so far

AIMS

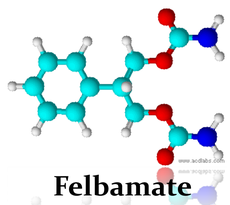
- ✓ Develop an animal model to assess the metabolic contribution of IDR's.
- ✓ Investigate the metabolic mechanisms of IDR's using a metabonomic approach.
- ✓ Evaluate in rats several drugs known to induce IDR's.

MATERIALS & METHODS

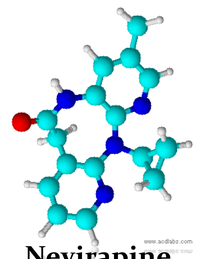
Immunologic Models



Drugs

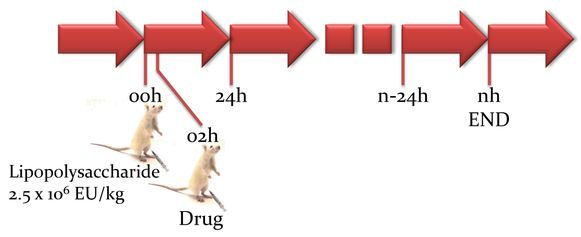


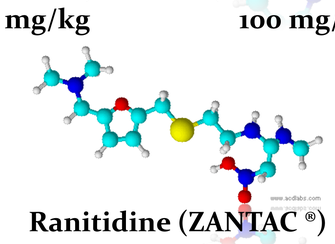
Felbamate (TALOXA ®) 800 mg/kg



Nevirapine (VIRAMUNE ®) 100 mg/kg

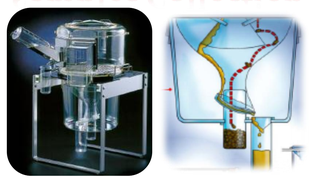
Metabolic Models





Ranitidine (ZANTAC ®) 30 mg/kg

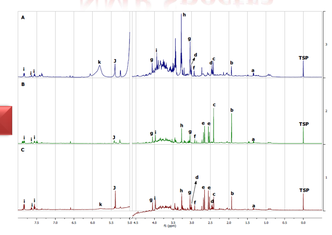
Samples Collection



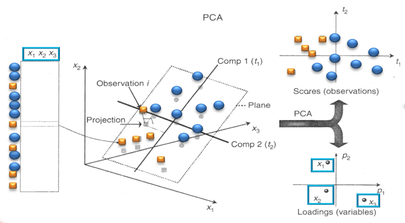
Samples Preparation

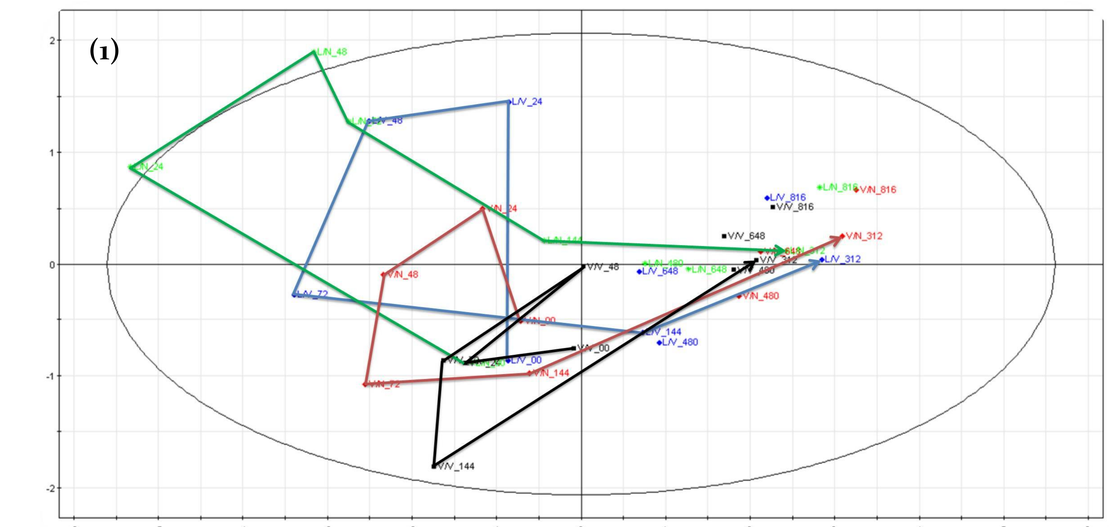
NMR Analysis 9.4 T

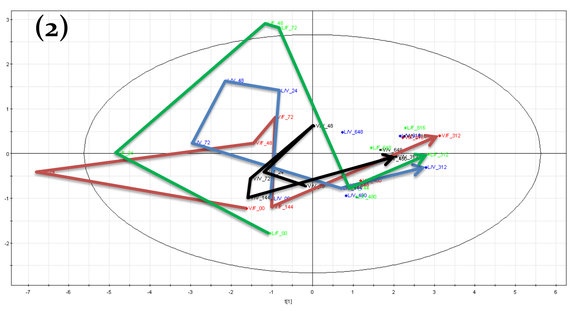
NMR Spectra



Multivariate Analysis







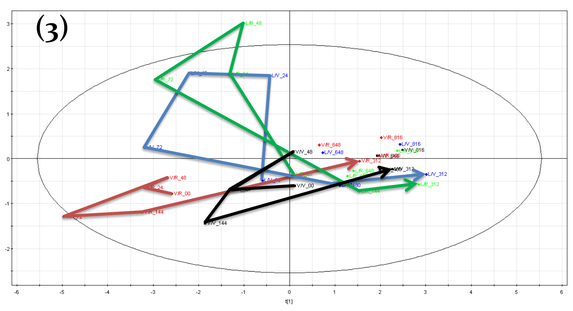


Fig.1: NMR PCA scores plots of 00 to 816 h posttreatement urine samples means and metabolic trajectories. Rats were treated with vehicle only (black) or vehicle and drug (red) or with 2.5 x 10^6 EU/kg LPS and vehicle (blue) or 2.5 x 10^6 EU/kg LPS and drug (green). Drugs : 100 mg/kg Nevirapine (1) ; 800 mg/kg Felbamate (2) ; 30 mg/kg Ranitidine (3)

DISCUSSION & CONCLUSION

- ✓ **Immunological model :**
  - Changes observed for Felbamate and Nevirapine, not for Ranitidine (fig.2).
  - Decrease in citrate, alpha-ketoglutarate and succinate
    - ➢ Reduction in Krebs cycle intermediates concentrations
      - ➢ Reduction of the performance of oxidative phosphorylation
  - Decrease 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.1)
    - ➢ 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.**

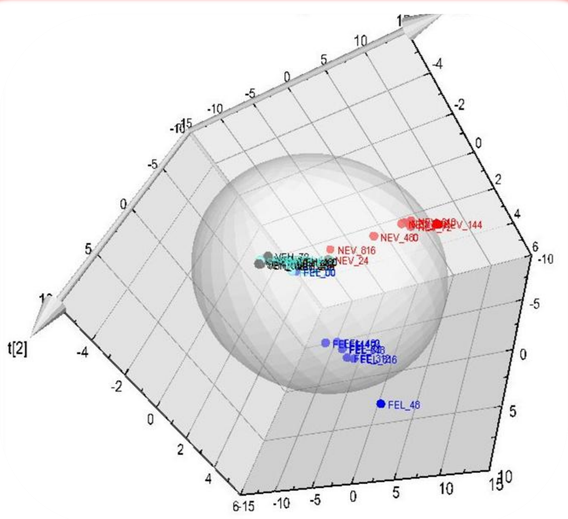


Fig.2: NMR PCA 3D scores plots of 00 to 816 h posttreatement urine samples. Rats were treated everyday with 800 mg/kg Felbamate (◆) or 100 mg/kg Nevirapine (◆) or 30 mg/kg Ranitidine (◆) or Vehicle (◆).

Nevirapine		Felbamate	
Myo-inositol Allantoin Glucose	Citrate a-ketoglutarate TMAO Taurine Hippurate	Glucose Felbamate & metabolites	Citrate a-ketoglutarate TMAO Taurine Hippurate Acetate Succinate

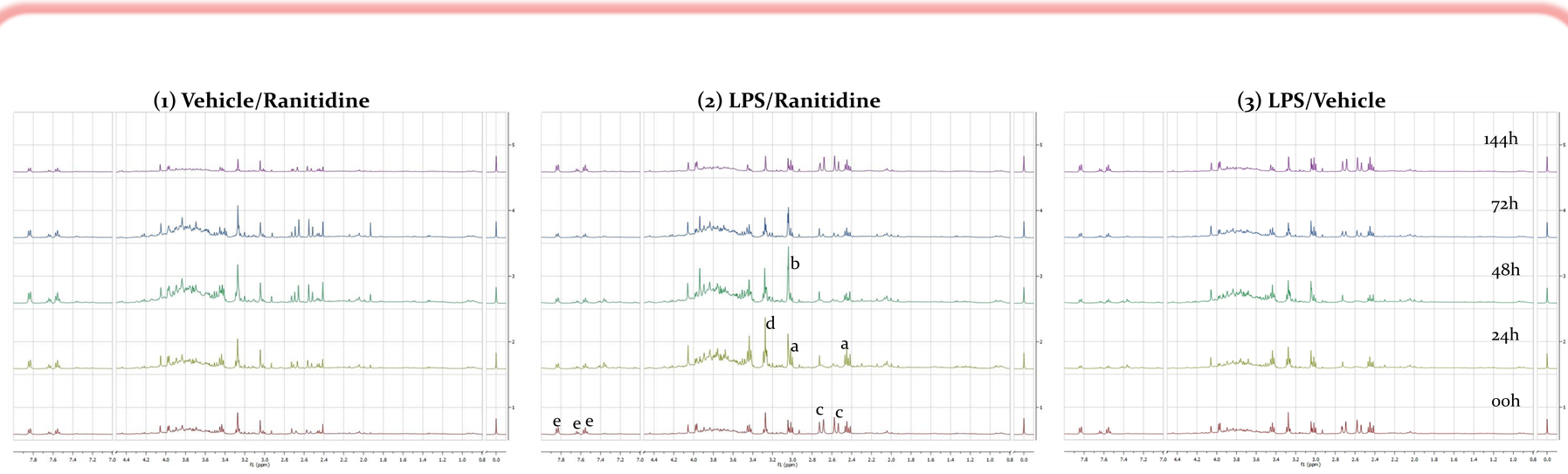


Fig.3: ^{1}H NMR spectra (400 MHz) of urine for "metabolic model" : Rats were pretreated with vehicle and after 30 mg/kg Ranitidine (1) or pretreated 2.5 x 10^6 EU/kg LPS and after 30 mg/Kg Ranitidine (2) or pretreated with LPS 2.5 x 10^6 EU/kg LPS and after vehicle (3). Peaks showing major differences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

Acknowledgements

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References

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