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Botulinum toxin in the treatment of chronic constipation in Parkinson's disease

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Constipation and defaecatory dysfunction occur approximately five times more frequently in patients with Parkinson's disease than in those without. Ineffective defaecation in Parkinson's disease has been correlated with failure of relaxation or with paradoxical contraction of the puborectalis muscle during straining. This contraction has been treated by surgical division of the muscle, a therapy that has often been unsuccessful and is accompanied by a prohibitively high rate of incontinence. We investigated the efficacy of botulinum toxin A injections in treating Parkinsonian patients with severe constipation due to outlet obstruction (puborectalis syndrome).

Keywords: Botulinum toxin, Parkinson's disease, constipation, puborectalis muscle

INTRODUCTION

Chronic constipation, defined as fewer than three bowel movements per week accompanied by straining at stool, is approximately five times more common in patients with Parkinson's disease than in the general population and its severity is directly related to the severity and duration of the disease (Edwards *et al.*, 1992). Constipation is classified as being due to either slow transit or outlet obstruction, and in Parkinson's disease elements of both causes usually co-exist. We focused on patients with prominent signs of outlet-obstruction type constipation as potential candidates for treatment with botulinum toxin type A. Outlet-obstruction constipation (sometimes known as anismus or puborectalis syndrome) has been attributed to dystonia of the pelvic floor sustained by a failure of relaxation, or to paradoxical contraction of the puborectalis muscle during straining (Wexner and Bartolo, 1995). Previous treatments have included surgical division of the puborectalis, but this surgical approach is often unsuccessful and is accompanied by a prohibitively high rate of incontinence. Local injection of botulinum toxin A as a non-surgical alternative for the treatment of outlet-obstruction type chronic constipation in Parkinson's disease was therefore assessed, and a prospective study is now under way to establish the prevalence of outlet-obstruction type constipation in Parkinson's disease.

CASE STUDY

A 55-year-old man with a 13-year history of Parkinson's disease presented with intractable constipation. The patient was a good responder to levodopa and dopamine agonists; at the time of our observation he was taking levodopa at 1400 mg/day, pergolide at 2 mg/day and domperidone at 30 mg/day. He had developed severe chronic constipation which had progressively worsened over the last 2 years. At presentation he had achieved no spontaneous evacuation for 6 months and was in great pain and distress. On examination he showed a mild slowing of intestinal transit with no signs of autonomic dysfunction, and colonoscopy gave an unremarkable picture. Assessment by defaecography showed a diminished change in anorectal angle on straining, suggestive of an outlet-obstruction type of constipation.

Methods and outcome evaluation

Thirty units of botulinum toxin A (BOTOX®, Allergan Inc., Irvine, California, USA) were injected into two sites on either side of the puborectalis muscle, under electromyograph guidance. Resting anal pressure, maximum voluntary contraction and pressure on straining were evaluated before treatment and 4, 8, 12 and 16 weeks afterwards. Changes in anorectal angle during straining were meas-

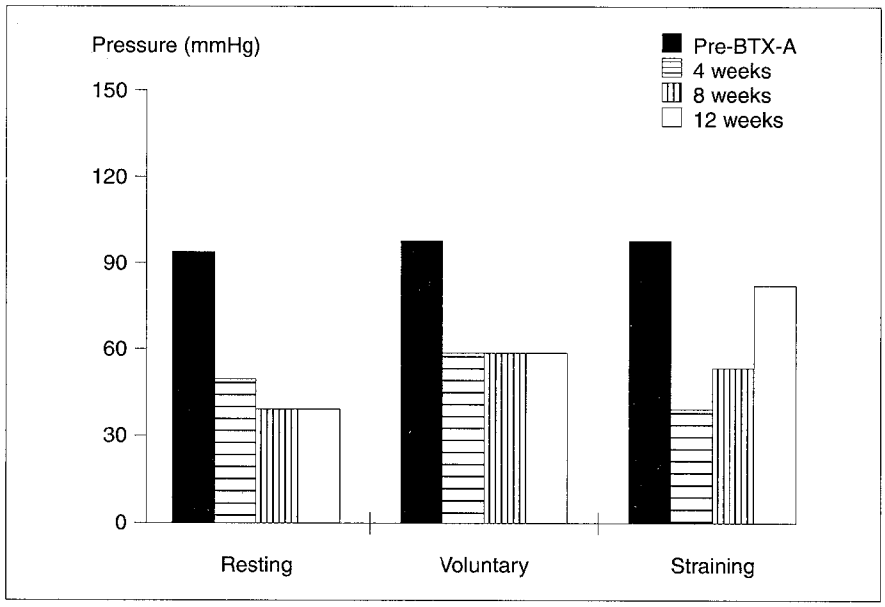

Fig. 1. Variation in resting, voluntary and straining pressures, measured by anorectal manometry, before (Pre-) and 4, 8 and 12 weeks after treatment with botulinum toxin A (BTX-A).

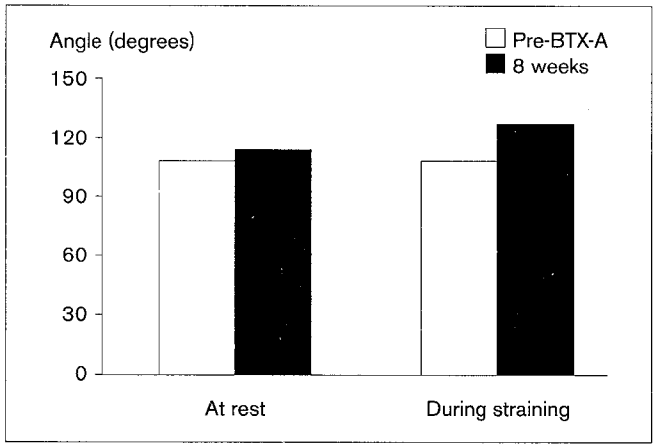

Fig. 2. Variation in anorectal angle, recorded by defaecography, before (Pre-) and 8 weeks after injection with botulinum toxin A (BTX-A).

ured by defaecography before and 8 weeks after treatment. At the 16-week evaluation, the patient complained of a relapse: the defaecation had worsened and was as severe as before treatment. Anal manometry revealed increased resting and on-straining values. The patient was retreated with 100 U of botulinum toxin A.

Results

Fig. 1 shows the fall in the manometric measurements following the first set of injections of botulinum toxin A. The reductions in resting and maximum voluntary pressures were sustained for 12 weeks following these injections, but pressure during straining gradually returned towards pretreatment values over this period. This prompted an increase in the subsequent injection dose to 100 U.

Fig. 2 shows the recorded changes in anorectal angle. The change in angle during straining was significantly increased 8 weeks after the botulinum toxin injection. Subjectively, the patient reported improved defaecatory function. In defaecography tests, the patient evacuated the barium paste without the need for laxatives and enemas.

ONGOING PROSPECTIVE STUDY

Following the success of botulinum toxin A therapy in this patient, a prospective study was started on the use of this toxin in Parkinsonian patients with constipation. The initial aim was to assess the proportion of patients who had outlet-obstruction type constipation and were suitable for consideration for a trial of botulinum toxin A therapy. All subsequent outpatients at the Gemelli Hospital with a diagnosis of idiopathic Parkinson's disease were asked to complete a questionnaire on defaecatory dysfunction. In those who responded positively, a proctological examination was performed to test the relaxation of the puborectalis muscle during straining. All cases suspected to have insufficient relaxation were studied in detail, and anorectal manometry and defaecography were performed.

This preliminary screening of 102 consecutive patients showed that 60 (58.8%) had constipation as defined above. However, only five of these (8.3%) were identified as hav-

ing prominent outlet-obstruction type constipation with insufficient relaxation or with paradoxical contraction of the puborectalis, suitable for entry into a trial of botulinum toxin A treatment. The present treatment group consists of four males and one female, aged 56–72 years, affected by Parkinson's disease for between 0.5 and 15 years. All reported a history of chronic assisted evacuation (by laxatives, enemas or suppositories). The recruitment phase of this study is ongoing. Ten patients will be enrolled in order to test the efficacy and tolerability of botulinum toxin A treatment.

CONCLUSIONS

The successful treatment with botulinum toxin A of intractable chronic constipation in a Parkinson's disease patient raises the possibility of a new therapeutic approach for this condition (Albanese *et al.*, 1997). Although chronic constipation is a common condition in patients affected by Parkinson's disease, careful assessment shows that perhaps only a minority, who are suffering from outlet-obstruction type constipation involving the puborectalis, may be suitable for this form of therapy (Hallan *et al.*, 1988; Joo *et al.*, 1996).

For the majority, increased transit time due to neurological damage to the myenteric plexus may be a more significant cause of constipation. In these subjects, the combined effects of autonomic dysfunction, dopaminergic drugs, chronic use of laxatives and diet may be important contributing factors. Alternative treatment options include the use of apomorphine (Christmas *et al.*, 1988; Edwards *et al.*, 1993), anal dilation (Maria *et al.*, 1996, 1997) and more complex procedures such as deep brain stimulation of the suprathalamic nucleus.

For those patients with puborectalis dysfunction, however, botulinum toxin A may be a useful treatment and our ongoing trial will evaluate this further.

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DISCUSSION

Question from the floor: We have discussed the cologastric reflex. With a full rectum, the patient is constipated, and the stomach stops emptying. In advanced Parkinson's disease, a proportion of the fluctuations that occur in motor behaviour with long-term treatment are caused by failure of gastric delivery (or absorption) of levodopa. Did you notice any effect on motor fluctuations when the constipation was relieved?

A. Albanese: No. I cannot say because we only have a few patients, but that's an intriguing point.