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Haloperidol-Induced Tardive Dyskinesia in Monkeys

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Abstract. In three cebus monkeys the chronic daily administration of haloperidol (0.5 mg/kg/day orally) created sedation and parkinsonism during the first 5–7 weeks. Later the animals developed signs reminiscent of acute dystonia, as seen in the clinic during treatment with neuroleptics. These signs were dose-dependent and in extreme cases included widespread tonic and clonic seizures. After 3 and 12 months, respectively, two of the cebus monkeys developed buccolingual signs (grimacing and tongue protrusion), similar to tardive dyskinesia in the clinic.

The tardive dyskinesia symptoms were reduced in a dose-dependent manner after each haloperidol administration, being most pronounced in the morning before haloperidol was given. Biperiden reduced acute dystonia but reinstated signs of tardive dyskinesia, which had been abolished by haloperidol. It is suggested that cebus monkeys may provide a useful animal model for the study of neurologic long-term complications from neuroleptic drugs.

Key words: Tardive dyskinesia – Acute dystonia – Haloperidol – Animal model.

Animal models of varying degrees of relevance have been used to study the mode of action of neuroleptics in inducing disorders of movement. However, earlier attempts to reproduce tardive dyskinesia in monkeys have generally been disappointing (Sassin, 1975; Marsden et al., 1975). Although dyskinetic patterns of movement have been observed during long-term chlorpromazine (Deneau and Crane, 1969; Paulson, 1973; Messiha, 1974) or haloperidol (Bédard et al., 1972; Weiss, 1975a, b) administration, the effects were generally not long-lasting and in most instances seem to have disappeared within hours following each dose of the neuroleptic agent. For these reasons and due to the reversibility of symptoms following anticholinergic drugs (Deneau and Crane, 1969), the effects so far reported more closely resemble acute dystonia rather than tardive dyskinesia (Marsden et al., 1975).

The present paper reports on the measurement of behavioural disturbances in chronically haloperidol-treated monkeys. It was found that three different categories of movement disorder could be distinguished: (1) a syndrome closely related to acute dystonia and parkinsonism in the clinic (AD-P syndrome), (2) buccolingual and other symptoms resembling tardive dyskinesia (TD syndrome), and (3) certain characteristic changes of general motor activity.

Five monkeys, two cynomolgus (Macaca fascicularis: 1.7 and 3.7 kg) and three Cebus apella (1.1–1.9 kg) were housed in individual cages (61 × 61 × 74 cm). Haloperidol was administered for 4–16 months once daily in the diet of the animals, generally added to apple juice. Care was taken to check that the whole amount was consumed within 30 min. The cynomolgus monkeys were given increasing doses of haloperidol from 0.5 to 8 mg/kg/day and their behavior was rated once monthly during 24 h following their regular oral dose.

The Cebus monkeys received oral haloperidol 0.5 mg/kg/day throughout the experiment except on test days, when ratings were performed. On these occasions administration was i.m. and the dose was varied as reported below. Behavior was recorded on videotape through a plexiglass window at the side of the cage before and at 5, 10, 15, and 30 min, 1, 2, 4, 6, 8, and 24 h after haloperidol administration. In some experiments biperiden, an anticholinergic drug, was given 70 µg/kg i.m. either alone, or together with (20 min before, or 20 min after) the regular daily haloperidol dose. The patterns of behavior were rated on three different rating scales[1], one for the AD-P

[1] The rating scales may be obtained on request from the authors

syndrome (measuring rigidity with tonic contractions, clonic seizures, and tremor), one for the TD syndrome (measuring abnormal activity within the oral, lingual, periocular, and masticatory regions) and one for motor activity (measuring amount of activity, speed of movements, and degree of arousal). Comparison of 18 videotaped recordings presented in randomized order to two independent raters yielded agreements from 95.8 to 100% for nine different subscales (mean 98.5%).

It was found that chronic administration of haloperidol created both AD-P and TD signs in 2 cebus monkeys, whereas one cebus displayed only the AD-P syndrome. In the two cynomolgus monkeys there was only a mild reaction after each administration, with sedation and slight parkinsonian symptoms.

The general behavior of all monkeys during the first month of haloperidol treatment was dominated by sedation, with lowered speed of movements and various degrees of drowsiness, from which the animals could be only briefly aroused by vigorous knocking signals. This drowsy state lasted for 6–8 h after each administration, whereafter behaviour returned to normal. In the 3 cebus monkeys there was a gradual change in the reaction to each dose, with elements of acute dystonia and parkinsonism becoming increasingly prominent after 5–7 weeks.

Following each oral administration of 0.5 mg/kg they had both tonic and clonic cramps for a couple of hours together with tremor and stiffness of movements. When strongly affected they would lie on the floor, clinging to the bars and typically with clonic seizures. They responded to signals and there were no generalized epileptic fits. In one female monkey there was a further development of the symptomatology 3 months after the start of treatment. It became obvious before each haloperidol administration that the animal had varying degrees of perioral twitchings and grimacing. In addition there was also a more or less conspicuous protrusion of the tongue, giving the monkey a strange appearance. These buccolingual signs were reduced or disappeared within half an hour following each haloperidol administration. In one more cebus monkey (male) a similar development appeared to take place after 12 months of haloperidol, whereas in the third cebus we have only seen acute dystonia during 14 months of treatment.

Generally signs of acute dystonia became maximal within 30 min and lasted for about 24 h after haloperidol administrations. The buccolingual TD signs which were marked before the injections were reduced to various degrees during the same time period as was also the rated motor activity. When the daily haloperidol dose was omitted, the signs of TD remained unchanged for at least 3 days (maximal period tested).

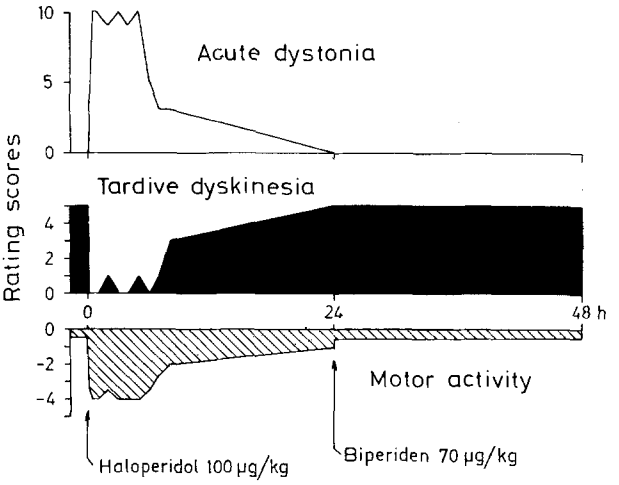

Fig. 1. Time curve of ratings of acute dystonia (*above*), buccolingual tardive dyskinesia signs (*black area, middle*), and motor activity (*hatched area, below*) following 100 µg/kg of haloperidol administered at zero time to a cebus monkey (4th month of treatment). On day 2 biperiden was substituted for haloperidol without apparent effect on behavior

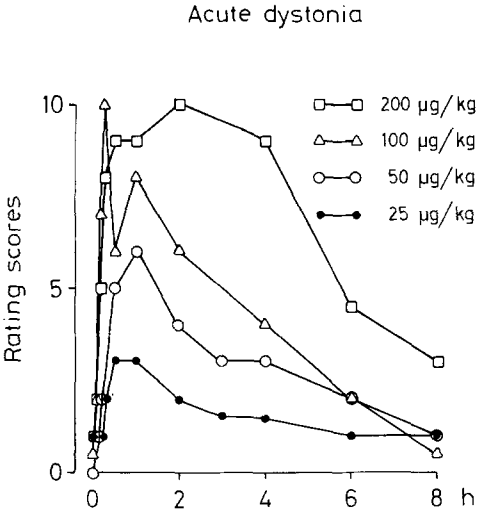

Fig. 2. Ratings of AD-P signs for 8 h after 25, 50, 100, and 200 µg/kg of haloperidol given i.m. at zero time on 4 separate days in a monkey which had received haloperidol daily for 3 months

Figure 1 shows that biperiden given on the 2nd day did not alter this pattern of behavior.

Figure 2 illustrates the AD-P ratings following various doses of haloperidol. There was a dose response relationship between 25 and 200 µg/kg. Figure 3 illustrates the symptom-reducing effects of the same doses on the TD syndrome. Also in this case there was an obvious dose-dependent response.

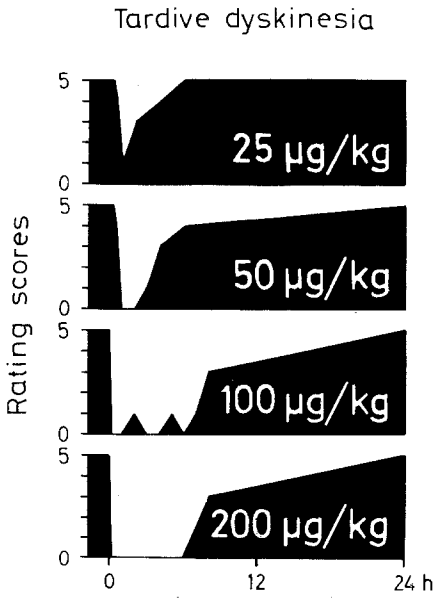

Fig. 3. Ratings of TD signs for 24 h after 25, 50, 100, and 200 µg/kg of haloperidol administered at zero time on 4 separate days in a monkey which had received haloperidol for 3 months

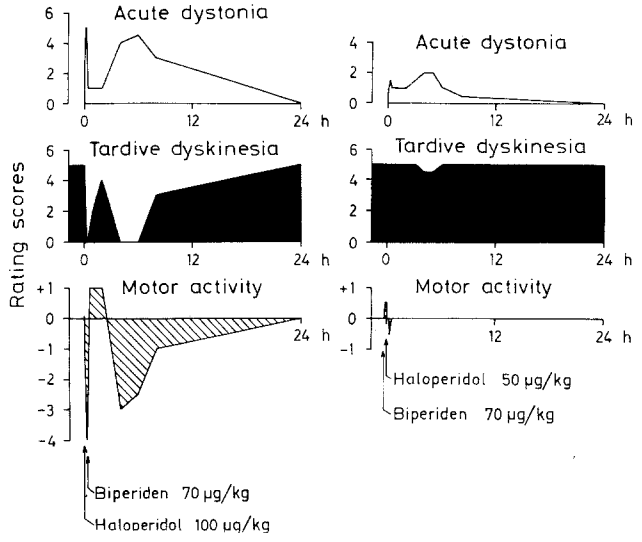

Fig. 4. Ratings of AD-P, TD and motor activity in a chronically haloperidol-treated monkey. *Left:* biperiden (70 µg/kg) given 20 min after haloperidol (100 µg/kg). *Right:* biperiden (70 µg/kg) given 20 min before haloperidol (50 µg/kg)

In one experiment (Fig. 4, left) biperiden was given 20 min after 100 µg/kg of haloperidol when the AD-P signs were rapidly increasing. The anticholinergic partly reversed the AD-P syndrome for about 4 h and at the same time there was a marked increase in motor activity with movements above normal speed. Biperiden temporarily reversed also the effect of haloperidol on TD. The usual alleviation of TD signs after haloperidol was interrupted by a second biperiden-induced peak of TD activity, lasting for 4 h. When biperiden (70 µg/kg) was administered 20 min before 50 µg/kg of haloperidol (Fig. 4, right) there was a nearly complete reversal of all haloperidol-induced changes in behavior (AD-P, TD alleviation, and motor activity).

The present paper is the first demonstration of two distinct dyskinetic syndromes in monkeys, one with several elements of acute dystonia and the other closely corresponding to tardive dyskinesia. The first-mentioned syndrome, which is a direct and dose-related effect of haloperidol, could be reversed by administration of biperiden. Tardive dyskinesia, on the other hand, which was temporarily controlled by haloperidol, became aggravated when biperiden was given (Fig. 4). All these observations are in good agreement with clinical reports of dyskinetic syndromes complicating antipsychotic medication in humans (Ayd, 1967; Crane, 1973) and we therefore suggest that the signs registered in cebus monkeys may provide a useful animal model of neuroleptic induced dyskinesias. The 2 cynomolgus monkeys displayed only slight symptoms in spite of high doses and similar observations have been reported in rhesus monkeys (Paulson, 1973). Thus, there might be species differences in this response to neuroleptic agents, where Cebus apella appears to be a particularly susceptible species.

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