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

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Introduction

Traditional Ayurvedic Indian medicine, preparations of Mucuna pruriens seeds (fig. 1) are used in the treatment of Parkinson’s disease (PD). It has been suggested that Mucuna preparations may possess some clinical advantages over conventional, synthetic L-DOPA/carbidopa preparations, including a rapid onset of action and longer on time without concomitant increase in dyskinesia (Katzenschlager et al. 2004; Kasture et al. 2009; Lieu et al. 2010). Alcoholic extracts of MP 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 methanolic 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 benzerazide (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 steriley implanted into left medial forebrain bundle, all displaying significant contralateral forelimb akinesia and amphetamine-induced rotations 3-3 weeks post-surgery.

Ten rats were assigned to a chronic “dose-finding” study (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 benzerazide 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 clinometer last, recorded on video and rated on a scale of 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 checked 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 ip in a volume up to 15 ml/kg. Benzerazide was used 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. 2002).

Results

Therapeutic effects in Mucuna pruriens (MP) seeds and of (synthetic) L-DOPA treatments without additives: Fig. 1. Therapeutic effect chronic treatment. Mucuna pruriens seed extract alone (series M1) showed significant therapeutic effect in comparison to baseline (p<0.05, Dunnet’s multiple comparison test). A significant contralateral forelimb akinesia and amphetamine-induced rotations were not observed in M1, M2 or D2 groups.

Effects of combined therapeutic treatments: Chronic Mucuna (M2) or L-DOPA (D2) treatments induced motor improvement that took days to build up and lasted for 3-4 days after cessation of treatment, i.e. similar to the long duration response of L-DOPA treatment. However, chronic treatment with these doses of Mucuna extract caused also more severe AIDs (predominantly dyskinesia, but also axial and orofacial dystonias) than L-DOPA alone.

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. similar 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 by peroral L-DOPA treatment. However, chronic treatment with these doses of Mucuna extract caused also more severe AIDs (predominantly dyskinesia, but also axial and orofacial dystonias) than L-DOPA alone.

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

• Mucuna extract lacking L-DOPA did not show any therapeutic effect.

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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