TOXICOLOGICAL STUDY ON RATS FED HALOPERIDOL : 80 WEEK CHRONIC TOXICITY TEST

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ABSTRACT — Haloperidol (HPL) was administered by presenting HPL-admixed food to 20 male and 19 female Sprague-Dawley rats from the age of 5 weeks at a target dose of 1.0 mg/kg/day for 80 weeks. The range of the actual daily dose was 0.48–1.11 mg/kg in males and 0.34–0.73 mg/kg in females. The control rats (13 males and 13 females) were given normal food. In the present study, the general condition and locomotor activity of these rats were examined.

1. The number of HPL-treated animals that died during the administration periods (11 males and 9 females) and the symptoms observed immediately before their death were comparable to those in the control group. Vacuous chewing movement developed in HPL-treated animals (12 males and 11 females) after the 28th week of administration. These movements showed a tendency of decrease after the 68th week. Blepharitis was observed in all females and 3 males of the HPL-treated group, but in none of the controls of either sex. Subcutaneous masses in the chest and abdomen were observed in 3 HPL-treated females and 6 control females, but there was no significant difference in their incidence between the two groups.

2. The body weight gain in the HPL-treated group was suppressed in males, but was promoted and then suppressed in females. The food consumption in the HPL-treated group was similar, but the water consumption was reduced in both sexes as compared with the control groups.

3. Locomotor activity was reduced in the HPL-treated group for both males and females, and no tolerance developed.

These results suggest that HPL does not have a possibility to cause death even by chronic administration at the doses examined in the present study. However, the occurrence of body weight losses and blepharitis indicated the need for particular attention to these symptoms during chronic administration.

KEY WORDS : Haloperidol, Chronic administration, General symptoms, Locomotor activity, Male and female rats.

INTRODUCTION

Haloperidol (HPL), a drug of the butyrophenone group, is the first choice in the treatment of

schizophrenia and is used more often than phenothiazines (Itoh *et al.*, 1979 ; Miyakoshi and Okuma, 1980). Because of the chronic nature of schizophrenia, the administration of HPL is often continued for a long period until death depending on the condition. Such a clinical situation suggests the necessity of toxicity studies on life-time

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administration of HPL. However, it is unclear whether life-time administration of HPL induces organic changes from the basal ganglia to the mid-brain.

Seay and Field (1967) and Waddington and Gamble (1980) reported toxicity studies of HPL in male rats, but there have been no studies in which HPL was administered over a period corresponding to the human life-span.

We conducted a chronic toxicity study in rats administered HPL. This report concerns the general condition and the amount of spontaneous locomotor activity in rats administered HPL for 80 weeks from the age of 5 weeks.

MATERIALS AND METHODS

Animals and breeding conditions: Four-week-old male and female Sprague-Dawley (SD) rats were purchased from Nihon Clea Ltd. and used for the experiments after the 5 day preliminary breeding (body weight at the beginning of preliminary breeding: males 98–122 g, females 82–97 g). The drug-treated group consisted of 20 males and 19 females, and the control group of 13 males and 13 females. Three animals each were housed in a polycarbonate cage (292×400×200 mm), and the administration was started at the age of 5 weeks. The animals were maintained in an animal room adjusted to a constant temperature ($23\pm 2^{\circ}\text{C}$) and humidity ($55\pm 10\%$) under a 12 hour light and dark cycle (light 7:00, dark 19:00), and tap water, sterilized using an immersed light source, was given *ad libitum*.

Drug and method of administration: HPL was provided by Shionogi Seiyaku & Co. HPL was mixed with food and pelleted, and was administered at a daily target dose of 1.0mg/kg. This pellet food was prepared on the assumption that both male and female rats consume on average 20 g of food per day. The animals were weighed once a week until the 12th week of the administration (16 weeks old) and once every 2 weeks thereafter. The HPL content of the food was adjusted according to the weight gain of the animals.

Locomotor activity: Locomotor activity was measured for 20 minutes with an animex activity meter (M-SE, Muromachi Kikai, Japan) at a sensitivity of $25\mu\text{A}$ and a turning set of $40\mu\text{A}$.

Measurement was performed in a dimly lighted room between 9:30 and 12:30 at 3-month intervals. The amount of locomotor activity was evaluated with respect to the number of spontaneous movements per animal during a 20-minute period, and compared with the value of age-matched control.

Observation and examination of the general condition: The general condition of the animals was observed every day except on Sundays. Amount of water consumption per day in groups of 3 rats each was measured once a week until the 12th week of HPL administration and once every 4 weeks thereafter. Amount of food consumption per day in same groups was measured twice a week. From these results, the mean daily amounts results, of water and food consumption per rat were estimated. Determination of the water and food consumption was made between 9:30 and 11:30 on a fixed day during the examination period.

The animals were killed due to marked general weakness or those died during the administration period were immediately necropsied, and the main organs were examined grossly. The brain, lungs, heart, liver, spleen, pancreas, stomach, small intestine, kidneys, adrenal glands, testes, ovaries, prostatic glands, uterus, submaxillary glands, and thyroid were excised and fixed in a 10% formalin solution for histopathological evaluation. Masses observed in subcutaneous or other regions were also fixed with formalin. The results of the histopathological examination and a blood biochemistry test will be described elsewhere.

Statistical analysis: Statistical significance of the values was examined by Fischer's exact probability test and Student's *t*-test.

RESULTS

Animals that died of weakness: As shown in Table 1, 5 control (38.5%) and 11 HPL-treated males (55.0%), and 4 control (30.8%) and 9 HPL-treated females (47.4%) died during the administration period. Although the mortality rate was higher in the HPL-treated animals than in the controls for both males and females, the differences between the groups were not statistically significant. And also there was no statisti-

Table 1. The number of rats that died during the treatment with haloperidol.

Sex	Group	No. of rats	Weeks after administration												Mortality (%)	
			32	42	46	48	50	64	68	70	71	72	74	76		80
Male	Control	13	1		2				1		1					38.5 (5/13)
	Haloperidol	20		1	2	3	1				1	1		2		55.0 (11/20)
Female	Control	13						1	1		1	1				30.8 (4/13)
	Haloperidol	19							1	2	1	2	1		2	47.4 (9/19)

cally significant difference in mortality between males and females of the HPL-treated group. Symptoms observed immediately before death included constipation (1 male: 5.0% and 1 female: 5.3%), marked weight loss (2 males: 10.0% and 3 females: 15.8%), dysbasia due to paralysis of the hind legs (1 male: 5.0%), and scoliosis (1 male: 5.0%) in the HPL-treated group. Similar symptoms were also observed in the controls, and there was no statistically significant difference in the incidence of these conditions between the two groups. Inflammatory lesions of the lungs (8 males: 40.0% and 5 females: 26.3%) and intestinal obstruction (2 males: 10.0% and 2 females: 10.5%) were the most notable of the gross necropsy findings in HPL-treated animals. Similar conditions were also observed in the controls with no statistically significant difference in their incidences. Furthermore, these symptoms observed immediately before the death of animals that expired during the administration period and necropsy findings suggested that there was no direct relationship between the administration of HPL and the death of the animals. However, it could not be determined whether the chronic administration of HPL can effect organic changes in the brain.

General condition: Masses considered to be mastadenomas were observed subcutaneously in the chest and abdomen of 3 HPL-treated females (15.8%) and 6 control females (46.2%), and their incidence was not significantly different between the two groups. The subcutaneous masses observed only in females were not considered to have been caused by HPL.

Vacuous chewing movements (VCMs) developed in both sexes of HPL-treated groups after the 7th week of administration (11 weeks

old), and it was gradually increased until the 27th week (31 weeks old). At the 28th week of administration (32 weeks old), VCMs developed in 59% of HPL-treated rats (12 males and 11 females), but not in 41%. However, the appearance of such VCMs showed a tendency to decrease after the 68th week.

Blepharitis was observed in HPL-treated animals. The condition was first noted in 3 females (15.8%) in the 12th week of administration (16 weeks old) and 3 males (15.0%) in the 18th week (22 weeks old) (Photo. 1). Table 2 shows the extent of blepharitis at each time during the administration period evaluated according to an arbitrary scoring system and expressed in a percentage. The score of blepharitis was rated as follows; 0: non blepharitis, 1: blepharitis in one eye, and 2: blepharitis in both eyes. In the present study, blepharitis was noted on only 3 HPL-treated males (15.0%), and disappeared by the 80th week of administration (84 weeks old). In contrast, the condition occurred in all HPL-treated females (100%) and did

Photo. 1. Blepharitis appeared in female rats treated with haloperidol for 28 weeks.

Table 2. Score percentages in incidence of blepharitis.

Sex	Group	Weeks after administration																
		12	16	18	20	24	28	32	36	40	48	52	54	60	64	68	72	80
Male	Control	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Haloperidol	—	—	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.8	8.3	8.3	8.3	8.3	8.3	5.9	—
Female	Control	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Haloperidol	7.9	23.7	23.7	26.3	31.6	36.8	39.4	47.4	55.3	60.5	63.2	76.3	81.6	92.1	100.0	100.0	100.0

Score ; No blepharitis : 0, Lateral blepharitis : 1, Bilateral blepharitis : 2.

not disappear spontaneously. In the control group, neither males nor females showed blepharitis. Thus, blepharitis occurred in only HPL-treated animals, and was severer in females than in males.

Body weight: Changes in body weight are shown in Fig. 1. The weight gain of HPL-treated males was slightly suppressed after the 2nd week of the administration (6 weeks old) and significantly suppressed ($P < 0.05-0.001$) after the 48th week (52 weeks old). HPL-treated females showed a greater body weight gain after the 4th week (8 weeks old), and the body weight gain was significantly greater ($P < 0.01$) from the 10th to the 24th week (14 to 28 weeks old) than in the control. The gain of body weight in the HPL-treated group became smaller thereafter and was suppressed after the 40th week (44 weeks old), resulting in a significantly smaller body weight ($P < 0.05-0.001$) than in the controls after the 56th week (60 weeks old).

Food and water consumption: Fig. 2 shows the mean daily relative food consumption at each time during the administration period. There were no statistically significant differences in the food consumption between the HPL-treated group and the control group in either males or females. The daily dose of HPL calculated from the food consumption corrected for the loss

during ingestion (about 10%) was 0.48–1.11 mg/kg for males and 0.34–0.73 mg/kg for females. The dose was about 1.6 times greater in males than in females.

Fig. 3 shows the mean daily relative water consumption at each time during the administration period. The water consumption was significantly less ($P < 0.05-0.001$) in the HPL-treated animals than in the controls from the 11th to the

Fig. 2. Changes in food intake of male and female rats during oral administration of haloperidol for 80 weeks. Male control group: $\triangle$ — $\triangle$, male haloperidol-treated group: $\blacktriangle$ — $\bullet$ — $\blacktriangle$, female control group: $\circ$ — $\circ$, female haloperidol-treated group: $\bullet$ — $\bullet$ — $\bullet$.

Fig. 1. Changes in body weight of male and female rats during oral administration of haloperidol for 80 weeks. Male control group: $\triangle$ — $\triangle$, male haloperidol-treated group: $\blacktriangle$ — $\bullet$ — $\blacktriangle$, female control group: $\circ$ — $\circ$, female haloperidol-treated group: $\bullet$ — $\bullet$ — $\bullet$. *, ** and ***: Significantly different from the value of control, $P < 0.05$, $P < 0.01$ and $P < 0.001$, respectively.

Fig. 3. Changes in water intake of male and female rats during oral administration of haloperidol for 80 weeks. Male control group: $\triangle$ — $\triangle$, male haloperidol-treated group: $\blacktriangle$ — $\bullet$ — $\blacktriangle$, female control group: $\circ$ — $\circ$, female haloperidol-treated group: $\bullet$ — $\bullet$ — $\bullet$. *, ** and ***: Significantly different from the value of control, $P < 0.05$, $P < 0.01$ and $P < 0.001$, respectively.

Fig. 4. Locomotor activities in male and female rats treated with haloperidol for 0, 11, 24, 38, 50, 64 and 76 weeks (closed circle). Activity counts per 20 min are expressed as mean $\pm$ S. E. *, **, and ***: Significantly different from the value of control (open circle), $P < 0.05$, $P < 0.01$ and $P < 0.001$, respectively.

40th week (15 to 44 weeks old) for males and from the 16th to the 52th week (20 to 56 weeks old) for females.

Amount of locomotor activity: The amount of locomotor activity (Fig. 4) in the 11th, 24th, 38th, 50th, 64th and 76th week of the administration period (15, 28, 42, 54, 68 and 82 weeks old) was significantly less ($P < 0.05$ – 0.001) in the HPL-treated animals than in the controls, being 79.0–85.8% in males and 65.4–77.1% in females of the respective controls. In the control group, the amount of the locomotor activity increased until the 64th week (68 weeks old) as compared with the values before the beginning of the administration in both males and females [males: 1172 ± 24 (counts/20 min) in the 0 week (before treatment), 1341 ± 32 in the 11th week and 1726 ± 104 in the 64th week; females: 1157 ± 21 in the 0 week, 1300 ± 20 in the 11th week and 1481 ± 70 in the 64th week], but reduced thereafter as compared with the level in the 64th week. However, the amount of locomotor activity in the HPL-treated group did not exhibit such an increase accompanying aging.

DISCUSSION

In the present study, HPL was mixed in food, and it was administered to male and female rats from 5 to 84 weeks after birth at an intended daily dose of 1.0 mg/kg. The actual dose calcu-

lated from the food consumption was 0.48–1.11 mg/kg in males and 0.34–0.73 mg/kg in females. The results of the present study were produced by these doses.

The first death in HPL-treated groups occurred after the 42nd week of the administration (46 weeks old) in males and after the 68th week (72 weeks old) in females. Deaths in these weeks occurred later in the HPL-treated group than in the control group in both males and females. The mortality rate during the administration period showed higher values in the HPL-treated group than in the control group in both males and females, but the differences between the groups were not statistically significant for either sex. Thus, there was no significant difference in mortality between the rats administered HPL for a long time and the controls, and the treatment was not considered to be directly related to the death of the animals. However, the delay in the occurrence of the first death in the HPL-treated group as compared with the control group is interesting. In the observation of life-time until death from the beginning of the experiment, the duration of life-time is shown from longest to shortest in the following order: the HPL-treated female group, the control female group, the HPL-treated male group, and the control male group. Although we consider that the changes of body weight and sedation induced by HPL administration and cage size accompanying body

weight gain in rat may have influence on the duration of life-time, these could not clarify in the present study. Marked weight loss accompanied by constipation observed immediately before death was also noted by Haneda *et al.* (1972) after the treatment of HPL in human, but this symptom was observed in present study not only in HPL-treated animals but also in untreated controls with no significant difference in the incidence.

Masses suspected to be mastadenoma were noted subcutaneously in the thoracoabdominal region in only females of both HPL-treated and control groups, but there was no statistical significant difference in their incidence between the groups. Phenothiazines in general induce enlargement of the mouse mammary glands, probably because the drugs act on the hypothalamus-hypophysial system to promote prolactin secretion (Itoh, 1978a). Moreover, a relationship between the antipsychotic effects of phenothiazines and prolactin secretion has been established (Meltzer *et al.*, 1979). No relationship has been observed, however, between the antipsychotic effects of butyrophenones and enlargement of the mammary glands (Mishkinsky *et al.*, 1969). In SD female rats mammary tumor is known to spontaneously occur with a high frequency (Durbin *et al.*, 1966; Morii and Fujii, 1973; Muraoka *et al.*, 1977). Accordingly, these masses observed in the present study were spontaneous tumors specific in SD rats, and are not considered to have been caused by HPL.

VCMs developed in both sexes of the HPL-treated group after the 28th week of administration (32 weeks old). The long-term treatment of neuroleptic drugs in human is known to produce a hyperkinetic movement disorder called tardive dyskinesia which is characterized by involuntary movement of the mouth, extremities and trunk (Hunter *et al.*, 1964; Jacobson *et al.*, 1974). In rats, it has been reported by many investigators (Clow, 1980; Gunne *et al.*, 1982; Waddington *et al.*, 1983) that chronic treatment with neuroleptic drugs often produces spontaneous mouth movements. In the present study, involuntary movement was not present in other body areas. Therefore, spontaneous involuntary movement in rats may be restricted to the oral region, as reported by Tamminga *et al.* (1990).

The incidence of blepharitis in the HPL-treated group was higher in females than in males. Blepharitis associated with chronic administration of HPL was first reported by Itoh *et al.* (1981) in male rats. According to their report, the eyelid lesions disappeared within a few days after drug withdrawal. In our study, blepharitis was noted on only 3 males although the HPL dose was 1.6 times greater in males than in females, and disappeared after the 80th week of continued administration. In contrast, the condition occurred in all females and did not disappear spontaneously, indicating a marked sex difference in the incidence of blepharitis. Although opacification of the cornea and lens, and degeneration of the pigmented retina are among the reported eye disorders induced by long-term administration of the phenothiazines (Siddall, 1965; Crane, 1971), no such eye abnormalities have been reported in relation to butyrophenones, especially HPL. In the present study, since no animals exhibited gross corneal opacification on macroscopic observation, no relation between the cause and effect is apparent.

Patients on chronic antipsychotic medication are known to show gains in body weight. Nagasaka (1964) reported that such body weight gains occur more frequently in females, and he pointed out that psychosomatic activity may exert an influence on the body weight gains. Sletten and Gershon (1966) suggested that chlorpromazine causes abnormalities in the adrenocortical function and secretion of antidiuretic hormones, which lead to alteration in the water balance and, thus, weight gains. Yamane *et al.* (1967) observed no characteristic findings considered to be related to weight gains by biochemical analyses of the blood of patients who had been administered phenothiazines for over 2 years. Furthermore, Kinoshita (1980) reported that HPL was associated with significantly smaller weight gains than phenothiazines. The effect of drugs on the body weight are considered to vary according to the species, sex, and individual differences of the animals as well as the dose, route of administration, and duration of the treatment. Sex differences in the effects of HPL on the rat body weight were first observed in the present study. The animals in our study were first treated with HPL when they were immature

(5 weeks old). Therefore, the increases in the body weight in females may be due to the effects of HPL on the actions of ovarian hormone or on their mediator mechanisms (Mook *et al.*, 1972; Wade and Zucker, 1970). However, the cause of the weight gains was not clear from our results.

Changes in the food consumption were similar between the HPL-treated group and the control group in both males and females. Therefore, HPL is not considered to affect the neural network related to feeding behavior at the doses used in the present study.

Water intake is known to be regulated primarily by excitation of cholinergic nerves in the lateral regions of the hypothalamus, and appears to be partly controlled by the osmotic receptor mechanism of the brain, regulatory mechanisms of angiotensin and vasopressin secretion, and antidiuretic hormones (Yamashita, 1986). The marked reduction in the water consumption of the HPL-treated animals may be due to the effects of the agent on these mechanisms. Our observation of the decrease in water consumption unaccompanied by changes in food consumption is consistent with the report of Itoh (1978b).

The amount of locomotor activity was evaluated at 3-month intervals from the beginning of the administration. The activity of males and females administered HPL was significantly reduced as compared with the controls, and none of the animals developed tolerance to the reduction of their activity. Many investigators also observed the absence of the development of tolerance of the activity to antipsychotic drugs (Asper *et al.*, 1973; Clow *et al.*, 1979; Waddington and Gamble, 1980; Carey and De Veauh-Gelss, 1984). Matsumoto *et al.* (1983) suggested that chronic HPL administration not only continuously blocks dopamine receptors of the nigro-striatal system but also affects the nucleus accumbens and tuberculum olfactorum of the meso-limbic system. Earlier studies indicated that the striatum develops tolerance against blocking of dopamine receptors during experimental chronic administration of HPL, but that the meso-cortical system shows no tolerance against acceleration of dopamine metabolism (Laduron *et al.*, 1977; Bacopoulos *et al.*, 1978). Bowers and Rozitis (1974) and Kaneno *et al.* (1978) also reported that the meso-limbic system, unlike the striatum, does

not develop tolerance to the blocking of dopamine receptors during the administration of chlorpromazine. Thus, antipsychotic drugs are reported to induce no tolerance against blocking of dopamine receptors and acceleration of dopamine metabolism, and turnover in the meso-limbic system and meso-cortical system, unlike those in the striatum, even after chronic administration.

The antipsychotic actions of HPL and its suppressive effect on locomotor activities are closely related with the meso-limbic and meso-cortical system (Scatton *et al.*, 1977; Bannon and Roth, 1983). Clinical evaluations have shown that no tolerance develops to the antipsychotic actions (Davis, 1975), and our results also indicated the absence of tolerance against the suppression of spontaneous exercise. These results suggest that the antipsychotic effects of HPL and its suppressive effects on spontaneous activity play a common role in the meso-limbic and meso-cortical systems.

Studies supported that dopamine plays an important role in the etiology of schizophrenia. Also, image analysis examination on the brain posed a question that chronic administration of antipsychotic drugs may produce irreversible lesions of brain tissue (Arioka *et al.*, 1975). Therefore, we consider that further examination on the effects of antipsychotic drugs on the brain tissue is necessary.

The above results suggest that HPL does not have a possibility to cause death even by chronic administration at the doses examined in the present study. However, the development of vacuous chewing movements, the occurrence of body weight losses and blepharitis indicated the need for particular attention to these symptoms during chronic administration of HPL. Also, the present study suggested that the effects of HPL on body weight changes and the incidence of blepharitis in rats are different between the sexes.

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