Propiverine-Induced Parkinsonism: A Case Report and a Pharmacokinetic/Pharmacodynamic Study in Mice

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Purpose. We present a case report of propiverine-induced Parkinsonism. We previously reported the induction of catalepsy by amiodarone, aprindine and procaine, which possess a diethylaminomethyl moiety and demonstrated selective blockade of dopamine D2 receptors by these drugs in mice. We hypothesized that drugs possessing a diethylaminomethyl structure may generally induce Parkinsonism and/or catalepsy.

Methods. Thus, we performed a study to examine whether oxybutynin, pentoxyverine and etafenone, as well as propiverine, induce catalepsy in mice.

Results. The intensity of drug-induced catalepsy was in the order: haloperidol > etafenone > pentoxyverine > propiverine > oxybutynin. *In vivo* occupancy of dopamine D_1, D_2 and mACh receptors in the striatum was also examined. The *in vitro* binding affinities to the D_1, D_2 and mACh receptors in the striatum synaptic membrane were within the ranges of 2.4–140 μM, 380–4,200 nM, and 1.2–2,800 nM, respectively.

Conclusions. These results support the idea that any drug possessing a diethylaminomethyl moiety may contribute to the induction of catalepsy, possibly by occupying dopamine receptors.

KEY WORDS: catalepsy; diethylaminomethyl; dopamine receptor; drug-induced Parkinsonism; propiverine; receptor occupancy.

INTRODUCTION

Drug-induced Parkinsonism is a serious side-effect of dopamine receptor antagonists such as neuroleptics (1,2). Some neuroleptics induce Parkinsonism dose-dependently and a relationship between the occurrence of drug-induced Parkinsonism and dopamine D_2 receptor inhibition ratio or dopamine D_2 receptor occupancy has been suggested (3). Moreover, we and other investigators have reported the induction of Parkinsonism by antiarrhythmic drugs (amiodarone and aprindine), and a local anesthetic (procaine) in both humans and mice (4–8), as well as by calcium channel blockers such as flunarizine and cinnarizine in patients treated for cerebral blood flow disturbances (9,10). These drugs all possess a diethylaminomethyl moiety in a similar conformation to that seen in a neuroleptic drug (haloperidol; Fig. 1), and in benzamide derivatives (metoclopramide and tiapride), which selectively block dopamine D_2 receptors. Moreover, we demonstrated that the induction of catalepsy in mice by amiodarone, aprindine and procaine was mainly due to blockade of the dopaminergic D_1 and D_2 receptors (8). In the present paper we describe a patient who developed Parkinsonism during treatment with propiverine hydrochloride (propiverine).

Case Report. The patient, a 72-year-old-man had been taking 2.5 mg of glibenclamide daily for several years for his diabetes. Propiverine, 20 mg daily before sleeping, was prescribed because of the appearance of nocturia. After the beginning of propiverine treatment, dysstasia, bradypragia and brachybasia appeared. Three months later, levodopa-dopa decarboxylase inhibitor (DCI) 200 mg daily was given for the treatment of Parkinsonism. Although no tremor, muscular rigidity, hypodynamia or enhanced deep reflex was recognized after one month of treatment, significant bradypragia and brachybasia were observed. Moderate encephalatrophy was also recognized by computed tomography. Propiverine was discontinued, and brachybasia disappeared within two weeks. No abnormality remained except for slight dysbasia. No tremor, muscular rigidity or mental symptom was observed.

Sugiyama has also reported three cases of Parkinsonism induced by propiverine (11). The mechanism of drug-induced Parkinsonism has not been fully established, but seems mainly to involve the blockade of dopamine receptors in the striatum by administered drugs (8,12). Moreover, propiverine possesses a similar partial conformation to that seen in drugs such as haloperidol, flunarizine and cinnarizine, all of which induce Parkinsonism (9,10,13,14). These results suggest the hypothesis that other drugs possessing a similar structural feature, such as propiverine, may also induce Parkinsonism and/or catalepsy. In this study, therefore, we conducted *in vivo* and *in vitro* experiments using mice to examine whether catalepsy is induced by the anti-pollakiuria agents propiverine and oxybutynin hydrochloride (oxybutynin), as well as pentoxyverine citrate (pentoxyverine), an antitussive agent, and etafenone hydrochloride (etafenone), used to treat ischemic heart disease. These drugs all contain a diethylaminomethyl moiety (Fig. 1).

MATERIALS AND METHODS

Animals

Male ddY mice, 5 weeks old, weighing 25–30 g, were purchased from Seac Yoshitomi Co., Ltd. (Fukuoka, Japan).

Drugs

The following drugs were gifts from the indicated companies: propiverine hydrochloride from Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan); oxybutynin hydrochloride from Hoechst Marion Roussel (Tokyo, Japan); pentoxyverine citrate from Sumitomo Pharmaceutical Co., Ltd., (Osaka, Japan); etafenone hydrochloride from Kissei Pharmaceutical Co., Ltd., (Nagano,

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ABBREVIATIONS: mACh, muscarinic acetylcholine; SCH23390, R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine; [^{3}H]QNB, [^{3}H]L-quinuclizinyl benzilate.

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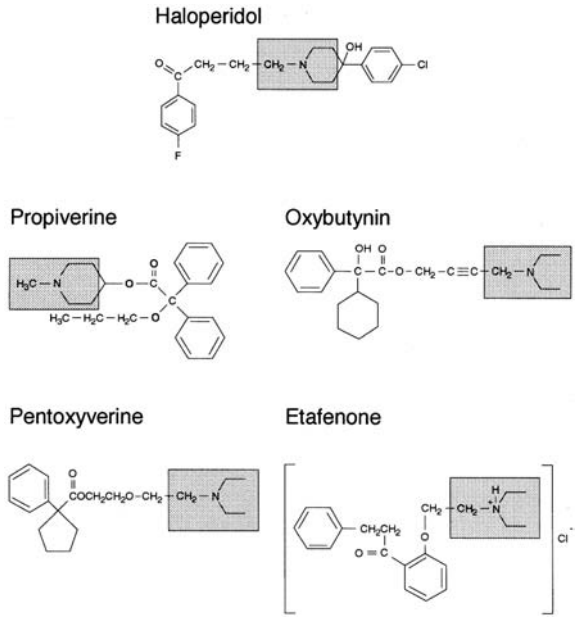

Fig. 1. The chemical structures of the test drugs. Shaded parts in the figure represent the similar conformation of a diethylaminomethyl moiety or side chain.

Japan); haloperidol and biperiden hydrochloride from Dainippon Pharmaceutical Co., (Osaka, Japan); nemonapride from Yamanouchi Pharmaceutical Co., Ltd. (Tokyo, Japan); propantheline bromide from Monsanto Co., Ltd. (Osaka, Japan). Clearsol I scintillation cocktail was purchased from Nakalai Tesque, Inc., (Kyoto, Japan), atropine sulfate monohydrate from Wako Pure Chemical Ind., Ltd. (Osaka, Japan) and R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2, 3, 4, 5-tetrahydro-1H-3-benzazepine (R(+)-SCH23390) hydro-chloride from Funakoshi Co., Ltd. (Tokyo, Japan). [^{3}H] SCH23390 (specific activity, 70.3 Ci/mmol), [^{3}H] raclopride (specific activity, 79.3 Ci/mmol), and [^{3}H] L-quinuclizinyl benzilate ([^{3}H] QNB; specific activity, 49.0 Ci/mmol) were purchased from NEN Research Products (MA, USA), and SOLVABLE from Packard (CT, USA). All other chemicals used in the experiments were of analytical grade.

Preparation of Drug Solutions

In the *in vivo* study, biperiden was dissolved in distilled water. Haloperidol was dissolved in 0.3% tartaric acid and diluted with saline. Propiverine, oxybutynin, pentoxyverine, etafenone, propantheline bromide and atropine sulfate monohydrate were dissolved in saline. The unlabeled drugs were injected in a volume of 2.5 ml/kg for intravenous administration and a volume of 10 ml/kg for other administration. The administration of the solvent alone was employed as a control.

In the *in vitro* study, propiverine, oxybutynin, pentoxyverine, etafenone, R(+)-SCH23390 and atropine sulfate monohydrate were dissolved in distilled water. Haloperidol and nemonapride were dissolved in 0.3% tartaric acid.

Measurement of Intensity of Catalepsy

Measurement of catalepsy was performed according to the method of Haraguchi *et al.* (13). Propiverine (10 to 75 mg/kg), oxybutynin (10 to 75 mg/kg), pentoxyverine (10 to 50 mg/kg) and etafenone (10 to 50 mg/kg) were intraperitoneally injected, and the results were compared with those obtained in the case of haloperidol (0.05 to 0.5 mg/kg) previously reported by us (8). Control animals received the respective solvent alone under the same conditions. Catalepsy was assessed at 0.5, 1.5, 3, and 4.5 h after administration of the drugs by the bar method; the front paws were gently placed on a horizontal metal bar 2 mm in diameter suspended 4 cm above the floor, and the length of time (seconds) the mouse maintained this abnormal posture was measured. The measurement of catalepsy was performed by an observer who had not prepared the drug solutions, according to the double blind method.

Effects of Central and Peripheral Anticholinergic Drugs on Catalepsy

Propiverine (75 mg/kg), oxybutynin (75 mg/kg), pentoxyverine (50 mg/kg), etafenone (50 mg/kg) or haloperidol (0.5 mg/kg) was intraperitoneally injected. Catalepsy was measured at 60 min after the injection of each drug under the same conditions as noted in the section on "Measurement of intensity of catalepsy", and then 10 mg/kg of biperiden, a central anticholinergic drug, or 2.5 mg/kg of propantheline, a peripheral anticholinergic drug, was administered subcutaneously or intravenously, respectively. After the injection of biperiden or propantheline, catalepsy was measured every hour for three hours. Animals that received the respective solvent alone under the same conditions were employed as controls.

In Vivo Dopamine D_1, D_2, and mACh Receptor Occupancy

Measurement of *in vivo* receptor occupancy was performed according to the method of Haraguchi *et al.* (13). Each drug or vehicle was administered intraperitoneally to mice under the same conditions as described in the section on "Measurement of intensity of catalepsy". At 85 min after the administration of haloperidol and at 25 min after the administration of the other drugs, a D_1-selective antagonist [^{3}H]SCH23390 (2 μCi/body), a D_2-selective antagonist [^{3}H]raclopride (2 μCi/body) or an mACh specific antagonist [^{3}H]QNB (2 μCi/body) was injected intravenously. After 10 min, the mice were decapitated and the striatum and cerebellum were isolated by dissection on a glass plate. Each sample was weighed in a vial, added to 1 ml of SOLVABLE and incubated at 50°C until a clear solution was formed, then 0.2 ml of 30% H_2O_2 was added and the vial was left at room temperature overnight. The solution was neutralized with 70 ml of 6 M HCl and 10 ml of Clear-sol I was added. Radioactivity was measured in a liquid scintillation counter (LS6500, Beckman Ins., CA, USA).

Dopamine and mACh receptor occupancies were calculated according to the following equations (1) and (2), respectively:

$$F1(\%) = (1 - (A - 1)/(B - 1)) \times 100 \quad (1)$$

where A and B are the ratio of radioactivities (striatum/cerebellum) in the presence and absence of a drug, respectively. The cerebellum was utilized as a dopamine receptor-free region to estimate the nonspecific binding of ligands.

$$F2(\%) = (1 - (A' - C)/(B' - C)) \times 100 \quad (2)$$

where A′ and B′ are the radioactivities in the striatum in the presence or absence of a drug, respectively. C is the nonspecific binding, which was determined by subcutaneous administration of non-labeled atropine (50 mg/kg) at 25 min before the administration of [^{3}H]QNB.

In Vitro Dopamine D_1, D_2, and mACh Receptor Binding Study

Membrane samples were obtained according to the method of Haraguchi *et al.* (15). The mice were decapitated and the striatum was rapidly isolated by dissection. The striatal tissue was weighed and homogenates were prepared in 100 volumes (w/v) of ice-cold 50 mM Tris-HCl buffer (pH 7.4) with a Teflon-on-glass tissue homogenizer. The homogenates were centrifuged (20,000 × *g* for 10 min at 4°C) twice with intermediate resuspension in ice-cold 50 mM Tris-HCl buffer (pH 7.4). The final pellets were resuspended in 200 and 300 volumes (w/v) of the buffer for dopamine and mACh receptors, respectively.

Aliquots of the membrane preparations were incubated with each drug and 0.3 nM [^{3}H]SCH23390 (for D_1 receptor binding) or 1 nM [^{3}H]raclopride (for D_2 receptor binding) for 15 min at 37°C in 50 mM Tris-HCl buffer (pH 7.4) containing (millimolar): NaCl, 120; KCl, 5; $CaCl_2$, 2; and $MgCl_2$, 1. For mACh receptor binding, aliquots of the membrane preparations were incubated with each drug and 0.2 nM [^{3}H]QNB for 30 min at 37°C in 50 mM Tris-HCl buffer (pH 7.4). The final tissue concentrations were 1 mg wet weight of the original tissue per 1 ml for D_1 and D_2 receptor binding and 2 mg/3 ml for mACh receptor binding. The amounts of protein in the cells were measured by Lowry's method (18).

The incubation was terminated by rapid pouring of the contents of the tubes over Whatman GF/C glass fiber filters under vacuum. The filters were rinsed twice with 5 ml of ice-cold 50 mM Tris-HCl buffer (pH 7.4) and placed in glass scintillation vials, then 8 ml of Clear-sol I was added.

Nonspecific binding was determined in the presence of 100 nM SCH23390, 1 μM nemonapride and 1 μM atropine for D_1, D_2 and mACh receptor binding, respectively.

K_i values were calculated according to the following equation:

$$R = (K_d + D)/(K_d \cdot (1 + I/K_i) + D) \quad (3)$$

where R is the specific binding ratio (ratio of [^{3}H] count in the presence of drugs to that in the absence of drugs), and D is the concentration of [^{3}H] ligand, I is the concentration of the drugs as inhibitors and K_d is the dissociation constant of the [^{3}H] ligand obtained from Scatchard analysis of saturation experiment data. Data analysis and simulations used the nonlinear least-squares method MULTI (17).

Statistical Analysis

Statistical analysis was performed by using Student's t-test. The criterion of statistical significance was a *P* value of less than 0.05.

RESULTS

Induction of Catalepsy

Time courses of the intensity of catalepsy induced after intraperitoneal injection of various doses of propiverine, oxybutynin, pentoxyverine, etafenone and haloperidol are shown in Fig. 2A–E. The intensities of drug-induced catalepsy at 30 min after administration were dose-dependent (Fig. 3). Catalepsy was observed for several hours after administration of each test drug with different dose dependencies among the drugs. The relative intensity of a drug was defined as the ratio of the inverse of the dose giving a duration of catalepsy of 5 sec to that of haloperidol (Fig. 3). The relative values of intensity of

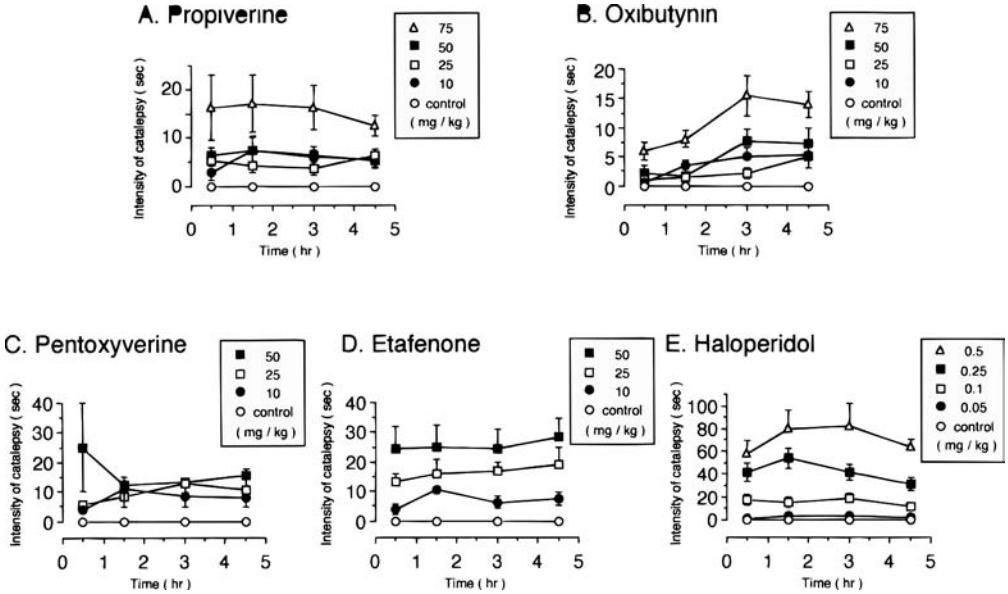

Fig. 2. Time courses of induced catalepsy. The intensity of catalepsy was assessed at 0.5, 1.5, 3 and 4.5 hr after i.p. administration of A; propiverine, B; oxybutinin, C; pentoxyverine, D; etafenone, compared with the case of haloperidol (E) previously reported by us (8). The catalepsy was measured as described in materials and methods. Data are means ± S.E. (n = 6–7).

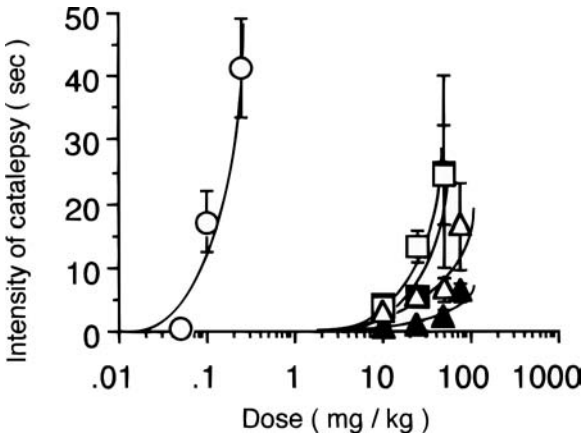

Fig. 3. Dose-dependent induction of catalepsy. Symbols: △; propiverine-, ▲; oxybutinin-, ■; pentoxyverine-, □; etafenone-, ○; haloperidol-induced catalepsy at 30 min after i.p. administration. Data are means ± S.E. (n = 6–7).

haloperidol, etafenone, propiverine, pentoxyverine and oxybutynin were 1.0, 0.02, 0.003, 0.002 and 0.0009, respectively (Table I).

Effect of Central and Peripheral Anticholinergic Drugs on the Catalepsy

Biperiden, a central anticholinergic drug, completely alleviated the catalepsy induced by all tested drugs to the baseline level (Fig. 4A–D). However, there was no change in catalepsy in the presence of propantheline, a peripheral anticholinergic drug (Fig. 5A–D).

In Vivo Dopamine D_1, D_2, and mACh Receptor Occupancy and Catalepsy

The values of intensity of catalepsy measured at 30 min after the administration of propiverine (75 mg/kg), oxybutynin (75 mg/kg), pentoxyverine (50 mg/kg) or etafenone (50 mg/kg) and at 90 min after the administration of haloperidol (0.5 mg/kg), and the *in vivo* dopamine D_1, D_2 and mACh receptor occupancies for the various drugs are shown in Table I. The *in vivo* occupancies of D_1, D_2 and mACh receptors were within the ranges of 25 to 74.5%, 17.3 to 87.2% and 9.7 to 98.0%, respectively.

In Vitro Dopamine D_1, D_2, and mACh Receptor Binding Affinity in Striatum Nervous Membrane

Figure 6 shows the inhibition of the *in vitro* binding of dopamine D_1, D_2 or mACh receptor-selective radioligands ([^{3}H] SCH23390 for D_1 receptor, [^{3}H] raclopride for D_2 receptor and [^{3}H] QNB for mACh receptor) to the striatum membrane in the presence of the test drugs. The K_d values of [^{3}H] SCH23390, [^{3}H] raclopride and [^{3}H] QNB obtained by Scatchard analysis were 0.22, 1.0 and 0.075 nM, respectively. The calculated K_i values of the test drugs are listed in Table II. The K_i values of the test drugs for dopamine D_1, D_2 and mACh receptors were in the ranges of 2.4 μM-137 μM, 376 nM-4.2 μM and 1.2 nM-2.8 μM, respectively. Propiverine showed the second strongest binding affinity for the D_1 receptor after etafenone. Oxybutynin and pentoxyverine showed very strong binding affinity for the D_2 receptor. Oxybutynin, pentoxyverine and etafenone all showed markedly strong binding affinity for the mACh receptor as compared with the dopamine D_1 and D_2 receptors, while propiverine exhibited comparable binding affinities for the mACh and dopamine D_1 and D_2 receptors.

DISCUSSION

We encountered a clinical case of propiverine-induced Parkinsonism, which we considered to have been probably due to blockade of dopamine D_1 and D_2 receptors by propiverine. Recently, we demonstrated that two antiarrhythmic drugs, amiodarone and aprindine, and a local anesthetic drug, procaine, induced catalepsy in mice (8). These drugs have a diethylaminomethyl moiety, like haloperidol and the benzamide derivatives metoclopramide and tiapride, which selectively block dopamine D_2 receptors. Moreover, it was suggested that the induction of catalepsy by these three drugs was due to the blockade of both dopamine D_1 and D_2 receptors (8). So, drugs possessing an alkylamine-type moiety, such as propiverine, that can adopt a similar conformation to that of the above drugs may also have the potential to induce Parkinsonism and/or catalepsy. In this study, we conducted *in vivo* and *in vitro* experiments using mice to examine whether catalepsy can be induced by two anti-pollakiuria agents, propiverine and oxybutynin, an antitussive agent, pentoxyverine, and a drug used to treat ischemic heart disease, etafenone, all of which possess a diethylaminomethyl group or a similar alkylamine structure (Fig. 1). Indeed, extrapyramidal syndrome was induced in the patient treated with propiverine.

Table I. Intensity of Catalepsy and *In Vivo* D_1, D_2, and mACh Receptor Occupancies of the Test Drugs

	Dose (mg/kg)	Intensity of catalepsy (sec)	Relative intensity	*In vivo* receptor occupancy (%)		
				D_1	D_2	mACh
Propiverine	75	28.0 ± 9.4	0.003	39.7 ± 2.8	24.4 ± 5.1	30.4 ± 4.8
Oxybutynin	75	2.9 ± 2.1	0.0009	29.2 ± 6.4	46.8 ± 1.4	98.0 ± 5.2
Pentoxyverine	50	43.3 ± 23.8	0.002	61.7 ± 8.9	17.3 ± 2.3	28.9 ± 5.5
Etafenone	50	50.6 ± 13.2	0.02	74.5 ± 1.4	69.2 ± 9.9	57.7 ± 13.3
Haloperidol	0.5	71.7 ± 7.9	1	25.0 ± 5.3	87.2 ± 6.5	9.7 ± 8.7

Note: [^{3}H]SCH 23390, [^{3}H]raclopride and [^{3}H]QNB were used for *in vivo* labeling of dopamine D_1, D_2 and mACh receptors, respectively. Relative intensity is the ratio of the inverse of the dose giving an intensity of catalepsy of 5 sec to that of haloperidol. Data are means ± S.E. (*in vivo* receptor occupancy; n = 3–4, intensity of catalepsy; n = 9–11).

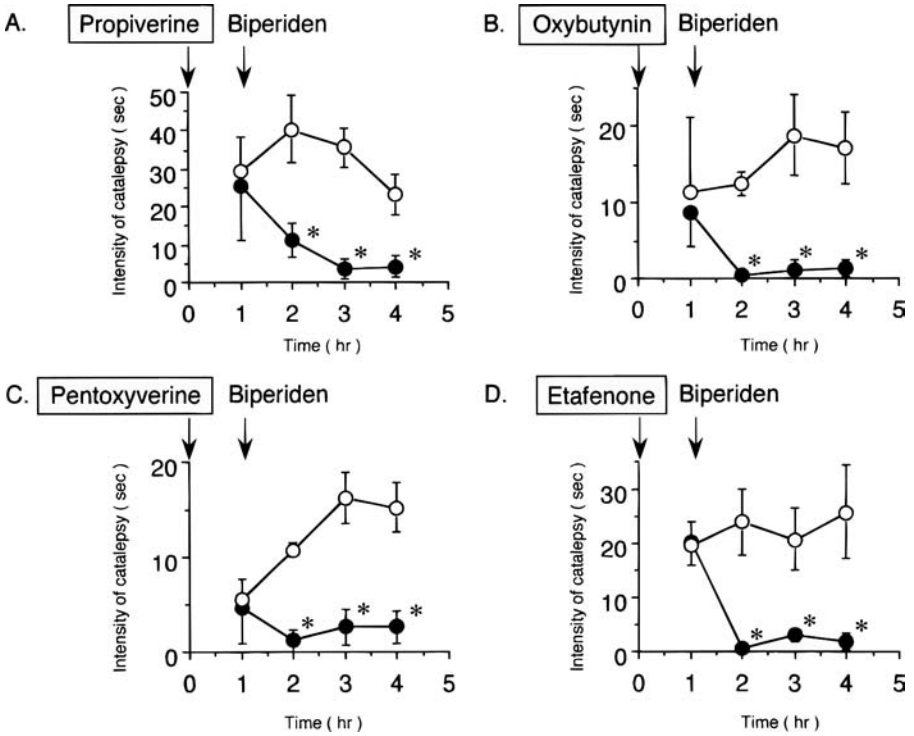

Fig. 4. Effect of biperiden on drug-induced catalepsy. Biperiden (●) or the solvent alone (○) was administered at 60 min after i.p. administration of A; propiverine (75 mg/kg), B; oxybutinin (75 mg/kg), C; pentoxyverine (50 mg/kg), D; etafenone (50 mg/kg). Data are means ± S.E. (n = 5–6). Significant differences from the drug alone; (*$p < 0.05$).

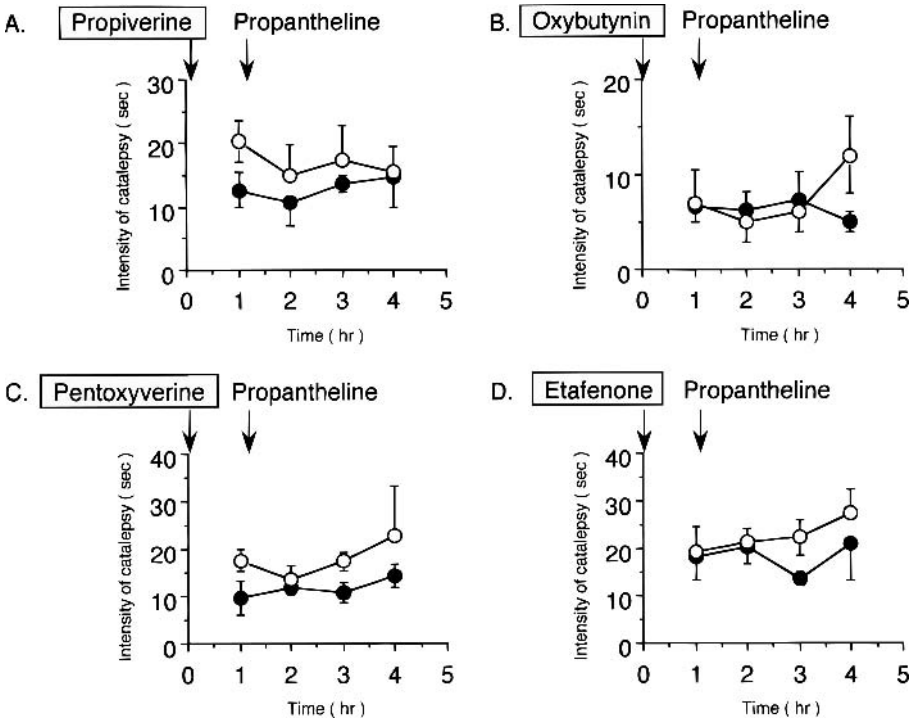

Fig. 5. Effect of propantheline on drug-induced catalepsy. Propantheline (●) or the solvent alone (○) was administered at 60 min after i.v. administration of A; propiverine (75 mg/kg), B; oxybutinin (75 mg/kg), C; pentoxyverine (50 mg/kg), D; etafenone (50 mg/kg). Data are means ± S.E. (n = 3). No significant differences from the drug alone.

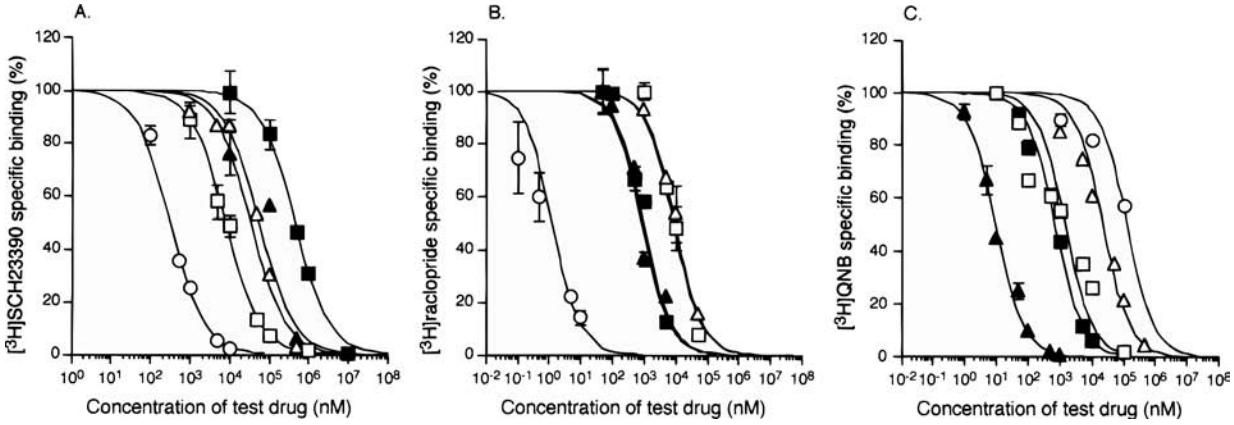

Fig. 6. Inhibition curves for binding of [^{3}H]SCH23390 (A), [^{3}H]raclopride (B) and [^{3}H]QNB (C) to mouse striatal membranes in the presence of haloperidol (◯), propiverine (△), oxybutinin (▲), pentoxyverine (■) or etafenone (□). Data are means ± S.E. (n = 3).

It is well known that catalepsy is induced in a dose-dependent manner by neuroleptics such as haloperidol (13,14). We found that catalepsy was also induced in a dose-dependent manner by propiverine, oxybutynin, pentoxyverine and etafenone (Figs. 2, 3). These results are consistent with the case report of propiverine-induced Parkinsonism in this paper. In the case of pentoxyverine, dose-dependency was not clearly apparent except at 30 min after the administration. The amplitude of catalepsy declined within 90 minutes, suggesting a possible rapid elimination of pentoxyverine. To determine whether the observed catalepsy can be attenuated by blockade of the cholinergic central nervous system, a central anticholinergic agent, biperiden, which is easily transported into the brain *in vivo* (18,19), was administered subcutaneously, and its effect on the drug-induced catalepsy was investigated. The catalepsy was almost completely alleviated in the presence of biperiden (Fig. 4A–D), whereas a peripheral anticholinergic drug, propantheline (20) was ineffective (Fig. 5A–D). These results suggest that drug-induced catalepsy can be attenuated by blocking the cholinergic central nervous system, which may be activated by blockade of the dopaminergic receptors.

Both *in vivo* and *in vitro* binding assays of these four drugs to the dopamine D_1, D_2 and mACh receptors were performed. As shown in Table I and II, each drug used in this study blocked the D_1 and D_2 receptors both *in vivo* and *in vitro*, suggesting that the dopamine D_1 and D_2 receptors are related to the drug-induced catalepsy and Parkinsonism. Propiverine, oxybutynin, pentoxyverine and etafenone, however, were high-affinity antagonists of the mACh receptor both *in vivo* and *in vitro*. This activity of the drugs may have the effect of reducing the intensity of drug-induced catalepsy in mice. This may explain why there is little published information about the induction of Parkinsonism by these four drugs in humans.

Table II. *In Vitro* K_i Values of the Test Drugs for D_1, D_2 and mACh, Receptors

	K_i (nM)		
	D_1	D_2	mACh
Propiverine	6520 ± 696	4150 ± 503	2780 ± 233
Oxibutynin	16700 ± 2180	376 ± 50.9	1.22 ± 0.12
Pentoxyverine	137000 ± 10400	419 ± 37.9	88.6 ± 4.94
Etafenone	2430 ± 239	3920 ± 517	184 ± 27.8
Haloperidol	60 ± 3.1	0.52 ± 2.90	16300 ± 610

Note: [^{3}H]SCH 23390, [^{3}H]raclopride and [^{3}H]QNB were used for *in vitro* labeling of dopamine D_1, D_2 and mACh receptors, respectively. Data are means ± S.D. (n = 3).

It has been reported that propiverine, oxybutynin, pentoxyverine and etafenone have a calcium channel blocking effect (21–24). A similar effect of amiodarone, aprindine and procaine was also reported (25–28). The diethylaminomethyl group is a common structure in local anesthetic drugs and may be important for the calcium channel blocking effect (27–29). Further, some drugs that exert their pharmacological effect by the blockade of dopaminergic receptors possess calcium channel blocking activity (30). Thus, the calcium channel blocking effect of drugs that possess a diethylaminomethyl moiety may play a role in the induction of catalepsy.

In conclusion, we suggest that the clinical case of propiverine-induced Parkinsonism presented in this paper may have been due to dopamine D_1 and D_2 receptor blockade by the drug. In an *in vivo* study in mice, catalepsy was induced by the administration of not only propiverine, but also pentoxyverine, etafenone and oxybutynin. Oxybutynin showed high *in vivo* and *in vitro* dopamine D_2 receptor occupancies, but also showed very high binding affinity to mACh receptors. This may be the reason why oxybutynin induced the lowest intensity of catalepsy among the five drugs. Our results suggest that, in the clinical setting, drugs that contain a diethylalkylamine moiety tend to induce catalepsy by occupying dopamine receptors, but this effect is alleviated by high anticholinergic activity.

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