IMPLICATIONS OF APITHERAPY REGARDING THE EVOLUTION OF BILIRUBIN IN ACETAMINOPHEN INDUCED INTOXICATION

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Summary

Acetaminophen is a drug substance with analgesic and antipyretic effects, with a frequent use in Europe and United States. Found in over 100 pharmaceutical products, it is one of the most common drugs with liver and kidney toxicity potential. The drug-induced affection was achieved by gavage administration of acetaminophen (100 mg/100 g), for 2 weeks. Administration of acetaminophen resulted in the increase of total, direct and indirect bilirubin levels. Administration of apitherapy products to the group of animals with acetaminophen induced toxicity determined the decrease of the values for total, direct and indirect bilirubin. Supplementation of apitherapy diet with Royal Jelly led to the decrease of total and indirect bilirubin levels, and the increase of the values for direct bilirubin.

Key words: apitherapy, bilirubin, acetaminophen

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Introduction

Acetaminophen is one of the most used analgesic and antipyretic substances, also characterized by liver and kidney toxicity (Perry et al., 1998).

Bilirubin is produced in macrophages by the enzymatic catabolism of the heme fraction from different proteins. The oxidation of heme generates biliverdin, which is afterwards metabolized to bilirubin (Wallach, 2001). Bilirubin circulates through the blood, being transported to the hepatic level as a soluble complex, i.e. bilirubin-albumin (Atanasiu and Mohora, 2004). The serum levels of bilirubin increase when its production surpasses its metabolism and excretion (Braunwald et al., 2003).

In the present experiment, the influence of apitherapy diet, single or in combination with Royal Jelly (RJ – supplement with many uses – Nicula et al., 2010), was studied in acetaminophen induced toxicity by evaluating the levels of total, direct and indirect bilirubin.

Material and methods

The experimental model included 6 groups of Wistar rats: control group standard food (group I - normal status, standard food), control group apitherapy diet (group II - normal status, apitherapy diet), control group apitherapy diet + RJ (group III - normal status, apitherapy diet and RJ), acetaminophen group (group IV - acetaminophen-induced toxicity, standard food), acetaminophen group + apitherapy diet (group V - acetaminophen-induced toxicity, treated with apitherapy diet), acetaminophen group + apitherapy diet + RJ (group VI - acetaminophen-induced toxicity, protected with apitherapy diet and RJ).

The drug-induced toxicity was achieved by gavage administration of acetaminophen (100mg/100g), for 2 weeks. The treatment consisted of apitherapy diet, single or in combination with RJ.

After 3 weeks of experiment, the laboratory animals were anesthetized with thiopental (dose of 1 ml/100 g from a
0.01% thiopental solution), blood samples were collected by the puncture of the cord with a Vacuette® system and submitted to the investigation of total, direct and indirect bilirubin levels.

The statistical interpretation of the results was performed with One-Way ANOVA test and Tukey’s post-hoc test. The results were given as mean ± standard deviation. The value of p<0.05 was considered significant.

Results and discussions

In animals with acetaminophen-induced toxicity (group IV), when compared to the other experimental groups, the increase of the following parameters was obtained: i) total bilirubin (0.138 ± 0.014 versus 0.115 ± 0.007, the value for group I; 0.138 ± 0.014 versus 0.095 ± 0.007, the value for group III) (fig.1), ii) indirect bilirubin (0.125 ± 0.01 versus 0.101 ± 0.01, the value characteristic for group I; 0.125 ± 0.01 versus 0.085 ± 0.007, the value registered for group III) (fig.2).

Administration of apitherapy diet to laboratory animals with acetaminophen-induced toxicity (group V) determines the decrease of bilirubin levels, in comparison with the unprotected group (group IV): i) total bilirubin (0.138 ± 0014 versus 0.101 ± 0.017) (fig.1), ii) indirect bilirubin (0.125 ± 0.01 versus 0.091 ± 0.01) (fig.2).

Supplementation of apitherapy diet with RJ in laboratory animals with acetaminophen-induced hepatopathy (group VI) leads to the decrease of bilirubin levels when compared to the untreated group (group IV): i) total bilirubin (0.138 ± 0014 versus 0099 ± 0017) (fig.1); ii) indirect bilirubin (0.125 ± 0.01 versus 0.087 ± 0.014) (fig.2).

It is known the fact that 80% of the circulating bilirubin derives from the old erythrocytes. The rest of it comes from other sources, such as the damage of the mature erythrocytes from the bone marrow or the metabolism of other proteins that contain heme - hepatic cytochromes, muscle myoglobin, enzymes. Thus, the increase of bilirubin levels for the group with acetaminophen induced hepatotoxicity may be not only due to the liver affection, but also due to the hematologic disorder sustained by the decrease of erythrocytes obtained in the present experiment (unpublished data) and by other experimental studies (Andriţoiu et al., 2011c). The obtained results are correlated with the results of other reported studies (Andriţoiu et al., 2010; Andriţoiu et al., 2011a, Andriţoiu et al., 2011b).
**Fig. 3** - Mean values and SD for conjugated bilirubin

The significant increase of conjugated bilirubin for the group treated with apitherapy diet and RJ (fig. 3) is surprising and may be explained, probably, by the supplementation of the apitherapy diet with RJ, as it is known the fact that the administration of this bee product is possible only after the evaluation of the serum protein electrophoresis.

**Conclusions**

1) Administration of apitherapy diet to the group that had previously received acetaminophen proved to be efficient in bringing the levels of total bilirubin to normal values.

2) Supplementation of the apitherapy diet with Royal Jelly for the group that had previously received acetaminophen demonstrated its efficacy by improving the total bilirubin levels.

3) Administration of apitherapy diet to the group with acetaminophen induced toxicity resulted in normal levels of indirect bilirubin.

4) Administration of apitherapy diet in combination with Royal Jelly to the group with acetaminophen induced toxicity proved its efficacy by improving the indirect bilirubin levels.

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**References**


