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Antagonism of Paracetamol and Ethanol Metabolism in Liver System p450 in Rabbits. Development of an Experimental Animal Model

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INTRODUCTION

In this experimental Study the contribution of the metabolic way of P450 after taking paracetamol hyperdose, and simultaneously the increase of hepatic necrosis after a chronic administration of alcohol is emphasized. Also we examined the possible mechanism of aversion of paracetamol metabolism, after acute ethanol administration, resulting in prevention of paracetamol induced hepatotoxicity.

MATERIALS AND METHODS

Totally 24 animals were used (male rabbits, New Zealand, 2.5-3 kg) and divided in four groups with 6 animals in each group. Group1 (G1): 2000 mg paracetamol/kg B.W., Group2 (G2): 1500 mg/kg B.W., Group3 (G3): alcohol administration for 7 months (50% of calories needs) and paracetamol administration at the end of this period (1500 mg/kg B.W.). Paracetamol was diluted in normal saline 0.9% and was given using a pediatric plastic catheter. The alcohol (20% solution) was mixed with water. Group4 (G4): Same as in G1 and also alcohol was given (solution 20% in dose 4g/kg B.W.). Blood samples were collected for biochemical evaluation and HPLC analysis (paracetamol levels and metabolites) at 6, 12 and 24 hours and 30 min., 2 h., 4 h. and 6 h. respectively. At the end of the experiment, the animals were euthanized and the liver was plugged in potassium chloride. Also, liver sections were fixed in formaldehyde for pathology examination.

RESULTS

G1: In 5/6 animals (83%) liver necrosis was observed. Biochemical data showed a moderate elevation of transaminases at 6 h. and a higher one at 12-h. *G2* : 1/6 animals (16%) had liver necrosis and the rest inflammatory changes only. *G3* : 3/6 animals (60%) had liver necrosis and high levels of transaminases (*10 higher than the normal levels) at 12 h. and 24 h. *G4*: In this group in 1/6 animals (16%) liver necrosis and a light elevation of transaminases were observed. Cytochrome P450 in the liver was measured by a Spectrum fluoremeter method. A significant elevation of P450 was found in G3, in comparison to G2, while a decrease of P450 activity was found in G4 in comparison to G1. In the alcoholic animals (G3) higher levels of glucoronide conjugate were observed, in comparison to G1. Concerning the sulfate conjugate, no significant differences were found. For the toxic metabolite of paracetamol, a significant increase was observed in G3, in comparison to G2. In G4, a decrease of toxic

metabolite was observed, in comparison to G1. In the animals in which liver necrosis was observed, increased levels of glucoronide conjugate and toxic metabolite were found.

CONCLUSIONS

We well know from our previous experimental work that the dose of 2000 mg/kg B.W. is the toxic dose. The dose of 1500 mg/kg B.W. produced also necrosis but in lower levels than G1. The use of alcohol in G3 (same dose with G2) produced higher hepatotoxicity because of the higher production of the toxic metabolite due to the induction of cytochrome P450 by alcohol. The preventive effect of the alcohol administration in the paracetamol induced hepatotoxicity, when given simultaneously is due to the metabolic priority of the alcohol in the cytochrome P450 metabolic system resulting in the aversion of paracetamol metabolism to other pathways and the production of less toxic metabolites.