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TREATMENT OF ADVANCED PARKINSON'S DISEASE WITH A SUSTAINED-RELEASE PREPARATION OF L-DOPA

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INTRODUCTION

About 50 per cent of patients with Parkinson´s disease develop a fluctuating response to chronic treatment with conventional L-Dopa preparations (Marsden et al, 1982; Marsden,1976). Based on the findings that these fluctuations can be compensated by constant-rate intravenous infusions of L-Dopa (Quinn et al,1984) oral sustained-release preparations have been developed to obtain stabilization of L-Dopa plasma levels. Following initial positive results with oral sustained-release L-Dopa (Madopar HBS) (Poewe et al, 1986) we have carried out an open trial with Madopar HBS.

PATIENTS AND METHODS

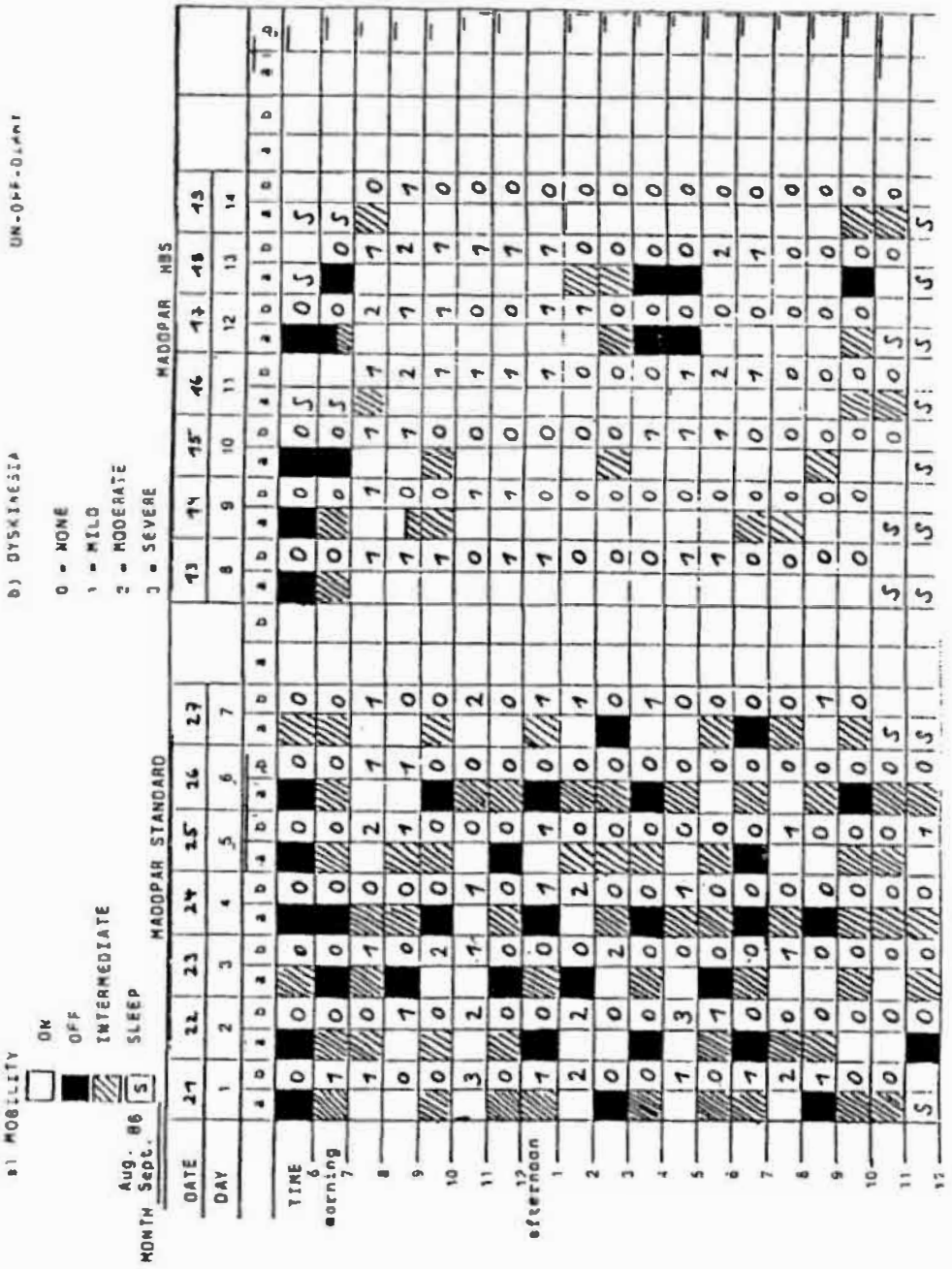
11 patients with advanced Parkinson´s disease and a fluctuating response to long-term treatment with conventional L-Dopa were included in this trial. Their clinical data are summarized in Table 1.

Table 1 Madopar HBS in advanced P.D./patient data

N= 11	6 male, 5 female
Age	59,8 (51-76) years
Duration	
- Disease	9,8 (5-19) years
- L-Dopa	6,0 (2-14) years
Hoehn and Yahr Stage	
- "on"	2,1
- "off"	4
L-Dopa dose	700 (350-1700) mg

In an in-patient phase of 2 to 4 weeks the response characteristics to their individual L-dopa regimen was assessed using self-scoring on-off diaries for hourly documentation of on-off swings as well as involuntary movements (AIM´s) (see figure 1). In addition, Parkinson´s disease symptoms were rated weekly during "on" and "off" phases using+.

Figure 1



When necessary the standard L-dopa regimen was modified to obtain the best possible clinical response. Patients were then switched to Madopar HBS in equivalent doses with adjustments of dose size and frequency until sufficient clinical effect had been achieved. In all patients 100 mg of standard L-dopa were added to their first morning dose and in two cases a further dose of 50 mg of conventional L-dopa was needed in the afternoon. Responders were followed as out-patients with bimonthly controls and clinical assessment was based on the patient's self-scoring on-off diary which was kept throughout the trial.

RESULTS

8 responders were treated with Madopar HBS for a mean period of 241 days. The mean daily dose of Madopar HBS was 900 mg averaging an increase of 64 per cent over the previous mean standard L-dopa of 550mg in this group of 8. Dosing frequency and dose intervals were only slightly different from standard L-dopa treatment (see Table 2).

Table 2 Madopar HBS in advanced P.D.-results in responders
N = 8

	conventional L-dopa	Madopar HBS
daily dose	550 (350-800) mg	900(400-1800)mg
No. of doses	5,6 (4-8)/d	5(3-8)/d
dose interval	3,1 (2-4) hrs	3,5(3-4,5) hrs
HRS "on"	7,7 (6-10)	12,5(10-14)
duration of HBS treatment		241(97-414)days

+ Columbia University Parkinson Scale (CURS) and Northwestern Disability Scale (NUDS).

Response fluctuations were considerably improved with a reduction of end-of-dose effects and an increase of total daily "on" time in all responders (see Table 2). Figure 1 gives an example of one responder's self-scoring on-off diary showing increased "on" time during one week of HBS treatment as compared to one week on standard L-dopa. Biphasic dyskinesias disappeared in three or five patients and were reduced in two, where there was only one episode after each morning dose (see Table 3).

Table 3 Madopar HBS in advanced P.D.-results in responders

	No. of patients improved with Madopar HBS
End of dose effects (N=8)	8
Nocturnal immobility (N=8)	4
Biphasic dyskinesia (N=5)	5
Off-period dystonia (N=2)	2

In all four patients with marked-time disabilities there was improvement of nocturnal akinesia. 2 patients of this group had had off-period dystonia which was abolished when on Madopar HBS.

5 of the 11 patients participating in the trial stopped Madopar HBS after a mean duration of 65 days. Three patients did not finish their adjustment phase (early drop-outs after 5,6 and 18 days, respectively) due to prolonged off-periods. Inspite of high total daily doses of Madopar HBS up to the twofold of prior conventional L-dopa therapy no sufficient clinical effect could be achieved. 2 of the 8 responders stopped Madopar HBS after 93 and 204 days, respectively, due to the unpredictability of onset and duration of response to Madopar HBS and to increases peak-dose chorea paralleling the prolonged "on" periods (see Table 4).

Table 4 Madopar HBS in advanced P.D./ reasons for treatment failures

(N = 5)

Duration of HBS	65(5-204)days
Reasons for stopping HBS	
- prolonged off-periods	3 pts.
- unpredictable response	2 pts.
- increased peak dose AIM´s	2 pts.

One of these patients also reported outbursts of disabling peak-dose choreic movements. In both patients peak-dose choreic movements led to functionally useless "on" periods and therefore to discontinuation of Madopar HBS. In 6 of the 8 responder patients there was no or only slight increase of peak-dose dyskinesias.

DISCUSSION

The sustained-release principle of Madopar HBS may lead to a reduction of dose-dependent fluctuations in motor performance, increase in nocturnal mobility and decrease in biphasic as well as off-period dystonia The observed increase in the total daily dose of L-dopa with Madopar HBS treatment corresponds to the decreased bioavailability of Madopar HBS which has been shown to be about 60 per cent of conventional L-dopa (Crevoisier et al, 1985). It is not always possible to overcome this problem by increasing the dose of sustained-release L-dopa: in 3 non-responders no clinical benefit could be achieved despite of an increase of 100 per cent over the previous standard L-dopa dose. Increased peak-dose chorea as observed in several patients of this study, particulary in the afternoon, may represent an "overlap effect" (Eckstein et al, 1973). It can be a reason for treatment failure by rendering "on" periods functionally useless as seen in 2 of the 8 responders of this series. The main disadvantage of sustained-release L-dopa in this study was the unpredictability of onset and duration of clinical effects. The controlled-release principle of Madopar HBS is based on a continuous release of L-dopa while the capsule remains floating in the stomach for prolonged periods of time (Poewe et al, 1986).
As the absorption site for L-dopa is the proximal small intestine the sustained-release principle of Madopar HBS can be influenced by erratic gastric activity (Nutt,1987). Individual differences in gastric activity may be responsible for the fact that not all patients complain about this problem. For a reliable and rapid "switch on" in the morning all patients needed conventional L-dopa in addition to their first dose of Madopar HBS. 4 of the responders took further so-called "back-up" doses of conventional L-dopa when needed, especially in the afternoon. Despite of the various shortcomings the results of this study show that Madopar HBS can be a useful alternative in the treatment of Parkinson patients with the L-dopa long-term syndrome.

REFERENCES

Chouza,C., Romero,S., De Medina.O. et al.(1985): Results of the substitution of Madopar Standard by Madopar HBS in parkinsonians with fluctuations in the therapeutic effect. Int.Workshop on the On-Off-Phenomenon in Parkinson´s Disease. Nov.14-16

Crevoisier,C.,Hoevels,B., DaPrada,M.(1985): Bioavailability of Madopar H8S in healthy volunteers. Int. Workshop on the On-Off-Phenomenon in Parkinson's Disease. Nov.14-16

Eckstein,B., Shaw,K., Stern,G.(1973): Sustained-release levodopa in parkinsonism. Lancet 1. 431-432

Marsden,C.D., Parkes,J.D.(1976): "On-off" effects in patients with Parkinson's disease on chronic levodopa therapy. Lancet 1,292-296

Marsden,C.D., Parkes,J.D., Quinn,N. (1982): Fluctuations of disability in Parkinson's disease: clinical aspects. In Movement Disorders, eds.C.D.Marsden. S.Fahns, pp.96-122 London:Butterworth Scientific

Nutt.J.G.(1987): Pharmacokinetics of Levodopa. In Handbook of Parkinson's Disease. Marcel Dekker Inc., ed.W.C.Koller,pp.339-354 New York-Basel

Poewe,W.H., Lees,A.J., Stern,G.M.(1986): Treatment of Motor fluctuations in Parkinson's disease with an oral sustained-release preparation of L-dopa:clinical and pharmacokinetic observations. Clin.Neuropharmacol. 9, 430-439

Quinn,N., Parkes,J.D., Marsden,C.D.(1984): Control of on/off phenomenon by continuous intravenous infusion of levodopa. Neurology 34,1131-36

Rinne,U.K.(1985): Madopar H8S in the long-term treatment of parkinsonian patients presenting fluctuations in disability. Int.Workshop on the On-Off-Phenomenon in Parkinson's Disease, Nov.14-16

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