Dokumenttyp: journal article

Autor(en) des Beitrags: Labedzki, A; Buters, J; Jabrane, W; Fuhr, U

Titel des Beitrags: Differences in caffeine and paraxanthine metabolism between human and murine CYP1A2.

Abstract: For the characterisation of murine models of CYP1A2 mediated metabolism in humans we compared the metabolism of caffeine and paraxanthine in human liver microsomes (LM) (two samples) and in LM from CYP1A2-null and wild-type mice. Inhibition experiments were carried out with the quinolones norfloxacin and pefloxacin and the substrate, caffeine. Additionally, in vivo pharmacokinetics of paraxanthine was determined in CYP1A2-null and wild-type mice. All LM produced the primary metabolites of caffeine and paraxanthine. In human LM, the main metabolite of caffeine was paraxanthine (K(M) 0.4 and 0.5 mmol L(-1)). In wild-type and CYP1A2-null mice LM, the main caffeine metabolite was 1,3,7-trimethylurate, but formation was not saturable. Apparent K(M) for paraxanthine formation from caffeine in wild-type and CYP1A2-null murine LM were 0.2 and 4.9 mmol L(-1), respectively. The main metabolite of paraxanthine was 1-methylxanthine in human (K(M) 0.13 and 0.2 mmol L(-1)) and in wild-type mice LM (K(M) 0.53 mmol L(-1)). In CYP1A2-null murine LM, the main paraxanthine metabolite was 7-methylxanthine. The quinolones competitively inhibited caffeine metabolism in human but not in wild-type or CYP1A2-null murine LM. No obvious differences were seen for blood pharmacokinetics and urinary metabolite excretion of paraxanthine between CYP1A2-null and wild-type mice. Thus, for paraxanthine, norfloxacin and pefloxacin interaction...
with CYP1A2 there were clear differences between mice and man. Our results suggest that an interspecies comparison is required for the metabolism of individual xenobiotics interacting with CYP1A2 prior to the use of mice models to predict its toxicity and/or pharmacological activity in man.