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Amantadine infusion in treatment of motor fluctuations and dyskinesias in Parkinson's disease

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Summary. Efficiency and safety of amantadine sulfate (AMS) infusions were investigated in late stage complications of Parkinson's disease (PD). In an open-label study, 21 PD patients suffering from motor fluctuations and/or dyskinesias were administered AMS infusions (PK-Merz®, 400 mg per day) during seven days. Oral AMS treatment followed. Significant improvement of UPDRS motor scores was observed between day 0 and day 7, remaining improved until day 21. Based on patients' diary notes, both severity and occurrence of hypokinetic "off" state significantly decreased (from 6.6 to 3.1 hours, $p < 0.001$, average "off" time per day) as well as dopaminergic-induced dyskinesias (from 2.5 to 1.3 hours, $p < 0.05$, average duration of dyskinesias per day). AMS infusions followed by oral administration appeared as a safe method for improvement of both motor fluctuations and dyskinesias in advanced PD. In advantage to simple oral therapy, AMS infusions allowed fast introduction of a profound and durable treatment effect.

Keywords: Parkinson's disease, amantadine, dopaminergic-induced dyskinesias, response fluctuations.

Introduction

After several years of duration of Parkinson's disease (PD), most patients manifest complications of the therapeutic response to dopaminergic treatment (Fahn, 1982). Motor fluctuations correspond to shortening of the effect of individual doses of levodopa associated with occurrence of hypokinesia before onset of the effect of the next dose or even unpredictably at any time (wearing-off, sudden-off, on-off). These signs are attributed to altered pharmacokinetics of levodopa, however, alterations in the functional state of the striatum dopaminergic receptors contribute thereto as well (Bravi et al.,

1994). Dyskinesias (involuntary movements of choreatic, dystonic or mixed character) appear either in the period of good motor effect of levodopa (peak-of-dose dyskinesia), or during transitional phases (beginning- and/or end-of-dose dyskinesia), or during the period of minimum motor effect of levodopa (off-dystonia). Dyskinesias are ascribed to altered pharmacodynamics following a long-term intermittent stimulation of dopamine receptors (Chase et al., 1993). In late stages of PD the patient often manifests with several kinds of the described complications, producing serious disability. The control of these complications is the most difficult task in the treatment of advanced PD.

Aim of this study was to verify the therapeutic effect of amantadine in late complications of PD. The favorable effect of this drug in PD was discovered by coincidence when PD patients unexpectedly exhibited improved mobility after taking amantadine as an influenza-prophylactic drug (Schwab et al., 1969). It was subsequently proved that amantadine has anticholinergic effects and that it also increases the dopamine concentration in the synapses — probably as result of improved release from the pre-synaptic vesicles (Danysz et al., 1997). Furthermore, amantadine was shown to be able to influence the signs of both PD and other parkinsonian syndromes by means of extra-striatal effect on the basal ganglia as an antagonist of glutamate NMDA receptors (Kornhuber et al., 1991; Stoof et al., 1992). Symptomatic effects of amantadine are widely used in treatment of early-stage PD in which the drug can at least temporarily alleviate the cardinal motor symptoms (Danielczyk, 1995). There is far less experience with administration of amantadine in late complicated stages of PD although as early as in 1971, Danielczyk suggested the use of amantadine in advanced PD (Danielczyk and Korten, 1971). So far, a few sporadic case-reports brought data on favorable effect of amantadine on motor fluctuations (Shannon et al., 1987) or dyskinesia (Adler et al., 1997). A recent double blind placebo-controlled study confirmed that oral amantadine can markedly improve motor response complications in PD (Verhagen Metman et al., 1998). These effects have incited a renewed clinical and research interest in amantadine (Greenamyre and O'Brien, 1991; Greulich and Fenger, 1995; Goetz, 1998). Therapeutic options have been significantly broadened by introduction of the infusion form of amantadine-sulphate. Amantadine-sulphate (AMS) becomes one of few available preparations for parenteral administration that can be used in acute hypodopaminergic states (akinetic crisis in PD, post-operative states, etc.) (Danielczyk, 1973; Müller et al., 1995).

In this open-label study, we aimed to test the therapeutic effectiveness of infusion treatment with AMS in late motor complications of PD. We also tested safety and tolerance of treatment with AMS, and we wanted to find out whether administration of AMS allows decreasing of dosage of other medication, especially that of levodopa.

Materials and methods

Patients

21 patients meeting the diagnostic criteria of PD (Ward and Gibb, 1990) were included after giving informed consent. The group consisted of 6 women, 15 men, with average age

59.1 years (SD 6.5), duration of the disease 9.6 years (SD 5.5) and duration of treatment with levodopa 7.1 years (SD 5.2). All the patients suffered from motor fluctuations, thirteen of them also presented with dopaminergic treatment induced dyskinesias. Patients with signs of delirium, confusion or dementia (the limit score of Mini-Mental-Status test MMS = 28) as well as the patients with narrow-angle glaucoma, adenoma of prostate, impairment of renal functions and cardiac insufficiency were not included in this study. All the patients were treated with combination of antiparkinsonian drugs, all of them were taking levodopa in average daily dose 830 mg (SD 460), some of them were taking also the dopamine agonists, anticholinergic drugs and selegiline. This treatment was administered in regular dosage at least one month before start of the study treatment.

Procedure

Upon the inclusion to the study the patients underwent basic neurological examination, simple psychometry (MMS) and a complete examination according to the Unified Parkinson's Disease Rating Scale (UPDRS). The patients performed the mobility state self-assessment every hour during day waking time and, by means of the symbols, noted three possible states in their Diaries: good mobility ("on"); rigidity and poor mobility ("off"); or involuntary movements (dyskinesia). The patients kept the Diary at least two days before admission to hospital (D-2, D-1). On the day of admission to hospital (D0) the patients were examined in the "on" state after the first or second daily treatment dose according to both motor part of the UPDRS (UPDRS III) and the dyskinesia scale (a modification of the Abnormal Involuntary Movement Scale — AIMS, rating involuntary movements on a five-graded scale from 0 = no dyskinesia to 4 = extremely disabling dyskinesia in face, neck, trunk and four extremities, with maximum score of 28). On the following day (D1) in the morning, the levodopa test was carried out after 12-hour discontinuation of all antiparkinsonian medication. At the beginning of the test both the UPDRS III and AIMS examinations were performed, and at about 9 AM 250 mg levodopa/benserazide (Madopar®) or 275 mg levodopa/carbidopa (Nakom®) was administered. The choice of preparation was based on the regular therapy by either Madopar® or Nakom® in each patient. Then, the examination was repeated every 15 minutes according to the above-mentioned scales until the end of the dose effect. After the levodopa test, the infusion therapy was launched by intravenous administration of 200 mg of AMS (one bottle of 500 ml) with careful observation of possible side effects of the treatment. If there were no adverse events relating to the first infusion, the infusion therapy continued by administration of 400 mg AMS (two bottles) daily from the day D2 to D7. The infusions were administered with a rate of 55 drops per minute, i.e. one bottle in 2.5 hours starting at about 9:30 AM and at 4:00 PM. During the hospital stay, from the day D2 to D4, the motor state was assessed similarly to D0 according to UPDRS III and AIMS in the "on" time daily at about 9 AM. On the days D5 and D6 the patients kept the Diary. On the day D7 the last AMS infusions were administered and clinical global impression (CGI) of the effect of the PK-Merz infusion therapy was assessed. UPDRS and AIMS were examined similarly to D0. On the day D8, the levodopa test was performed under exactly the same conditions as on D1. Furthermore, from the day D8 the treatment was converted to oral therapy with PK-Merz 1 or 2 tablets 3 times daily (100 mg in each tablet), according to the patient's state and tolerance, combined with levodopa and other antiparkinsonian drugs. Adjustment of levodopa dose could be performed. On the day D9, UPDRS and AIMS were performed. From the day D10 the patients were conducted on the outpatient basis with stable medication including AMS tablets. On the days D19 and D20 the patients performed self-assessment in their Diaries. On the day D21 a final check-up, including complete UPDRS, AIMS and CGI, was performed under exactly the same conditions as previous assessments. Furthermore, blood count and biochemical screening were performed on D1 and D8.

The following indexes were assessed: The motor state (UPDRS part III, D0 compared with D7 and D21), presence and severity of dyskinesia (UPDRS part IV, items 32–

35, and AIMS, D0 compared to D7 and D21). The daily duration of both the "off" and dyskinetic states (in hours) were calculated based on the Diary notes, D-2, D-1 compared to D5,6 and D19,20. Furthermore, the latency, intensity and duration of the levodopa dose effect were analyzed on D8 comparing to D1: In the levodopa test, the decrease of the motor score by at least 20% was considered as onset of the effect. The minimal UPDRS III score was recorded as the "best on" and mean dyskinesia score was calculated as a sum of AIMS scores divided by the number of observations during the test. The daily dose of levodopa on D0 was compared to that on D21. Finally, individual tolerance, safety and occurrence of complications during the AMS treatment were assessed.

Statistics

As normal distribution of measured values was rejected by means of calculating skewness and kurtosis, we used non-parametric tests for data analysis. Friedman test served for comparisons of multiple repeated measures of UPDRS and AIMS and of daily time spent in "on", "off", and dyskinesia. Wilcoxon signed ranks tests were used for post-hoc analyses and to compare paired values (UPDRS II and IV obtained on D0 and D21, levodopa test parameters from D1 and D8).

Results

The patients' motor state improved significantly during the infusion therapy (Fig. 1): UPDRS III score, mean ± SD = 25.7 ± 17.1 on D0 compared to 15.3 ± 13.4 on D7 (i.e. the decrease by 40%). The motor state remained improved also during the subsequent oral medication until D21 (UPDRS III, 15.6 ±

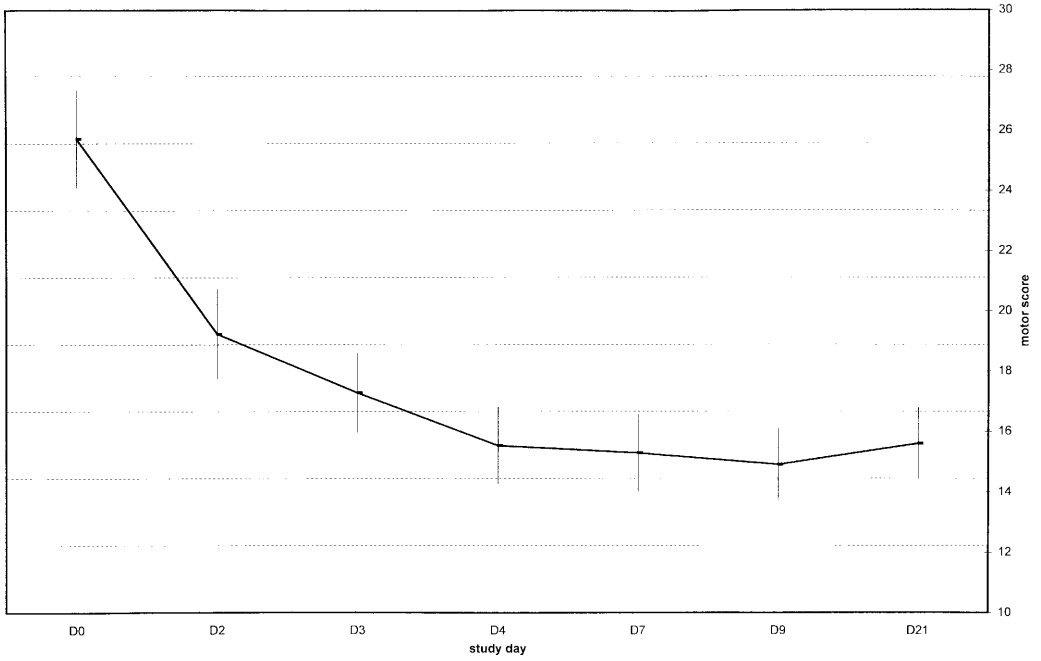

Fig. 1. UPDRS III motor scores in 21 PD patients during the treatment with amantadine-sulphate (mean values ± SEM)

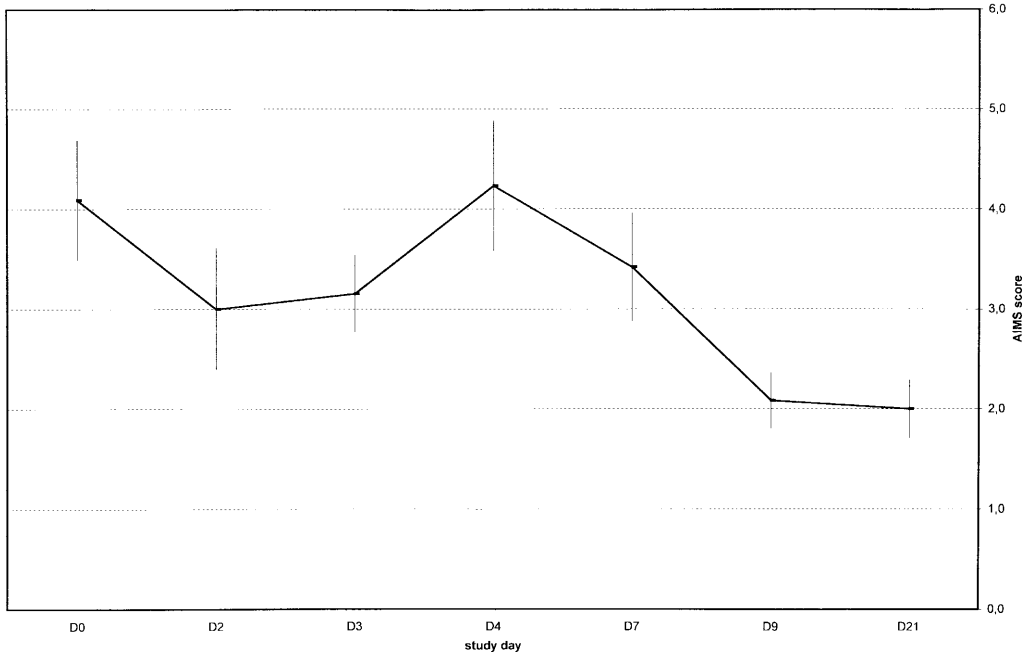

Fig. 2. Dyskinesia scores in 13 PD patients during the treatment with amantadine-sulphate (mean values ± SEM)

12.5). This result was statistically significant, Friedman $X^2 = 45.7$, $p = 0.0001$; D21 compared to D0, Wilcoxon $Z = -3.625$, $p < 0.001$ (with Bonferroni's correction for multiple comparisons).

The occurrence and severity of dyskinesia, according to the appropriate UPDRS IV subscore, did significantly decrease between D0 and D21 (3.19 ± 2.73 compared to 1.90 ± 1.94, $Z = -2.708$, $p < 0.01$). According to AIMS scores (Fig. 2), there was no significant change in dyskinesia severity by the end of infusion therapy, however a trend to alleviation of dyskinesias was shown on D9 and D21 compared to D0 (mean ranks 3.3, 2.85, and 4.9, $X^2 = 8.69$, $p = 0.19$).

According to the Diary records (Fig. 3), average duration of the "off" state decreased from mean 6.6 ± 3.1 hours on D-2, D-1 (before the infusion therapy was started) to 4.1 ± 2.8 hours on D5,6 (during the infusion therapy) which represents a 38%-improvement. On D19,20 (i.e. 12 days after the infusion therapy was terminated) the mean duration of the "off" state further decreased to 3.1 ± 3.1 hours per day which represents a 53%-improvement compared to D-2, D-1. This result was statistically significant, $X^2 = 13.46$, $p < 0.001$; D19,20 compared to D-2, D-1, $Z = -3.50$, $p < 0.001$ (Bonf. correction). The average occurrence of dyskinesia decreased from mean 2.5 ± 2.5 hours on D-2, D-1 to 1.7 ± 2.2 hours on D5,6, and to 1.3 ± 2.2 hours on D19,20, representing a 48%-improvement compared to D-2, D-1. The change was statistically significant, $X^2 = 9.48$, $p < 0.01$; D19,20 compared to D-2, D-1, $Z = -2.35$, $p < 0.05$ (Bonf. correction).

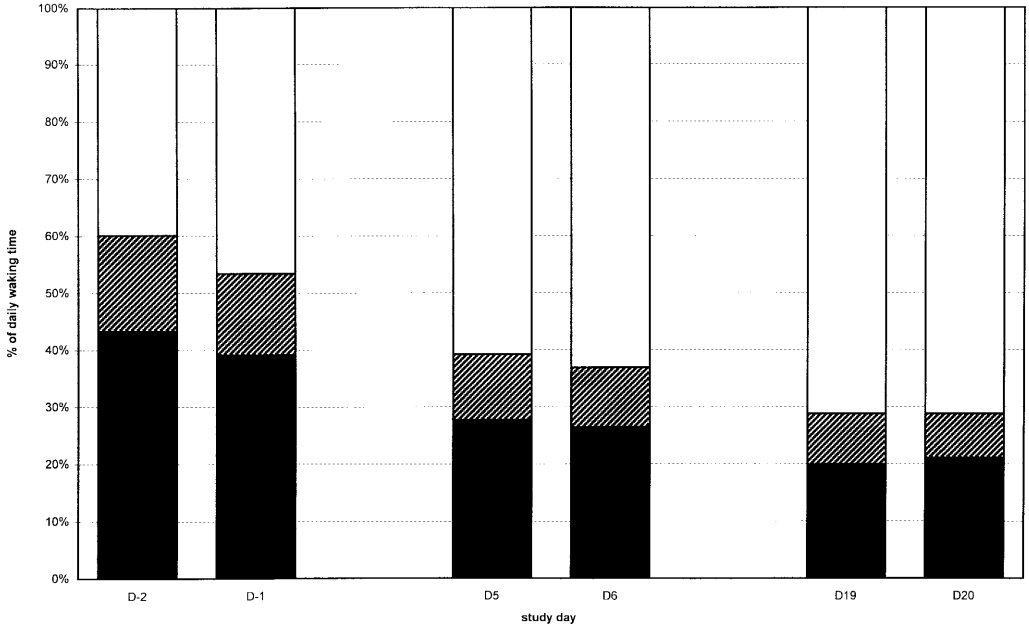

Fig. 3. Average duration of daily "off" state and dyskinesias according to the self-evaluation Diaries — proportion of daily waking time. Black bars: "off" state; striped bars: dyskinesias; empty bars: "on" without dyskinesia. D-2, D-1: before the infusion therapy with amantadine-sulphate was started. D5, 6: during the infusion therapy. D19, 20: before the end of the study, on oral treatment

During the levodopa tests, mean dyskinesia score and both the "off" and "best on" motor scores significantly decreased between D1 and D8 (Table 1). Neither latency of onset nor duration of the effect of the levodopa dose changed on D8 compared to D1.

The average daily dose of levodopa decreased at the end of the study (772 ± 436 mg) compared to the initial dose (830 ± 460 mg, $p < 0.05$). On CGI assessment, a marked improvement was mostly noted by both the patient and physician at the end of the study and the administration of the tablet form of

Table 1. Levodopa test in 21 PD patients before (D1) and after (D8) infusion therapy with amantadine-sulphate, mean values (SD)

Measure	D1	D8
UPDRS III "off"	39.1 (19.4)	30.5 (17.4)***
UPDRS III "on"	14.4 (11.7)	10.9 (9.4)**
latency of effect (min)	44.5 (26.8)	49.3 (30.0)
duration of effect (min)	148.0 (58.1)	156.0 (60.4)
average AIMS score (n = 12)	2.1 (2.4)	1.4 (1.7)*

Wilcoxon Signed Ranks Test, comparison between D1 and D8: *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

AMS was decided to continue in 19 patients (mean daily dose, 350 ± 100 mg, range 300–600 mg).

Out of 21 patients who were involved in the study, one patient had to discontinue the infusion therapy due to decrease of the blood pressure and tachycardia in the D6. The state of another patient deteriorated by D21. The daily duration of the "off" state was significantly reduced (from 7 hours to about 15 minutes), however, after transitional alleviation of the dyskinesia during the infusion therapy, invalidating involuntary movements got accentuated in the third week of the study. The compliance of the patient was not high enough to adequately decrease the levodopa doses. Therefore, the therapy with AMS was terminated in this patient on D21. Another patient, a 65-year-old man with previous history of dopaminergic induced hallucinations, reported vivid colorful dreams on D2 in the morning (after the first AMS infusion given on D1). In this case, it was decided to continue the treatment with 200 mg AMS (one bottle) daily. Vivid dreams persisted only during the infusion series and disappeared thereafter. No side effects occurred in the other patients.

Discussion

The cure with AMS in our patients was associated with pronounced alleviation of the parkinsonian symptomatology that was expressed by average decline of the motor UPDRS score by 40%. The improvement was apparent during the first few days of the one-week-lasting infusion therapy, and the improved mobility state persisted during the continued treatment with the oral form of the drug. The patients' Diary records are the most convincing evidence of the functional effect of the therapy, which pointed out that the daily period of the "off" state was reduced to less than half. Remarkably, the initial effect of the infusion therapy was intensified during the subsequent period so that levodopa daily dosage could be slightly reduced in some patients. Furthermore, the cure favorably influenced both the intensity and occurrence of the dyskinesias: there was a noticeable trend towards the decrease of the dyskinesia scores and the daily duration of dyskinesias was significantly shortened.

The results of levodopa tests are remarkable from the aspect of the assumed pharmacological mechanisms of amantadine. In comparison with the tests performed at the beginning of the study, there was a marked decrease of the motor UPDRS scores after the infusion cure — not only in the maximum values that correspond to the "off" state but also in the minimum "on" scores. The decrease of the "on" scores jointly with unaltered latency and duration of the effect of a dose of levodopa suggest that the effects of AMS might be mediated on a level different from the dopaminergic nigro-striatal synapses.

Besides its non-specific dopaminergic effect, amantadine can exhibit slight anticholinergic and more important antiglutamatergic potencies (Kornhuber et al., 1991; Schmidt et al., 1992; Danysz et al., 1997), suggesting that the observed effects of AMS may be connected with the glutamatergic mechanisms. This theoretical assumption can be supported by the results of several

previous studies. Dyskinesia after administration of levodopa in monkeys with artificially induced PD equivalent (the toxic MPTP model) was efficiently inhibited by administration of a selective inhibitor of the NMDA receptors (LY235959) without negative impact on favorable effect of dopaminergic therapy on other signs (Papa and Chase, 1996). Another NMDA antagonist, remacemide, significantly potentiated favorable effect of the dopaminergic therapy on hypokinetic signs in the rat model of PD, without inducing the motor hyperactivity corresponding to the dyskinesia (Greenamyre et al., 1994).

A plausible explanation is based on the functional model of the basal ganglia system (Albin et al., 1989). Despite the model extremely simplifies the function of basal ganglia, it may be used as a background for explanation of pathophysiological and pharmacological mechanisms of extrapyramidal disorders (Hallett, 1993). If a patient with hypokinetic signs of PD and intermittent dopaminergic-induced dyskinesias is administered an inhibitor of glutamatergic NMDA receptors, an effect on several different levels may be expected. The inhibition of glutamatergic transmission between the subthalamic nucleus and the internal pallidum inhibits the indirect striato-pallidal tract, the hyperactivity of which leads to hypokinesia and rigidity. This may result in alleviation of the main signs of PD — to certain extent independently from current level of dopamine in the striatum. The blockade of NMDA receptors in the cortex and striatum may suppress abnormal thalamo-cortical and cortico-striatal hyperactivity underlying dopaminergic induced dyskinesias, thus suppressing the involuntary movements. In our study, the dynamics of the course of the patients' state suggests that the initial loading infusion dose of AMS might influence especially the subthalamo-pallidal glutamatergic transmission, thus exhibiting significant antihypokinetic effect. There was a certain delay in suppression of involuntary movements observed in some patients — as late as not before transition to oral therapy. This may reflect different pharmacodynamic properties of NMDA receptors in the thalamo-cortical and cortico-striatal systems. However, the alleviation of dyskinesias might be also related to the fact that the protocol allowed adjusting levodopa doses as an indirect result of AMS treatment.

In this short term study we did not observe previously described adverse effects of amantadine, such as livedo reticularis, edema of lower extremities, disorders of micturition due to enlargement of the prostate, etc. (Bailey and Stone, 1975). Both cardiac arrhythmias and orthostatic dysregulation of the blood pressure rank among occasional side effects of amantadine. Indeed, in one patient we had to discontinue the infusion administration of AMS due to fluctuation of the blood pressure and tachycardia which subsided after discontinuation of the therapy. Clinical experience also show increased risk of psychotic disorders in conjunction with administration of amantadine, especially after higher dosage and combined administration with other antiparkinsonian drugs. We encountered vivid dreaming in one patient with previous history of dopaminergic induced hallucinations. The patient was yet able to complete the infusion series with a lower dose of AMS. We ascribe the fact that we did not observe more severe psychotic complications in our group

to relatively strict inclusion criteria of the study (individuals with cognitive loss were excluded as well as those over the age of 65 years — except for one such a patient). Due to safety reasons, we keep on observing these criteria at routine indications of the AMS infusion cure in late-stage PD.

In conclusion, the study proved that the infusion series of AMS has favorable effect in patients with late complications of PD. In advantage to simple oral add-on therapy, the effects of AMS infusions promptly appeared since the initial days of treatment and moreover, it promoted further amelioration beyond the end of infusion series. The improvement of the patients' mobility state was due to alleviation of the main PD signs and to decreased occurrence and severity of the hypokinetic "off" states and dopaminergic-induced dyskinesias. This was of indubitable and significant functional effect for the patients. The persistence of antiparkinsonian and antidyskinetic effects suggests that in the late-stage PD the infusion cure with AMS may induce convalescence and long-term stabilization of the imbalance in the basal ganglia neurotransmission.

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