HISTOPATHOLOGIC CHANGES IN LIVER AND SMALL INTESTINE INDUCED BY KETOROLAC AND KETOGAL REPEATED ORAL TREATMENT IN MICE

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Introduction: Ketorolac is a powerful non-steroidal anti-inflammatory drug (NSAID), with a great analgesic activity. Despite the excellent therapeutic activity, the chronic use of ketorolac has long been limited owing to the high incidence of gastrointestinal and kidney side events. In our previous studies, we demonstrated that ketorolac-galactose conjugate (ketogal) was able to reduce ulcerogenicity, while preserving the high pharmacological efficacy of ketogal, both in a single oral administration and in a repeated oral treatment. Here, in order to corroborate these data and to assess ketogal toxicity, we evaluated histological aspect of small intestine and liver.

Materials and methods: Swiss CD1mice were orally treated for 5days with ketorolac (10 mg/kg) and equimolecular dose of ketogal (16.3mg/kg). Then, histological evaluations were performed: in particular, the presence of fibrosis in liver sections was assessed.

Results: In mice treated with ketorolac we observed severe vacuolations and erosion of the intestinal villi with edematous areas. On the contrary, ketogal pointed out a significant improvement of the intestinal morphology, which appears to be comparable to the control group. Regarding the liver, ketorolac treatment highlighted a sinusoidal spaces impairment and a vacuolation of the hepatocyte's cytoplasm. In mice treated with ketogal there is a general improvement in the tissue histology even if the hepatocyte's vacuolation persists in some areas. Histological results on small intestine and liver clearly showed that our prodrug is able to induce lower intestinal and liver damage than ketorolac.

Discussion and conclusions: These data obtained in small intestine and liver, together with those already published on stomach and kidney, would seem to confirm a better safety profile of the ketogal compared to ketorolac. Although ketorolac side effects are minimized by the combined use of gastroprotectors (proton-pump inhibitor), it is known that they also have side effects and are related to the onset of neurodegenerative diseases. So, the possibility of administrating only one drug would seem to be the best alternative in terms of health and public spending. Further study will be carried out to better understand if the morphological improvement observed after ketogal treatment also influence the metabolic state of these organs.