Single dose oral toxicity study of Cetirizine in juvenile rats

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SUMMARY

A single dose oral toxicity study of Cetirizine was carried out in juvenile rats. Pups of Sprague-Dawley rats Crj:CD(SD), age 3 weeks were treated orally with Cetirizine at a single dose of 0, 100, 200, 300, 450, 670 or 1000 mg/kg. Each dose group consisted of 5 males and 5 females. After administration, the animals were observed for general signs and body weight changes for 14 days, then killed and examined pathologically. The results obtained are as follows:

1) Deaths were observed in the 300 mg/kg and higher groups. Four males and three females died in the 300 mg/kg group, and every animal died in the 450 mg/kg and higher dose groups.

2) Decrease of spontaneous activity was observed in both sexes of every administration group, and this sign appeared earlier and in more animals in the higher dose groups. In addition, crouching, prone position and lateral position appeared in the high dose groups. No abnormal signs were observed the day after administration among the surviving animals. The test article did not affect the body weight of the surviving animals.

3) In the necropsy of dead animals, rhinorrhea, foamy fluid in the tracheal cavity, non-contraction of the lungs, hemorrhage in the lungs, linear reddish brown or brown coloration in the glandular stomach, thoracic fluid and hemorrhage in the thymus were found. Histopathological examination of the tissues from the 1000 mg/kg group showed a congestive edema in the lungs, and dilation of capillaries in the mucosa, hemorrhage in the mucosa and mucosal necrosis of upper layer of the glandular stomach. No abnormal changes attributable to the test article were detected during necropsy after the terminal sacrifice.

In conclusion, the LD₅₀ value of Cetirizine for juvenile rats was estimated to be between 200 and 300 mg/kg in this study.
I. Materials and Methods

1. Test animals
SPF rats of Sprague-Dawley strain Crj:CD(SD), 10 males and 20 females were obtained from Charles River Japan, Inc. on December 17, 1990. The age of the males was 11 weeks old and that of the females was 10 weeks old at the time of arrival. The animals were subjected to acclimation for 1 week. During this period, their general sign was examined and body weight was measured. All of the healthy animals were used for breeding.
4. Administration

1) Route and procedure
Cetirizine, dissolved in water for injection (Japan Pharmacopoeia Grade), was administered by gavage. The amount for each administration was 10 ml/kg, and the volume for each animal was calculated from the body weight measured shortly before administration. Animals were kept from food 16 hours prior to and 4 hours after administration.

2) Dose levels and their justification
In a preliminary test (dose: 2000, 1000, 200 mg/kg; each group consisted of 3 males and 3 females), a temporary depression in spontaneous movement was observed in the 200 mg/kg group, and all the animals died in the 1000 and 2000 mg/kg groups. Therefore, a dose of 1000 mg/kg was adopted for the highest dose in this study. Dosages for lower levels were set to be 670, 450, 300, 200, 100 mg/kg with a common ratio of about 1.5. The control group animals were similarly treated with water for injection (J. P. Grade, 10 ml/kg).

5. Observation and measurement
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
Body weight was determined on the day of administration, and 1, 2, 3, 5, 7, 11 and 14 days after administration. Dead animals were weighed before necropsy.

6. Pathological examination
Fourteen days after administration, all surviving animals were anesthetized with ether, killed by exsanguination from the abdominal aorta and necropsied. Dead animals were necropsied as soon as possible.
7. Statistical analysis

The lethal dose was estimated based on the cumulative deaths occurring in 14 days after administration. The body weight data were analyzed by the F test. In case of homogeneous variance, the t test was employed. In a non-homogeneous case, Aspin-Welch's t test was applied.
II. Results

1. Preterminal mortalities
   No animals died in the 100 and 200 mg/kg groups, 4 males and 3 females died in the 300 mg/kg group, and every animal died in the 450 mg/kg and higher dose groups. All the deaths were observed within 6 hours after administration except 3 cases; 1 male and 1 female in the 300 mg/kg group and 1 female in the 450 mg/kg group were found dead the next morning.

2. General signs
   No abnormal signs were observed in the males or females of the control group throughout the 14 day observation period. Decrease of spontaneous activity was seen in every administration group. In the 100 mg/kg group, this sign was observed in 2 males 1 hour after administration, in 3 males after 2 and 3 hours, and in 2 females after 2 hours. Each animal recovered after 1 - 3 hours of suffering.
   Among the 200 mg/kg and higher dose groups, the appearance of depression spontaneous movement was earlier and in more animals in the higher dose groups. In addition, crouching, prone position and lateral position were found in the higher dose groups. All the surviving animals appeared normal from the day after administration with a few exceptions. A few animals of the 300 and 200 mg/kg groups lost hair and suffered from incrustation on the dorsal skin from 7 to 9 days after administration on. However, these changes were slight and no dose dependency of these changes were observed.
   In many lethal cases, decreased body temperature and rigor were seen shortly before death.

3. Body weight changes
   No significant body weight differences were observed between the control animals and the surviving animals in the 100, 200 and 300 mg/kg groups.
III. Discussion and Conclusion

The aim of this study was to examine the single dose toxicity of Cetirizine in juvenile rats. Three week old rats were treated orally with Cetirizine at a single dose of 0, 100, 200, 300, 450, 670 or 1000 mg/kg. Each group consisted of 5 males and 5 females. After administration, the animals were observed for clinical signs and body weight changes for 14 days, then killed and examined pathologically. No animals died in the 100 and 200 mg/kg groups, 4 males and 3 females died in the 300 mg/kg group, and every animal died in the 450 mg/kg and higher dose groups. All the deaths were observed within 6 hours after administration except 3 cases; 1 male and 1 female in the 300 mg/kg group and 1 female in the 450 mg/kg group were found dead the next morning.

Decrease of spontaneous activity was observed in every administration group. This sign appeared earlier and in more animals in the higher dose groups. In addition, crouching, prone position and lateral position were seen in the higher dose groups. All the surviving animals appeared normal from the next day after administration. No effect of the test article was observed on the body weight of the surviving animals in the 100, 200 and 300 mg/kg groups.

In the necropsy of dead animals, rhinorrhea, foamy fluid in the tracheal cavity and thoracic fluid were observed. During the histopathological examination of the 1000 mg/kg group animals, slight or moderate congestive edema and hemorrhage were observed in the lungs and severe edema in the glandular stomach. These changes indicated a severe circulatory disturbance and hypofunction of the lungs. It is known that acute intoxication with anti-histamine drugs could cause circulatory and respiratory collapse resulting in death. Therefore, the deaths in this study appeared to be attributed to a similar cause. The main change found in the glandular stomach of animals that died within 2 hours after administration was edema in the mucosa. Mucosal hemorrhage and mucosal necrosis of upper layer of the submucosa were seen in the animals that died later. No effects of the test article were detected in the animals of terminal sacrifice.
In conclusion, the LD$_{50}$ of Cetirizine at a single oral administration for juvenile rats (3 weeks of age) was between 200 and 300 mg/kg in this study.