Botulinum Toxin Treatment of Lateral Axial Dystonia in Parkinsonism

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Abstract: Lateral axial dystonia (LAD) has been described in patients with Parkinson’s disease (PD), but treatment might be more controversial than treatment of LAD in other neurological conditions. Our study was designed as a blinded cross-over with botulinum toxin (BTX) and placebo in order to investigate the efficacy of BTX in PD LAD. Nine patients with LAD who failed to experience benefit from oral medications were randomly assigned to 2 groups, 4 patients received BTX and 5 placebo as a first treatment, and were switched-over to BTX or placebo in the following treatment session, performed 3 months after the first session. Each patient was evaluated at baseline, 2 and 4 weeks after injection and after 3 months follow-up with the Trunk Dystonia Disability Scale (TDDS), a Visual Analogue Scale (VAS) and a goniometric measurement of the lateral displacement. Patients were videotaped at each visit. None of the patients of the placebo group experienced benefit from treatment. BTX treatment was effective in 6 patients. One patient reported subjective benefit, with improvement of VAS score and mild improvement of TDDS score, but with no improvement of flexion degree. Two patients did not report any benefit. Four patients opted to continue to receive BTX treatment for 2 years after the cross-over study. Our study shows that BTX could be considered a possible treatment for LAD in parkinsonism. © 2007 Movement Disorder Society

Key words: lateral axial dystonia; parkinsonism; botulinum toxin; Parkinson’s disease.

Pisa syndrome1 or pleurothotonus2 or extensor truncal dystonia3 are synonymous of a lateral axial dystonia (LAD) characterized by contraction of the trunk musculature with marked flexion of the thoraco-lumbar spine and backward axial rotation, resulting in tonic lateral flexion of the trunk, which may be painful and impair function.

LAD has been described among symptoms of tardive neuroleptic dystonia, in patients with dementia treated with cholinesterase inhibitors, in patients with idiopathic primary dystonia and, as case reports, in patients with probable Parkinson’s disease (PD), Alzheimers disease, and multiple system atrophy.

The use of the term “Pisa syndrome” is controversial, as some authors recommend to differentiate “pleurothotonus” from “Pisa syndrome,” which should be limited to tardive neuroleptic syndromes, whereas other authors propose that the term “Pisa syndrome” should be used as synonymous with “pleurothotonus,” followed by the term defining etiology.

A recent study, focused on clinical differences between lateral flexion in PD and Pisa syndrome, noticed that the initial development of lateral flexion in PD is subclinical but its progression is rapid and it is caused by a component of dystonia added to rigidity.

Earlier studies showed that injection of botulinum toxin (BTX) into lower paraspinal muscles can improve truncal dystonia of patients affected by primary or tardive neuroleptic dystonias.

Studies on pharmacologic treatments of primary or tardive dystonia showed also that high doses of anticholinergics, tetrabenazine, and clozapine could be partly effective.

Treatment of LAD appearing in parkinsonian patients might be more controversial as tetrabenazine and high
doses of anticholinergics might worsen parkinsonian symptoms or cognitive functions; further controversy arises from a report describing LAD linked to pergolide, thus suggesting that LAD could also be a feature of distonic-dyskinetic complications of dopaminomimetic treatment in PD.

The aim of our study was to investigate in a double blind randomized cross-over pilot study the effect of BTX injection on LAD in patients affected by levodopa (L-dopa)-responsive parkinsonism.

PATIENTS AND METHODS

Patients Selection and Definition of LAD

In our local cohort of 1,400 patients with parkinsonism, we identified 92 patients (6.6%) with L-dopa responsive parkinsonism affected by bent spine on the antero-posterior or lateral axis. In 30 patients spine X-rays or MRI showed moderate-to-severe degeneration of bone structures; thus the origin of axial dystonia could not be disentangled as being preceding or secondary to bone degeneration. In 62 patients (44.4%) bent spine was not accompanied by bone structure degeneration, 36 (26%) patients had anterior axial flexion, with the classic feature of camptocormia, and 26 (19%) patients presented with lateral flexion of the trunk (3–4 points at item 28 of the UPDRS III motor subscale).

Lateral bending was measured on a wall goniometer on the two planar positions, antero-lateral and lateral. Two patients had a torsional bending with antero-lateral (6–8 degrees) and lateral bending by 6–8 degrees. The fulcrum of bending (indicating the level on the spine where binding originated) was at L1-L2 in one and at L2-L3 in the other. In all the other patients (24, 1.7%) bending was only lateral and fulcrum was at L2-L5 level.

Test-retest evaluations of goniometric measurement showed that only 5 degrees were consistently assessed by different raters. Consistency among examiners (L.B., V.S., S.V.) for 1–4 degrees was 40–60%. Coincidence of evaluations among raters was 100% only in patients with 5–10 degrees of more bending. Therefore, all measurements were approximated to 5 degrees.

EMG recordings of the paraspinal muscles were performed in patients with lateral flexion and showed patterns of denervation or myopathic activity only in two patients.

In 24 patients (1.7%), EMG of the paraspinal muscles ipsilateral to the bending side, recorded with coaxial needles while laying laterally on the bed and in standing posture, amplified with a 20,000 gain and band pass filtered at 20–2,000 Hz, showed a pattern of continuous muscle activity while standing, without positive sharp waves or fibrillation potentials. Continuous activity disappeared when patients lay down on one side producing a complete relaxation of the paraspinous muscles with electrical silence. Contralateral paraspinous muscles showed occasional bursting activities of motor unit potentials, without a consistent pattern among patients. EMG of the paraspinous muscles was also recorded with patients laying in prone (face down) position on the examination bed, with a pillow under the abdomen in order to induce moderate antero-posterior bending at the lumbar level: patients were asked to press down against the bed with the shoulder contralateral to EMG explored paraspinous muscles. This maneuver induces in normal conditions the maximal relaxation of the contralateral paraspinous muscles. In all patients with continuous activity of paraspinous muscles ipsilateral to the bending side, the contralateral shoulder press maneuver did not induce relaxation and continuous activity persisted. Thus, the contraction of paraspinous muscles ipsilateral to the bending side was considered as typical of dystonic contraction.

In all patients with lateral trunk flexion, drug treatments were adjusted for 2–9 months by increasing oral antiparkinsonian medication dosages and/or adding COMT inhibitors according to patient needs. Twelve patients had initially end-of-dose deterioration; in 6 patients lateral bending increased during off state by 5–10 degrees, and treatment adjustment led to disappearance or reduction of “off” states with occurrence of moderate dyskinesias (1–2 UPDRS item 32), whereas lateral bending persisted with the same approximate degree of inclination observed in “on” state. Twenty patients failed to experience improvement of lateral flexion from adjustment of oral antiparkinsonian medication dosage (no change in UPDRS III item 28). Goniometric evaluations were performed at mid-day 1 hour after the second L-dopa administration (evaluation in “on”) and in the morning 2–4 hours after awakening, to avoid sleep benefit, without treatment (evaluation in “off”). No difference between “on” and “off” evaluations were observed. In all the 20 patients further drug treatment of lateral bent spine was attempted. Trihexyphenidyl (8–12 mg/day) was administered in 14 patients; in 12 the occurrence of confusion and disorientation or hallucinations prompted the discontinuation of the anticholinergic drug in 1–6 days. In 2 patients, trihexyphenidyl was withdrawn after 20–26 days because of the occurrence of hypotension. Clozapine (6.25–25 mg) was administered in the same patients: no improvement of lateral trunk flexion was observed; 8 patients complained of excessive daytime somnolence or confusion; in all clozapine was withdrawn after 1 to 8 weeks.
Sixteen of the 20 patients suffered from dystonia-related pain of variable intensity. In 5 of the 16 patients, a new spine X-ray examination evidenced the occurrence of osteoporotic vertebral bone degenerations not observed in the initial X-ray assessment. These patients were excluded from the blinded study. Only 11 patients were therefore considered eligible for the study. Hoehn/Yahr stage, UPDRS III motor subscale scores, MMSE scores of the 11 patients were compared with same scores of the 81 patients affected by axial dystonia by means of a Student t test: no differences were observed.

The inclusion criterion was as follows: presence of painful LAD not responding to oral medications in patients with at least a 12-month history of L-dopa and dopaminomimetic treatment responsive parkinsonism. Treatment responsiveness was stated as improvement of UPDRS part III motor evaluation by 30% or more after 1 month of treatment optimization and difference by 20% or more between evaluation in “on” (1 hour after the second L-dopa daily administration) and “off” (15 hours after the last L-dopa and dopaminoagonist administration, at least 2 hours after awakening). No patients with wearing-off or unpredictable “off” complications were admitted to the study. For inclusion to the study, LAD should have not changed in “on” and “off” conditions by more than 5 degrees according to limits of evaluation.

Exclusion criteria were as follows: previous exposure to BTX or to neuroleptic drugs.

LAD was defined as follows: LAD is a lateral flexion of the trunk by ≥15 degrees toward one side as measured on a wall goniometer, which increased during walking and disappeared in the recumbent position, in the absence of mechanical restriction to trunk movement, such as ankylosis or clinical or radiological signs of degenerative vertebral or skeletal disease developed before the appearance of the lateral flexion. LAD must be characterized by a continuous EMG activity of lumbar paraspinous muscles ipsilateral to the bending side, appearing only when the patient is standing or walking, disappearing in lateral recumbent position, in absence of EMG signs of denervation or myopathic potentials.

Study Design

A blinded cross-over study design was devised in order to avoid the known placebo effect of treatment in PD patients. Two patients refused to participate. Nine patients were involved in the study. Figure 1 shows the flow chart of the study. All the patients were on a stable and optimal dose of antiparkinsonian drug, according to their needs. The study was conducted according to the declaration of Helsinki, and subsequent revision and was approved by our ethical committee. The study design followed the CONSORT statement recommendations. Patients (and their caregivers) signed a written informed consent to participate to the study.

Patients were randomly assigned to 2 groups; 4 patients received BTX and 5 placebo as a first treatment, and were switched over to BTX or placebo in the following treatment session, performed 3 months after the first session. Randomization and substance preparation were done by a nurse unaware of the injection protocol and of the purpose of the study, who assigned serial numbers to patients and to the placebo- or BTX-containing vials and took care of the switch over procedure. We used BTX toxin type A obtained in 500-U vials as Dysport (Ipsen): the toxin was reconstituted with 4 mL of saline solution and gently shaken, to a final concentration of 125 U/mL. 125 U of BTX toxin were injected under electromyographic control, as the depth of injection varies according to the thickness of the adipose panicle overlying paraspinals muscles, by a neurologist blinded to treatment in 4 sites into the paraspinal muscles 2 to 2.5 cm lateral to spinous processes at level L2-L5 on the side of the trunk flexion, for a total dose of 500 U. The 500 U Dysport dose corresponded, according to the conversion coefficients, to the 150 U Botox administered to patients affected by LAD due to tardive dystonia in a previous study. Dilution to 125 U/mL was selected with the purpose to enhance diffusion in the muscle bulk. For each patient, sites of injection were registered at each treatment session on an anatomical illustration. Four milliliters of saline solution were used as placebo and injected with the same modalities as BTX containing solution. Figure 2 shows sites of injections and an example of goniometric evaluation at baseline.

Each patient was evaluated at baseline, 2 and 4 weeks after injection and after 3 months follow-up. In addition to complete neurological examination, patients were rated with the UPDRS III motor subscale and H/Y scale. Patients were videotaped at each visit by an examiner blind to treatment, who also administered the Trunk Dystonia Disability scale (TDDS). A mobile wall goniometer was used to calculate the degrees of trunk inclination; pain secondary to dystonia was rated with a visual analogue scale (VAS) ranging from 0 (no pain) to 10 (worst imaginable pain). All measurements were performed in “on” conditions 1 hour after the regular morning antiparkinsonian drug administration.

After the blinded assessment, BTX treatment was repeated every three months for 2 years in patients 1, 2, 7, 9 and twice in patient 3,4,8.
Statistical Analysis

Wilkoxon signed-ranks matched-pairs test was used to evaluate the differences in bending degree, TDDS and VAS between placebo and BTX treatments. All

the comparisons were repeated using a paired t-test and results were concordant. Correlation between test scores was analyzed by Spearman rho. The study was originally planned to be conducted on 11 patients, which would have yielded a power greater than 0.80 for all comparisons, assuming $\alpha = 0.05$ and the following parameters: a difference of 10 points in the mean bending degree across groups, with standard deviation (SD) = 10; a difference of 3 points in the mean TDDS across groups, with SD = 3; a difference of 25 mm in the mean VAS across groups, with SD = 15.

Two patients refused to participate. However, we found larger differences than expected across groups, being able to achieve a statistical power of 0.88 for both bending degrees and VAS; 0.75 for TDDS.
RESULTS

Demography, clinical rating scores, disease duration, LAD duration, daily l-dopa equivalent doses, and evaluation scale scores at baseline and at 1 month after BTX treatment or placebo are shown in Table 1. None of the patients of the placebo group experienced benefit from treatment.

Six patients treated with BTX showed improvement in grading of LAD, function (TDDS) and pain (VAS); two patients did not benefit from treatment. One patient reported subjective benefit in VAS score, but only TDDS score improved, while the degree of bending was unmodified. The improvement of lateral bending in patients responding to BTX treatment was by 50% to 85.7%. TDDS showed a mean improvement of 4 points with the maximum of 6 in 3 patients (patients 1, 2, and 4) and a minimum of 1 in one patient (patient 7). All the patients responding to the treatment showed a marked improvement of their posture. Seven patients experienced a remarkable improvement of dystonia-induced pain. Mean VAS scale improvement was 31.4 mm with a maximum of 55 mm in 1 patient (patient 2) and a minimum of 19 mm in 1 patient (patient 8) (24.1–76.4%).

Wilkoxon signed-ranks matched-pairs test between placebo and active treatment showed significant effects for all tested scales (*P* < 0.01 for every measurement). LAD, lateral axial dystonia; MMSE, mini mental state examination; UPDRS, unified Parkinson’s disease rating scale; H/Y, Hoehn/Yahr; TDDS, trunk dystonia disability scale; VAS, visual analogue scale.

### TABLE 1. Clinical rating scores, disease duration, demography at baseline, and mean evaluation scale scores at baseline and at one month after BTX treatment or placebo

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<th>4</th>
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<th>7</th>
<th>8</th>
<th>9</th>
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*P* values: for every measurement (goniometric evaluation, TDDS, VAS) comparison between BTX and baseline or placebo.

DISCUSSION

BTX treatment was effective on LAD of 6 of 9 patients affected by l-dopa responsive parkinsonism, with improvement of goniometric grading and of TDDS and VAS scores; in one patient, only subjective benefit, with reduction of VAS and TDDS scores, was reported.

Following the cross-over study, 7 patients opted to continue to receive BTX treatment on a 3-month repeated schedule. After 1 year, the reduction of LAD, as measured on the goniometer and with TDDS, was by 25% to 40% better than after the first active treatment in 6 patients.

In one patient measurements showed no difference with measurements performed after the first active treatment. In 4 patients treatment was regularly repeated for 2 years: after 1 year of treatment, trunk dystonia was less pronounced in terms of grading and TDDS compared to baseline (20–45%), thus showing no worsening in comparison with measurement performed after 1 year. The duration of efficacy of BTX treatment was probably longer than the planned 3 months interval between treatment sessions, as patients 1, 2, 7, 9 spontaneously reported for treatment every 4 to 6 months, instead of the 3 months schedule.

In patient 8 (whose improvement was only subjective, without evidence of reduction on the goniometric scale) the treatment was repeated two further times, but no improvement was observed.
Statistical comparisons showed significant differences between placebo or baseline and active treatments.

In 4 patients treatment was regularly repeated for 2 years on a 3-month basis: follow-up measurements showed that trunk dystonia was less pronounced after one/two years of treatments in terms of grading and TDDS compared to baseline. The duration of efficacy of BTX treatment was also apparently longer than 3 months as four patients reported every 4 to 6 months.

BTX seems to be well-tolerated and effective and it could be considered a possible treatment in parkinsonian patients with LAD not responding to changes of dopaminomimetic treatments.

A previous study had shown that BTX administration, performed with the same methods as in our study, was effective in LAD due to primary or tardive dystonias.

Further comments should be addressed to the definition of LAD suggested in the present study.

LAD in parkinsonism is apparently a rare and controversial entity, as only sporadic single case description in PD patients (or other parkinsonisms) are reported in peer-reviewed literature. Only one study, published on a non-peer-reviewed journal supplement, detailed incidence and feature of LAD in a restricted PD patient population.

In order to perform the blinded BTX study, prevalence and characteristics of LAD were reviewed in our patient population. LAD appeared as a consistent though rare (1.7%) complication in the course of L-dopa responsive parkinsonism, and was scarcely (6/26, 22%) sensitive to dopaminomimetic treatment adjustment and wearing-off correction. High doses of anticolinergics and clozapine treatments could not be used because of frequent occurrence of cognitive side effects (12/14, 86%). In 5 of the 16 patients (31%) pre-selected for our study, bone degeneration occurred in 6 to 9 months, while LAD was left untreated. Therefore LAD is probably a complication deserving adequate treatment.

In order to show the effect of BTX, a definition of LAD, with strict exclusion and inclusion criteria has been proposed. We augur that more researchers in the field will be interested in discussing this entity.

**LEGENDS TO THE VIDEO**

**Segment 1.** Patient 1 at baseline and after BTX treatment. Patient 1 is a 70-year-old violin player with a 5-year history of parkinsonism, treated with L-dopa at the dose of 500 mg/day (b.i.d.) and ropinirole 6.5 mg/day (t.i.d.). He came at our observation because of painful thoracolumbar lateral flexion of 30 degrees toward the left side, causing difficulty in standing and walking, and increment of rest tremor in the right hand; he had a 10-year history of RBD; UPDRS III motor subscale score was 19, with 4 points at item 28 (posture), H/Y stage was 2 and MMSE was 22. He was initially treated by fractioning of L-dopa to the dose of 150 mg/QID, with entacapone to 800 mg/day and increment of ropinirole to 15 mg/day, with a 7-point improvement of UPDRS motor score, and no improvement of LAD. Trihexyphenidyl 4 to 12 mg/day was tried to control LAD, but the drug was withdrawn because of the occurrence of confusion and hallucinations. Clozapine up to 25 mg/day was not tolerated because of excessive daytime somnolence.

**Segment 2.** Patient 2 at baseline and after BTX treatment. Patient 2 is a 71-year-old woman with a 2-year history of left hand rest tremor. She was referred to our clinic because of a 25-degree LAD toward the right side developed concomitantly with parkinsonian tremor, worsening when walking. UPDRS III motor subscale score was 14, with 3 points at item 28 (posture), H/Y stage was 2, MMSE score was 21; she had RBD. The patient was treated for the first 6 months with pramipexole at the dose of 2.1 mg/day and L-dopa at the dosage of 400 mg/day, increased in the following six months to 600 mg/day with improvement of UPDRS motor score by 9 points, and transient reduction of LAD. In these months she also occasionally complained of complex visual hallucinations, followed by recurrence of lateral bending with the same degree. She was treated with clozapine, 12.5 to 25 mg/day. During clozapine treatment LAD neither improved nor worsened and after 2 months, she decided to withdraw the drug because hallucinations had remitted. She was admitted to the trial 3 months after clozapine withdrawal.

**REFERENCES**


