THE EFFECT OF SELEGILINE AND BROMOCRIPTINE IN THE PROPHYLAXIS OF PERPHENAZINE-INDUCED PSEUDOPARKINSONISM IN RAT: A COMPARATIVE STUDY

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Abstract

Parkinsonism is a neurodegenerative disease that is defiend by certain symtom as muscle rigidity , impaired movement , tremor and disorientation of body. The aim of the present study was to compare the efficacy of selegiline and bromocriptine in the prevention of experimentally induced pseudoparkinsonism in rat. Perphenazine (5mg/kg) was used (IP) as the inducing agent. Different groups of rats were pretreated by either selegiline (2.5, 5, 10, and 20mg/kg), or effective dose of bromocriptine (30mg/kg). The degree of prevention of catatonic reaction was compared with control group. The results showed all selegiline-treated groups had significant reduction in the catatonic reaction relative to sham treated group. In addition, 20mg/kg selegiline had more intensive effect to reduce the catatonic reaction than bromocriptine (30mg/kg). Selegiline seems to be a suitable drug to prevent perphenazine–induced catatonia in rat.

Keywords:

Pseudoparkinsonism, Selegiline, Bromocriptine, Catatonic reaction, Rat

Introduction

The term Parkinsonism refers to a clinical complex first described by James Parkinson in 1817 and named it shaking palsy or paralysis agitans. This disease is characterized by four manifestations; resting tremor, rigidity, increased resistance to passive movement, akinesia and loss of normal postural reflexes (1). Previous studies have demonstrated a close relationship between the extrapyramidal reaction following neuroleptic drugs in man and the catatonic reaction in rat. Perhaps the model used in this study is a further understanding upon the possible comparative efficacy of selegiline and bromocriptine in the prevention of drug induced extrapyramidal reaction in human(2).

The exact mechanisms that lead to the development of parkinsonism is unknown. However, the process of neuronal injury can result from interaction of various factors ranging from environmental, to intrinsic susceptibility of the neurons to injury. The intrinsic factors can be due to susceptibility to exotoxic injury and production of toxic free radicals as products of cellular metabolism. Oxidative stress induced by dopamine metabolism may underlie the selective vulnerability of dopaminergic neurons (3,4,5). The mere reduction of the dopaminergic input to the neurons of the neostriatum and aging *per se* does not warrant the development of this disease,

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although with aging there is decrease in the dopaminergic neurons in brain. However, the reduction needs to be between 80 to 90% before the development of this syndrome(6). Parkinson disorder can be iodiopathic, that is the classically described by Parkinson, or caused by other factors, among them is drug-induced; in this case it is termed pseudoparkinsonism. The latter has been used in experimental animal models for studying the effects of various pharmacological interventions for assessment of effectiveness of drugs used in the treatment of this disorder. In this study, using an experimental model proposed earlier by Morpurgo in 1962 (2,7), which is based on the perphenazine-induced catatonic reaction. This term describes the failure of the animal to correct spontaneously an unphysiological posture of the body. The aim of this study was to compare the effectiveness of bromocriptine (dopamine agonist) and selegiline (MAOI) in the prevention of perphenazine-induced pseudoparkinsonism in rat.

Materials

Male and female rats of NMRI strain, weight ranged from 140g to 180g were used throughout the study. They were housed in polycarbonate cages in groups of 10 and had access to standard laboratory pellet food and tap water. A 12hr light/dark cycle was maintained. Room temperature was set at 23±2C$^{\circ}$ with a relative humidity of 45-55%.

Methods

The animals were pre-treated by an injection of 5ml/kg (IP) either of the following drug solutions Contain 2. 5, 5, 10, 15 and 20mg/kg selegiline, most effective dose of bromocriptine (30mg/kg) (7) and normal saline (5ml/kg) (Sham treated group). After 30 minutes, all animals received an IP injection of 5mg/kg perphenazine hydrochloride. The catatonic responses were recorded after 20, 40, 60, 90, 120, 180 and 240 minutes after the perphenazine injection. The scoring of catatonic reaction was adopted from those reported by Morpurgo(2,7), using perphenazine (5mg/kg), various stages of catatonia were induced in rats. The scoring adopted were based on a three-stages model as follow:

Stage 1: when the rat placed on a flat table, the animal did not move, but on gentle touch, it showed movement, allocated score = 0.5.

Stage 2: one of the front paws of the rat was palced on a 3cm high block, if the rat did not correct its position within 10 seconds, it received a score of 0.5. Similarly, the second paw was placed on the block and scored the same way.

Stage 3: one of the front paws was placed on a 9cm high block and the other paw left hanging. A positive catatonic reaction was gauged by the failure of the animal to correct the imposed position within 10 seconds and was given a score of 1. Similar procedure was used with the other paw. Thus, if a rat was in full catatonia, a total cumulative score of 3.5 was assigned.

The drugs to be tested were administered 30 minutes prior to perphenazine injection. The scoring was initiated 20 minutes after perphnazine injection. In order to evaluate the anti-parkinsonism effects of the drugs administered, further periodic scoring were made at 20, 40, 60, 90, 120, 180 and 240 minutes after perphenazine administration.

Statistical analysis of the data collected were made by use of non-parametric method of Kruskal-Wallis method of analysis. A P value less than 0.05 was considered the level of significance.

Results

The means of the scoring for all groups under investigation are reported and summarized in Table 1. The results showed selegiline, at doses 2.5, 5 and 10mg/kg, produced a dose-dependent and significant reduction of catatonic responses 90, 120 and 180 minutes post-perphenazine administration in comparison with sham

treated group. While with 15 and 20mg/kg selegiline induced reduction was extended to cover all the period of the experiment (240 minutes) after perphenazine administration. Furthermore, there were significant differences between the 20mg/kg selegiline with other selegiline-treated groups. The degree of significance of differences was dose related, being maximal when compared with 2.5mg/kg and minimal with 15 mg/kg (Fig 1).

The results of effective dose of bromocriptine (30mg/kg) compared with 20mg/kg selegiline, showed that there was greater degree of reduction of catatonic responses in selegiline-treated group at 180 and 240 minutes post-perphenazine treatment (Fig 2) .

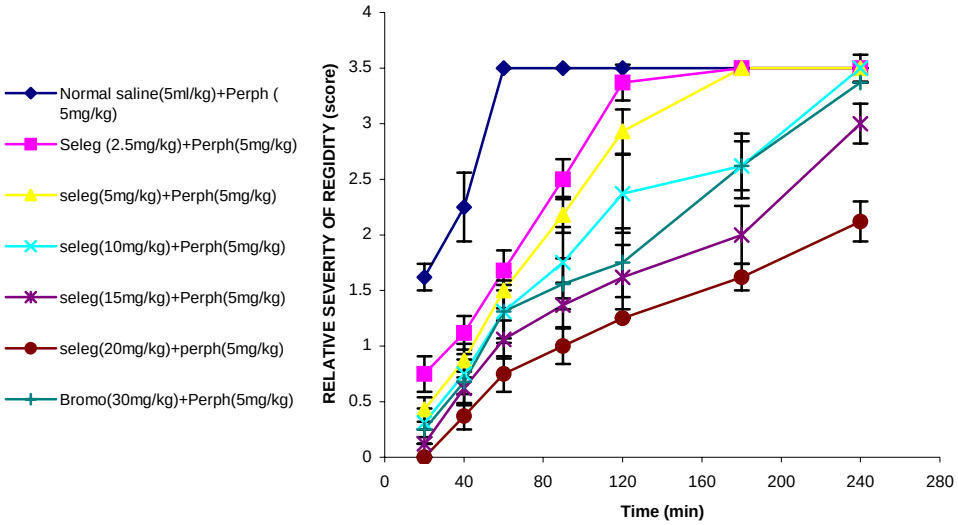

Fig. 1: The effect of different doses of selegeline on perphenazine-induced regidity in rats.

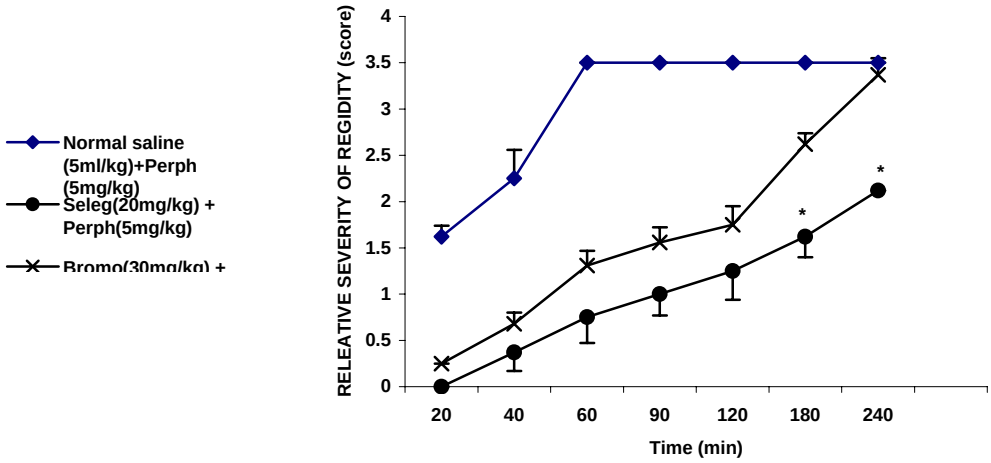

Fig. 2: Comparison of the effect of selegeline and bromocriptine on perphenazine-induced regidity in rats. Differences between two drugs are shown as *($p<0.05$)

Table 1: Mean ± SEM perphenazine-induced (5 mg/Kg) catatonic reaction scores at various intervals in pretreatment with sham treated group (normal saline), selegiline (S) or bromocriptine (B) groups in rat.

	Minutes following administration of perphenazine						
Group	20	40	60	90	120	180	240
Control	1.62±0.12	2.25±0.31	3.5±0	3.5±0	3.5±0	3.5±0	3.5±0
S(2.5)	0.75±0.16*	1.12±0.15*	1.68±0.18*	2.5±0.18*	3.37±0.16	3.5±0	3.5±0
S(5)	0.43±0.11*	0.87±0.15*	1.5±0.16*	2.18±0.16*	2.93±0.20*	3.5±0	3.5±0
S(10)	0.31±0.13*	0.75±0.18*	1.31±0.24*	1.75±0.31*	2.37±0.35*	2.62±0.29*	3.5±0
S(15)	0.12±0*	0.62±0.15*	1.06±0.17*	1.37±0.2*	1.62±0.29*	2±0.26*	3±0.18*
S(20)	0±0*	0.37±0.12*	0.75±0.16*	1±0.16*	1.25±0.2*	1.62±0.12*#	2.12±0.18*#
B(30)	0.25±0*	0.68±0.20*	1.31±0.28*	1.56±0.23*	1.75±0.31*	2.62±0.22*	3.37±0

*P <0 .05 Relative to sham treated group # P< 0.05 Relative to bromocriptine treated group.

Discussion

The results from this study demonstrate that selegiline was an effective drug in reducing acute perphenazine-induced catatonic muscular rigidity in rats. This effect was shown to be dose-dependent and at 20mg/kg was even more significantly potent than most effective dose of bromocriptine (30 mg/kg).

The aim of this study was to compare the efficacy of selegiline with bromocriptine, and the results demonstrated that effective dose of selegiline to be a more suitable and more potent than bromocriptine in preventing perphenazine-induced catatonia. Further advantages for this drug, is its reported neuroprotective action, and its favorable modulating effect on the wearing off phenomenon effects when used in combination with L-dopa (8).

L-dopa is considered as the golden choice in the treatment of Parkinsonism. However, due to short half life, various side effects, and most importantly the wearing off effect with accompanying switching on/off effects, made many physicians not recommend its use until there is compelling need of the patients for such treatment (9). Furthermore, recent evidences implicate the oxidative stress produced from metabolism of dopamine as the causative factor for the accelerated the dopaminergic neuronal damage (10).

On the other hand, idiopathic parkinsonism has been recently classified into three distinct phase (11). In the first phase, the disabilities are mild, it is recommended that selgiline to be used as the drug of choice. If needed a central acting anticholinergic agent, may be added. This will reduce nocturnal muscular rigidity (12). In order to reduce the peripheral effects that may develop following the use of the anticholinergic drug, a peripheral acting anticholinestrase such as pyridostigmine may be added. In the second stage of the disease, the use of L-dopa is recommended. Normally, in order to reduce the peripheral side effects associated with conversion of L-dopa to dopamine in the peripheral site, a dopa-decarboxylase inhibitor such as benserazide or carbidopa is given concurrently. Furthermore, in order to reduce the long term side effects of L-dopa, a dopaminergic receptors agonist, is given (13).

Conclusion

It seems that selegiline is a suitable drug both in the first phase of the disease as a single agent, and possible, in combination with L-dopa, in the second stage of the disease.

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