SAFETY STUDIES OF EGF + GHRP6 COMBINATION THERAPY FOR THE TREATMENT OF ACUTE PHASE OF CEREBRAL INFARCTION

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Introduction

Epidermal growth factor (EGF) and growth hormone releasing peptide-6 (GHRP-6) showed physiological and pharmacological properties in experimental, clinical events, highlighting cytoprotective effects in liver, heart tissues, and striking in the treatment of burns, wound healing, surgical degenerative processes, and tissue degeneration in radioepidermitis radiodermatitis cytostatic extravasation ulcers circulatory insufficiency results.

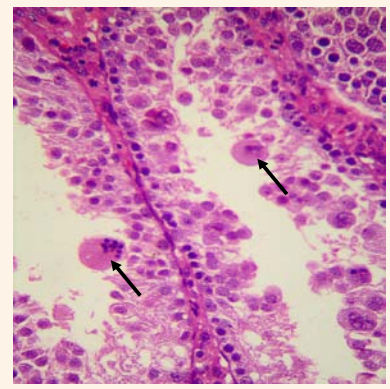
Methods

Objective: Based on the results of EGF + GHRP-6 combination in these contexts and in order to translate these findings to clinical trials, there was a need to evaluate the toxicological profile using safety studies of this combination as a single product.

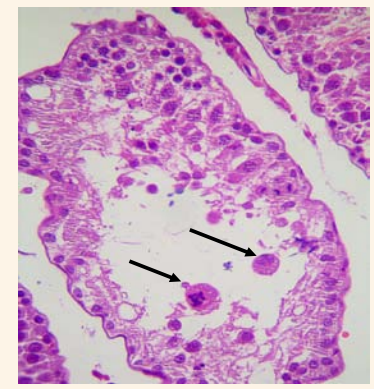
Methods: Several studies were carried out, including a first wave study (a single administration of doses up to 280 times the therapeutic dose (TD)), a repeated dose study (14 administrations up to 10 times the TD) and a local tolerance study (15 administrations up to 180 times the TD). The animal species used as test systems were: Cenp:Wistar Rats or F1 rabbits (NZ x Semi-Giant), young males and females, administered with intravenous and intraperitoneal injections. In each of the studies, five experimental groups were established: Untreated control group, Placebo group, and three dose levels, calculated from human TD and the average body weight of animals in the studies. In the local tolerance study an irritation index was determined by classifying the level of irritation of the product. In general, studies also allowed us to assess the reversibility of unwanted effects via a satellite group and residual effects on the target organs, physiological and metabolic tolerance, clinical evaluations and body weight analysis, food consumption, hematological and biochemical parameters, and macroscopic and microscopic findings in organs and tissues.

Results

In the fist wave and local tolerance studies, no observations or values that could indicate toxic effects of the product were found. No anatomical or behavioral abnormalities were evidenced. A progressive increase of body weight was shown, corresponding to a normal food intake during the study. The values obtained in hematology and biochemistry pathology were normal as they were within the physiological range for the species. In the macroscopic observations there were no signs attributable to the test substance in any organ of the studied animals. In the local tolerance study, the irritation rate was zero (0) for all treated groups, corresponding to the Non-irritating category of the used scale. Moreover, in the repeated dose study testicular atrophy was observed in the middle (60 times the TD) and high (180 times the DT) doses. This was an irreversible event within 15 days after the last application of the test substance, and was consistent with the values of organ weights reported for these groups.



Testicle. Focal atrophy. Presence of giant cells (black arrows) in an animal received 180 times the TD. H&E. 40X.



Testicle. Focal atrophy. Giant cells (black arrow) in an animal of the Satellite group who had received 180 times the TD. H&E. 40X.

Conclusions

The combination of epidermal growth factor (EGF) and growth hormone releasing peptide-6 (GHRP-6) when repeatedly applied at doses greater than 60 times the TD, it elicit adverse effects in the male reproductive system; and at doses up to 10 times the TD, it is classified as non-toxic and non-irritating.