INTRODUCTION

The nuclear hormone receptors PXR and CAR are known to regulate hepatomegaly. PB, a nongenotoxic hepatocarcinogen, activates CAR and induces hepatomegaly (characterised by hypertrophy and hyperplasia using Cyp2b10 induction and cell proliferation as respective markers). CAR-mediated cell proliferation is a key event in PB-induced hepatocarcinogenesis. Mice devoid of the CAR receptor cannot activate the Cyp2b10 gene or induce the hyperplastic response in response to PB dosing.

To compare the activation of the human and murine receptors, PB was administered via the diet for 7 days at four escalating doses to huPXR/huCAR mice and C57BL/6 (WT) mice. Hepatocellular proliferation (S-phase) and hepatic microsomal pentoxyresorufin-O-depentylation (PROD) was measured, along with the PB levels achieved in the plasma at termination.

METHODS

Male WT C57BL/6 mice were obtained from Harlan (UK) and male huPXR/huCAR mice were obtained from Taconic Farms (NJ, USA). All mice were 10-12 weeks old at the beginning of the study.

PB was administered in the diet at 0, 200, 500, 750 and 1000 ppm to both strains of mice for 7 days. S-phase was determined using implanted osmotic pumps containing bromodeoxyuridine (BrdU) solution, followed by immuno- cytochemistry. Cyp2b10 induction was assessed by measuring the levels of microsomal PROD. Additionally, terminal plasma samples were assessed by reverse phase LC-MS/MS for PB levels.

RESULTS

Table 1 details a number of parameters including dose level achieved in the diet and food consumption. As the latter parameter was higher at several doses in the huPXR/huCAR mice, the PB levels measured in the terminal plasma samples were also elevated. Both strains demonstrated a dose related increase in liver/body weight ratios.


tables

Table 1: Various parameters concerning dietary PB administration, terminal PB levels and liver/body weight information. *Values in bold are statistically significant (P < 0.05) using the Student’s T-Test (n=10).

Table 2: S-phase labelling index in huPXR/CAR mice vs. WT mice following PB administration

Figure 1: PROD assessment in huPXR/CAR mice vs. WT mice following PB administration

Figure 2: S-phase labelling index in huPXR/CAR mice vs. WT mice following PB administration

CONCLUSION 1

- The PB dose-response was equivalent in both the WT and huPXR/huCAR mice with respect to Cyp2b10 induction, when the terminal plasma PB level was taken into account.

REFERENCES


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