# Effect of experimentally induced liver cirrhosis on CYP3A induction in male Wistar rats

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Drug-drug interactions are a remarkable problem in health care since they are responsible for a great number of adverse drug reactions, especially in elderly patients who are often under polymedication. Since metabolism is the main pathway of drug elimination and cytochromes P450 (CYPs) are the major enzymes involved, most drug-drug interactions arise from either inhibition or induction of CYP enzymes. Although induction has long been investigated in patients with cirrhosis, highly discrepant results have been obtained; moreover, the mechanism underlying the possible effect of cirrhosis on induction has not been clarified. Because of ethic constraints, human studies thus far performed often lack rigorous methodology. Therefore, animal studies are necessary to clarify the influence of liver disease on CYP induction. This study was designed to compare CYP3A induction in healthy rats and rats with experimentally induced liver cirrhosis stratified according to the degree of liver dysfunction. We focused on CYP3A1 and CYP3A2 enzymes, which are closely related to human CYP3A4.

We used 3 groups of male Wistar rats, one of healthy animals and two groups of rats with carbon tetrachloride ($CCl_4$)-induced cirrhosis. The severity of liver cirrhosis was determined on the basis of histological examination (Ishak score), the presence or absence of ascites, and laboratory data (PT, albumin, AST and ALT).

Each group was divided in 2 subgroups of 6 rats, one treated with vehicle (olive oil), the other with the prototypical CYP3A inducing agent dexamethasone (DEX), which activates the PXR nuclear receptor. The inducing effect was assessed by measuring the activity of CYP3A1 and CYP3A2, using liver microsomes obtained from normal and $CCl_4$-treated rats. 4-OH-hydroxilation of midazolam (MDZ) was used as a validated marker reaction for CYP3A1 and CYP3A2. Western blot analysis and quantitative RT-PCR were performed to evaluate protein and gene expression, respectively, of the two CYP3A isoforms.

Our data show that DEX treatment significantly increased $V_{max}$ of 4-OH-midazolam (4-OH-MDZ) formation in healthy and non ascitic rats, whereas no statistically significant induction of this metabolic reaction was observed in ascitic animals. CYP3A1 gene and protein expression was markedly increased by DEX treatment in all groups of rats, whereas gene and protein expression of CYP3A2 increased significantly in healthy and non ascitic rats, but not in those with ascites.

In conclusion, our data show that the inducibility of CYP3A1 mRNA and protein is well preserved in cirrhosis, regardless of the degree of liver dysfunction, whereas that of CYP3A2 is markedly reduced when liver dysfunction becomes severe. Since the inductive effect of DEX on 4-OH-MDZ formation is severely curtailed only in ascitic rats, CYP3A2 is probably the most important CYP3A isoform catalyzing this metabolic reaction in male Wistar rats.