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PAPER

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Background: Dyskinesias are a transient but severe complication of subthalamotomy in some patients.
Patients and methods: Three patients with Parkinson's disease undergoing bilateral micro-recording guided surgery of the subthalamic nucleus (STN) are described; deep brain stimulation (DBS) was used in one case, and subthalamotomy in the other two. Prior to surgery, levodopa induced dyskinesia had improved ($\leqslant$50%) under treatment with amantadine (400 mg/day, po) in all three patients. The patient treated with DBS developed severe dyskinesia a few days after discharge and began self medication with amantadine but showed no improvement. This suggested a possible lack of response to amantadine for treatment of dyskinesias induced by surgery of the STN.
Results: Both patients treated with bilateral subthalamotomy developed unilateral choreoballistic movements immediately after surgery, despite not taking levodopa (L-dopa). Patients were scored using the dyskinesia scale and started treatment with 400 mg amantadine (po) for 4 days within the first postoperative week with no effect on dyskinesia score or its phenomenology. Amantadine was therefore discontinued. One month after surgery both patients were free of involuntary movements with an improvement of about 60% in the ''off'' state UPDRS motor score. Six month follow up showed maintained antiparkinsonian benefit, without need for levodopa treatment and complete absence of dyskinesia.
Conclusion: The present findings suggest that: (i) amantadine probably exerts its anti-dyskinetic effect by acting on the ''indirect'' pathway; (ii) the pathophysiological mechanisms of subthalamotomy induced dyskinesias may differ from those involved in L-dopa induced dyskinesias; (iii) dyskinesias induced by STN surgery resolve spontaneously as compensatory mechanisms develop.

We observed that amantadine was unable to relieve dyskinesias induced by deep brain stimulation (DBS) of the subthalamic nucleus (STN) in a patient with Parkinson's disease (PD) whose levodopa induced dyskinesias (LIDs) had been well controlled by this drug prior to surgery. This is an interesting observation for two reasons. Firstly, the mechanism of action of amantadine on LID is not well understood.[1] Secondly, experimental observations in monkeys suggest that LIDs and dyskinesias induced by blockade of the STN and of its connections share a common pathophysiological mechanism.[2] Subthalamotomy is a surgical treatment option when special circumstances make DBS therapy inapplicable,[3] however it may be associated with hemichorea-ballism.[4] We therefore decided to prospectively test the effect of amantadine on LIDs in a series of patients enrolled in a subthalamotomy protocol, and to repeat the study in those patients developing hemichorea-ballism after surgery.

METHODS

Patients were evaluated using the CAPSIT protocol and subjected to serial levodopa (L-dopa) tests for 6 months prior to surgery.[5] The motor section of the UPDRS and timed arm tests (time to tap the index finger between two points 30 cm apart for 20 successive cycles) were performed. Dyskinesias were evaluated by means of the CAPSIT rating scale in the ''on'' state. The surgical procedure was performed under local anaesthesia and lesion guided by the micro-recording technique.

Two patients presented with postoperative choreoballistic movement disorders; one had undergone bilateral subthalamotomy and the other had received a combination of unilateral STN-DBS and contralateral subthalamotomy. Having obtained their consent, the patients were prospectively challenged to a 4 day trial with 400 mg amantadine (100 mg twice daily po).

A case report of the original observation of DBS induced involuntary movements unresponsive to amantadine is presented, as well as the observations on both patients prospectively evaluated.

Case 1 (original observation)

The patient was 73 year old male with PD who underwent bilateral STN-DBS because of severe levodopa related motor complications. He had suffered severe LIDs which had previously responded to amantadine treatment. One month after surgery he returned for the first postoperative evaluation. At that time, the patient had achieved a reduction in L-dopa dose from 2000 to 500 mg/day, with a marked improvement in limb rigidity and limb bradykinesia, and complete disappearance of resting tremor. Speech, postural instability, and gait initiation were only minimally improved under the initial setting (right: 3.9 V, 90 μs, 135 Hz monopolar 0−00; and left: 3.6 V, 90 μs, monopolar 00−0), so a different setting was programmed (right: 4.3 V, 120 μs, 185 Hz, bipolar +0−0; and left: 3.6 V, 120 μs, 185 Hz bipolar +0−0). After 1 h at the outpatient clinic under the new parameters, the patient reported a subjective release sensation of gait freezing, and mild chorea was observed in the right foot. Over the next few days, dyskinesias in the right foot became progressively more severe and spread to involve the entire limb. The patient suppressed L-dopa entirely without any modification in involuntary movements. The dyskinesias became so severe 1 day later that the patient

Abbreviations: DBS, deep brain stimulation; LID, levodopa induced dyskinesia; L-dopa, levodopa; PD, Parkinson's disease; STN, subthalamic nucleus

self-prescribed 400 mg/day of amantadine. In contrast to the situation prior to surgery, after 48 h on amantadine he did not observe any modification in involuntary movements. When examined again in the outpatient clinic, parkinsonian motor features had worsened due to complete L-dopa withdrawal, and severe choreoballistic involuntary movements were observed in the right lower limb. Stimulation settings were returned to previous values and involuntary movements disappeared completely within 10 min. The patient was subsequently retreated with L-dopa (375 mg/day) attaining adequate control of parkinsonism without dyskinesia.

Case 2

The patient, a 66 year old woman with a 20 year history of severe disabling PD, met all clinical criteria required by CAPSIT for candidates for stereotactic surgery. She received 825 mg L-dopa and 18 mg ropinirole daily. UPDRS motor score during the "off" medication state was 65 points and corresponded to stage IV on the Hoehn and Yahr scale. Treatment with oral amantadine 400 mg/day generated a marked anti-dyskinesia effect but after 5 weeks the drug had to be withdrawn because of severe ankle oedema.

The patient underwent micro-recording guided bilateral stereotactic subthalamotomy. Some 5–10 min after the third lesion of the left STN (second surgery) was performed, the patient developed progressively increasing ballistic movements involving the right side of the body, including both limbs and face. The movement peaked in severity and became very intense 6 h after the procedure, gradually stabilising after 24 h. Treatment with levodopa was not resumed after surgery. Ballistic dyskinesias were observed on the right side of the body 48 h after surgery, and scored as severe in both upper and lower limb muscles, and mild and choreic in the trunk and face. Patient global judgement was that involuntary movements were severe, producing patient distress and moderate disability. A 4 day trial of 400 mg/day of oral amantadine produced no changes in dyskinesia intensity. The patient's general physical condition remained good, despite the movements, and there was a marked reduction in the severity of signs of PD. It was therefore decided to continue patient follow up without adding any further treatment. One month after surgery, the patient was free of spontaneous involuntary movements on 200 mg/day piribedil as her only treatment (fig 1A). Improvement in motor symptoms persisted 6 months later, without recurrence of dyskinesias.

Case 3

A 39 year old male suffering from PD since the age of 32, and having met all clinical criteria required by CAPSIT for candidates was treated with stereotactic surgery for PD. Daily dose of L-dopa was 850 mg. Motor UPDRS score in the "off" state was 66 and the Hoehn and Yahr scale was graded as IV. He achieved 1 month relief from drug induced involuntary movement (a 50% reduction in the dyskinesias scale) with 400 mg of amantadine daily. The patient underwent micro-recording guided unilateral stereotactic subthalamotomy on the left side, and an electrode for STN-DBS was implanted on the right side. Involuntary movements on the right side were not observed in the operating room but were noticed when the patient was moved to his room. Initially, they were choreic in nature, of mild intensity, and restricted to the upper and lower limbs, sparing the face, neck, and trunk. The morning after surgery the patient remained without L-dopa. The dyskinesias increased and became ballistic in the upper limb. They were rated as moderate in severity and as inducing tolerable discomfort. Full day evaluation with the patient hospitalised revealed no changes in the nature or intensity of the movements. A daily dose of 400 mg of amantadine started 24 h later and maintained for 4 days had no effect on the severity or characteristics of the dyskinesias. The patient remained well controlled in terms of his PD without L-dopa after 1 month of follow up (fig 1B). At that time, the dyskinesias had almost disappeared. Subsequently, adequate control of the parkinsonism was achieved and no resurgence of dyskinesias under treatment with ropinirole 6 mg/day was observed.

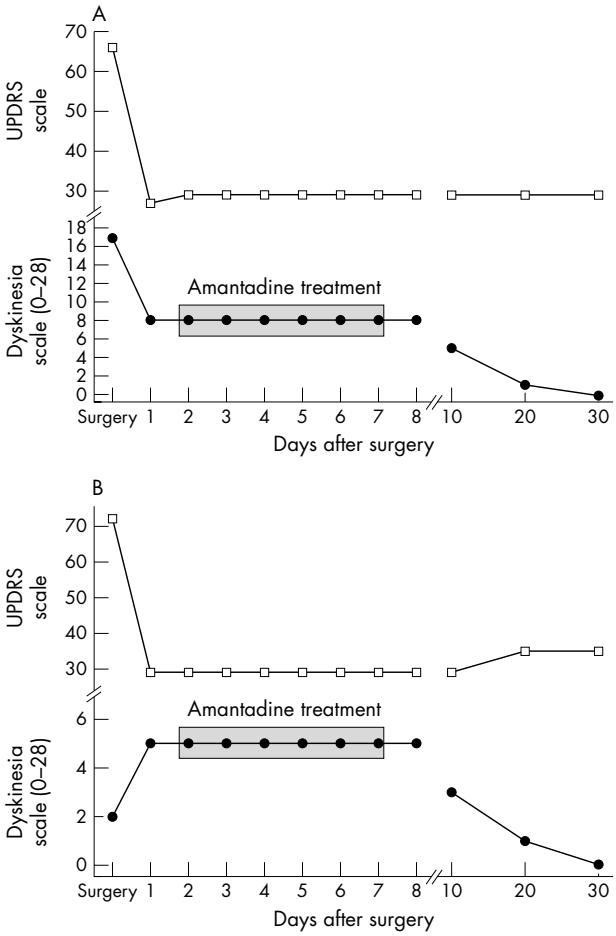

Figure 1 (A) Patient 2. Temporal evolution of the UPDRS motor and dyskinesias scores induced by subthalamotomy, and lack of effect of treatment with amantadine. For day 1, scores correspond to the morning before surgery in the "off" state, and at the end of surgery in the operating room. Subsequently, motor and dyskinesias scores were recorded once a day. Shaded rectangle corresponds to period of treatment with amantadine. (B) Patient 3. Temporal evolution of the UPDRS motor and dyskinesias scores induced by subthalamotomy and lack of effect of treatment with amantadine. For day 1, scores correspond to the morning before surgery in the "off" state, and at the end of surgery in the operating room. Subsequently, motor and dyskinesias scores were recorded once a day. Shaded rectangle corresponds to period of treatment with amantadine.

DISCUSSION

Amantadine proved very efficacious against LIDs in these three patients before surgery, in keeping with previous reports,[6 7] but completely failed to improve the hemichorea-ballism induced by STN surgery. This preliminary report therefore suggests that in PD: (a) interruption of the "indirect basal ganglia" circuit blocks the antidyskinetic effect of amantadine; (b) hemichorea-ballism following subthalamic blockade/lesion and LIDs do not share the same pathophysiological mechanisms; and (c) subthalamotomy induced dyskinesias tend to resolve spontaneously.

Amantadine is known to act as a non-competitive NMDA antagonist[8] and oral administration of the usual therapeutic doses achieves brain levels that block NMDA receptors.[9] Preclinical studies suggest that development of L-dopa related motor complications is associated with enhanced phosphorylation of NMDA receptors on striatal medium spiny neurons.[1–10] Protein phosphorylation serves as a major regulatory mechanism for NMDA receptors, and an increased state of phosphorylation of NMDA receptors is linked to enhanced synaptic efficacy.[11] As a result, cortico-striatal glutamatergic input is amplified, leading to altered striatal gabaergic output, which in turn could cause expression of motor complications.[11] It has been hypothesised that amantadine exerts its anti-dyskinetic effect by normalising striatal NMDA receptor mediated hyperfunction at the striatal level.[12] NMDA receptors in the striatum are largely expressed in medium spiny neurons containing D-1 receptors,[13] therefore modulating basal ganglia output activity in the ''direct'' circuit.[14] However, the profound anti-dyskinesia effect previously present in the patients described here, was lost after blockade/lesion of the STN, suggesting amantadine effects are strictly dependent on the integrity of the ''indirect circuit''.

Recently, in the rat 6-hydroxydopamine model, amantadine was found to increase STN firing, unlike the NMDA-receptor antagonist MK 801, which significantly reduced STN neuronal activity.[1] These findings suggest that amantadine may reduce LIDs by shifting the mean firing rate of the STN to higher levels, and help explain why its anti-dyskinetic effect is lost after lesion of the STN. Altogether, our clinical observations and the experimental data indicate that amantadine probably acts against LIDs mainly through modulation of abnormal neuronal activity in the ''indirect'' circuit. In parkinsonian monkeys, subthalamotomy improved motor function and induced dyskinesias quite similar to those observed in our patients.[3] These dyskinesias were not modified by administration of levodopa, which prior to the lesion had induced typical LIDs in MPTP monkeys, nor by anti-dopaminergic drugs such as reserpine, the D-2 antagonist sulpiride, or the D-1 antagonist SCH 31390.[3] A similar experience has been reported in previously normal people who developed hemiballism after stroke and also in PD patients.[15] It seems likely, therefore, that both the pharmacological sensitivity and the pathophysiology of hemichorea-ballism observed following lesions of the STN are different from those mediating LIDs in PD. This is consistent with the lack of anti-dyskinetic effect of amantadine seen in these patients, as well as the difficulty in managing postsurgical hemichorea-ballism in PD using the normally recommended pharmacological agents (that is, dopamine receptor blockers).[16]

The general experience, albeit limited, regarding the course of hemichorea-ballism observed following subthalamotomy, is in accordance with the findings described here. By and large, the dyskinesia undergoes self resolution,[16] but can occasionally be severe enough to require active therapy.[4–16] In such instances, amantadine is not likely to be useful.

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