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Dose- and time-dependent therapeutic and adverse effects of Mucuna pruriens extracts in the 6-OHDA rat model of Parkinson's disease

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Introduction

In traditional Ayurvedic Indian medicine, preparations of Mucuna pruriens seeds (L-Dopa) are used in the treatment of Parkinson's disease (PD). It has been suggested that Mucuna preparations may posses some clinical advantages over conventional, synthetic L-DOPA/carbidopa preparations, including a rapid onset of action and longer on time without concomitant increase in dyskinesias (Katzenschlager et al. 2006; Kasture et al. 2010; Lieu et al. 2010). Alcoholic extracts of M. seeds are rich in L-DOPA, but other, as yet unknown compounds may contribute to its therapeutic effects.

Objectives

In 6-hydroxydopamine (6-OHDA) lesioned rats we determined:

1. Therapeutically effective doses of a methanol extract of Mucuna pruriens seeds and of (synthetic) L-DOPA without additives.
2. Abnormal involuntary movements (AIMs) during chronic treatment at therapeutically effective doses.
3. Dose-dependent effects of Mucuna extract and L-DOPA in the presence of benserazide (peripheral decarboxylase inhibitor).
4. Effects of a Mucuna preparation lacking L-DOPA.

Materials and Methods

Twenty-four 6-hydroxydopamine (6-OHDA) lesioned rats were used (Sprague Dawley, males, 8 µg 6-OHDA free base in 2 µl saline, 0.1% ascorbic acid sterilely injected into left medial forebrain bundle), all displaying significant contralateral forelimb akinesia and amphetamine-induced rotations (2-3 weeks post-surgery).

Ten rats were assigned to a chronic "dose-finding" series (M1, two periods of 4 weeks treatment) and 14 rats assigned to a comparative study of therapeutic and adverse effects of chronic Mucuna versus L-DOPA treatments without additives (series M2-D2, 4 daily injections in week 1, 5 injections in week 2 and 7 injections in week 3). After a wash-out period of 4 weeks the latter group of 14 rats was used to study effects of Mucuna and L-DOPA in the presence of benserazide and of Mucuna extract lacking L-DOPA.

Forelimb akinesia, therapeutic and adverse effects (i.e. abnormal involuntary movements, AIMs) of Mucuna or L-DOPA treatments were assessed using the cylinder test, recorded on video and rated on a scale from 0-6 (Lundblad et al. 2002).

Mucuna extracts containing ca. 20% L-DOPA (dry weight extract) were prepared and the chemical profiles of different batches were determined by HPLC and mass spectrometry to ensure reproducible quality. A Mucuna extract lacking the major constituent L-DOPA was prepared by preparative HPLC. Mucuna or L-DOPA preparations were solubilized in saline, 1% ascorbic acid and administered i.p. in a volume of 12.5 mg/kg. Benserazide was added at a dose of 15 mg/kg.

Rats were killed and brains dissected one week after the last Mucuna or L-DOPA injection. Dopamine and 5-hydroxytryptamine (5-HT) levels in ipsilateral and contralateral striatum were determined by HPLC with electrochemical detection (Gramsbergen et al. 2003).

Results

Materials and Methods

Twenty-four 6-hydroxydopamine (6-OHDA) lesioned rats were used (Sprague Dawley, males, 8 µg 6-OHDA free base in 2 µl saline, 0.1% ascorbic acid sterilely injected into left medial forebrain bundle), all displaying significant contralateral forelimb akinesia and amphetamine-induced rotations (2-3 weeks post-surgery).

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Conclusions

• Chronic Mucuna treatments induced a sustained motor improvement that took days to build up and lasted for 3-4 days after cessation of treatment, i.e. to the long duration response of L-DOPA treatment. Determination of the lowest, therapeutically effective doses required therefore repeated dosing.

• Mucuna extract was more effective than (synthetic) L-DOPA at equivalent L-DOPA doses of 12.5-25 mg/kg i.p. However, chronic treatment with these doses of Mucuna extract caused also more severe AIMS (predominantly limbic, but also axial and orofacial dyskinesias) than L-DOPA alone.

• Co-treatments with benserazide in Mucuna or L-DOPA-sensitized rats, did not reveal differences in therapeutic or adverse effects of Mucuna or L-DOPA.

This study in 6-OHDA lesioned rats did not reveal clinical benefits of Mucuna treatment over conventional L-DOPA therapy.

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References


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