Pharmacology Biochemistry and Behavior, Vol. 58, No. 4, pp. 947–953, 1997

0091-3057/97 $17.00 + .00

ELSEVIER

PII S0091-3057(97)00314-6

The Common Marmoset (*Callithrix jacchus*) as a Model for Neuroleptic-Induced Acute Dystonia

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Received 29 May 1996; Revised 27 January 1997; Accepted 19 February 1997

FUKUOKA, T., M. NAKANO, A. KOHDA, Y. OKUNO AND M. MATSUO. *The common marmoset (*Callithrix jacchus*) as a model for neuroleptic-induced acute dystonia.* PHARMACOL BIOCHEM BEHAV **58**(4) 947–953, 1997.—To examine whether acute dystonia is induced by neuroleptic treatment, common marmosets were treated with haloperidol orally twice a week over 25 weeks until dystonic behavior was elicited. Movement disorders such as acute dystonia were observed 6 weeks after the initial treatment, and had appeared in all treated animals by 25 weeks. Once these movement disorders were induced, they consistently reappeared after further treatment with haloperidol, and once haloperidol dosing was discontinued, the episodes vanished. Then, various neuroleptic drugs (bromperidol, chlorpromazine, risperidone thioridazine, sulpiride, tiapride, and clozapine) or a nonneuroleptic drug (diazepam) were administered orally instead of haloperidol in the above animals. All the neuroleptic drugs except for clozapine elicited similar abnormal behavior, while diazepam failed to induce any dystonia. An anticholinergic drug, trihexyphenidyl, which is known to reduce acute dystonia in patients, was also given orally to the above haloperidol-sensitized animals, followed by further treatment with haloperidol 30 min later. This clearly suppressed the induction of dystonia by haloperidol. The similarity between these findings for haloperidol-pretreated common marmosets and clinical findings suggests that the present model is useful for predicting the potential of antipsychotics to induce acute dystonia in humans. © 1997 Elsevier Science Inc.

Dystonia Extrapyramidal side effects Haloperidol Common marmoset Animal model

SINCE chlorpromazine was introduced into psychiatric practice in 1952, various neuroleptic drugs have been developed. However, the usefulness of those drugs has been limited due to development of undesirable extrapyramidal side effects (EPS) at therapeutic doses. Acute EPS, such as dystonia, akathisia, and drug induced-Parkinsonism, occurs in up to 75% of patients taking such drugs (3). Therefore, the development of new antipsychotic drugs with no or fewer acute EPS is a high priority.

Animal models are used to predict whether drug-induced EPS will occur. Although catalepsy in the rat was traditionally used for this purpose, the predictability of EPS was found to be low with clinical results (8). Recently, it was reported that nonhuman primates pretreated with neuroleptic drugs are useful for prediction of acute EPS in humans, and particularly the acute dystonia, which is the earliest common adverse effect in clinical cases (15). Old world species, including rhesus monkeys (1,9,22,23), cynomolgus monkeys (13), and baboons (17), are reported not to be satisfactorily sensitive for models of dystonia, while new world species, including cebus monkeys (13,26,27) and squirrel monkeys (14), appear to be more likely candidates.

A smaller new world species, the common marmoset (*Callithrix jacchus*), has recently been established as an experimental animal, and its uses in science have been expanding. In the present study, we examined whether common marmosets are good species for prediction of EPS using neuroleptic drugs with EPS-inducing potential.

The terms dyskinesia and dystonia have been used by various research groups in primate investigations to designate a battery of movement disorders consisting of bizarre posture, contorted posture and various types of abnormal movements. We record abnormal movements as dyskinesias and abnormal posture as dystonia (14), but we use the term "dystonia" to designate both

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dyskinetic and dystonic syndromes in this article. The term "acute" here indicates that phenomena are elicited by an "acute" treatment, distinguished from tardive dyskinesia in humans.

METHOD

Subjects

The subjects were three male and three female adult common marmosets (*Callithrix jacchus*), 16–19 months old, and weighing 380–430 g (bred by Japan E D M, Gifu Pref., Japan). They were individually housed in stainless steel cages (415 × 700 × 870 mm) in animal rooms kept at a constant temperature of 28 ± 2°C and humidity of 50 ± 20% with a 12-h light–dark cycle and an air exchange rate of more than 10 times per hour. They were fed standard marmoset pellets (CMS-1, CLEA Japan, Inc.), multivitamins, powdered milk, and boiled chicken meal once daily, and given tap water ad lib.

Observation Procedures

The observers were blind to the drugs and dose each animal received for the duration of the study. Monkeys were observed in their home cages just before, and 15, 30, 60, 120, 240, 360, and 480 min after drug administration on treatment days and one to three times on nontreatment days. All animals were examined for 4–6 min at each observation.

The observers recorded results on prepared checklists. Dystonias were divided into several categories on the basis of results of a pilot study and the approach used by another research group (14) and recorded separately. They were body writhing movements (neck or trust), persistent extension of limbs, oral dyskinesias (abnormal tongue protrusions, licking movements, biting movements), abnormal behavior (persistent pushing of the head against a cage wall or ceiling), and an abnormal gait characterized by repeated circling, adducted hindlimbs, and elevated rump. Other neurological symptoms of motor behavior including sedation, hyperactivity, ptosis in the form of blepharoptosis, and tremors were also assessed during each session. After each observation, catalepsy was evaluated. Animals were caught and placed upside down on a steel net leaning against the room wall. If the animal remained in an immobile posture over 5 s on the net, catalepsy was considered to be present, because normal marmosets never remain immobile in these circumstances.

The absolute value of the score without catalepsy corresponds to 0 = signs not present or normal behavior; 1 = signs present once during each observation (4–6 min); 2 = signs repeatedly present during each observation; and 3 = signs continuously present during each observation.

Drugs

In the first experiment, all animals were given haloperidol at 1.25 mg/kg orally twice weekly until they exhibited dystonic movements. Although continuous treatment with haloperidol induced movement disorders in patients and in some primates investigations, intermittent administration also sufficed to induce dystonic movements in nonhuman primates (20,27). Intermittent administration was chosen to reduce stress to animals in this study.

Then, after dystonic reactions had been clearly elicited by repeated haloperidol treatment, the following drugs were administered orally to observe each response in the above haloperidol-sensitized monkeys as the second experiment: haloperidol (0.12, 0.36, and 1.2 mg/kg—synthesized at Sumitomo Pharmaceuticals Co., Ltd.), bromperidol (0.12, 0.36, and 1.08 mg/kg—extracted and purified from Impromen®, Yoshitomi Pharmaceutical Industries, Ltd., Osaka, Japan), chlorpromazine (2, 6, and 20 mg/kg—Sigma Chemical Co., St. Louis, MO), thioridazine (1.8, 5.4, and 18 mg/kg—Sigma), sulpiride (12, 36, and 120mg/kg—Sigma), tiapride (2.5, 7.5, 25, and 75 mg/kg—extracted and purified from Gramalil®, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan), risperidone (0.12, 0.36, 1.2, and 3.6 mg/kg—synthesized at Sumitomo Pharmaceuticals Co., Ltd.), clozapine (9, 27, and 90 mg/kg—synthesized at Sumitomo Pharm.), diazepam (0.4 and 4 mg/kg—Wako Chem., Tokyo, Japan), and vehicle as the control. In addition, trihexyphenidyl (0.2 and 2 mg/kg—Sigma) was administered orally, followed by further treatment with haloperidol (1.25 mg/kg) 30 min later. All monkeys were observed for abnormal movements prior to the administration of drugs. All drugs were suspended in 0.5% methylcellulose (Nacalai Tesque, Inc., Kyoto, Japan) solution, and were administered by intubation in a volume of 1 ml/kg.

Evaluation of Results

Monkey behavior was always compared with data for pretreatment and nontreatment sessions with the same individual during the 1.25 mg/kg haloperidol administration. The results with various drugs were compared with the effects of 1.25 mg/kg haloperidol and those of other drugs. Monkeys were also given 1.25 mg/kg haloperidol after every four treatments with other drugs to confirm that their basic responses remained steady during the experiments. Because normal common marmosets never exhibit any dystonic movements and other neurological signs, the differences obtained between drug and control values under blind conditions were sufficiently clear to render statistical tests unnecessary.

The protocol of this study was approved by our Animal Care Committee, and animals used in this study were maintained in accordance with the "Guide for Care and Use of Laboratory Animals" of the Institute of Laboratory Animal Resources,

TABLE 1

EFFECTS OF HALOPERIDOL (1.25 mg/kg) IN COMMON MARMOSETS

	Anim. No.					
	Male			Female		
Signs	1	2	3	1	2	3
Body writhing	12	26	18	12	9	17
Body extension	18	28	8	28	16	10
Oral dyskinesia	22	6	9	17	10	25
Abnormal gait	6	8	8	26	11	6
Abnormal movement*	22	—	12	27	16	19
Hyperkinesia	10	25	8	—	—	—
Sedation	1	1	1	1	1	1
Reduced response to observers	1	1	1	1	1	1
Ptosis	1	1	1	1	1	1
Tremor	1	1	1	1	1	1
Catalepsy	1	1	1	1	1	1

Six normal common marmosets were administered 1.25 mg/kg haloperidol twice a week for 32 weeks. Distonic or other neurological movements were observed after each treatment. Number shows the first week when those signs appeared.

*Abnormal movement consisted of persistent pushing with the head against a cage wall or ceiling, inability to grasp the cage and perch, and rhythmical hand swinging.

FIG. 1. Abnormal posture, neck extension after haloperidol administration at 1.25 mg/kg.

National Research Council, Department of Health, Education, and Welfare, Publication No. (NIH) 85-23, revised 1985.

RESULTS

Effects of Haloperidol

All monkeys exhibited sedation, reduced responses to observers, catalepsy, and ptosis after every treatment from the first administration of haloperidol. The duration of these signs gradually reduced with the progress of dosing, but dystonia, characterized by writhing movements, persistent extension of limbs, oral dyskinesias, abnormal behavior, and an abnormal gait appeared constantly. Table 1 shows general categories and weeks with stable eliciting of signs. After 6 weeks of administration, two monkeys began to display an abnormal gait, and all animals subsequently displayed various movement disorders by 25 weeks. Their abnormal gait was characterized by circling, retrogression, stiff leg movements, and steady gaze. When animals were prone on the cage floor, they exhibited neck or trust writhing movements (Fig. 1). Abnormal movements consisted of persistent pushing with the head against a cage wall or the ceiling, inability to grasp the cage and perch, and rhythmical hand swinging. At this time, when they were caught and pressed to the room wall, they swung not only their hands but all their limbs. Oral dyskinesias included purposeless licking, biting cage bars, and abnormal tongue protrusion (Fig. 2). These episodes almost always disappeared by the next day, and once haloperidol administration ceased, these episodes vanished. However, once these symptoms were elicited in each individual, they reliably reappeared with haloperidol treatment. There were individual differences in frequencies, duration, and categories of types of dystonia.

FIG. 2. Oral dyskinesia, abnormal tongue protrusion after haloperidol administration at 1.25 mg/kg.

Hyperkinesia was present in all males, and one male in particular would fling himself crash into the walls and ceiling of the cage. The removal of impediments such as a food box may be helpful in preventing the animals from injuring themselves.

Effects of Other Neuroleptics

Various drugs were administered in turn to the abovementioned haloperidol-sensitized common marmosets once they displayed no abnormal behavior in each session. The basic dose was established in line with the clinical dose for each drug, and the challenge doses were selected from 0.3-, 1-, 3-, 10-, or 30-fold the basic dose.

TABLE 2

OVERALL INCIDENCE OF DYSTONIA AFTER TREATMENT WITH NEUROLEPTIC AND NONNEUROLEPTIC DRUGS IN HALOPERIDOL-SENSITIZED COMMON MARMOSETS

Drugs	Basic dose (mg/kg)	Multiples of Basic Dose				
		0.3	1	3	10	30
Haloperidol	0.12	—	2*	6	6	—
Bromperidol	0.36	0	6	6	—	—
Chlorpromazine	2.00	—	0	6	6	6
Thioridazine	1.80	—	0	2	5	—
Sulpiride	12.00	—	0	2	5	—
Tiapride	2.50	1	0	—	4	6
Risperidone	0.12	—	3	6	6	—
Clozapine	9.00	—	0	—	0	0
Diazepam	0.40	—	0	—	0	—
Trihexyphenidyl†	0.20	—	6	—	2	—
Vehicle‡	0	—	0	—	—	—

Six haloperidol-sensitized common marmosets were administered various neuroleptic and non-neuroleptic drugs.

*Number shows the number of animals displayed dystonia. The maximal number is 6.

†Trihexyphenidyl was treated before 1.25 mg/kg haloperidol administration.

‡Vehicle was 0.5% methylcellulose solution.

Table 2 and Figs. 3 and 4 show results of the trials. Haloperidol was tested at the doses of 1-, 3-, and 10-fold its basic dose (0.12, 0.36, and 1.20 mg/kg). Two monkeys displayed dystonia at 0.12 mg/kg, while all animals were affected with 0.36 mg/kg and the largest dose. Similar results were observed for treatment with risperidone. Although haloperidol induced a larger variety of types of movement disorders than risperidone, no clear differences were observed between these two drugs in frequency or duration. Chlorpromazine elicited clear-cut dystonia at 3- and 10-fold its basic dose (6 and 20 mg/kg), but only slight effects were observed at 2.0 mg/kg. Bromperidol induced clear-cut dystonia in all monkeys at the basic dose (0.36 mg/kg). Sulpiride and thioridazine caused the same changes in five out of six monkeys at 10-fold basic dose of each, and tiapride elicited abnormalities in four out of six monkeys at 10-fold basic dose and in all monkeys given the 30-fold dose.

The dystonia could not be distinguished from those induced by intermittent previous haloperidol administration at 1.25 mg/kg in the same individuals. Regarding other neurological signs, catalepsy appeared linked to dystonia. However, ptosis was not consistently induced by those neuroleptic treatments. Tremor was often observed in all treated monkeys, but not in a dose-related fashion.

Clozapine failed to elicit dystonia even at 30-fold its basic dose. Sedation and reduced responses to observers were noted, and erection was often observed for all males after higher doses of clozapine and thioridazine, and unsteady gait was apparent after treatment with both of these drugs.

The nonneuroleptic agent diazepam was also examined using haloperidol-sensitized six monkeys. At 4.0 mg/kg, diazepam elicited no dystonia, but did induce a slightly unsteady gait by all monkeys.

After treatment with the anticholinergic drug trihexyphenidyl (2.0 mg/kg), haloperidol at 1.25 mg/kg either failed to elicit dystonia or had reduced effects in all monkeys.

Vehicle (0.5% methylcellulose solution) alone induced no abnormal signs including dystonia or other neurological signs in any animals.

DISCUSSION

Various primate species, for example, rhesus monkeys (1,22,23), cynomolgus monkeys (13), baboons (17), green monkeys (2), cebus monkeys (10,13,26,27), and squirrel monkeys (14), have been tested for induction of dystonia by treatment with neuroleptics. Haloperidol has been the most common drug used in such studies. The observed behavior in all these species was qualitatively similar in onset and time course to that of common marmosets in the present study. Although the dose and frequency of treatment used differed among the studies in the literature, cebus monkeys and squirrel monkeys (new world species) appear to be more susceptible to induction of acute dystonia than do old world monkeys. Porsolt and Jalfre (23) reported that 4–24 months was required for all of three rhesus monkeys to develop dystonia, while green monkeys required 4–14 months to develop this condition (2). Gunne and Barany (13) indicated that cynomolgus monkeys failed to suffer dystonia, although they were the species most typically used in the preclinical investigations. In baboons, Meldrum et al. (17) observed acute dystonia in only 3 out of 25 monkeys, but the duration of treatment was not specified. In the case of new world primates, acute dystonia has been elicited after 130–317 days in cebus monkeys (26), and Liebman and Neale (14) reported that all squirrel monkeys used in their study exhibited dystonia within 25 weeks.

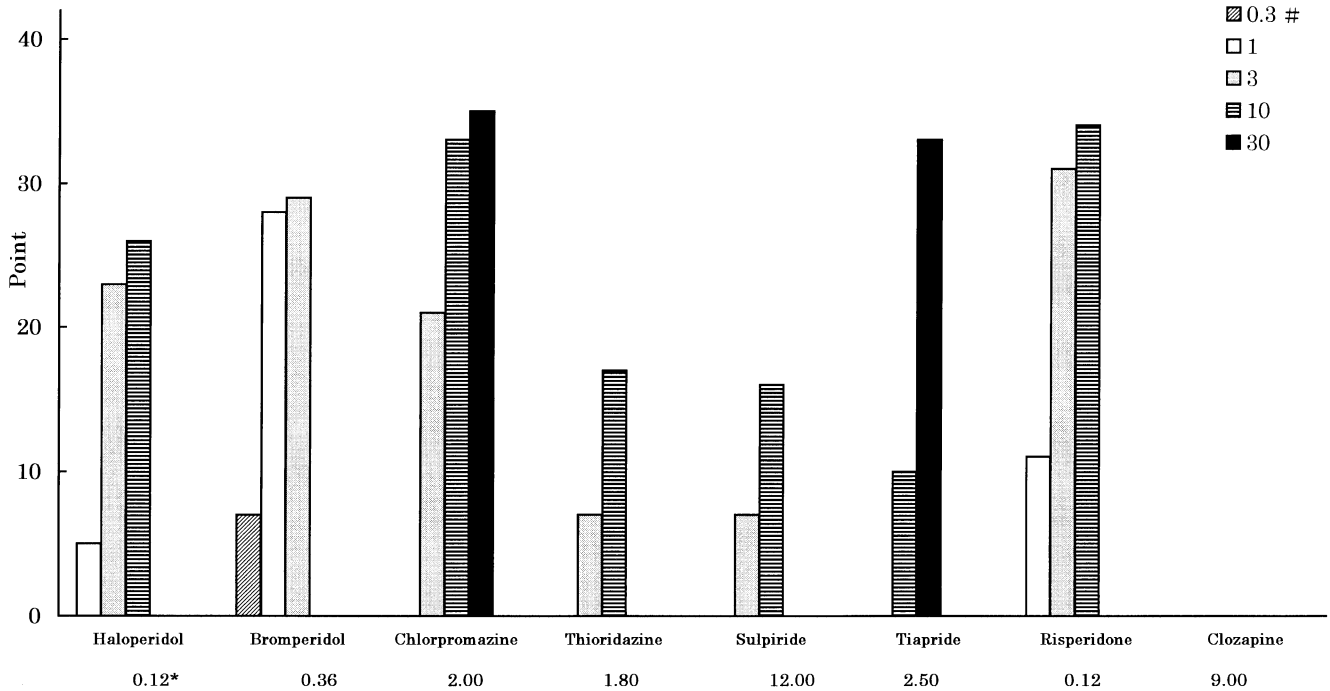

FIG. 3. Points assigned for dystonia during each session in six haloperidol-sensitized common marmosets. The observation points was 7 after each drug administration for each individual. The maximal number of points was 42. *Shows the basic dose of each drug and # shows the number of times the basic dose.

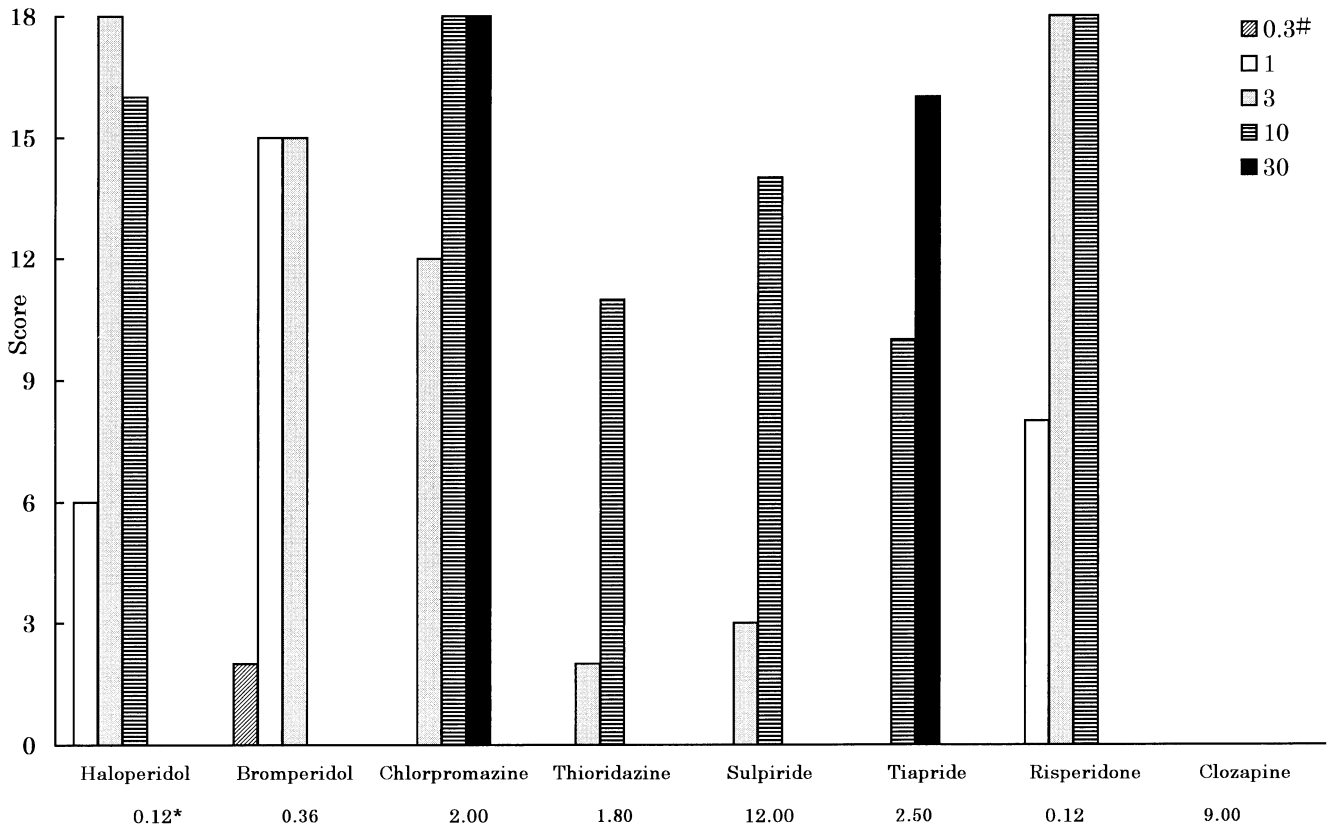

FIG. 4. The maximal score for appearance of dystonia by each dose of drug in six haloperidol-sensitized common marmosets. The score was recorded as 0–3. The maximal score for each session was 18. *Shows the basic dose of each drug and # shows the number of times of the basic dose.

In our study, all common marmosets, a new world primate species, exhibited dystonia after 6–25 weeks of treatment. Our results confirm that new world species are useful for prediction of development of dystonia and suggest that common marmosets will be useful in studies requiring haloperidol-sensitizable monkeys. We also studied four rhesus monkeys in a parallel experiment under the same conditions as for common marmosets. However, only one of four these animals exhibited slight oral dyskinesia after 21 weeks of treatment, until 1 year (data not shown). Our investigations confirm that the common marmoset is more susceptible to haloperidol-induced acute dystonia than is an old world species (rhesus monkey). Thus, there is a considerable difference in susceptibility to acute dystonia between new and old world monkey species. The reason for this difference remains unclear, and additional study for species difference is needed. Although old world species are phylogentically closer to humans than are new world species, there are physiological similarities to and differences from humans in both old world species and new world species. Old world species with the exception of apes are not always physiologically closer to humans than are new world species. The response to neuroleptics of new world species is closer to that of humans than is that of old world monkeys.

Dose-related effects of treatment with various neuroleptic drugs were found in haloperidol-sensitizable common marmosets in the present study. The butyrophenones haloperidol and bromperidol induced dystonia at near-clinical doses. Our findings for the traditional neuroleptic haloperidol are similar to those obtained for squirrel monkeys (14) and rhesus monkeys (23). Another butyrophenone, bromperidol, elicits clear-cut dystonia in common marmosets. And a typical neuroleptic, chrolpromazine, also induced dystonia at near-clinical doses. Thus, findings similar to clinical results were obtained for some typical neuroleptics in the present study. Porsolt and Jalfre (23) reported that sensitivity differed among rhesus monkeys for phenothiazines and was particularly low for chlorpromazine and thioridazine. However, squirrel monkeys along with common marmosets responded with dystonia to both drugs (14). Clinical findings indicate that thioridazine causes dystonia at much higher doses than butyrophenones. This finding correlates well with the clinical findings that this drug causes fewer EPS episodes than do other typical neuroleptics (11).

Our observations of the effects of benzamides, sulpiride and tiapride, are similar to those for these drugs in squirrel monkeys (19) and rhesus monkeys (23). Both benzamides also induced dystonia at lower doses than haloperidol. Clozapine, an atypical neuroleptic, has been examined by several researchers in haloperidol-sensitized primates including squirrel monkeys (14), rhesus monkeys (23), and cebus monkeys (4). None of these species demonstrated dystonia the same as that observed clinically (15). However, sedation, hypersalivation, ptosis, ataxia, and/or tremors were observed. In our study, clozapine failed to induce dystonia, and other neurological signs were similar to the results of other species, although salivation and ptosis were not clearly induced and all males also displayed erection. Another atypical neuroleptic,

risperidone, elicited dose-related dystonia in common marmosets at almost the same dose as haloperidol, particularly at dose above 0.36 mg/kg. Although its antipsychotic effect was similar to that of haloperidol, risperidone under 6 mg/man induced EPS to a lesser extent than did haloperidol in humans (21). On the other hand, EPS induction at higher doses with risperidone are similar to those with haloperidol (16,21). The present results with common marmosets correlated well with clinical findings. The benefit ratio of antipsychotic efficacy dose ranges is approximately 3:1(7). Studies of other neuroleptic-sensitized primates have shown that the dystonia-inducing threshold dose is the same for risperidone and haloperidol (5–7), and dose-related curves similar to those in this study were also found for both drugs (7).

Thus, the more typical drugs induced dystonia at lower doses, while the more atypical drugs did at higher doses in haloperidol-sensitized common marmosets. And the results with common marmosets also support the conclusion that high dose of risperidone produce EPS similar to that induced by haloperidol, as found both humans and other species of nonhuman primates (7,16,21,24), although risperidone has the advantage of requiring a lower dose for efficacy with lower risk of EPS than does haloperidol.

A nonneuroleptic, diazepam, also failed to produce dystonia in our study. Therefore, neuroleptic-induced dystonia in common marmosets appears to be distinguishable from those due to nonneuroleptics. The anticholinergic drug, trihexyphenidyl, can certainly suppress haloperidol-induced dystonia in the common marmoset as it also does in humans, and as earlier reported for cebus monkeys (26), baboons (17) and squirrel monkeys (14). In addition, dystonia was induced after individual acute administration of drugs in each common marmoset. The effects of anticholinergic drugs in primates are similar to findings for neuroleptic-induced dystonia in humans. Although development of human dystonic reactions does not require a pretreatment period, unlike the case for the common marmoset and other primate models. Rupniak et al. (25) described that these movement disorders of primate models are strikingly similar to the characteristics of neuroleptic-induced acute dystonia, and not tardive dyskinesia.

All the marmoset males exhibited hyperkinesia, and one male in particular would fling himself crashing into the cage walls and ceiling. Similar movements were observed during dystonic episodes in cebus monkeys treated with haloperidol (2,26) and fluphenazine (10). This syndrome constitutes part of an idiosyncratic dystonic syndrome in new world species or more closely resembles akathisia in humans. There was no discrimination about correlation between development of akathisia and gender (15). However, female monkeys exhibited hyperkinesia in the Cebus studies. Further study may be needed to determine the significance of this behavior. Administration of neuroleptic in combination with ritanserin might be helpful to prove it, because ritanserin is a relatively selective antagonist of serotonin ($5\text{-}HT_2$) receptors and has clinically beneficial effects in reducing neuroleptic-induced akathisia (18).

Other neurologic signs including tremor, catalepsy, and ptosis were induced by various neuroleptics, but no clear dose dependency was observed, and catalepsy and ptosis were also noted after treatment with diazepam. Catalepsy in animals might be a counterpart of Parkinsonism in humans, because it results from insufficient interaction of dopamine with dopamine receptors in the basal ganglia (12). However, catalepsy is not sufficient as a particular sign in neuroleptic-sensitized primates, for example, common marmosets and squirrel monkeys (14), for prediction of the human drug-induced Parkinsonism.

The findings of the present study suggest that common marmosets are good species for prediction of extrapyramidal side effects and for screening of new neuroleptics candidates. Recently, application of common marmosets has increased in a number of fields, because of their several advantages as experimental animals. In psychopharmacological studies, nonhuman primates play very important roles, but the use of primates involves certain difficulties, for example, handling, infection, and commercial availability. In general, these problems can be ignored with common marmosets, because they are purpose-bred animals and, therefore, easier to obtain and handle than other primate species. The size of marmosets is small, and their body weight ranges from 250–400 g, about half that of squirrel monkeys and similar to that of rats. Thus, use of this monkey can be recommended for the screening of new drug candidates, because large amounts of test material are not usually available in the early stages of drug development.

ACKNOWLEDGEMENTS

We thank Mr. Hirohiko Yamada for supporting our study and Dr. Yoshikuni Tanioka (Central Institute for Experimental Animals) for his specialist advice concerning the use of common marmosets, and express our gratitude to Mr. Takayuki Iwaisako and Atsushi Matsumoto for their expert technical assistance. We also thank Dr. Yukihiro Ohno (Research Center, Sumitomo Pharmaceuticals Co., Ltd.) for supplying several drugs.

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