Evaluation of liver metabolism following phenobarbital treatment in the Götttingen minipig

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INTRODUCTION
Rodent models are often used to study biochemical mechanisms of toxicity and to establish the toxicological mode of action (MOA) for observed adverse chemical-induced effects. Phenobarbital (PB), a barbiturate sedative known for its liver enzyme inducing effects, has been shown to induce liver CYP2B, CYP3A and UGT enzymes in rodents, leading to increased thyroid hormone clearance followed by increased thyroid stimulating hormone and subsequent stimulation of cell proliferation in the thyroid, producing thyroid tumors after long-term exposure. This pathway is not completely investigated in nonrodent models. In this study, two groups of 3 male Göttingen minipigs were orally administered either with PB at 15 mg/kg/day in capsules (treated group) or with empty capsules (control group) for 6 days followed by evaluation of phase I and II liver enzymes (mRNA expression and enzyme activities), gene expression profiles in the liver, circulating thyroid hormone levels and a standard toxicological exam.

RESULT
The expected pharmacological effects of daily PB administration were observed in treated animals, including mild to moderate sedation. No significant effects on body weights, hematology or clinical pathology were observed in the PB-treated group. PB increased liver weights (absolute by 46% and relative by 41%) and produced mild, diffuse hepatocellular hypertrophy following 6 days of oral administration. PB treatment led to a reduction in plasma concentrations of T3 (by 27% and 47%) and T4 (by 15% and 20%) at 24 hours and after 6 days of administration, respectively, versus predose values. PB induced approximately 2-fold increases in enzymatic activities of CYP3A429 and CYP4A24, a 5-fold increase in CYP1A2 and a 14-fold increase in CYP2B22 compared to the control group, with increases also observed in mRNA expression of these genes. CYP2B22, CYP2A19, CYP2C42, CYP3A39 and CYP3A46 were among the top 20 upregulated genes, and a 1.6-fold increase in T4-specific UGT enzyme activity was observed in the PB-administered group.

CONCLUSION
This study demonstrates that several early biochemical key events in the liver following PB-administration in rodents are also present in PB-treated minipigs. Further investigation is needed to determine whether long-term PB exposure in minipigs can lead to the adverse outcomes observed in rodents. It is concluded that the minipig is a useful model for the studies of effects on metabolism and the tissue consequences of xenobiotics on the liver-thyroid axis.
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