Preterm piglets as a translational model for premature babies: focus on hepatic drug metabolism

Laura Buyssens¹, Thomas Thymann², Melkamu Tessema³, Miriam Ayuso¹, Chris Van Ginneken¹, Steven Van Cruchten²

¹Applied Veterinary Morphology, Department of Veterinary Sciences, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium
²Comparative paediatrics and nutrition, Department of Veterinary and Animal Sciences, University of Copenhagen, Grønnegårdsvej 15, 1870 Frederiksberg C, Denmark

Corresponding author: tel.: + 32 (0)3 265.24.38 ; e-mail: laura.buyssens@uantwerpen.be

INTRODUCTION

Children and especially (premature) neonates are the most vulnerable group in the human population with regard to the use of medicinal products. Due to the associated risks and ethical concerns, studies in juvenile animals may be warranted for safety assessment of drugs in development. In this study, we investigated the preterm and term piglet as a translational model for preterm and term infants. More specifically, the early Phase I biotransformation capacity was investigated focusing on hepatic CYP3A activity.

METHODS

• Birth: Preterm (Gestational day (GD)105-107, N=38) & Term (GD115-117, N=56)
• Age at euthanasia: (Postnatal) Day 0, 5, 11, 19 & 26
• Two technical replicates, four biological replicates, CYP3A baculosomes as positive control

Liver samples snap frozen, stored at -80°C

Isolation liver microsomes by different homogenisation, centrifugation & ultracentrifugation steps

Determination protein concentration: BCA assay

Determination CYP3A4-specific activity: Luciferin-IPA assay

RESULTS AND DISCUSSION

Figure 1: Formation of D-Luciferin in pmol/min/mg microsomal protein (MP). The mean value of 2 technical replicates for each animal is represented by a purple cube (female), orange dot (male) or blue triangle (positive control). Upper (dotted) and lower (dashed) horizontal lines represent the LLOQ and LLQ, respectively. Different letters indicate significant (p<0.05) differences between the age groups.

• CYP3A activity was detectable, but under the LLOQ for preterm and term Day 0, 5 and preterm Day 11 samples. (Only values above LLOQ were used for statistical analysis)
• There was no significant difference in CYP3A activity between term Day 11 and term Day 19 (p=0.812) and term Day 19 and preterm Day 26 (p=0.799)
• A significant difference was observed between term Day 26 on the one hand and term Day 11 (p=0.0008), term Day 19 (p=0.0007) and preterm Day 26 (p=0.0145) on the other hand

CONCLUSIONS AND PERSPECTIVES

• Hepatic CYP3A activity is detectable but under the LLOQ for the youngest age groups (preterm and term Day 0 & 5, preterm Day 11) and increases with age in other age groups
• Gestational age rather than postnatal age affects development of CYP3A activity
• These age groups will be further investigated for other biotransformation enzymes in order to further characterise the piglet as a translational model for paediatrics

ACKNOWLEDGEMENTS