

DAILY VERSUS INTERMITTENT HALOPERIDOL ADMINISTRATION: EFFECTS ON CATALEPSY OF MICE

José Francisco Navarro, Juan Manuel Manzanque, Mercedes Martín-López
and Francisca Vera
Universidad de Málaga

Drug effects on behaviour are closely related to the temporal patterns of their administration. Numerous studies have demonstrated that regular (daily) versus intermittent dosing of any drug can determine whether tolerance or sensitization is developed. The aim of this study was to examine if daily (10 days) or intermittent (every other day and every two days) administration of haloperidol (0.75 mg/kg, ip) could affect differentially to catalepsy of male (experiment 1) and female mice (experiment 2). Catalepsy was measured by means of the 'bar test', being evaluated 120 minutes after the last administration of haloperidol or saline. In both experiments, as compared with controls, catalepsy increased significantly in mice treated with a single injection of haloperidol, as well as in the groups treated with haloperidol intermittently, although a marked tolerance to haloperidol-induced catalepsy after daily administration of the drug was observed. However, only the group of female mice treated with haloperidol every two days showed significantly more catalepsy than those treated daily or every other day, suggesting that the effect of several schedules of drug administration can affect differentially to male and female mice.

Efectos de la administración diaria versus intermitente de haloperidol sobre la catalepsia de ratones. Los efectos conductuales de los fármacos están estrechamente relacionados con los patrones temporales de su administración. Numerosos estudios han demostrado que la administración diaria o intermitente de un fármaco puede determinar el desarrollo de tolerancia o sensibilización a sus efectos. El objetivo de este trabajo fue examinar si la administración diaria (10 días) o intermitente (día sí/día no y cada dos días) de haloperidol (0.75 mg/kg, ip) podía afectar diferencialmente la conducta cataléptica de ratones machos (experimento 1) y hembras (experimento 2). Para la evaluación de la catalepsia se utilizó el 'test de la barra', siendo los animales evaluados a los 120 minutos de la última inyección de haloperidol o salina. En ambos experimentos, se observó un incremento significativo de la conducta de catalepsia tras la administración aguda y la administración intermitente de haloperidol, en comparación con el grupo control, así como una marcada tolerancia a los efectos catalépticos tras su administración repetida. Sin embargo, únicamente el grupo de las hembras mostró significativamente más catalepsia tras la administración intermitente (cada dos días) que tras la inyección diaria, sugiriendo que el efecto de diferentes programas de administración de haloperidol puede tener distintos efectos en ratones machos y hembras.

mental animals (Navarro, Muñoz, Rivas, Miñarro and Simón, 1992). Likewise, after its repeated administration a clear development of tolerance to cataleptic effects can be also observed (Navarro, Martín, Puigcerver and López, 1993; Manzaneque, Arenas and Navarro, 1995a, b; Ushijima, Mizuki and Yamada, 1995).

The development of tolerance (or failure to develop) to the effects of neuroleptics has evident implications for their clinical use. The study of the tolerance phenomena to the behavioural effects of neuroleptics has been a focus of those interested in the consequences of prolonged exposure to drugs that act on CNS (Antelman, 1988).

The factors that determine whether or not tolerance will develop to a particular drug action are many. Among them, intermittency appears to be a key element (Post, 1980). Numerous studies have demonstrated that the development of tolerance to a given effect of a drug seems to be closely related to the type of schedule used. Thus, it has been showed that daily versus intermittent dosing of haloperidol can determine whether tolerance or intolerance is developed. In this respect, when inter-injections intervals are too brief, tolerance becomes more likely to occur (Antelman, 1988; Barnes, Robinson, Csernansky and Bellows, 1990; Carey and DeVaugh-Geiss, 1980). For example, Masuda, Mura and Itoh (1982) reported that haloperidol-induced catalepsy in ddY strain male mice increased with intermittently oral administration of haloperidol (0.6, 1.2 or 4.8 mg/kg) whereas decreased with daily administration of the drug during 21 days (1.2 or 4.8 mg/kg). This tendency was clearer when haloperidol was administered every four days than every two days.

The main aim of this study is to examine whether daily or intermittent (every other day and every two days) haloperidol

administration has different effect on catalepsy of male and female mice. Additionally, we attend to confirm the development of tolerance to the cataleptic effects of haloperidol previously described in mice as well as to explore the possible existence of gender differences in the effects of haloperidol on catalepsy behaviour.

Materials and methods

Animals

100 OF.1 strain albino mice (50 males in the experiment 1 and 50 females in the experiment 2) weighing 25-30 g were obtained from "Servicio de Animales de Laboratorio", Granada (Spain). Animals arrived in the laboratory at 42 days of age and were housed in transparent plastic cages (24 x 13.5 x 13 cm) in groups of five under standardized lighting conditions (light: 20:00-8:00), a constant temperature and laboratory chow and tap water available *ad libitum*. All animals underwent a seven-day adaptation period to the laboratory before experimental treatments began.

Drug administration

In both experiments, haloperidol (Haloperidol®, Sintex Latino Laboratories, Madrid, Spain) was diluted in saline and administered acutely, daily (for ten consecutive days) or intermittently (every other day and every two days). Control animals received 0.9% sodium chloride (see experimental design in Table 1). Consequently, in both experiments, besides the control group, four experimental groups (ten animals per group) were used. In all experimental groups, a dose of 0.75 mg kg⁻¹ of haloperidol (in 0.01 ml g⁻¹) was administered.

Table 1
Experimental desing

	Days									Test (120')	
	1	2	3	4	5	6	7	8	9		10
Group 1 (saline; SS)	S	S	S	S	S	S	S	S	S	S	S
Group 2 (acute; SH)	S	S	S	S	S	S	S	S	S	S	H
Group 3 (chronic; HH)	H	H	H	H	H	H	H	H	H	H	H
Group 4 (intermittent 1; SHSH)	S	H	S	H	S	H	S	H	S	H	H
Group 5 (intermittent 2; HSSH)	H	S	S	H	S	S	H	S	S	H	H

H: Haloperidol; S: Saline

Behavioural test

Catalepsy was measured by means of the bar test. An aluminium bar of 5 mm in diameter was placed 4 cm above the floor. The animals forepaws were gently put on the bar and the time it took the animal to place at least one paw on the floor was measured. If 1 min elapsed without movement the test was interrupted. Successive behavioural evaluations of catalepsy were carried out two hours after the administration of haloperidol or saline. Between determinations, the mice were kept in their home cages. Individual animals were tested in a random order.

Statistical analysis

Non-parametric Kruskal-Wallis tests were used to assess the variance of the behavioural measures over different treatment groups. Subsequently, appropriate paired comparisons were carried out using Mann-Whitney U-tests to contrast the catalepsy in different treatment groups.

Results

Experiment 1

Kruskal-Wallis analysis showed that there was a significant variance in cata-

lepsy behaviour over different treatment groups ($p < 0.02$). As can be seen in Figure 1, paired comparisons revealed that, as compared with controls, catalepsy increased significantly in male mice treated with a single injection of haloperidol ($p < 0.01$), as well as in the groups treated with haloperidol intermittently ($p < 0.02$). Likewise, a marked tolerance to haloperidol-induced catalepsy after daily administration of the drug was observed. Thus, mice chronically treated with haloperidol showed statistically significant reduced catalepsy scores as compared with singly treated group ($p < 0.01$).

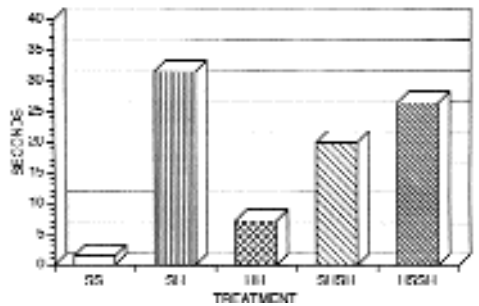


Figure 1. Effects of haloperidol on catalepsy in male mice. «U» Mann-Whitney: $p < 0.01$ SS vs SH, SH vs HH $p < 0.02$ SS vs SHSH, SS vs HSSH

Experiment 2

Kruskal-Wallis analysis showed that there was a significant variance in catalepsy behaviour over different treatment groups ($p < 0.001$). As can be seen in Figure 2, paired comparisons revealed that, as compared with controls, catalepsy increased significantly in female mice treated with a single injection of haloperidol ($p < 0.01$), as well as in the groups treated with haloperidol intermittently ($p < 0.01$). Moreover, like in the experiment 1, a clear tolerance to haloperidol-induced catalepsy after daily administration of the drug

was found. Mice treated daily with haloperidol showed statistically significant reduced catalepsy scores as compared with singly treated group ($p < 0.05$). Animals treated with haloperidol every two days showed significantly more catalepsy than those treated daily ($p < 0.01$) or every other day ($p < 0.05$).

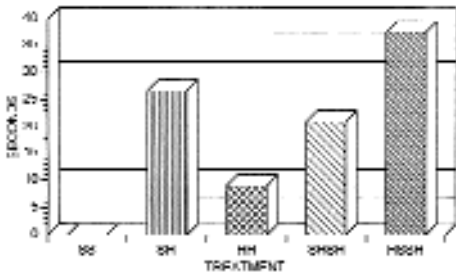


Figure 2. Effects of haloperidol on catalepsy in female mice. «U» Mann-Whitney: $p < 0.01$ SS vs SH, SS vs SHSH, SS vs HSSH, HSSH vs HH, HSSH vs SHSH, $p < 0.05$ SH vs HH

Discussion

This study is concerned with the possible role of the type of drug administration schedule used (regular versus intermittent) on catalepsy induced by haloperidol in mice.

Our results confirm previous studies demonstrating a development of tolerance to haloperidol-induced catalepsy both in

male (Navarro et al., 1993) and female mice (Manzanque et al., 1995a, b).

The overall picture of the effects on haloperidol-induced catalepsy was similar in both daily and intermittently treated mice. Nevertheless, some interesting effects due to the temporal pattern of drug administration can be observed. Thus, although in male mice no significant differences between daily and intermittent groups on catalepsy were found, female mice treated with haloperidol every two days showed significantly more catalepsy than those treated daily or every other day. Therefore, these data indicate that the effect of several schedules of haloperidol administration can affect differentially to male and female mice. In this respect, gender differences in the effects of haloperidol on catalepsy after its acute administration has been also reported in mice (Navarro, Vera, Puigcerver and Martín-López, 1993).

If catalepsy is considered as an appropriate animal model for the extrapyramidal side effects of neuroleptics the findings found in this study can be clinically relevant. Thus, they suggest that, in females, a daily administration schedule might produce less extrapyramidal side effects than an intermittent administration schedule (every two days), in spite of the fact that the daily treated animals received a higher global amount of the drug.

In conclusion, the development of tolerance or intolerance to haloperidol-induced catalepsy in mice seems to be closely related to the type of administration schedule used.

References

- Antelman, S.M. (1988). Time-dependent sensitization as the cornerstone for a new approach to pharmacotherapy. *Drug Development Research*, 14, 1-30.
- Barnes, D.E., Robinson, B., Csernansky, J.G. and Bellows, E.P. (1990). Sensitization versus tolerance to haloperidol-induced catalepsy: multiple determinants. *Pharma-*

- cology Biochemistry & Behavior*, 36, 883-887.
- Carey, R.J. and DeVeugh-Geiss, J. (1984). Treatment schedule as a determinant of the development of tolerance to haloperidol. *Psychopharmacology*, 82, 164-167.
- Manzaneque, J.M., Arenas, M.C. and Navarro, J.F. (1995a). Tolerance to cataleptic effects of haloperidol after repeated administration in female mice. *Medical Science Research*, 23, 549-550.
- Manzaneque, J.M., Arenas, M.C. and Navarro, J.F. (1995b). Influence of ovariectomy on haloperidol-induced catalepsy in female mice. *Medical Science Research*, 23, 623-625.
- Masuda, Y., Murai, S. and Itoh, T. (1982). Tolerance and reverse tolerance to haloperidol catalepsy induced by the difference of administration interval in mice. *Japanese Journal of Pharmacology*, 32, 1186-1188.
- Navarro, J.F., Muñoz, A.L., Rivas, T., Miñarro, J. and Simón, V.M. (1992). Efectos del haloperidol sobre la catalepsia en ratones machos. *Psicothema*, 4, 369-377.
- Navarro, J.F., Martín, J.M., Puigcerver, A. and López, E. (1993). Tolerance to cataleptic effects of haloperidol after repeated administration in male mice. *Medical Science Research*, 21, 387-388.
- Navarro, J.F., Vera, F., Puigcerver, A. and Martín-López, M. (1993). Gender differences in catalepsy of mice after haloperidol administration. *Medical Science Research*, 21, 815-816.
- Post, R.M. (1980). Intermittent versus continuous stimulation: effect of time interval on the development of sensitization or tolerance. *Life Sciences*, 26, 1275-1282.
- Ushijima, I., Mizuki, Y. and Yamada, M. (1995). Development of tolerance and reverse tolerance to haloperidol- and SCH23390-induced cataleptic effects during withdrawal periods after long-term treatment. *Pharmacology Biochemistry & Behavior*, 50, 259-264.

Aceptado el 27 de mayo de 1996