The neonatal Göttingen Minipig as translational model for drug disposition in perinatal asphyxia

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Introduction

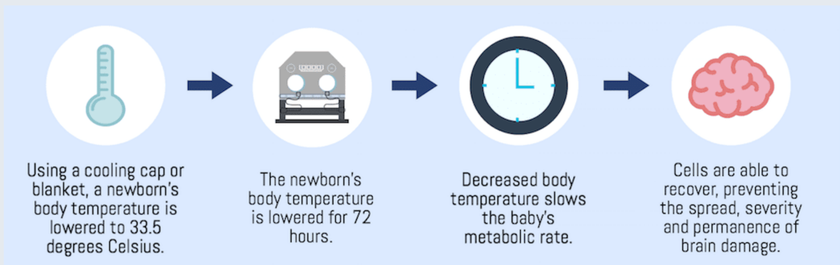
Oxygen deprivation

Perinatal asphyxia

Brain damage

Treatment of perinatal asphyxia (PA)

Therapeutic Hypothermia (TH)



Add-on drug treatment

Fentanyl
Midazolam
Topiramate
Phenobarbital

We hypothesized that **TH and PA** have an impact on CYP-mediated drug disposition. Because TH and PA cannot be studied separately in the clinical context, we used the **neonatal Göttingen Minipig** as translational model.

Methods

in vivo

in vitro

Gene expression

Göttingen Minipig Liver

↓

RNA

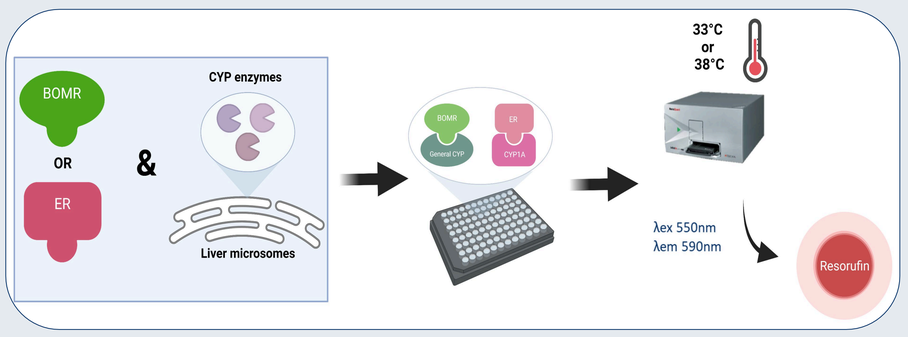
↓

cDNA & PCR + gel electrophoresis

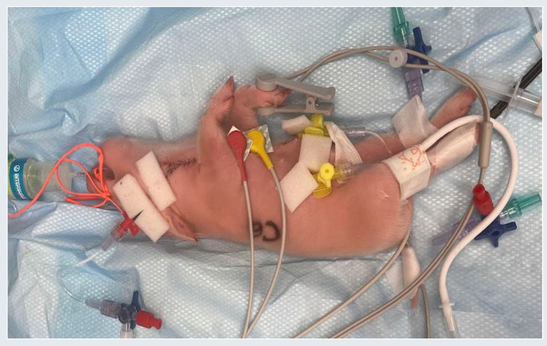
↓

Quantabio qPCR

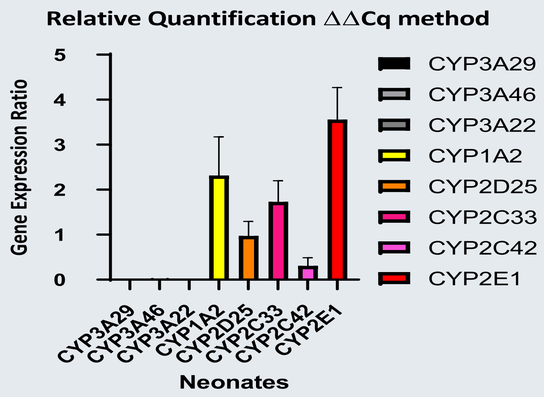
Fluorometry



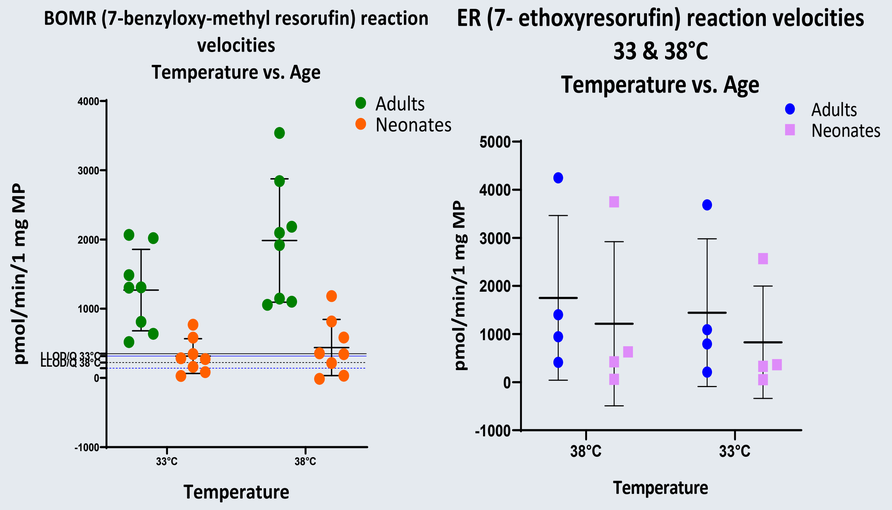
Results



- **Perinatal asphyxia can be induced in neonatal Göttingen Minipigs,** and the effect of perinatal asphyxia and therapeutic hypothermia on drug disposition can be studied separately, **for 24h.**



- **Neonates** have **lower CYP3A22, 29 & 46 gene expression** compared to adults. No difference in gene expression for CYP2E1, CYP2D25, CYP2C42 & 33, CYP1A2 were observed in neonates, compared to adults.



- **Neonates** have a **lower general CYP activity** as compared to adults. CYP activity, CYP1A2 in particular, is reduced in adults due to **cooling treatment.**

Conclusions

- **PA** can be induced in neonatal Göttingen Minipigs, and the effect of **PA and TH** on drug disposition can be studied separately, for **24h**.
- In vitro investigations showed **significant lower CYP3A22, 29 & 46 gene expression** and **significant lower general CYP activity in neonates** compared with adult Göttingen Minipigs. Once Göttingen Minipig liver microsomes were exposed to **in vitro cooling**, the **CYP activity** for adults **decreased significantly**.

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