Single dose oral toxicity study of Cetirizine in juvenile dogs

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SUMMARY

A single dose oral toxicity study of Cetirizine was carried out in juvenile dogs. Three-week-old Beagles were treated orally with Cetirizine at a single dose of 0, 30, 100 or 300 mg/kg. Each dose group consisted of 1 male and 1 female. After administration, the animals were observed for general signs and body weight changes for 14 days, then killed and recorded the major organ weights and examined macroscopically. The results obtained are as follows:

1) No animals died in any dose group.
2) In 30 minutes after administration, vomiting and depression of spontaneous movements appeared in the 100 and 300 mg/kg groups, and salivation in the 300 mg/kg group. All of these signs disappeared within 2 hours after administration.
3) Body weight loss was observed in both animals of the 300 mg/kg group after 1 day of administration.
4) No treatment related changes were observed in organ weights and macroscopic findings.

In conclusion, the approximate lethal dose of Cetirizine for juvenile dogs was more than 300 mg/kg in this study.
1. Materials and Methods

1. Test animals
   Beagle dogs (6 males and 6 females) were obtained at the age of 3 weeks from the Fuji Animal Farm Inc. on February 5, 1991. These animals had been fed with synthetic milk and weaning food from the age of 2 weeks, and weaned at the age of 3 weeks. They were judged to be healthy by examination of their surface, behavior and stools. The animals were transferred to an animal room and subjected to acclimation for 2 days. During this period, their physical condition was observed, and body weight and food consumption were measured. Healthy animals were used for the study. The age of the animals at administration was 3 weeks, and the body weight range was 0.82 - 1.00 kg for the males and 0.90 - 1.08 kg for the females.

2. Environmental conditions
   The animal room was maintained at 22±2 °C and 50±10 % relative humidity. The room was ventilated with fresh air at an exchange rate of 12 times per hour and light was provided from 6 a.m. until 6 p.m. daily. Each animal was housed in a stainless steel cage (70 × 69 × 84 cm). A heating panel was supplied to each cage for warming.
   A paste food which was prepared by mixing 80 g of pellet feed, 30 g of powdered milk and 250 ml of warm water was supplied to each animal daily in four feedings. Animals had free access to tap water obtained from a public supply.

3. Allocation
   Four males and 4 females were selected, and each dog was allocated to one of the treatment groups the day before administration. Clinical observation, body weight and litter of origin were taken into account during this procedure.

4. Administration

1) Route and procedure
   Animals were fasted for 17 hours prior to administration. The test article in gelatin capsules (Japan Pharmacopoeia Grade) was
administered orally in the morning. The animals in the control group received the same number of empty capsules as the animals in the high dose group. Feeding at 9 a.m. was omitted on the administration day.

2) Dose levels and groups

Four groups were employed as follows:

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg)</th>
<th>Number of Animals</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (gelatin capsules)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cetirizine, low dose</td>
<td>30</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cetirizine, medium dose</td>
<td>100</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cetirizine, high dose</td>
<td>300</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

3) Selection of dosage levels

In the previous oral acute toxicity study of the test article in adult beagles, vomiting was observed in the 160 and 320 mg/kg groups, and nervous in the 320 mg/kg group. Therefore, a dose of 300 mg/kg was adopted for the high dose in this study. Dosages for medium and low levels were set to be 100 and 30 mg/kg, respectively, according to a common ratio of 3.

5. Observations and measurements

1) General signs

Animals were frequently observed within 6 hours after administration, and twice a day, once in the morning and once in the afternoon, for 14 days thereafter.

2) Body weight

Each animal was weighed on the day of administration, and after 1, 2, 3, 4, 7, 10 and 14 days of administration.

3) Food consumption

Daily food intake was measured once in the acclimation period, and after 1, 2, 3, 4, 7, 10 and 13 days of administration.
6. Pathological examination

1) Necropsy
All the animals were anesthetized by injection of a 6.0 % sodium pentobarbital solution into the cephalic vein of the foreleg, killed by exsanguination from the bilateral axillary arteries and necropsied.

2) Organ weight measurement and storage
The liver, heart, thymus, spleen, lungs, kidneys and adrenals of necropsied animals were weighed. Organ weight per kg body weight was calculated using the body weight obtained on the necropsy day. These organs were fixed in 10 % neutral-buffered formalin and stored. The eyeballs were fixed in Davidson's solution and stored in the 10 % neutral-buffered formalin.
II. Results

1. Clinical signs
   No animals died during the observation period.
   In the 100 mg/kg group animals, retching and depression of spontaneous movement appeared from 10 - 15 minutes after administration. Within 30 minutes after administration, they vomited frothy mucus twice. These signs disappeared within 45 minutes after administration. In the 300 mg/kg group, depression of spontaneous movement and salivation appeared from 6 minutes after administration. Each animal in this group vomited 3 times within 30 minutes after administration, and a test article-like white material was observed in a vomitus of the female. Salivation disappeared in 28 minutes or 1 hour after administration, and depression of spontaneous movement recovered in 1.5 or 2 hours after administration in the male or female, respectively.
   Other observed changes were various types of stool, such as soft, mucous, watery-mucous and watery stool during observation period. However, the incidence of these abnormal stools was the lack of a dose response. These types of stool are common to juvenile beagles, and were also observed before administration.

2. Body weight
   Body weight loss was observed in both animals of the 300 mg/kg group after 1 day of administration. However, they showed a similar body weight gain to that of the control animals thereafter. No abnormal body weight was observed in other animals.

3. Food consumption
   No remarkable changes were observed throughout the observation period.

4. Pathological examination
   1) Necropsy findings
      A hemocyst in the tricuspid valve of the heart was found in the male in the 100 mg/kg group, the male in the 300 mg/kg group and the female in the 30 mg/kg group. A white or red patch was seen in the capsule of the spleen of the female in the 30 mg/kg and the male in the 100 mg/kg
group. No other macroscopic abnormalities were detected in any animal at necropsy.

2) Organ weight
Absolute and relative adrenal weights increased in the male of the 300 mg/kg group. There were no significant effects toxicologically on the weight of the other organs in any animal.
III. Discussion and Conclusion

The purpose of this study was to assess the oral toxicity of a single dose of Cetirizine in juvenile dogs. Beagle dogs (3 weeks old) were treated orally with Cetirizine at a dose of 0, 30, 100 or 300 mg/kg once. Each dose group consisted of 1 male and 1 female. After administration, the animals were observed for general signs and body weight changes for 14 days, then killed and examined pathologically. No animals died in any group. Therefore, it was concluded that the approximate lethal dose of the test article for juvenile dogs was more than 300 mg/kg.

Within 30 minutes after administration, vomiting and depression of spontaneous movement appeared in the 100 and 300 mg/kg groups, and salivation appeared in the 300 mg/kg group. These signs disappeared within 2 hours after administration. Vomiting, calm and salivation were also observed in the acute oral or intravenous toxicity study of Cetirizine in adult dogs. Therefore, the signs observed in this study were considered to be related to the administration of the test article. Body weight loss was observed in the both animals of 300 mg/kg group after 1 day of administration. However, this change was slight and transient, and they showed normal body weight gain thereafter.

In organ weights and macroscopical examination, absolute and relative adrenal weights were increased slightly in the male of the 300 mg/kg group. However, the adrenal weights of the female in this group were not increased. Since individual variation of organ development in juvenile dogs is large, this weight increase was not considered to be related to the administration of the test article. A hemocyst was found in the tricuspid valve of the heart in 2 animals of the administration groups. This change is known to be congenital, and was regarded to be insignificant in this acute toxicity study. Another change was a white or red patch in the capsule of the spleen in the female of the 30 mg/kg group and the male of the 100 mg/kg group. Since no dose dependency of these changes in the heart and spleen was observed, these changes were not considered to be related to the test article.