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Persistence of Central Effects of Pirlindole, a Short-Acting Monoamineoxidase Inhibitor, in the Presence of a Monoamineoxidase Inhibitor

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ABSTRACT

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Pirlindole, a tetracyclic drug, is known to have a reversible and short-lived monoamineoxidase inhibitory activity. When administered after a supramaximal inhibitory dose of a classic monoamineoxidase inhibitor, pirlindole continues to antagonize reserpine-induced ptosis and oxotremorine-induced akinesia in mice. These results indicate that some central effects of pirlindole are partially independent of its monoamineoxidase inhibitor activity.

Key words: pirlindole, antidepressant, monoamineoxidase inhibitors

INTRODUCTION

The tetracyclic compound pirlindole, briefly and reversibly inhibits monoamineoxidase in vivo and in vitro [Mashkovsky et al., 1975; Mashkovsky and Andrejeva, 1981; Martorana and Nitz, 1979]. Martorana and Nitz [1979] consider that pirlindole's monoamineoxidase inhibitor activity is unlikely to be related to its antidepressant activity in view of its very short duration of action. Unlike imipramine, pirlindole is devoid of anticholinergic activity [Martorana and Nitz, 1979] and has low, if any, cardiac toxicity [Fiedler et al., 1983].

In this study we have attempted to verify the hypothesis that in the same range of doses, pirlindole possesses two different effects that could contribute to its antidepressant activity.

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TABLE 1. Effect of Pirlindole (Alone or Associated With Pargyline) on Palpebral Ptosis in Mice (20 per Group)

Treatment	Pargyline (mg/kg PO)	Pirlindole (mg/kg IP)	Ptosis mean index ± SEM (min) 30	60	90	120	150	180
a	0	0	3.05 ± 0.16	3.4 ± 0.16	3.55 ± 0.15	3.65 ± 0.15	3.60 ± 0.15	3.7 ± 0.14
b	128	0	2.1 ± 0.16	2.55 ± 0.16	2.6 ± 0.15	3.00 ± 0.15	2.95 ± 0.15	3.1 ± 0.14
c	0	64	2.1 ± 0.16	2.25 ± 0.16	2.25 ± 0.16	2.5 ± 0.15	2.70 ± 0.15	2.95 ± 0.14
d	128	64	1.6 ± 0.16	1.6 ± 0.16	1.9 ± 0.15	2.2 ± 0.15	2.30 ± 0.15	2.4 ± 0.14
Tukey test			*a bcd*	*a bc d*	*a bcd* *b d*	*a bcd* *b d*	*a bc d* *b d*	*a bc d*

Pargyline, reserpine, and pirlindole were administered 24 hr, 4 hr and 30 min, respectively, before the test. Analysis by Tukey test for multiple comparison at $p < .01$. Results are expressed as follows: Groups jointly in italics are not significantly different. For example *a bc d* means $a > b = p < 0.01$, $a > c = p < 0.01$, b and c are not significantly different $b > d$, $c > d$ and $a > d = p < 0.01$.

Two tests, sometimes used for the screening of antidepressants—antagonism of reserpine-induced ptosis and antagonism of oxotremorine-induced akinesia—were used.

MATERIALS AND METHODS

Male NMRI mice weighing 22–25 gm were used. Homogeneously bred animals were supplied by CERJ, Genest Ste. Isle, France.

The compounds used for the various tests were suspended in arabic gum or dissolved in distilled water and administered in a volume of 0.25 ml per gram body weight in mice.

Reserpine-Induced Ptosis in Mice

Pirlindole was administered 4 hr after a solution of reserpine (2.5 mg/kg IP) dissolved in acetic acid and diluted. Ptosis, scored according to Rubin et al. [1957], was evaluated every 30 min.

Oxotremorine-Induced Akinesia in Mice

The method of Francès et al. [1980] was used. Pirlindole was administered 30 min before oxotremorine (0.25 mg/kg IP). Immediately after administration of oxotremorine, the mice were placed individually in small boxes (20 × 10 × 10 cm) for observation. Groups of ten mice were used and akinesia was evaluated at repeated intervals.

Statistical Analysis

Statistical analysis was done using the Tukey test [Zar, 1984].

RESULTS

Reserpine-Induced Ptosis in Mice

Table 1 shows that pirlindole antagonizes reserpine-induced ptosis in mice. The effects of pirlindole and pargyline were additive.

Oxotremorine-Induced Akinesia in Mice

Table 2 shows that oxotremorine-induced akinesia is clearly antagonized by pirlindole (32–64 mg/kg IP) in the presence or in the absence of pargyline (Table 3).

DISCUSSION

Pirlindole was able to antagonize oxotremorine-induced akinesia in mice, a test in which tricyclic antidepressants but not monoamineoxidase inhibitors are active [Francès et al., 1980]. It was also effective in another test of antidepressant activity (reserpine-induced ptosis), even

TABLE 2. Effect of Pirlindole on Oxotremorine-Induced Akinesia in Mice (20 per group)

Pirlindole (mg/kg IP)	Percentage of akinetic mice at a given time (min)			
	10	30	60	90
0	85	85	85	100
32	45	55	65	65
64	0	0	0	35

Pirlindole and oxotremorine were administered 30 and 10 min, respectively, before the test.
Statistical analysis: For 10 min DDL = 2, $\chi^2 = 15.38 = p < 0.001$; for 30 min DDL = 2, $\chi^2 = 10.44 = p < 0.01$; for 60 min DDL = 2, $\chi^2 = 11.5 = p < 0.01$; for 90 min DDL = 2, $\chi^2 = 19.0 = p < 0.01$.

TABLE 3. Effect of Pirlindole (Alone or Associated With Pargyline) on Oxotremorine-Induced Akinesia in Mice (20 per Group)

Treatment	Pargyline (mg/kg PO)	Pirlindole (mg/kg IP)	Percentage of akinetic mice at 30 min
a	0	0	85
b	128	0	90
c	0	64	10
d	128	64	25

Pargyline, pirlindole, and oxotremorine were administered at 24 hr, 1 hr and 30 min, respectively, before the test. Analysis by Tukey test for multiple comparison at $p < 0.001$, after data transformation using arc sin $\sqrt{p}$ *ba dc*.
For complete explanation see Table 1.

in the presence of a supramaximal dose of pargyline, a monoamineoxidase inhibitor [Zirkle and Kaiser, 1964].

From their biochemical experiments, Mashkovsky and Andrejeva [1981] concluded: "It has been shown that pirlindole inhibits the neuronal uptake of noradrenaline. Thus, the drug possesses features of a dual mechanism of action inhibiting the neuronal uptake of monoamines as well as the activity of monoamineoxidase." It seems probable that the effects of pirlindole observed in our two experimental conditions are related to the inhibitory effect of the drug on the neuronal uptake of noradrenaline.

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