Tr. J. of Medical Sciences
29 (1999) 627-629

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S-Aroylmethyl N, N-Disubstituted Dithiocarbamates With Antiparkinson Activity

Received: September 07, 1998

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Abstract: Seven S-aroylmethyl N,N-disubstituted dithiocarbamate derivatives have been synthesized and their effects on oxotremorine induced tremor have been investigated on mice pretreated with the proparkinsonian drug haloperidol. While the compound **1f** inhibited oxotremorine-induced tremors at doses of 50 mg/kg and 100 mg/kg levels, compounds **1a, 1c** and **1e** had this effect at the dose of 100 mg/kg. The compounds **1b, 1d** and **1g** had no effect on oxotremorine-induced tremors in mice. These results suggest that some of these derivatives have central antimuscarinic effects and antiparkinson activities.

Key Words: Dithiocarbamate, antiparkinson activity

Introduction

The aim of this study was to investigate the central antimuscarinic effects and antiparkinson activities of some dithiocarbamate derivatives on mice. It is well known that the dithiocarbamate derivatives have pharmacological properties such as antimicrobial and anticholinergic activities (1-12). In our previous studies, we synthesized and demonstrated the anticholinergic activities of some N,N-disubstituted dithiocarbamate derivatives on guinea pig ileum (13-17). The aim of the present study was to investigate antiparkinson activities of some S, N, N-trisubstituted dithiocarbamate derivatives on mice.

Material and Method

All compounds used in this study were synthesized and their structures were elucidated by previously used spectroscopic methods (17). The formulas of compounds are given in the Table 1.

Pharmacology

Antiparkinson activity

In the present study, male albino mice (25-30 g) were used. They were housed in plastic cages and maintained at 20 ±2 ˚C in a room with a 12 h light-dark cycle. Water was freely available throughout and standard laboratory chow was given *ad libitum*. The animals were pretreated with haloperidol (0.5 mg/kg, i.p.) 10 min before the test. Saline, atropine (2,4 mg/kg) or the test compounds (50 and/or 100 mg/kg) were injected i.p. 30 min. before i.p. injection of oxotremorine (200 mg/kg). Five minutes after the injection of oxotremorine, the tremors were scored separetely for each mouse during 15 min of observation. The tremor intensities were scored over 5-min periods by a person who did not know which drug had been given the animals follows: 0, none, 1, slight (or slow tremor of head); 2, moderate (or fast tremor of head, trunk or limbs); and 3, severe (or intensely fast tremor). Total tremor score was expressed as the sum of the scores for 5 min periods during 15 min of observation (18). One dose of a test compound or atropine was used in each animal. The results were expressed as means ± S.E.M. of number (n) of experiments.

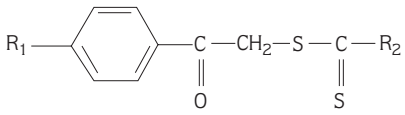
Statistical analysis

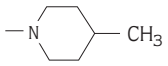
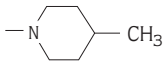
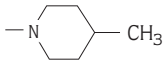
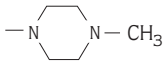
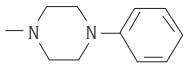
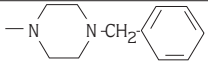
ANOVA (Tukey B test) were employed.

Results and Discussion

The results of antiparkinson activity studies are shown in Table 2. The cholinergic-dopaminergic balance in the basal ganglia is disarranged in parkinson's disease.

Table 1. Formulas of the compounds 1a-g.



Compound	R_1	R_2
1a	H	
1b	H	
1c	OCH_3	
1d	OCH_3	
1e	OCH_3	
1f	OCH_3	
1g	OCH_3	

An alternative approach to restore the normal balance of cholinergic and dopaminergic influences with antimuscarinic drugs has been attempted (19). All these compounds studied have been found to possess peripheral antimuscarinic action (17). Because of their structures, they are highly lipid soluble, so they can enter the cerebrospinal fluid from the circulatory system.

Table 2. The effects of atropine and the compounds 1a-g on exotremorine-induced tremors in mice (N:10). *: $p<0.05$ as compared to control group.

	Tremor Score	
Compound	50 mg/kg	100 mg/kg
1a	-	5.57 ± 0.35*
1b	-	7.67 ± 0.42
1c	8.45 ± 0.15	6.75 ± 0.29*
1d	8.30 ± 0.13	7.96 ± 0.32
1e	8.33 ± 0.12	6.88 ± 0.56*
1f	7.00 ± 0.07*	6.92 ± 0.22*
1g	8.60 ± 0.18	8.25 ± 0.22
Atropine (2,4 mg/kg)	4.17 ± 0.17 *	
Control	8.61 ± 0.15	

The antiparkinson activities of the compounds were shown against oxotremorine-induced tremors at the two dose levels in mice. All compounds may have potent anticholinergic activities (17). In particular, the compound carrying 4-methoxyphenyl group in its structure (**compounds 1c**) also showed antiparkinson activity at the dose level of 100 mg/kg. The compounds carrying methoxy group in their structures showed higher activity against acetylcholine-induced contractions than the others (17). Since the amounts of compound **1a-b** were insufficient, it was not possible to investigate these compounds at a dose level of 50 mg/kg. The introduction of second nitrogen atom into the piperidine ring generally decreased the activity. Additionally, enlargement of the piperidine ring to the homopiperidine isomer also decreased activity. In methoxy derivatives, the activities of 4-phenylpiperazine (**compound 1e**) and 4-benzylpiperazine (**compound 1f**) analogs (at 100 mg/kg) were found to be approximately equipotent.

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