Psychopharmacology (1984) 84:310–314

Psychopharmacology

Fluphenazine-induced acute and tardive dyskinesias in monkeys

Beverly Kovacic[1] and Edward F. Domino[2]

[1] Lafayette Clinic, Division of Pharmacology, 951 E. Lafayette, Detroit, MI 48207, USA
[2] University of Michigan, Department of Pharmacology, Ann Arbor, MI 48109-0010, USA

Abstract. Five *Cebus apella* monkeys were treated with biweekly injections of fluphenazine enanthate (0.1–3.2 mg/kg IM). Three of these completed 1 full year of treatment, one injured its leg after 6 months of treatment and was killed, and another died of unknown causes after 9 months of treatment. All monkeys displayed abnormal movements corresponding to the early appearing extrapyramidal symptoms of neuroleptic-treated patients. These consisted initially of slowing or absence of volitional movement, trembling of the hands, trembling of the entire body, and general drowsy behavior. As treatment progessed, a variety of abnormal postures and movements appeared after each injection that were not exacerbated by drug withdrawal and, as tested at the end of the year, could be abolished or prevented with benztropine mesylate (0.2–0.5 mg/kg IM). The three monkeys that completed 1 year of treatment with fluphenazine were then withdrawn from the drug. After withdrawal, all three developed movements similar in appearance to those of patients with tardive dyskinesia (TD). Reinstitution of fluphenazine treatment, as tested in one monkey, abolished all movements resembling TD.

Key words: Fluphenazine enanthate – *Cebus apella* – Primates – Extrapyramidal symptoms – Dystonia – Dyskinesia – Tardive dyskinesia

Tardive dyskinesia (TD) is one of the most problematic side effects of antipsychotic medication. The American Psychiatric Association's task force on TD (Baldessarini et al. 1980) has urged that, in preclinical studies of the disorder, maximum use be made of the newer primate models of TD such as that developed by Gunne and Bárány (1976) in which *Cebus apella* monkeys were given long-term treatment with haloperidol. We have developed a monkey model of TD (Kovacic and Domino 1982) by treating *C. apella* monkeys with fluphenazine enanthate (FPZ). The present paper gives more detailed information regarding this model and reports on acute effects of FPZ observed in the animals.

Materials and methods

Five feral-born female *C. apella* monkeys, each weighing approximately 2 kg, started in this study. None of these animals had been used previously in research. One of the monkeys (Karman) was estimated by veterinarians to be geriatric, another monkey (Elly) was found to be carrying a dead infant in utero during the 10-week quarantine period just before the start of the study, and the other animals were estimated to be middle-aged to geriatric. The monkeys were housed individually in a room controlled for temperature and humidity. Food and water were continuously available. Three of the animals (Karman, Elly, Ginger) completed 1 full year of neuroleptic treatment and maintained stable body weights throughout the entire study. A fourth animal (K-014) dislocated her knee after only 6 months of neuroleptic treatment, developed gangrene (dry), and was killed; except for the leg, no gross pathologic lesions were found on necropsy. The fifth monkey (K-013) died after 9 months of neuroleptic treatment from undetermined causes.

Elly developed a chronic skin infection during the late months of her year of neuroleptic treatment, along with weakness and raspy breath. She was treated for this condition at various times with a vitamin B complex and penicillin G (Flo-cillin, Bristol, Syracuse, NY, USA; 15,000 IU/kg). A fungal infection in this animal was treated effectively with griseofulvin (Grisfulvin, McNeil, Fort Washington, PA, USA; 15 mg/kg orally) approximately 5 days/week from the third through the sixth month after her year of neuroleptic treatment.

Drugs. Doses of the following drugs refer to the salt: FPZ (Prolixin enanthate, Squibb, Princeton, NJ, USA), biperiden lactate (Akineton, Knoll, Whippany, NJ, USA), benztropine mesylate (Cogentin, Merck, Sharp and Dohme, West Point, PA, USA), and benzathine penicillin G plus procaine penicillin G (1 : 1) (Flo-cillin). Haloperidol was provided by McNeil Laboratories (Fort Washington, PA, USA) and was prepared by dissolving 50 mg in 25 ml of a 40% lactic acid solution and bringing the final volume to 100 ml with 0.9% NaCl. The dose of haloperidol refers to the free base.

The monkeys were treated with IM FPZ every other week. During the first 2 months of treatment, the dose was raised in half-log increments from 0.1 to 3.2 mg/kg. At the high dose, the animals stopped eating and drinking so the dose was dropped back to 1 mg/kg for 4 months, then raised to 3.2 mg/kg and held there for the last 6 months of the year.

From the fourth to the eighth month of FPZ treatment, attempts were made to add haloperidol to the treatment regimen by adding 0.5 mg/kg to food (fruit or juice) daily.

Offprint requests to: B. Kovacic

However, the animals would not reliably eat the drugged food and decreased food and water intake became a problem, causing the attempt to be abandoned.

Assessment of behavior. During the first 6 months of the year of FPZ treatment, the monkeys were observed directly in their home cages by a trained technician. The procedure consisted simply of standing in the monkey room for several minutes and viewing each animal separately for a minute or so. The animals were not observed on a rigid schedule, but were inspected several times per day, 5 days per week, during normal working hours. The authors also observed the animals frequently. During the last 6 months of the year of FPZ treatment, another trained technician viewed each animal for a minute or so between 7–9:00 AM and logged the behavior observed. The animals were always sitting or lying quiet at that time of day. For the remainder of the day, all observations and log entries were made by one of the authors, who viewed the animals during normal working hours approximately once an hour for the first 3 days after FPZ injection and, except for weekends and holidays, approximately four times a day for the remainder of each 2-week interval between FPZ injections. During the last 3 months of FPZ treatment, regardless of the day or time, if a monkey was showing a reaction involving abnormal postures and/or movements, the animal was then usually observed at least once an hour until it no longer displayed such a reaction. Such hourly observations often continued past 9 PM on the first 3 days after injection, were rarely needed after 11 PM, and were not made after midnight even if an animal was still displaying abnormal postures or movements. For the remainder of the study, the technician continued to log behavior once between 7–9:00 AM. One of the authors observed and recorded behavior several times per day during normal working hours.

At the start of the study, before any drugs were administered, one of the technicians videotaped each animal for several minutes in a cage fitted with a Plexiglas door. The technician also videotaped each animal for several minutes at approximately monthly intervals during the first 6 months of FPZ treatment so as to show reactions to FPZ. The tapes were later reviewed by one of the authors.

Effect of anticholinergic drugs on acute reactions to FPZ. During the months 7–9 of FPZ treatment, biperiden lactate (0.02–0.04 mg/kg IM) was administered during episodes of acute dystonic-dyskinetic reactions to FPZ.

The ability of benztropine mesylate to affect the monkeys' abnormal movements was examined during the last 2 weeks of the year of FPZ treatment. Shortly after an animal went into an episode of acute dystonic-dyskinetic reaction to FPZ, it was given benztropine mesylate (0.2–0.5 mg/kg IM).

Effect of short courses of FPZ on fading TD. During the months that followed the full year of chronic FPZ, Ginger, Elly, and Karman all developed abnormal movements resembling TD. At 2.5 months after the last FPZ injection, Ginger's TD-like symptoms were fading and a second course of FPZ treatment was begun for this animal. The course consisted of an injection of FPZ (3.2 mg/kg IM) every other week for 4 weeks (i.e., a total of three injections). The first injection abolished TD symptoms completely.

Benztropine (0.3–0.6 mg/kg IM) was then used as needed to treat or prevent acute reactions to FPZ. Ginger's TD reappeared after the short (second) course of treatment. At 3.5 months after the end of the second course, Ginger's TD was a gain fading and a third course of FPZ, similar to the second, was begun.

Results

Acute reactions to FPZ. During month 1 of chronic FPZ treatment, predominant effects seen in all monkeys were sedation (general drowsy behavior, decreased interest in the environment), reduction or absence of motor activity, slowing of volitional movement, trembling of the hands (at rest and when manipulating food), and trembling of the entire body. During the following months, these symptoms (evident for the entire 2-week interval between injections) remained and a variety of abnormal postures, abnormal movements, and displays of motor restlessness appeared. These included the following effects that were displayed by all monkeys: Incessant quadrupedal circling, sudden flinging of oneself into walls or ceiling of cage (often appearing glassy-eyed and unresponsive to stimuli just before a fling), bizarre postures while thrashing about or while moving in slow motion, sustained abnormal postures including 'crucifixion' postures (with extremities clinging to walls or ceiling, often with severe rigidity and trembling), and retrocollis. All of these abnormalities have been observed in other primate studies (Bedard et al. 1977; Casey et al. 1980; Deneau and Crane 1969; Deuel 1969; Weiss et al. 1977).

In addition to the above, acute effects characteristic to each animal were observed. Karman had oral dyskinesias that first appeared during the month 7 of treatment. She would hold her mouth wide open and protrude her tongue far to the side, holding it out for many seconds at a time, sometimes moving her jaw up and down rhythmically. Sometimes she would gnaw on the cage wall, ceiling, or floor, protruding her tongue far through the mesh, either straight out or curving downward to the side, moving her tongue irregularly.

Ginger often held her right arm in a characteristic posture. She held the arm straight up with the wrist flexed so that the palm of her hand was parallel to the top of her head. Often when in this position, she would make bicycling movements with her legs while either staying in one location or while prancing around the cage. Sometimes she was quite graceful about this, giving the appearance of dancing. During the later months, she was not graceful and this characteristic behavior became a signal that flinging was imminent if not prevented by pulling the 'squeeze wall' forward.

Elly and K-013 would lie on the floor on their backs and, while remaining on their backs, would rotate constantly for hours. Their elbows were scraped raw from this activity. Nystatin-neomycin ointment (Panalog, Squibb, Princeton, NJ, USA) was applied to the elbows and bulky bandages were used to prevent further injury and permit healing. While rotating, the animals' arms and legs would often thrash about or flex and extend rhythmically.

The acute abnormal postures, movements, and displays of motor restlessness occurred in episodes that had their

Table 1. Example of one monkey's (Karman) frequency of display of abnormal postures and movements during the last 3 months of a year of chronic treatment with fluphenazine enanthate. Shown are the 2-week intervals following injection (3.2 mg/kg IM) on Mondays (approximately 8 AM) on weeks 41 and 43. The animal was observed (approx 1 min/observation period) at least once during the hours indicated. Symbols are as follows: P = protruding tongue, mouth usually wide open, jaw often goes up and down; G = gnawing cage wall, with tongue usually protruding far through mesh; T = thrashing about in a poorly coordinated manner, assuming bizarre postures; R = retrocollis; F = flinging violently into walls or ceiling of cage; C = crucifixion posture with severe rigidity and trembling. A dash indicates that the animal was observed but was not displaying abnormal postures or movements

Clock (hour)	Week 41					Week 42					Week 43					Week 44				
	Mon	Tue	Wed	Thur	Fri	Mon	Tue	Wed	Thur	Fri	Mon	Tue	Wed	Thur	Fri	Mon	Tue	Wed	Thur[a]	Fri[a]
7 AM	–	–	–	–	–	–	–		–		–	–	–	–						
8	Inj									–	Inj		–		–	–	–			
9	–	R											–					R		
10	–	–		R		–	–	–	–	–	–	–	–	F		–	–	–		
11	–	–	–		–	G	–				–	–	–	–						
12 noon	–	R	–			G		–			PT	–	–							
1	P	R	–	R		PG					P	R	–	–	–					
2	P	R	–	RC	–	PG	–			–	PT	R	–	–		–	–	–		
3	P	R	–	–	–	PT		–	–		PT	R	–	–						
4	PGT	F	–	–		T					PT	R	–	–	–					
5	PGT	T	T	–	–	T	–				PT	R	–	–			RC			
6	T	T	PG	–	–	T		R	–	R	PT	T	R	–		–	–			
7	PT	–	G	–		–		–		–	–	T	–					–		
8	–		G	–								T	–							
9			G									T	–							
10			PT									T	–							
11			PT									–	–							

[a] Holiday (no observation)

peak occurrence during the first 3 days after each injection. Usually a monkey would have one episode on the day of injection and another on day 2 or 3 after injection. During an episode, any or many of the various abnormal postures, movements, and displays of restlessness could occur. For two monkeys (Elly and Karman) episodes of reaction often lasted for several hours at a stretch. During the later months of the year of FPZ treatment, episodes occurred not only during the 3 days after injection but also sporadically throughout the remainder of the 2-week period between injections (Table 1).

Stress, especially the stress of eye contact with the investigators, appeared to precipitate episodes of drug reaction.

Effect of anticholinergic drugs on acute reaction of FPZ. At the doses used, biperiden lactate had no clear-cut effect on episodes of acute dystonic-dyskinetic reactions to FPZ. Benztropine mesylate very effectively terminated such episodes.

Symptoms resembling TD. Within a few months after cessation of chronic treatment with FPZ, Elly, Ginger, and Karman all displayed symptoms similar to TD. Such symptoms worsened under stress.

Karman had a finger dyskinesia. She would keep spreading, then relaxing the fingers of her right hand. This symptom was clearly present at several weeks after treatment, remained for 11 months, and then faded.

Elly displayed a reaction analogous to human pacing. She constantly moved in a stereotyped and rhythmic fashion, back and forth, from one particular upper corner of her cage to another. The behavior drew unsolicited comments attesting to its abnormality from two veterinarians unfamiliar with the nature of the study. The reaction developed gradually but was very pronounced during the months 3–5 after the year of treatment with FPZ. During these months, Elly was being treated with griseofulvin for a fungal infection, as described.

Ginger displayed several TD-like symptoms. The first to appear was a rhythmic up-and-down movement of the jaw, first seen on day 20 after FPZ was discontinued. Other symptoms appeared during the next few weeks. The tongue could often be seen moving inside the mouth, forward and back repetitively, occasionally protruding slightly past the lips. There were frequent bouts of choreic arm and finger movements and of constant shifting of weight.

Effect of short courses of FPZ on fading TD. At 2.5 months after the year of chronic FPZ, when Ginger's TD was fading, a 4-week course of FPZ abolished TD completely. No symptoms were observed during the 4-week period but, 21 days later, they started to reappear in full force. The first symptom to reappear was abnormal tongue movement, which was similar to the former movement. During the following weeks, all other symptoms reappeared and pelvic rocking was added to the monkey's repertoire of abnormal movements. Stress worsened the movements.

At 3.5 months after the end of the 4-week course of FPZ, when Ginger's TD was again fading, another 4-week course of FPZ was begun. Again, the first injection eliminated symptoms of TD. They reappeared starting at 14 days after the last injection and were still present, though fading, several months later.

An oral dyskinesia difficult to classify. During the last month of the full year of FPZ treatment and for several months thereafter, Karman occasionally protruded her

tongue straight out (about 0.5–1 cm) flatly through otherwise closed lips and held it out for about 1 min. This 'flat tongue' usually occurred only when she was calm and there were no other symptoms. Unlike acute reactions to FPZ, this symptom was not affected by benztropine. Unlike TD symptoms, it was not exacerbated by stress.

Discussion

Results of this study confirm and extend those of Gunne and associates (Gunne and Bárány 1976; Bárány et al. 1979), who treated *C. apella* chronically with haloperidol. There are similarities between their work and the present study. In all of these studies, chronic neuroleptic treatment of Cebus monkeys produced two distinct motor syndromes; one corresponding to the early appearing extrapyramidal symptoms of neuroleptic patients, the other corresponding to TD. During month 1 of treatment, acute effects consisted mainly of sedation and parkinsonian-like symptoms. In the following months, abnormal postures and movements appeared similar to the dystonias and acute dyskinesias of neuroleptic-treated patients. These were at their worst after each administration of neuroleptic. Reversible TD turned into persistent TD after repeated neuroleptic treatment. Thus, one of Gunne's monkeys displayed TD that was reversible after 5 months of treatment but appeared irreversible after a further 12 months of treatment. In the present study, in the monkey that received three courses of FPZ, the duration of display of robust symptoms was longer after the third course of treatment than after the first or second. A difference between the Gunne studies and the present one is that Gunne's animals displayed TD during treatment whereas, in the present study, the disorder was not observed until after drug withdrawal.

Biperiden had no consistent effect on acute symptoms in the present study, but the dose employed (0.02–0.04 mg/kg IM) was probably too low in view of the drug's effectiveness at tenfold (dietary) doses used by Gunne and Bárány (1976) and Bárány et al. (1979).

As to whether any one combination of drug and species is more effective than others for producing TD in nonhuman primates, among haloperidol-treated Cebus monkeys, Gunne and associates have so far treated 14 *C. apella* monkeys and four of these (given 0.05–1 mg/kg for 3–34 months) developed TD (Häggström et al. 1981). However, Weiss and associates (Weiss et al. 1977; Weiss and Santelli 1978) treated *C. albifrons* and *C. apella* monkeys with haloperidol (0.25–1.0 mg/kg for 82–115 weeks), but none of the six animals displayed TD. Therefore, TD has appeared in 20% (four of 20) of Cebus monkeys treated with haloperidol. Among other species of primates treated with haloperidol, TD has appeared in two of 21 rhesus (Bedard et al. 1977; Paulson 1972, 1973), but not among 31 squirrel, eight green, or two iris monkeys (Casey et al. 1980; Gunne and Bárány 1976; Liebman and Neale 1980; Weiss and Santelli 1978). Chlorpromazine has been administered chronically to a total of 35 rhesus monkeys (Deneau and Crane 1969; Paulson 1972, 1973; McKinney et al. 1980), but only four (11%) displayed TD (McKinney et al. 1980). The contention that TD was produced in the chlorpromazine-treated rhesus monkeys of Paulson (1972, 1973) is not tenable, because in those particular animals dyskinesias worsened after each injection and were not exacerbated by drug withdrawal.

Among FPZ-treated animals, Häggström et al. (1981) reported that they have induced irreversible TD in two of six *C. apella*. In the present study, three of five *C. apella*, treated mainly with FPZ but also given some haloperidol, displayed TD. Combining all FPZ-treated Cebus monkeys, 45% (five of 11) exhibited TD. The data are too meager to draw firm conclusions, but they suggest that *C. apella* may be more prone to develop TD than rhesus, squirrel, or green monkeys, and that use of FPZ increases the likelihood of inducing TD. The latter suggestion is consistent with recent clinical (Csernansky et al. 1981; Smith et al. 1978; Gibson 1978; Ezrin-Waters et al. 1981) and rodent (Waddington 1982) studies, which present evidence that FPZ may be associated with more TD than other neuroleptics.

The acute effects of FPZ seen in this study are consistent not only with the results of Gunne and associates but also with those of most other nonhuman primate studies. The abnormal postures and movements that appear after several weeks of neuroleptic treatment have been designated the 'acute dyskinetic syndrome' (ADS) by Liebman and Neale (1980). Once established in a monkey, the syndrome is elicited with each administration of neuroleptic and the animal is considered 'primed' for ADS. The present study provides evidence that monkeys can also be primed for TD since, when TD symptoms are fading, they can be restored to full force with a short (4 week) course of FPZ.

Episodes of ADS had their peak occurrence during the first 3 days after each injection. This agrees with the study of Johnson (1973) in which dystonic reactions of patients treated chronically with FPZ occurred within 72 h after injections. Also, in humans (as in the present study) side effects of FPZ are just as likely to occur after 6 months of treatment as during the first 3 months (Johnson and Freeman 1973).

One monkey was treated with griseofulvin for a fungal infection at a time when 'pacing-like' behavior after neuroleptic withdrawal was pronounced. This raises the possibility that the 'pacing' behavior was an effect of griseofulvin rather than of neuroleptic withdrawal. That seems unlikely, however, since stereotyped motor abnormalities are not listed among the side effects of griseofulvin (Sande and Mandell 1980). The authors know of no reason to suspect that the fungal infection itself altered the course of, or resulted from TD.

References

Baldessarini RJ, Cole JO, Davis JM, Gardos G, Preskorn SH, Simpson GM, Tarsy D (1980) Tardive dyskinesia: A task force report of the American Psychiatric Association. American Psychiatric Association, Washington DC

Bárány S, Ingvast A, Gunne LM (1979) Development of acute dystonia and tardive dyskinesia in Cebus monkeys. Res Commun Chem Pathol Pharmacol 25: 269–279

Bedard P, Delean J, LaFleur J, LaRochelle L (1977) Haloperidol-induced dyskinesias in the monkey. J Can Sci 4: 197–201

Casey DE, Gerlach J, Christensson E (1980) Dopamine, acetylcholine and GABA effects in acute dystonia in primates. Psychopharmacology 70: 83–87

Csernansky JG, Grabowski K, Cervantes J, Kaplan J, Yesavage JA (1981) Fluphenazine decanoate and tardive dyskinesia: A possible association. Am J Psychiatry 138: 1363–1365

Deneau GA, Crane GE (1969) Dyskinesia in rhesus monkeys tested with high doses of chlorpromazine. In: Crane GE, Gardner R (eds) Psychotropic drugs and dysfunction of the basal ganglia. US Public Health Service, Washington DC, pp 12–14

Deuel RK (1969) Neurological examination of rhesus monkeys treated with high doses of chlorpromazine. In: Crane GE, Gardner R (eds) Psychotropic drugs and dysfunction of the basal ganglia. US Public Health Service, Washington DC, pp 15–18

Ezrin-Waters C, Seeman MV, Seeman P (1981) Tardive dyskinesia in schizophrenic outpatients: Prevalence and significant variables. J Clin Psychiatry 42: 16–22

Gibson A (1978) Depot injections and tardive dyskinesia. Br J Psychiatry 132: 361–365

Gunne LM, Bárány S (1976) Haloperidol-induced tardive dyskinesia in monkeys. Psychopharmacology 50: 237–240

Häggström JE, Anderson U, Gunne LM (1981) A primate model for tardive dyskinesia: Postmortem biochemical findings. In: Perris C, Sruwe G, Jansson B (eds) Biological psychiatry. Elsevier North Holland, Amsterdam, pp 837–839

Johnson DAW (1973) The side effects of fluphenazine decanoate. Br J Psychiatry 123: 519–522

Johnson DAW, Freeman HL (1973) Drug defaulting by patients on long-acting phenothiazines. Psychiatr Med 3: 115–119

Kovacic B, Domino EF (1982) A monkey model of tardive dyskinesia (TD): Evidence that reversible TD may turn into irreversible TD. J Clin Psychopharmacology 2: 305–307

Liebman J, Neale R (1980) Neuroleptic-induced acute dyskinesias in squirrel monkeys: Correlation with propensity to cause extrapyramidal side effects. Psychopharmacology 68: 25–29

McKinney WT, Moran EC, Kraemer GW, Prange AJ Jr (1980) Long-term chlorpromazine in rhesus monkeys: Production of dyskinesias and changes in social behavior. Psychopharmacology 72: 35–39

Paulson GW (1972) Dyskinesias in rhesus monkeys. Trans Am Neurol Assoc 97: 109–110

Paulson GW (1973) Dyskinesias in monkeys. Adv Neurol 1: 647–650

Sande MA, Mandell GE (1980) Antimicrobial agents: Miscellaneous antibacterial agents; antifungal and antiviral agents. In: Gilman AG, Goodman LS, Gilman A (eds) The pharmacological basis of therapeutics. Macmillan, New York, pp 1222–1248

Smith RC, Strizich M, Klass D (1978) Drug history and tardive dyskinesia. Am J Psychiatry 135: 1402–1403

Waddington JL (1982) Tardive dyskinesia, fluphenazine decanoate, and haloperidol. Am J Psychiatr 139: 703–704

Weiss B, Santelli S, Lusink G (1977) Movement disorders induced in monkeys by chronic haloperidol treatment. Psychopharmacology 53: 289–293

Weiss B, Santelli S (1978) Dyskinesias evoked in monkeys by weekly administration of haloperidol. Science 200: 799–801

Received June 17, 1982; Final version May 23, 1984