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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

In 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/carbostrophen preparations, including a rapid onset of action and longer on time without concomitant increase in dyskinesias (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 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 benzerazide (peripheral decarboxylase inhibitor).
4. Effects of Mucuna preparation lacking L-DOPA.

Materials and Methods

Twenty-five 6-OHDA-lesionated (6-OHDA) lesioned rats were used (Sprague Dawley, male, 8 μg 6-OHDA free base in 2 μl saline, 0.1% ascorbic acid steriologically injected into left medial forebrain bundle), all displaying significant contralateral forelimb akinesia and amphetamine-induced rotations 3-5 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). All 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 reproducibility quality. A Mucuna extract lacking the major constituent L-DOPA was prepared by preparative HPLC. Mucuna or L-DOPA preparations were solubilised in saline, 1% ascorbic acid and administered i.p. in a volume up to 10 ml/k. 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

Figure 1: The therapeutic dose range of Mucuna extract (fig. 1) or L-DOPA in 6-OHDA-lesionated rats, for different dose-response parameters. 1= M1, 2= M2, 3= M2 and D2, 4= M2 and D2.

Figure 2: Adverse effects of chronic Mucuna treatment, Mucuna treatment (Muc), L-DOPA treatment (L-DOPA) and Mucuna + L-DOPA treatments (Muc + L-DOPA). *p<0.05 **p<0.01, One way ANOVA, Tukey’s multiple comparison tests versus day of drug treatment. Series M2 and D2, N=7 vs N=7.

Figure 3: Long duration response following chronic Mucuna or L-DOPA treatments (last week of chronic treatment, week 3+4). Figures show mean basal akinesia in series M2 (dark blue) and D2 (pink). Tukey’s multiple comparison tests versus day of drug treatment, Series M2 and D2, N=7 vs N=7.

Figure 4: Therapeutic effect vs. L-DOPA without benzerazide. *p<0.05, **p<0.01, ***p<0.001, One way ANOVA, Dunnett’s multiple comparison tests versus baselines (0). Series M1, N=10 rats.

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 ip.

• However, chronic treatment with these doses of Mucuna extract caused also more severe AIBs (predominantly dystonias, but also axial and oral dyskinesias) 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

Kasture, S., Pontis, S., Pinna, A., Schintu, N., Spina, L., Longoni, R., Simola, N., Ballero, M. and Morelli, M. (2009) Assessment of symptomatic and neuroprotective efficacy of mucuna pruriens seed and of (synthetic) L-DOPA treatments at equivalent DOPA doses of 12.5-25 mg/kg ip. However, chronic treatment with these doses of Mucuna extract caused also more severe AIBs (predominantly dystonias, but also axial and oral dyskinesias) 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.