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Comparative behavioural effects of typical and atypical antipsychotic drugs in rhesus monkey

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Abstract

Behavioural effects of typical and atypical antipsychotic agents were compared in unrestrained rhesus monkey (*Macaca mulatta*) living in social colonies. The behaviours were categorized as social, solitary and abnormal. They were studied with the help of video cameras fixed in the observation chamber. The behavioural effects were recorded on videotape and analyzed for significant changes. Chlorpromazine (2.5–10 mg/kg, i.m.), haloperidol (0.01–0.04 mg/kg, i.m.), risperidone (0.05–0.2 mg/kg, p.o.) and clozapine (5–20 mg/kg, p.o.) induced significant alterations in parameters of social and solitary behaviour. Chlorpromazine produced a marked decrease in locomotor activity whereas haloperidol showed marked extrapyramidal effects. Risperidone produced minimal extrapyramidal effects and sedation compared to haloperidol and chlorpromazine. Clozapine had intermediate extrapyramidal effects similar to those of chlorpromazine but it produced hypersalivation and dose-related sedation. Thus, risperidone had advantages over the other antipsychotics used in this study because it did not produce salivation, had minimal extrapyramidal effects and caused less sedation. These antipsychotic drugs produced many behavioural effects in the rhesus monkey that were similar to their clinically observed effects. A study of behavioural effects in the monkey can thus be a useful predictive tool in the preclinical development of new antipsychotics.

Keywords: Behaviour; Chlorpromazine; Haloperidol; Risperidone; Clozapine; (Rhesus monkey)

1. Introduction

Antipsychotic agents have proved to be very useful in the management of schizophrenia. The classical antipsychotic drugs, however, relieve only the positive symptoms (hallucination, paranoia and delusions) and their effects on negative symptoms (apathy, social withdrawal) appear to be far from satisfactory (Crow, 1986; Bleich et al., 1988). They also produce extrapyramidal side effects. Clozapine and risperidone are new antipsychotic drugs that have lessened extrapyramidal side effects (Ichikawa and Meltzer, 1999; Stip, 2000). Even though unique clinical characteristics of clozapine have generated much interest, its use is limited due to the occurrence of agranulocytosis and marked sedation and salivation (Krupp and Barnes, 1992; Duncan et al., 1999). Considerable importance is being placed on behavioural tests in animals (rats) that have characterized the difference between clozapine and more typical antipsychotic drugs (Sanger and Perrault, 1995; Chesler and Salamone, 1996). Risperidone, a benzisoxazole derivative, belongs to a new class of antipsychotic drugs. It has been demonstrated to be an effective agent for the treatment of schizophrenia. Like clozapine, and in contrast to typical neuroleptics, it relieves both positive and negative symptoms of schizophrenia (Moller et al., 1995; Hippius, 1999). The incidence of extrapyramidal side effects is less (Chouinard et al., 1993) and there is no report of agranulocytosis.

The behavioural effects of typical and atypical antipsychotics have not been studied in the rhesus monkey. Analysis of behaviour alterations in nonhuman primates can provide cogent information concerning effects on human behaviour. They are also useful for studying extrapyramidal side effects since symptoms such as dystonia and parkinsonism occur in monkeys and clinically and in

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humans and have a similar time course in both species. Additionally, the close correlation between drug type, dose and the liability of producing extrapyramidal side effects offers an opportunity to evaluate new compounds for their extrapyramidal side effect liability during preclinical development (Liebman and Neale, 1980; Casey, 1993).

In the present study behavioural effects of atypical neuroleptics, clozapine and risperidone, have been compared with those of two commonly used typical neuroleptic drugs, chlorpromazine and haloperidol, in rhesus monkeys.

2. Materials and methods

The subjects for the study were social colonies of 3–5 year old active and healthy adult rhesus monkeys (*Macaca mulatta*) weighing 4–6 kg. Each colony comprised eight monkeys (one male and seven females) housed in a $20 \times 12 \times 8'$ cage. Six colonies of monkeys were used for the present experiments. The monkeys were kept under controlled conditions of temperature (22 ± 2 °C), humidity (55–60%), ventilation (10–15 air change per h with 100% fresh air) and light (300 lx intensity) and a 12-h light/dark cycle to maintain their physiological rhythm. A balanced diet was provided in the morning and evening and water was available ad libitum from an automatic watering system. The animals were allowed 4–6 weeks time to stabilize their behaviour in the new surroundings. To reduce the stress induced by handling and dosing, a single experimenter handled the animals. During the period of habituation, the monkeys were caught and removed from the cage once a week and given saline intramuscularly or orally.

The animals were observed for behaviour prior to (baseline control) and after drug or vehicle treatment. A checklist of social, solitary and abnormal behavioural responses based on a modified version (Palit et al., 1997) of the parameters described by Schlemmer and Davis (1983) was used. Behavioural responses were videotaped from an adjacent room as described by Palit et al. (2001). On any 1 day, a female from the group was injected with the drug. The following parameters of behaviour were observed.

2.1. Social behaviour

2.1.1 Social groom: discrete picking or spreading of hair of a co-inhabitant.
2.1.2 Approach: walking or running towards another animal from a distance of at least 1 m to within an arm's length so that it could touch the other animal.
2.1.3 Body jerk: quick voluntary jerks of the body while looking directly at another animal in close proximity.
2.1.4 Huddle: two animals sitting together with at least one monkey's arm embracing the other animal.
2.1.5 Contact: touching the body of another animal without any social interaction or huddling.
2.1.6 Threat: eyebrows up, ear back, mouth open with only lower teeth visualized, staring at another animal, with or without a specific low-pitched vocalization.
2.1.7 Chase: pursuit of other animals for purpose of attack.
2.1.8 Attack: vigorous, hostile, biting and/or hair pulling of another monkey.
2.1.9 Yield: moving away from a location, so that a more dominant monkey may occupy it.

2.2. Solitary behaviour

2.2.1 Feeding: the pattern of manipulation and mastication of foods.
2.2.2 Drinking: drinking water from automatic watering system.
2.2.3 Locomotion: the number of ambulations from one point to a distant point (1 m).
2.2.4 Self-groom: discrete picking or spreading of hair.
2.2.5 Scratch: scratching at a single specific location (scratching of the leg followed by scratching of the arm would be scored as two scratches).
2.2.6 Vigilance: changes of visual field by head and eye movement.
2.2.7 Vocalization: the number of clearly audible sounds produced by the observed animal.
2.2.8 Respiratory rate: number of respirations per minute in sitting posture.
2.2.9 Pupil size.
2.2.10 Lying down: assumes horizontal position on the cage floor.
2.2.11 Resting with eyes open: maintaining a relaxed posture and initiating no active behaviour for 30–60 s while eyelids remain open for more than 30 s.
2.2.12 Resting with eyes closed: similar to 2.2.11 but with eyelids shut for more than 30 s.

2.3. Abnormal behaviour

2.3.1. Catalepsy

1 = unnatural stance for < 5 min; 2 = unnatural stance between 5 and 10 min; 3 = unnatural stance between 10 and 20 min; 4 = unnatural stance for > 20 min.

Locomotion and vigilance were scored by the frequency of occurrence during each 60-s observation interval. Pupil size was recorded as normal, constricted or dilated. Salivation was graded as + = occasional, ++ = interrupted and +++ = continuous. Catalepsy was given a score of 1–4. All other behaviour patterns were scored as present (1) or absent (0). Respiratory rate was counted with the help of a stopwatch.

The initial behavioural score of the animal was taken as the normal score. Each monkey was observed for 1 min every 10 min for 2 h. The scores of each behaviour from 12 such observations were summed and the total represented the day's score for that monkey. The mon-

keys were also observed at 4, 6, 8 and 24 h post treatment for any significant alteration in behaviour. A minimum interval of 10 days was allowed before re-using the monkey to ensure washout of the effect of the previous dose.

Statistical analysis was performed for all behavioural data with the Mann–Whitney *U*-test.

2.4. Routes of drug administration

Chlorpromazine (Rhone-Poulenc, India) and haloperidol (Searle India) were used in injectable form and were administered intramuscularly. Risperidone and clozapine (Sigma, USA) were dissolved in sterile 0.9% saline and given orally. The control group received an equivalent volume of normal saline by the same route. The doses of test drug were extrapolated from doses used clinically.

3. Results

The effects of various drugs are summarized in separate tables. Only those parameters are listed in a particular table, which were significantly affected by at least one dose of the test drug. The scores for remaining parameters have not been shown so as to save space.

3.1. Behavioural effect of chlorpromazine

Chlorpromazine produced behavioural changes in a dose-dependent manner. The changes produced by the 2.5 mg/kg dose were not significant. The results are summarized in Table 1.

3.1.1. Social behaviour

A dose of 5 mg/kg produced a significant decrease in body jerk, contact or threat. The higher dose (10 mg/kg) produced a significant decrease in score for approach, and attack also.

3.1.2. Solitary behaviour

The 5 mg/kg dose decreased feeding, drinking, locomotion and vigilance and increased the time of resting with eyes closed. A higher dose (10 mg/kg) produced similar but more marked effects in all these parameters of solitary behaviour. Miosis was observed with both doses.

3.1.3. Abnormal behaviour

Catalepsy was observed for 5 min at the dose of 5 mg/kg and 5–10 min after 10 mg/kg.

3.1.4. Start and duration of action

The effects started 30 min after drug administration and lasted for up to 1–2 h with 2.5 mg/kg, 2–3 h with 5 mg/kg and 3–6 h with 10 mg/kg. The peak effect of all the doses was observed between 40–60 min after administration.

Table 1
Effect of chlorpromazine on behavioural responses of rhesus monkeys

Response	Median score (range), $n=5$			
	Control	Chlorpromazine (mg/kg, i.m.)		
		2.5	5	10
Social				
Approach	2 (0–4)	1 (0–1)	1 (0–3)	0[a] (0–1)
Body jerk	2 (0–3)	2 (1–2)	1[b] (0–2)	0[a] (0)
Contact	2 (0–2)	1 (1–3)	0[a] (0–1)	0[a] (0)
Threat	2 (1–3)	2 (1–4)	0[a] (0–1)	0[a] (0)
Attack	1 (1–2)	1 (0–2)	1 (0–1)	0[b] (0–1)
Solitary				
Feeding	2 (1–3)	2 (1–2)	1[b] (0–1)	0[a] (0)
Drinking	2 (1–3)	2 (0–3)	0[a] (0–1)	0[a] (0)
Locomotion	10 (7–12)	8 (8–10)	5[a] (4–6)	2[a] (1–3)
Self groom	1 (0–2)	1 (0–2)	1 (0–1)	0[b] (0–1)
Vigilance	12 (8–14)	10 (9–12)	6[a] (4–8)	3[a] (2–4)
Lying down	0 (0–2)	1 (1–3)	1 (0–2)	2[b] (0–2)
Resting with eyes closed	0 (0–2)	1 (0–1)	3[a] (1–3)	4[a] (2–6)
Pupil	Normal	Normal	Constricted	Constricted
Abnormal				
Catalepsy	0	0	1	2[a]

[a] $P<0.01$ significant difference from control.
[b] $P<0.05$ significant difference from control.

3.2. The effect of haloperidol

The response to haloperidol was also dose related. The effects of the lowest dose (0.01 mg/kg) were in the same direction as the effects of higher doses but were not significant. The scores are summarized in Table 2.

3.2.1. Social behaviour

The dose of 0.02 mg/kg produced a significant decrease in scores for approach, body jerk, threat and attack. The highest dose of haloperidol (0.04 mg/kg) decreased these social interactions more markedly (Table 2).

3.2.2. Solitary behaviour

The 0.02 mg/kg dose significantly decreased feeding, drinking, locomotion, self-groom and vigilance and increased the time of resting with eyes closed. The highest dose (0.04 mg/kg) produced a more marked decrease in these solitary activities and in addition, significantly increased the score for lying down.

3.2.3. Abnormal behaviour

The highest dose (0.04 mg/kg) produced a marked cataleptic posture, which persisted for more than 20 min. Cataleptic posture was also observed with the 0.02

Table 2
Effect of haloperidol on behavioural responses of rhesus monkey

Response	Median score (range), $n=5$			
	Control	Haloperidol (mg/kg, i.m.)		
		0.01	0.02	0.04
Social				
Approach	2 (0–4)	2 (1–3)	1[a] (0–2)	0[b] (0)
Body jerk	2 (0–3)	2 (0–2)	1[a] (0–1)	0[b] (0–1)
Threat	2 (1–3)	2 (1–2)	0[a] (0–1)	0[b] (0–2)
Attack	1 (1–2)	1 (0–2)	0[a] (0–2)	0[a] (0–1)
Solitary				
Feeding	2 (1–3)	2 (1–2)	1[a] (0–1)	0[b] (0)
Drinking	2 (1–3)	2 (1–2)	1[a] (0–2)	0[b] (0–1)
Locomotion	10 (9–12)	8 (7–9)	5[b] (4–6)	2[b] (2–3)
Self groom	1 (0–2)	1 (0–1)	0[a] (0–1)	0[a] (0–1)
Vigilance	12 (8–14)	11 (10–13)	8[a] (8–10)	5[b] (4–8)
Lying down	0 (0–2)	1 (0–1)	1 (0–2)	2[b] (1–3)
Resting with eyes closed	0 (0–2)	0 (0–1)	1[a] (0–2)	2[b] (1–2)
Abnormal				
Catalepsy	0	0	1	4[b]

[a] $P<0.05$ significant difference from control.
[b] $P<0.01$ significant difference from control.

mg/kg dose but the duration was less than 5 min (Table 2).

3.2.4. Start and duration of action

The start of action was 30–40 min and the peak effect was observed 60–80 min after drug administration. The effects lasted 1–2 h for 0.01 mg/kg, 2–4 h for 0.02 mg/kg and 4–8 h for 0.04 mg/kg dose of haloperidol.

3.3. Behavioural effect of risperidone

The effects of the lowest dose (0.05 mg/kg) were not significant. The results are summarized in Table 3.

3.3.1. Social behaviour

Risperidone (0.05–0.2 mg/kg, p.o.) produced a dose-dependent decrease in certain parameters of social and solitary behaviour. The 0.1 mg/kg dose produced a significant reduction in scores for approach, body-jerk, threat and attack. The highest dose, 0.2 mg/kg, produced a more marked decrease in the scores for all these parameters and also for contact (Table 3).

3.3.2. Solitary behaviour

Effects on solitary behaviour were also seen with the dose of 0.1 mg/kg. It produced a significant decrease in locomotion and vigilance. The effect on some other parameters included in Table 3 was not significant. The highest dose (0.2 mg/kg) decreased the parameters of solitary behaviour (feeding, drinking, locomotion, self-groom and vigilance) significantly. The scores for lying down and resting with eye closed were significantly increased (Table 3).

3.3.3. Abnormal behaviour

A minimal extrapyramidal effect was observed with the 0.2 mg/kg dose only and it was not significant.

3.3.4. Start and duration of action

The action started in 30 min, the peak effect was observed 45–60 min after drug administration and the effect lasted for 1–2 h for 0.05 mg, 2–3 h for 0.1 mg/kg and 2–4 h for the 0.2 mg/kg dose of risperidone.

3.4. Behavioural effect of clozapine

The results are summarized in Table 4. All the doses tested produced significant behavioural effects, which increased in a dose-dependent manner.

3.4.1. Social behaviour

The lowest dose of clozapine (5 mg/kg, p.o.) produced a significant decrease in the score for threat. At the dose of 10 mg/kg, it produced a significant decrease in scores for approach, body jerk, contact and threat. The highest dose (20 mg/kg) produced a marked decrease in all the social activities listed in Table 4.

3.4.2. Solitary behaviour

For solitary behaviour, the lowest dose of clozapine, 5 mg/kg, significantly decreased locomotion. The next higher dose (10 mg/kg) produced an even more marked decrease in locomotion. In addition, the scores for self-groom and vigilance were decreased. The time of lying down and resting with eyes closed was increased. The effect of the highest dose (20 mg/kg) on all these param-

Table 3
Risperidone induced behavioural changes in rhesus monkeys

Response	Median score (range), $n=5$			
	Control	Risperidone (mg/kg, p.o.)		
		0.05	0.1	0.2
Social				
Approach	2 (0–4)	2 (0–3)	0[a] (0–1)	0[b] (0)
Body jerk	2 (0–3)	2 (1–2)	1[a] (0–2)	0[b] (0–1)
Contact	2 (0–2)	1 (0–2)	1 (0–1)	0[b] (0)
Threat	2 (1–3)	2 (0–3)	1[a] (1–2)	0[b] (0–1)
Attack	1 (1–2)	1 (0–2)	0[a] (0–1)	0[a] (0–1)
Solitary				
Feeding	2 (1–3)	2 (1–3)	1 (0–2)	0[b] (0)
Drinking	2 (1–3)	2 (0–3)	1 (0–1)	0[b] (0–1)
Locomotion	9 (7–12)	5 (3–7)	4[a] (2–4)	1[b] (0–2)
Self groom	1 (0–2)	2 (0–2)	1 (0–2)	0[a] (0–1)
Vigilance	12 (8–14)	9 (8–12)	6[a] (5–9)	4[b] (3–5)
Resting with eyes closed	0 (0–2)	1 (0–3)	2 (1–3)	2[a] (1–3)
Abnormal behaviour				
Catalepsy	0	0	0	1

[a] $P<0.05$ significant difference from control.
[b] $P<0.01$ significant difference from control.

Table 4
Behavioural effect of clozapine in rhesus monkeys

Response	Median score (range), $n=5$			
	Control	Clozapine (mg/kg, p.o.)		
		5	10	20
Social				
Approach	2 (0–4)	1 (0–1)	0[a] (0–1)	0[b] (0)
Body jerk	2 (0–3)	1 (0–3)	0[a] (0–1)	0[b] (0)
Contact	2 (0–2)	1 (0–2)	0[a] (0–1)	0[b] (0)
Threat	2 (1–3)	1[a] (0–2)	1[a] (1–2)	0[b] (0)
Attack	1 (1–2)	1 (1–2)	1 (0–2)	0[a] (0–1)
Solitary				
Feeding	2 (1–3)	2 (1–4)	1 (0–1)	0[b] (0)
Drinking	2 (1–3)	2 (0–2)	1 (0–1)	0[b] (0)
Locomotion	9 (7–12)	6[a] (4–7)	3[a] (2–3)	1[b] (0–2)
Self groom	1 (0–2)	1 (0–2)	0[a] (0–1)	0[a] (0–1)
Vigilance	12 (8–14)	9 (8–10)	6[a] (4–7)	4[b] (2–4)
Lying down	0 (0–2)	1 (0–1)	2[a] (2–4)	4[b] (4–6)
Resting with eyes closed	0 (0–2)	1 (0–1)	2[a] (1–4)	3[b] (1–4)
Abnormal				
Catalepsy	0	0	0	2[b]
Salivation	–	–	++[a]	+++[b]

Salivation grade: + = occasional, ++ = interrupted, +++ = continuous.
[a] $P<0.05$ significant difference from control.
[b] $P<0.01$ significant difference from control.

eters was more marked. It also reduced the scores for feeding and drinking.

3.4.3. Abnormal behaviour

No abnormal behaviour was observed at 5 mg/kg but the 10 mg/kg dose produced interrupted salivation. The highest dose of 20 mg/kg produced significant catalepsy along with continuous salivation.

3.4.4. Start and duration of action

The effect started in 30 min and the peak effect was observed 50–60 min after drug administration. The effects lasted for 2–3 h for 5 mg/kg, 3–4 h for 10 mg/kg and 4–6 h for 20 mg/kg of clozapine.

4. Discussion

Extensive data are available about the effect of psychotherapeutic drugs on rodent behaviour but rodents do not properly mimic human behaviour. The results with primates such as the rhesus monkey appear to provide better correlation (Palit et al., 1998). The rhesus monkey has a more evolved central nervous system than do the rodents. Rhesus monkeys also exhibit defined patterns of social behaviour (Vellucci, 1990; Beirnstein et al., 1993) resembling those of human behaviour. Analytical study of behavioural effects in nonhuman primates can, therefore, provide useful information regarding effects of drugs on human behaviour (Cluttenbrock, 1974; Sassernath and Chapman, 1976).

Chlorpromazine produces a marked decrease in several parameters of social and solitary behaviour. It also produces catalepsy. The alterations in social and solitary behaviour are indicative of general apathy and sedation activity. Similar effects have been reported for humans (Stitzer et al., 1981). The cataleptic immobility of monkeys after chlorpromazine treatment resembles the extrapyramidal effects observed in patients (Breir et al., 1999). Higher doses of chlorpromazine produced miosis in the monkey. This effect has also been reported in humans and may be due to the known α-adrenoceptor blocking activity of chlorpromazine (Baldessarini, 2001).

Haloperidol induced changes in social and solitary behaviour and catalepsy; similar effects have been reported for other nonhuman primates and humans (Hicks, 1990; Casey, 1996). Catalepsy has been reported for the cebus monkey (Casey, 1993, 1996). The dose-dependent extrapyramidal effects observed in the present study have also been reported for humans and nonhuman primates (Casey, 1996; Peukens, 1995).

Clozapine produced a decrease in social interaction and solitary behaviour and an increase in resting activity, which indicates its sedative effect. This sedation and decreased locomotor activity have also been reported for human beings (Casey, 1996; Vrtunski et al., 1998). Hypersalivation and catalepsy, observed only with a higher dose, have also been reported for humans, cebus and squirrel monkeys (Casey, 1996). Worrel et al. (2000) have recently reported hypersalivation in patients treated with clozapine.

Risperidone belongs to a new series of atypical antipsychotic drugs, which have a low incidence of extrapyramidal side effects (Casey, 1996, 2000) at therapeutic doses. High doses, however, produce extrapyramidal side effects similar to those of a typical neuroleptic, haloperidol, in humans and nonhuman primates (Marder and Meibach, 1994; Casey and Hansen, 1995; Peukens, 1995; Stip, 2000). In this present study, extrapyramidal effects were seen only with the highest dose. Risperidone also produced sedation and loss of appetite with high doses but there was no salivation as was observed with clozapine (Tables 3 and 4). The non-sedative effect of risperidone and haloperidol as well as the sedative action of clozapine and chlorpromazine in monkeys parallel the clinical experience (Kane et al., 1988; Marder and Meibach, 1994).

The results of the present study show that chlorpromazine produced marked sedative and intermediate extrapyramidal effects along with miosis. Haloperidol produced marked extrapyramidal side effects but less sedation. Both drugs blocked only the positive behavioural effects induced by amphetamine and had no effect on negative behavioural responses in rhesus monkeys (Palit, 1995). Risperidone was less sedative and also had a lower propensity to cause extrapyramidal side effects with lower doses in monkey as has also been reported for humans (Casey, 2000). Clozapine has the advantage of being able to block both the positive and negative behavioural responses induced by amphet-

amine and produced much reduced extrapyramidal side effects (Kane, 1992; Meltzer and Stahl, 1992). Other effects with clozapine including sedation, hypersalivation observed in monkeys are also found in humans (Worrel et al., 2000).

This study thus provides information on the effects of typical and atypical antipsychotics on social, solitary and abnormal behaviour of rhesus monkey living together. The data are consistent with the reported clinical effects of these agents. The behavioural effects in monkeys appear to have greater predictive value regarding clinical spectrum of activity than do the effects in rodents. Our results suggest that social and solitary behaviour in nonhuman primates should form a useful component of preclinical studies on new CNS active compounds to predict their clinical effects.

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