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Preliminary Study for the Toxicity Study on Sodium Hyaluronate (Na-HA) in Rats by Repeated Oral Administration for 13 Weeks

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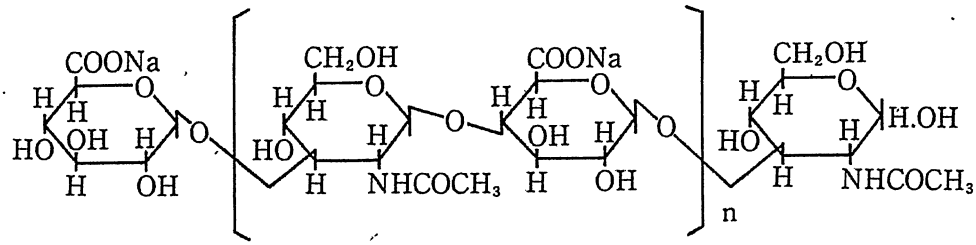
Abstract

Sodium hyaluronate (Na-HA) was given orally to SD-rats at dose levels of 12.5, 25 and 50 mg/kg/day for 13 weeks, additional study was conducted by the dose levels of 3.13 and 6.25 mg/kg/day. A control group received the phosphate buffered physiological saline solution. Furthermore, 1% methylcellulose solution group was set. The following changes occurred : a significant suppression in body weight gain rate and body weight gain rate in male of the 25 mg/kg and higher groups, sporadic decrease of food consumption in male of the 50 mg/kg group, no difference was found in food efficiency of each group. A significant increase in serum Na and Cl concentration were found in female of 25 mg/kg and higher groups.

No relation to the administration of the test substance were noted in general signs, water consumption, urinalysis, hematology, blood chemistry, autopsy and histopathology in both



Formula : $(C_{14}H_{20}NNaO_{11})$ n
Mol. Wt. : 401.30×n
n : 1,500～3,000

Fig. 1 Chemical structure of sodium hyaluronate (Na-HA)

sexes.

From the above results, it is considered that the dose level of the main study should be at 3.13, 6.25, 12.5, 25 and 50 mg/kg/day, as same as in this preliminary study. A necessity was suggested to investigate the effect of sex hormone, because the changes found in the 25 mg/kg and higher groups were different among sexes.

Introduction

Hyaluronic acid is one of typical glycosaminoglycans which are distributed in animal connective tissues, and it is a linear polysaccharide constructed out of repeated unit of N-acetyl-D-glucosamine and D-glucuronic acid. Sodium hyaluronate (Na-HA) derived from rooster combs is now being developed for the treatment of coneal epithalial diseases. LD_{50} values of mice, rats and rabbits by single oral dose are reported to exceed 2,400, 800 and 1,000 mg/kg, respectively[1]. However, toxicity of Na-HA by repeated oral dose is not reported. Before the conduct of repeated oral dose study, this preliminary study was conducted to set its dose levels and obtain its fundamental knowledge of evaluation items. This report describes the results of preliminary study for the toxicity on Na-HA in rats by repeated oral administration for 13 weeks.

Materials and Methods

1. Test substance

Na-HA (M. W. : 870,000～890,000) is a odorless, transparent and viscous 1% solution of sodium, hyaluronate dissolved in phosphate buffer physiological saline solution. The chemical structure of Na-HA is shown in **Fig. 1**.

2. Animals and animal husbandry

Male and female SD-rats (Crj:CD, SPF) of 4-weeks old were purchased from Chales River