**Human maturation of CYP450 enzymes, excerpts**

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The biotransformation rate of all three substrates increased with age, comparable with human maturation of CYP450 enzymes. The MPPGL decreased from birth till 8 weeks of age followed by an increase till 6–7 months of age. Significant sex differences in protein abundance were observed for CYP1A2, CYP2A19, CYP3A22, CYP4V2, CYP2C36, CYP2E_1, and CYP2E_2.

CYP450 enzymes are the most important phase I drug metabolizing enzymes, located on the smooth endoplasmic reticulum and highly expressed in liver compared to other tissues in pigs (Antonovic and Martinez, 2011; Nielsen et al., 2017). They metabolize between 70 and 80% of the human drugs used, most frequently by hydroxylation (Matalová et al., 2016). The ontogeny of the human CYP450 enzymes is rather well known. For example CYP2C9 enzyme activity increases rapidly after birth reaching adult values around 3 months of age, whereas CYP1A2 reaches adult values around 10 years of age (Alcorn and McNamara, 2002; Johnson et al., 2006; Matalová et al., 2016). In contrast to men, the ontogeny of CYP450 enzymes in pigs remains largely unknown.

In general, CYP3A4, CYP2C9, and CYP2E1 are estimated to contribute to the metabolism of over 50% of human drugs currently on the market (Alcorn and McNamara, 2002).

## Ie: CYP450 Enzyme Activity

The biotransformation rate of midazolam in pigs showed a steep increase during the first weeks of life followed by a gradual increase till 6–7 months of age.

The human maturation curves are in line with the results found in the current study. Edginton et al. (2006) reported an enzyme activity greater than adult values around the first year or two of life. This higher activity is also observed in 4-week-old piglets compared to 8-week-old piglets (Figure 1).

The enzyme activity of tolbutamide in pigs, which is a specific human CYP2C9 substrate, increased gradually to a plateau with adult values reached at 8 weeks of age.

Hu (2015) noticed a slightly different maturation curve in pigs, where no plateau was reached at 20 weeks of age. In humans, Johnson et al. (2006) reported a similar maturation curve as observed in the current study, where adult values are reached around 6 years of age.

the chlorzoxazone activity gradually increased during the first 8 weeks of life, reaching a plateau at 6–7 months of age. When expressed as nmol/min/g liver, the activity remained constant during the first 8 weeks of life and increased when reaching puberty.

However, when looking at the individual age categories it seems that only at 6–7 months of age CYP3A22 showed a high correlation with midazolam biotransformation. In the younger age categories other CYP450 proteins seem to be involved in the biotransformation. This might be an indication that during development other CYP450 enzymes take over when the CYP450 of interest is not yet abundant enough.

At 2 days of age only 14% of CYP450 proteins are present compared to the 6- to 7-month-old pigs, which is reflected in a very low biotransformation rate of the three substrates. Four- and eight-week-old piglets have around 50% of CYP450 proteins compared to the 6- to 7-month-old pigs. At 6–7 months of age, the amount of CYP450 proteins is considered to be at maximum adult values with 100% CYP450 proteins present in the liver.

Conclusion: This (Porcine) study provides more insight in the ontogeny of CYP450 mediated phase I metabolism in pigs, which can be used to support pediatric preclinical research. **Further research is required to evaluate age-related changes in CYP450 biotransformation involvement and the regulating developmental mechanisms.** Also, other relevant CYP450 enzymes and substrates should be evaluated.