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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 seed (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 increases in akinesias (Katzenschlager et al. 2004; Kasture et al. 2010; 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.

Materials and Methods

Twenty-four 6-hydroxydopamine (6-OHDA) lesioned rats were used (Sprague Dawley, males, 6–8 g). 6-OHDA free base in 0.1% ascorbic acid stereotaxically 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 the 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 additones (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 (peripheral decarboxylase inhibitor).

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 in equivalent L-DOPA treatments. Equalised L-DOPA doses of 12.5-25 mg/kg i.p. were ineffective in week 2 and 3, in injections per week during 4 weeks, cylindertest 40-50 min. after dosing). Doses equivalent to 12 and 25 mg DOPA/kg i.p. (60-125 mg extract/kg) were not effective in week 2 and 3, in injections per week during 4 weeks, cylindertest 40-50 min. after dosing). Doses equivalent to 12 and 25 mg DOPA/kg i.p. (60-125 mg extract/kg) were not effective in week 2 and 3.

• Mucuna extract treatments without benserazide showed a significant improvement in overall (M1: vs. M2, N=7 vs N=7.

• The chronic Mucuna + benserazide treatment was equally effective as L-DOPA in benserazide treatment. Mucuna + benserazide treatments were assessed using the cylinder test, recorded on video and rated on a scale of 0-6 (Lundblad et al. 2003).

• Mucuna extract lacking a dose of 15 mg/kg. Rats were killed at the end of the study 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).

Acknowledgements

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References


• 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.

Figures

Figure 1. Essential amino acid composition of the seed and the leaf of Mucuna pruriens. The data are given as a percentage of the total amino acid content.

Figure 2. Mucuna seeds and pods of Mucuna pruriens.

Figure 3. Mucuna extract containing L-DOPA. Treatment of 6-OHDA lesioned rats with Mucuna extract at DOPA doses of 12.5 mg/kg (week 1+2, blue), 20 mg/kg (week 2+3, dark blue) and 25 mg/kg (day 26, pink). Baseline akinesia is scored at the baseline (0).

Figure 4. Dose-dependent effects of Mucuna pruriens seed extract on dopamine levels in the ipsilateral and contralateral striatum of 6-OHDA lesioned rats. *p<0.05, **p<0.01, ***p<0.001, One way ANOVA, Dunnett’s multiple comparison test. N=10 for M1, N=7 for M2 and D2.

Figure 5. 5-HT levels in ipsilateral and contralateral striatum. Contralateral levels were similar in treatment groups. Ipsilateral (lesioned) levels in M1 group slightly higher than M2 and D2 groups. One-way ANOVA, Tukey’s multiple comparison test. N=10 for M1, N=7 for M2 and D2.

Figures

Figure 6. Long duration response following chronic Mucuna or L-DOPA treatments (last 12 injections). Mucuna extract at dose 25 mg/kg i.p. (day 26, pink). Baseline akinesia is scored at the baseline (0).

Figure 7. Reversal of contralateral forelimb akinesia following increasing doses of Mucuna extract (3-4 mg/kg i.p.), with statistical analysis of data (Mann-Whitney U test, **p<0.01, **p<0.001). 

Figure 8. Reversal of forelimb akinesia (therapeutic effect) and AIMs (adverse effects) by chronic Mucuna extract treatment at DOPA doses of 12.5 mg/kg (week 1+2, blue), 20 mg/kg (week 2+3, dark blue) and 25 mg/kg (day 26, pink). Baseline akinesia is scored at the baseline (0).

Figure 9. Reversal of contralateral forelimb akinesia and amphetamine-induced rotations (total of 2 hours recording) prior to Mucuna or L-DOPA treatments without additones (series M2-D2, N=7 vs N=7.

Figure 10. Reversal of contralateral forelimb akinesia and amphetamine-induced rotations (total of 2 hours recording) prior to Mucuna or L-DOPA treatments without additones (series M2-D2, N=7 vs N=7.

Figure 11. Therapeutic effect Mucuna vs. L-DOPA without benserazide.

Figure 12. Therapeutic effect Mucuna vs. L-DOPA without benserazide.

Figure 13. Therapeutic effect Mucuna vs. L-DOPA without benserazide.

Figure 14. Therapeutic effect Mucuna vs. L-DOPA without benserazide.

Figure 15. Therapeutic effect Mucuna vs. L-DOPA without benserazide.