The hepatoprotective effect of carvedilol, prazosin, metoprolol and prazosin plus metoprolol against paracetamol-induced hepatotoxicity in rabbits

A thesis

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Abstract

Background

Paracetamol is a widely used over-the-counter analgesic and antipyretic, it is a major cause of acute liver failure that represents a significant clinical problem. Paracetamol mainly metabolized by the liver and acute oral overdose with paracetamol can be extremely serious due to severe hepatotoxicity with centrilobular necrosis. In paracetamol toxicity, there is evidence that plasma catecholamine levels were significantly elevated.

Adrenergic blockers like (carvedilol, prazosin and metoprolol) are known to have beta and/or alpha adrenergic blocking activities with additional antioxidant effect, which explains most of their pharmacological actions that is involved in protection against disease or chemical induced hepatotoxicity. In view of these findings, it is thought that they could have a beneficial effect in paracetamol-induced hepatotoxicity.

Aim

To investigate the possibility of hepatoprotective effects of adrenergic blockers (carvedilol, prazosin, metoprolol and prazosin plus metoprolol) in paracetamol-induced hepatotoxicity in rabbits.

Materials and methods

The experiment was carried out on thirty six locally bred sexually mature domestic male rabbits, they were randomly divided into six groups according to treatments (six in each) as follows: Group 1 (negative control group): Animals in this group received distilled water orally for nine days. Group 2 (paracetamol treated group): regarded as a positive control group, animals in this group received a single daily dose of paracetamol (1gm/kg/day, orally) for nine days. Group 3 (carvedilol + paracetamol treated group), group 4 (prazosin + paracetamol treated group), group 5 (metoprolol + paracetamol treated group) and group 6 (prazosin + metoprolol + paracetamol treated group): Animals in these groups were given paracetamol in the same manner as in the second group but they were pretreated with a single daily dose of the following adrenergic blockers:

carvedilol (10 mg/kg/day, orally), prazosin (0.5 mg /kg /day, orally), metoprolol (10 mg/kg/day, orally), and a combination of metoprolol (10 mg/kg/day, orally) and prazosin (0.5 mg/kg/day, orally) respectively, one hour before paracetamol treatment for nine days. The rabbits were sacrificed at day 10.

The response to treatments was evaluated by histopathological examination of the liver, measurement of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and total bilirubin. Assessment of oxidative stress was made by measurement of malondialdehyde (MDA) and glutathione (GSH) in serum and liver homogenate.

Results

There were complete absence of histopathological changes in five of six rabbits on the combination of prazosin + paracetamol treated rabbits, improvement with very mild histopathological changes in one rabbit in comparison with the moderate to sever hepatotoxicity that was observed in paracetamol treated rabbits. There were normal histopathological pictures in the control group rabbits. In rabbits on paracetamol treatment, there was a significant elevation of serum levels of the following parameters in comparison to control group, malondialdehyde (MDA) (0.5 ± 0.29 vs. 0.2 ± 0.03 µmol/l), aspartate aminotransferase (AST) (31 ± 8.06 vs. 11.5 ± 3.14 U/I), alanine aminotransferase (ALT) (15.8 ± 8.23 vs. 6.5 ± 1.87 U/I), alkaline phosphatase (ALP) (75.4 ± 27 vs. 38.2 ± 20.5 IU/L) and total bilirubin (0.79 ± 0.56 vs. 0.3 ± 0.14 mg/dl), and significant depletion in serum glutathione (GSH) in comparison to control group (10.5 ± 4.03 vs. 19.9 ± 10.9 nmol/ml). Similarly, significant elevation of malondialdehyde (MDA) in liver homogenate was seen in paracetamol treated rabbits in comparison to control (3958 ± 1016 vs. 2206 ± 580 nmol/g).

On histopathological examination, three from six rabbits on carvedilol + paracetamol treated group appeared completely normal and mild to moderate histopathological changes in the other three rabbits. Significant reduction of serum levels of the following parameters in comparison to paracetamol treatment, malondialdehyde (MDA) (0.2 ± 0.1vs. 0.5 ± 0.29 µmol/l), alkaline phosphatase (ALP) (41.9 ± 19.7 vs. 75.4 ± 27 IU/L)

and total bilirubin (0.31 ± 0.22 vs. 0.79 ± 0.56 mg/dl). Similarly, significant reduction in malondialdehyde (MDA) was observed in liver homogenate in comparison to paracetamol treatment (2113 ± 567 vs. 3958 ± 1016 nmol/g).

Hepatotoxicity of paracetamol was not affected by metoprololol treatment. Slightly and insignificant changes were noticed in liver function enzymes tests and oxidative stress parameters. There were mild histopathological changes in all six rabbits on prazosin + metoprolol + paracetamol treatment in comparison to paracetamol treated group. Significant reduction of serum levels of these parameters in comparison to paracetamol treated rabbits were seen, malondialdehyde (MDA) (0.23 ± 0.09 vs. 0.5 ± 0.29 µmol/l), alkaline phosphatase (ALP) (39.2 ± 2.91 vs. 75.4 ± 27 IU/L) and total bilirubin (0.34 ± 0.14 vs. 0.79 ± 0.56 mg/dl). Similarly, significant reduction in malondialdehyde (MDA) was observed in liver homogenate in comparison to paracetamol treatment (2356 ± 935 vs. 3958 ± 1016 nmol/g). Changes in serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and glutathione (GSH)(in both serum and tissue homogenate) also observed but did not achieve statistical significance.

Conclusions

Carvedilol and prazosin have hepatoprotective effects in paracetamol-induced hepatotoxicity, combination of prazosin and metoprolol have moderate, while metoprolol alone has a little hepatoprotection.