Effects of antiparkinsonian drugs on neuroleptic-induced extrapyramidal signs in monkeys

Antiparkinsonian drugs with central anti-acetylcholine action are often used to counteract the pronounced extrapyramidal signs caused by neuroleptic drugs such as butyrophenones and phenothiazines because the signs are usually considered undesirable in psychiatric therapy. Since some neuroleptic drugs have been reported to induce the similar signs in monkeys (Courvoisier, Ducrot & Julou, 1957; Larochelle, Bedard & others, 1971; Dreyfuss, Beer & others, 1972), we have studied the effects of antiparkinsonian drugs on neuroleptic-induced cataleptic features correlated with the extrapyramidal signs in male cynomoglus monkeys (*Macaca irus*, 3·7–4·2 kg) induced by the subcutaneous injection of haloperidol (1 mg kg^{-1}) or perphenazine (2 mg kg^{-1}).

The monkeys after the haloperidol injection showed the extrapyramidal signs, that is, mask-like faces, hypokinesia of the limbs, spontaneous abnormal posture characterized by involuntarily rotatory movements of the head and the body, and maintenance of imposed abnormal posture with rigidity. The haloperidol-induced cataleptic features reached their greatest severity within 30 min, lasted for more than 6 h, and then disappeared after 24 h. The monkeys after perphenazine injection, also showed cataleptic features, these were caused within 30 min, lasted for more than 30 h and were similar to those induced by haloperidol.

Ethopropazine hydrochloride (5 mg kg^{-1}), benztropine mesylate (2 mg kg^{-1}), trihexyphenidyl hydrochloride (2 mg kg^{-1}) and 6,6,9-trimethyl-9-azabicyclo[3,3,1]non-3βyl α,α-di(2-thienyl) glycolate hydrochloride (PG-501, 2 mg kg^{-1}) respectively were administered subcutaneously to each of four monkeys 30 min before the injection of haloperidol or perphenazine and those drugs were evaluated according to a blind-testing method. In Fig. 1, the effects of the antiparkinsonian drugs on the haloperidol- and perphenazine-induced cataleptic features are presented.

PG-501 as well as trihexyphenidyl showed a clear antagonistic effect on the haloperidol-induced cataleptic features, while ethopropazine and benztropine were less

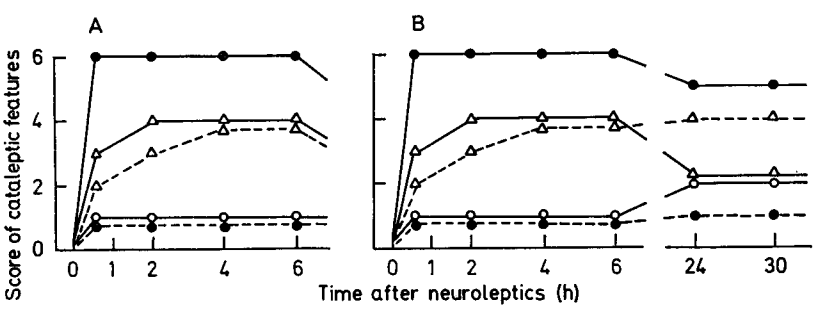

FIG. 1. Effects of antiparkinsonian drugs on haloperidol-induced cataleptic features (A) and perphenazine-induced cataleptic features (B). —●—: Saline; --●--: PG-501, 2 mg kg^{-1}; —⊙—: trihexyphenidyl, 2 mg $kg;^{-1}$; —△—: benztropine, 2 mg kg; --△--: ethopropazine, 5 mg kg^{-1}. The drugs were administered subcutaneously 30 min before the injection of haloperidol (1 mg kg^{-1}) or perphenazine (2 mg kg^{-1}). Each point represents the mean score obtained for a group of 4 monkeys.

Score of spontaneous abnormal posture: 6, extreme abnormal posture characterized by involuntary movements of the head and the body; 4, moderate intensity of the abnormal posture and hypokinesia of the limbs; 2, slight intensity of the abnormal posture and weak hypokinesia of the limbs; 0 No spontaneous abnormal posture.

Score of imposed abnormal posture: 6, maintenance of imposed abnormal posture with marked rigidity of the limbs when the monkeys were laid on side or back; 4, moderate intensity of the imposed posture (their limbs with moderate rigidity were kept in abnormal positions though they were not laid on side or back): 2, slight intensity of the imposed posture with weak rigidity of the limbs; 0, no maintenance of imposed abnormal posture.

antagonistic than trihexyphenidyl. Furthermore, PG-501 and trihexyphenidyl antagonized the perphenazine-induced cataleptic features for more than 30 h. Benztropine produced less antagonistic activity over 6 h, but the moderate effect was observed 24 h after perphenazine injection. Ethopropazine also showed a moderate antagonistic effect on the perphenazine-induced cataleptic features.

The evaluation of antiparkinsonian drugs in animals is generally not satisfactory, because of the difficulty in producing the extrapyramidal signs similar to the clinical symptomatology. Monkeys with tremor induced by the brain stem lesions have been used for the evaluation of antiparkinsonian drugs by Vernier & Unna (1956). Larochelle & others (1971) have reported that benztropine showed a reversible effect not only on the tremor in monkeys with the brain lesions, but also on the thioproperazine-induced catatonia in unoperated monkeys. The technique which induced the tremor in the monkeys with the lesions is not convenient for the evaluation of antiparkinsonian drugs because a satisfactory tremor does not appear to be obtained easily. Dreyfuss & others (1972) have reported that the baboon treated chronically with fluphenazine exhibited extrapyrimadal signs such as tremor, motor retardation and rigidity with tremor as a prominent feature, but those signs were not antagonized by low doses of benztropine or trihexyphenidyl.

Although tremor is characteristic of Parkinson's disease, the cataleptic features induced acutely by the neuroleptic drugs seem to be of importance as indicators for the evaluation of antiparkinsonian drugs in monkeys. The cataleptic features were antagonized by the antiparkinsonian drugs such as PG-501, trihexyphenidyl, benztropine and ethopropazine. PG-501, a new antiparkinsonian drug which was a potent antagonist of the tremorine-induced tremor in mice (Kojima, Nose & others, 1971), has been reported to reverse effectively the extrapyramidal signs induced by some neuroleptic drugs in man (Tanaka, Ogawa & others, 1972).

Our results are in agreement with findings reported by Morpurgo (1965) concerning protective effects of antiparkinsonian drugs against the perphenazine-induced cataleptic features in rats. The results indicate that this method may be useful for evaluation of antiparkinsonian drugs in monkeys.

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