Liver cell death induced by 4-aminopyridine in a repeated dose (28 days) oral toxicity study in rats: Gene expression profile of hybrid cell death

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INTRODUCTION

4-Aminopyridine (4-AP) is an orphan drug indicated for the treatment of neuromuscular disorders. There is a great controversy around the use of this drug because of its narrow safety index and because a large number of adverse effects have been reported. Moreover, it was shown to induce cell death in different cell lines, being reported mainly apoptosis and necrosis as the principal pathways of cell death mediated by blockage of K channels or the Na, K-ATPase, but until now it was not described in vivo cell death induced by 4-aminipyridine.

AIM

Provide new subchronic toxicity data and specifically, evaluate if 4-AP (2, 4 and 10 mg/kg) is able to induce in vivo cell death process in liver.

METHODS.

A repeated dose (28 days) oral toxicity study, at therapeutic range of doses, was conducted in rat livers. The anatomical pathology, the biochemical and hematological parameters were analyzed.

RESULTS

The leucocytes number, LDH and AST enzymatic activity were increased at all dose but the erythrocytes number, the hemoglobin concentration, FAL and ALT enzymatic activity were increased only at highest dose studied. However, glucose levels decreased at all doses.

CONCLUSIONS

The present work shows for the first time in vivo cell death on liver induced by 4-AP and the biochemical and the gene expression profile shows that the cell death is mediated by necrotic and apoptotic pathways.

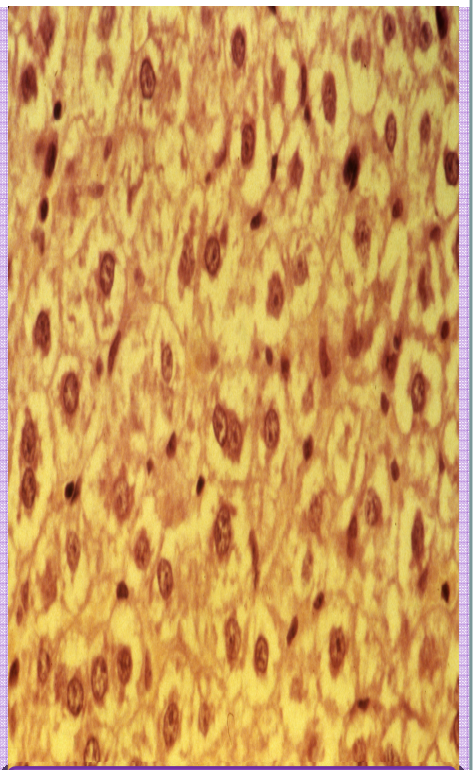

Fig. 1. Liver of animal treated with 4-AP at dose of 10 mg/kg (×300).