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Comparison of the anticholinergic effects of the serotonergic antidepressants, paroxetine, fluvoxamine and clomipramine

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Abstract

Paroxetine, a selective serotonin reuptake inhibitor, shows relatively high affinity for muscarinic acetylcholine receptors compared to other selective serotonin reuptake inhibitors. To determine whether paroxetine has anticholinergic effects in vivo, we examined the effects of paroxetine on oxotremorine-induced tremor, spontaneous defecation and passive avoidance performance using mice and compared the results with those using fluvoxamine, another selective serotonin reuptake inhibitor, and clomipramine, a tricyclic antidepressant with serotonin selectivity. The potency of antidepressant activity as determined in the tail suspension test was paroxetine>fluvoxamine>clomipramine. Paroxetine and clomipramine inhibited oxotremorine-induced tremor, reduced spontaneous defecation and impaired passive avoidance performance, while fluvoxamine did not have similar effects. A comparison of ED_{50} values showed that the ratio of anticholinergic effect to antidepressant activity was fluvoxamine, >3.2; paroxetine, 2.1–2.6; clomipramine, <0.8. These results suggest that paroxetine may induce fewer adverse anticholinergic effects than clomipramine, but more than fluvoxamine.

Keywords: Paroxetine; Fluvoxamine; Clomipramine; Antidepressant; Anticholinergic effect; (Mouse)

1. Introduction

Serotonin and/or noradrenaline reuptake inhibition is related to the therapeutic effect of antidepressants (Wong et al., 1975). On the other hand, blockade of neurotransmitter receptors by antidepressants causes unpleasant, but harmless, reactions, such as dry mouth or sedation, as well as severe toxic reactions, such as cardiac arrest (Owens et al., 1997). Compared to tricyclic antidepressants, selective serotonin reuptake inhibitors are selective for serotonin reuptake rather than noradrenaline reuptake and show very low affinity for neurotransmitter receptors (Hyttel, 1994). Due to their lack of receptor antagonism, selective serotonin reuptake inhibitors are almost devoid of life-threatening side effects, even though they show almost equipotent therapeutic efficacy as tricyclic antidepressants (Anderson and Tomenson, 1994; De Jonghe and Swinkels, 1997; Hiemke and Hartter, 2000). Therefore, selective serotonin reuptake inhibitors have been replacing tricyclic antidepressants as a first-choice antidepressant medication (Mendlewicz and Lecrubier, 2000).

Among selective serotonin reuptake inhibitors, paroxetine shows relatively high affinity for muscarinic acetylcholine receptors (Thomas et al., 1987; Hyttel, 1994). Indeed, the affinity of paroxetine for muscarinic acetylcholine receptors is compatible to that of tricyclic antidepressants (Thomas et al., 1987; Owens et al., 1997). Thus, the probability that paroxetine induces anticholinergic side effects, for example, dry mouth, constipation, urinary retention, sinus tachycardia, memory dysfunction and so on, is expected to be higher than that of other selective serotonin reuptake inhibitors. However, no previous study has compared in detail the anticholinergic side effects induced by paroxetine to those induced by other antidepressants. Therefore, in this study the effects of paroxetine on oxotremorine-induced tremor, spontaneous defecation and passive avoidance behavior were examined and compared with those of fluvoxamine, another selective serotonin reuptake inhibitor,

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and clomipramine, a tricyclic antidepressant that inhibits serotonin reuptake more selectively than noradrenaline reuptake (Hyttel, 1994). In some experiments, a muscarinic acetylcholine receptor antagonist atropine and a benzodiazepine anxiolytic diazepam were also examined as references.

2. Materials and methods

2.1. Animals

Male ICR (for tail suspension test) or ddY (for other tests) mice were purchased from Nihon SLC (Shizuoka, Japan) when they were 4 or 5 weeks old. They were housed in a room adjusted to 22–25 °C and 50–70% humidity with lights on between 7:00 and 19:00 at least 1 week prior to use. Water and rodent chow were available ad libitum during this acclimatization period. All studies were performed according to the guidelines of the Animal Care and Use Committee of Pharmaceutical Research Center, Meiji Seika Kaisha.

2.2. Drugs

Fluvoxamine maleate (Meiji Seika, Tokyo, Japan), paroxetine hydrochloride (extracted from Paxil tablets, SmithKline Beecham, by Pharmaceutical Research Center, Meiji Seika), clomipramine hydrochloride (Sigma, St. Louis, MO), atropine sulfate (Sigma) and diazepam (Wako, Osaka, Japan) were dissolved or suspended in 0.25% Tween 80/saline. Oxotremorine sesquifumarate (Sigma) was dissolved in saline. All drugs were prepared on the day of use and injected intraperitoneally in a volume of 10 ml/kg.

2.3. Tail suspension test

Thirty minutes after the administration of antidepressants, each mouse was suspended individually by its tail from a hook connected to a strain gauge that was adjusted to detect all movements of the animal (Neuroscience, Tokyo, Japan). The mice were suspended in separate chambers so that they could not see each other. The movements of mice were measured for 7 min, and digitized and processed at 1-min intervals using multipurpose analysis software, Super Scope II (GWI, Somerville, MA). The threshold level was set at 5% of the body weight of each individual mouse to exclude the effects of respiration movement. The immobility time was defined as the total duration that the animal showed no movement. The experiments were carried out between 9:00 and 16:00.

2.4. Anti-oxotremorine test

Fifteen minutes after the administration of fluvoxamine, paroxetine or clomipramine, mice were treated with 1 mg/kg oxotremorine. In another experiment, atropine was treated instead of antidepressants. The intensity of tremor was observed 15 min after the injection of oxotremorine and scored on a scale of 0 to 2 (0, absent; 1, moderate; 2, intense), as described by Ogren et al. (1985). The experiments were carried out between 13:00 and 16:00.

2.5. Spontaneous defecation test

Mice were treated with antidepressants just before lights-off at 19:00. Immediately after treatment, they were individually placed in a cage with free access to water and chow. One hour after treatment, the number of fecal pellets was counted. Atropine and diazepam were also examined using the same procedure. Prior to the experiment, each mouse was acclimated to the experimental environment for 2 days.

2.6. Passive avoidance test

A two-compartment light/dark apparatus (30 × 9 × 9 cm) was used. Thirty minutes after treatment with antidepressants or atropine, an acquisition trial was carried out in which each mouse was placed individually in the light compartment. When the animal entered the dark compartment, a foot shock of 0.3 mA was delivered through the grid floor of the dark compartment until the animal returned to the light compartment. The latency to enter the dark compartment, and the latency to escape from the dark compartment were recorded. If the mouse did not enter the dark compartment for up to 60 s, it was excluded from further experiments. In the retrieval trial performed 24 h later, the number of animals that did not enter the dark compartment for 600 s was counted. The experiments were carried out between 13:00 and 17:00.

2.7. Statistical analysis

The effects of each antidepressant on oxotremorine-induced tremor were statistically analyzed by Dunnett's multiple permutation comparison test, and the ED_{50} value of each antidepressant for suppressing tremor (score 0 or 1) was calculated by the probit method. The immobility time in the tail suspension test and the number of pellets in spontaneous defecation were calculated as the mean ± S.E.M. and statistically analyzed by Dunnett's multiple comparison test. ED_{50} values were calculated by linear regression analysis. In the passive avoidance test, the median and interquartile range of the entrance and escape latencies in the acquisition trial were calculated and analyzed by the Steel multiple comparison test. Furthermore, the percentage (%) of mice that did not enter the dark compartment in the retrieval trial was calculated and compared by Dunnett's multiple permutation comparison test. The ED_{50} value of each antidepressant for decreas-

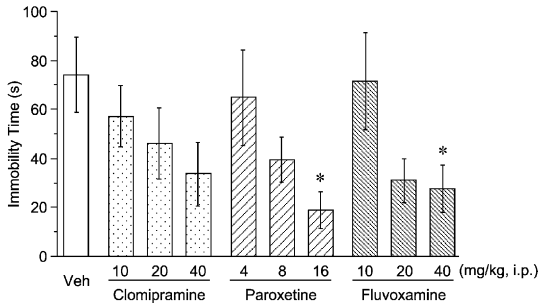

Fig. 1. Antidepressant activities of clomipramine, paroxetine and fluvoxamine in the tail suspension test in mice. The results are expressed as mean ± S.E.M. of the immobility time during 7 min of suspension. *$P<0.05$ vs. vehicle by Dunnett's multiple comparison test. Each group consisted of 13–16 mice.

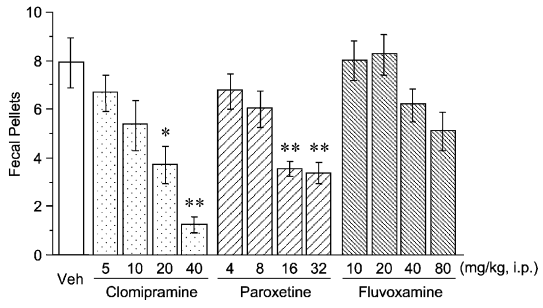

Fig. 2. Effects of clomipramine, paroxetine and fluvoxamine on spontaneous defecation in mice. The results are expressed as mean ± S.E.M. of the number of fecal pellets. *$P<0.05$, **$P<0.01$ vs. vehicle by Dunnett's multiple comparison test. Each group consisted of 12 mice.

ing this percentage was also calculated by the probit method.

3. Results

3.1. Decrease in the duration of immobility in the tail suspension test

The duration of immobility during 7 min of suspension is shown in Fig. 1. All of the antidepressants examined reduced the duration of immobility dose-dependently. The decreases induced by paroxetine 16 mg/kg and fluvoxamine 40 mg/kg were statistically significant, whereas clomipramine only tended to reduce the duration ($P=0.10$). The ED_{50} values of clomipramine, paroxetine and fluvoxamine for decreasing immobility to 50% of the value in the vehicle-treated group were 32.8, 9.0 and 24.4 mg/kg, respectively.

Table 1
Effects of clomipramine, paroxetine and fluvoxamine on the oxotremorine-induced tremor in mice

Treatment	Dose (mg/kg, i.p.)	Score		
		2	1	0
Vehicle	–	10	2	0
Clomipramine	5	8	3	1
	10	3	9	0[a]
	20	1	7	4[b]
	40	1	3	8[b]
Paroxetine	4	10	2	0
	8	10	2	0
	16	6	6	0
	32	4	7	1[a]
Fluvoxamine	10	11	1	0
	20	9	3	0
	40	9	3	0
	80	10	2	0

The results are expressed as the number of animals with scores of 2, 1 or 0.
[a] $P<0.05$ vs. vehicle by Dunnett's multiple permutation comparison test. Each group consisted of 12 animals.
[b] $P<0.01$ vs. vehicle by Dunnett's multiple permutation comparison test. Each group consisted of 12 animals.

3.2. Antagonism of oxotremorine-induced tremor

Table 1 shows the effects of clomipramine, paroxetine and fluvoxamine on oxotremorine-induced tremor. Oxotremorine at 1 mg/kg induced tremor in all of the mice; 10 of 12 mice showed intense tremor, and the other two mice showed moderate tremor. Clomipramine and paroxetine each inhibited oxotremorine-induced tremor dose-dependently. Clomipramine at a dose of 10 mg/kg or higher and paroxetine at 32 mg/kg significantly inhibited tremor. On the other hand, fluvoxamine did not affect oxotremorine-induced tremor at up to 80 mg/kg. The ED_{50} values of clomipramine and paroxetine at inhibiting oxotremorine-induced tremor were 6.4 and 18.5 mg/kg, respectively. Atropine also inhibited oxotremorine-induced tremor dose-dependently with the minimum significant dose of 0.5 mg/kg (data not shown).

3.3. Reduction in spontaneous defecation

Atropine reduced spontaneous defecation dose-dependently with the minimum significant dose of 0.2 mg/kg, whereas diazepam did not alter defecation at 3 mg/kg (the number of fecal pellets with vehicle, atropine 0.2 mg/kg and diazepam 3 mg/kg treatment was 8.4 ± 1.8, 3.2 ± 1.0 and

Table 2
Effects of clomipramine, paroxetine and fluvoxamine on the entrance and escape latencies in the acquisition trial of the passive avoidance test in mice

Treatment	Dose (mg/kg, i.p.)	Entrance latency			Escape latency		
		n	Latency (s)		*n*	Latency (s)	
Vehicle	–	14	14.5	(9–19)	14	2	(1–3)
Clomipramine	10	14	15.5	(7–17)	13	1	(1–2)
	20	14	12	(7–15)	14	1	(1–2)
	40	14	10	(8–12)	14	3	(2–6)
Paroxetine	8	14	8.5	(6–14)	14	1.5	(1–3)
	16	15	9	(6–10)	15	2	(1–2)
	32	15	15	(10–22)	13	2	(1–4)
Fluvoxamine	20	16	11	(7–9)	15	2	(1–2)
	40	15	10	(8–16)	15	1	(1–2)
	80	14	8	(7–9)	14	1.5	(1–4)

The results are expressed as median values with interquartile range in parenthesis.

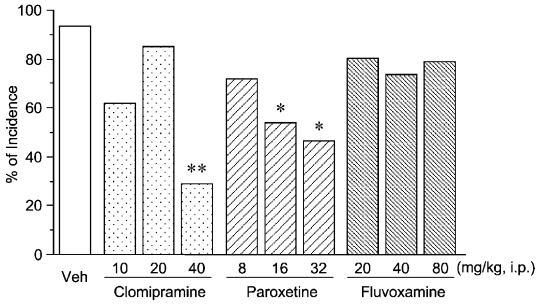

Fig. 3. Effects of clomipramine, paroxetine and fluvoxamine on passive avoidance learning behavior in mice. The results are expressed as the percentage (%) of mice that did not enter the dark compartment in the retrieval trial. $*P<0.05$, $**P<0.01$ vs. vehicle by Dunnett's multiple permutation comparison test. Each group consisted of 13–15 mice.

8.3 ± 1.7, respectively; mean ± S.E.M.). Clomipramine, paroxetine and fluvoxamine reduced spontaneous defecation dose-dependently (Fig. 2). The effects of clomipramine and paroxetine were significant with minimum effective doses of 20 and 16 mg/kg, respectively and the ED_{50} values of clomipramine and paroxetine for reducing the number of fecal pellets to 50% of that in the vehicle-treated group were 15.7 and 18.8 mg/kg, respectively. Fluvoxamine even at the highest dose, 80 mg/kg, neither has a significant effect ($P=0.06$) nor reduces the number of fecal pellets to 50% of that in the vehicle-treated group.

3.4. Impairment of passive avoidance performance

None of the antidepressants affected either the entrance latency or the escape latency in the acquisition trial at the doses tested (Table 2). The percentages of mice that did not enter the dark compartment in the retrieval trial are shown in Fig. 3. Clomipramine significantly decreased this percentage at 40 mg/kg. Paroxetine also significantly decreased this percentage at 16 and 32 mg/kg. However, fluvoxamine did not have a significant effect at up to 80 mg/kg. The ED_{50} values of clomipramine and paroxetine for inducing a passive avoidance deficit were 27.7 and 23.3 mg/kg, respectively. Atropine also decreased the percentages with the minimum significant dose of 0.5 mg/kg (data not shown).

4. Discussion

Several clinical studies have indicated that selective serotonin reuptake inhibitors have fewer adverse anticholinergic effects than tricyclic antidepressants. For example, with regard to the three antidepressants examined in the present study, paroxetine and fluvoxamine have been reported to induce fewer adverse anticholinergic effects, such as dry mouth and constipation, than clomipramine (Zohar and Judge, 1996; Ravindran et al., 1997; Pigott and Seay, 1999; Mundo et al., 2000). Although the incidence of the anticholinergic effects produced by each selective serotonin reuptake inhibitor has not yet been compared in detail (Donoghue, 2000), constipation has been reported to be more common with paroxetine than with other selective serotonin reuptake inhibitors (Finley, 1994).

The anticholinergic effects of selective serotonin reuptake inhibitors have not been examined in animal studies, except for the few cases described below. Therefore, in this study we compared the anticholinergic effects of paroxetine to those of another selective serotonin reuptake inhibitor, fluvoxamine, in mice. A tricyclic antidepressant with serotonin selectivity, clomipramine, was also examined as a positive reference drug to consider the likelihood that paroxetine and fluvoxamine would induce anticholinergic effects clinically.

In advance of the evaluation of anticholinergic effects, we firstly examined the antidepressant activity of these antidepressants using the tail suspension test to compare the dissociation between the anticholinergic effects and antidepressant activity of each antidepressant. The tail suspension test is a convenient model in which many antidepressants reduce immobility time, which is taken as an indication of antidepressant activity (Steru et al., 1985). In this study, all three antidepressants were effective, although the effect of clomipramine did not reach statistical significance within the doses examined. However, the antidepressant activities of the antidepressants were similar to those reported previously (Perrault et al., 1992; Teste et al., 1993; David et al., 2001; Fujishiro et al., 2001), and were well correlated to clinical doses.

We then examined in vivo anticholinergic effects of the antidepressants to assess the antagonism of oxotremorine-induced tremor. In the present study, clomipramine and paroxetine as well as atropine suppressed oxotremorine-induced tremor. Several reports have indicated that tricyclic antidepressants including clomipramine inhibit oxotremorine-induced tremor (Dufour et al., 1989; Katoh et al., 1995). Furthermore, paroxetine has been reported to suppress tremor at doses similar to those of two tricyclic antidepressants, imipramine and amitriptyline (Yamamoto et al., 1989). The results obtained with clomipramine and paroxetine are similar to those in the previous reports, which may be due to their potent in vitro muscarinic acetylcholine receptor-binding properties (Thomas et al., 1987; Hyttel, 1994; Owens et al., 1997). On the other hand, fluvoxamine did not affect oxotremorine-induced tremor at the doses examined. These results suggest that the ability of paroxetine to induce an anticholinergic effect is compatible to those of tricyclic antidepressants, whereas fluvoxamine is much less potent. To examine these possibilities, we also examined these antidepressants with regard to spontaneous defecation and passive avoidance performance, since constipation and memory dysfunction are known to be observed with antidepressant medications as their peripheral and central anticholinergic effects, respectively.

While all three antidepressants dose-dependently reduced spontaneous defecation, significant effects were observed only with paroxetine and clomipramine. Amitriptyline, which has the most potent affinity for muscarinic acetylcholine receptors among tricyclic antidepressants (Owens et al., 1997), has also been reported to reduce spontaneous defecation (Abe and Saito, 1998). However, the number of fecal pellets of rodents has been reported to increase when they were exposed to stress and fear, and these increases in defecation are reportedly abolished by treatment with anxiolytics such as diazepam and buspirone (Miyata et al., 1992; Krysiak et al., 2000). Therefore, the decrease in defecation by antidepressants might be due to their anxiolytic effect observed with serotonergic antidepressants (Den Boer et al., 1995). However, in the present study, defecation was reduced by atropine but not by diazepam at an anxiolytic dose, 3 mg/kg. These results indicate that anticholinergic effects rather than anxiolytic effects were detected under our experimental conditions, probably because the mice were acclimated to the experimental environment prior to the experiment.

Tricyclic antidepressants such as imipramine and amitriptyline, but not the selective serotonin reuptake inhibitor fluoxetine, have been reported to induce amnesia in passive avoidance and maze performance in mice (Kumar and Kulkarni, 1996). Numerous studies have shown that muscarinic acetylcholine receptor antagonists such as scopolamine induce amnesia in learning and memory experiments (Egawa et al., 1997; Imanishi et al., 1997). In the passive avoidance paradigm, the amnesia-inducing effects of muscarinic acetylcholine receptor antagonists are most evident when they are administered before the acquisition trial (Rush, 1988). In this study, clomipramine, paroxetine but not fluvoxamine, when administered before the acquisition trial, elicited amnesia in the passive avoidance test. Atropine also induced amnesia. Although antidepressants are known to have analgesic effects (Yamamoto et al., 1989; Sawynok et al., 2001), the escape latency measured in the acquisition trial was not influenced by treatment with antidepressants. Therefore, the amnesia observed with clomipramine and paroxetine seems to be the result of their anticholinergic effects rather than their analgesic effects. The finding that the entrance latency in the acquisition trial was also not influenced by treatment with antidepressants indicates that these antidepressants did not induce sedation at the doses used.

The ED_{50} values of the three antidepressants in all of the tests are summarized in Table 3, which also gives the ratios of the ED_{50} values for the antagonism of oxotremorine-induced tremor, reduction of spontaneous defecation and induction of a passive avoidance deficit to the ED_{50} value for antidepressant activity. The ratios for clomipramine in the three paradigms for evaluating anticholinergic effects were consistently below 0.8. Since fluvoxamine did not have any obvious anticholinergic effects in these paradigms, the ratios were greater than 3.2 in all of the tests using the highest dose, 80 mg/kg.

Table 3
ED_{50} values (mg/kg, i.p.) of clomipramine, paroxetine and fluvoxamine in the following tests; tail suspension (TS), antagonism of oxotremorine-induced tremor (OT), reduction of spontaneous defecation (SD) and induction of a passive avoidance deficit (PA) in mice

	TS	OT	SD	PA
Clomipramine	32.8	6.4 (0.2)	15.7 (0.5)	27.7 (0.8)
Paroxetine	9.0	18.5 (2.1)	18.8 (2.1)	23.3 (2.6)
Fluvoxamine	24.4	>80 (>3.2)	>80 (>3.2)	>80 (>3.2)

The number in parenthesis represents the ratio to the ED_{50} value obtained in the tail suspension test. Since an ED_{50} value could not be calculated for fluvoxamine in the latter three paradigms, apparent ratios were calculated using the highest dose, 80 mg/kg.

Paroxetine showed ratios between 2.1 and 2.6. Based on the in vitro potencies of muscarinic acetylcholine receptor-binding and the inhibition of serotonin reuptake reported by Hyttel (1994), among selective serotonin reuptake inhibitors, fluvoxamine has the highest ratio of muscarinic acetylcholine receptor-binding affinity to the inhibition of serotonin reuptake while paroxetine has the low ratio, which is still larger than that of the tricyclic antidepressant clomipramine. These ratios are consistent with the results in Table 3. These results support the notion that not only the antagonism of oxotremorine-induced tremor but also the reduction of spontaneous defecation and the induction of a passive avoidance deficit observed with clomipramine and paroxetine were related to their in vitro muscarinic acetylcholine receptor-binding abilities. However, the spontaneous defecation test and passive avoidance test are sensitive not only to an anticholinergic drug as demonstrated in this study, but also other mechanisms than anticholinergic effect. Furthermore, it is well known that clomipramine binds not only to muscarinic acetylcholine receptors but also to other neurotransmitter receptors such as α_1-adrenoceptors, histamine H_1 receptors and serotonin 5-HT_{2A} receptors (Hyttel, 1994). Therefore, it cannot be denied that the reduction of spontaneous defecation and the induction of passive avoidance deficit induced by clomipramine are due to other mechanisms than its anticholinergic effect. This might be a reason why ED_{50} values of clomipramine are varied compared to those of paroxetine in following three tests, the antagonism of oxotremorine-induced tremor, reduction of spontaneous defecation and induction of a passive avoidance deficit.

The rank order of the ratios obtained here also parallels the results in clinical reports which indicate that paroxetine has fewer adverse anticholinergic effects than tricyclic antidepressants (Zohar and Judge, 1996; Ravindran et al., 1997), but more than other selective serotonin reuptake inhibitors (Finley, 1994). Indeed, our finding that clomipramine has the lowest ratio is consistent with these clinical reports. The present results suggest that there are more adverse anticholinergic effects with paroxetine than with fluvoxamine or other selective serotonin reuptake inhibitors.

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