Achalasia: outcome of patients treated with intrasphincteric injection of botulinum toxin

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Abstract

Background—To evaluate the safety and clinical efficacy of botulinum toxin (BT) in patients with achalasia followed up for six months.

Methods—Fifty five symptomatic patients with manometrically proven achalasia were included in a multicentre prospective trial. Before and two weeks and two months after intrasphincteric injection of BT, symptoms of dysphagia, regurgitation, and chest pain were scored on a 0-3 scale, and lower oesophageal sphincter pressure (LOSP) was assessed. The symptom score was determined again at six months, clinical improvement being defined by ≤ 3 , relapse by > 3 , and failure as a relapse after two injections or loss to follow up.

Results—Except for transient chest or epigastric pain (22%), no side effects were observed. There was a significant decrease in LOSP after treatment. Symptom scores were significantly improved at two weeks (2.0 (SD 1.6)), two months (1.7 (1.8)), and six months (1.9 (2.0)) compared with pretreatment values (5.1 (1.8), $p < 0.001$). At six months, 33 patients had clinical improvement (27 after one injection), 17 were considered failures, and five had just relapsed. Although there was a trend for age (older patients being more responsive), age, sex, prior duration of symptoms, initial symptom score, weight loss, LOSP, magnitude of oesophageal contractions, vigorous or non-vigorous achalasia, previous dilatations, and radiological features were not predictive of results.

Conclusions—This multicentre series confirms that intrasphincteric injection of BT is a safe procedure, resulting in clinical improvement in 60% of patients with achalasia at six months. The therapeutic role of BT in achalasia needs further evaluation with regard to other alternatives.

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Keywords: achalasia; botulinum toxin; oesophageal motor disorders

Achalasia is a well defined primary oesophageal motor disorder characterised by a lack of peristalsis and a hypertonic lower oesophageal sphincter (LOS), with incomplete relaxations.¹ Treatment modalities consist of cardio-

myotomy and pneumatic dilatation, both of which are intended to relieve functional obstruction of the distal oesophagus. The symptomatic efficacy of these treatments ranges from 60% to 80%.²⁻⁷ The risk of perforation after dilatation is estimated to be 1-6%.⁵ Mortality related to these treatments is about 0.2%.^{6,7}

Intrasphincteric injection of botulinum toxin (BT) has been recently proposed as an alternative to pneumatic dilatation or surgery in the treatment of achalasia.⁸⁻¹⁰ BT has been shown to inhibit acetylcholine release from nerve endings, thereby inducing muscular paresis.¹¹⁻¹³ The effect of BT is reversible due to the sprouting of terminal axons that form new synaptic contacts on adjacent muscle fibres.¹⁴ BT has been used therapeutically in diseases producing hypertonia of skeletal muscles,^{11,13,15} but its use in smooth muscle is very recent. In vitro studies have shown that BT is also able to inhibit electrically stimulated smooth muscle contraction by blocking the presynaptic release of acetylcholine, without affecting the non-adrenergic non-cholinergic response.^{16,17} Pasricha *et al* showed that injection of BT into the LOS of piglets strongly decreased resting LOS tone.¹⁸ In a single centre trial, this same group recently reported that BT can be used for the treatment of achalasia. Their initial experience showed a 64% improvement rate (20/31 patients) at six months.⁸⁻¹⁰ However, it has not yet been clearly established whether these results can be reproduced in less specialised centres and in conditions of routine practice.

In this context, we conducted a prospective multicentre study of BT in achalasia in order to assess the feasibility of treatment as well as to provide additional data on its efficacy and safety.

Patients and methods

PATIENTS

The diagnosis of achalasia was manometrically determined on the basis of complete aperistalsis, together with either hypertonia of the LOS or incomplete relaxations of the LOS.¹ Symptomatic patients with achalasia (as defined above) were included. Patients under 18 years of age or over 80, pregnant or breastfeeding women, patients with previous oesophageal myotomy or those with secondary achalasia, and patients in whom BT was contraindicated (those using antibiotics, myorelaxants, or curare, or those with muscular

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disorders or severe ulcerative oesophagitis ($\geq$ grade 2 in the Savary-Miller classification)) were excluded.

The study was approved by the Ethics Committee of Nantes (Centre de Protection des Personnes des Pays de Loire Numéro 2), and written informed consent was obtained from all patients.

STUDY DESIGN AND PROCEDURE (fig 1)

The study was designed as a multicentre (12 centres) prospective open trial. During the month before BT injection, patients underwent a pretherapeutic work up including clinical assessment, oesophageal manometry, 24 hour pH monitoring, and oesophagography. Endoscopic ultrasonography (n=18) was performed only when the clinician considered that secondary achalasia had to be excluded.^{19 20}

Oesophageal manometry was performed after an overnight fast according to the method customarily used in each centre (a multilumen manometric catheter perfused by a low-compliance pneumohydraulic capillary infusion system). When it proved impossible to pass the manometric probe through the LOS, it was placed endoscopically. LOS pressure was determined by the slow pull-through method. Before each swallow, the patient was given 5 ml of water in the mouth. Resting mean LOS pressure was determined by calculating the mean of end expiratory readings recorded on each opening, both in abdominal and thoracic segments, under and above the pressure inversion point, respectively. LOS relaxation was determined by calculating the percentage of relaxations after each swallow (complete, incomplete, or absent). Gastric pressure was established as zero baseline, and the degree of relaxation of LOS was determined by reference to this baseline. A relaxation of 80% was considered complete. Finally, the amplitude of swallow induced waves in the oesophageal body was measured. Vigorous achalasia was considered to be present when the mean amplitude of pressure waves in the oesophageal body was >30 mm Hg. This value corresponded to the lower limit of normal adopted by all centres.

For the procedure, patients were hospitalised for 24 hours. Botulinum toxin (Botox®, Allergan France, Mougins, France) was injected following an overnight fast, either with (propofol, Diprivan®, ICI Pharma, Cergy, France) (n=25) or without general anaesthesia (n=30). Before BT injection, complete flexible

upper gastrointestinal endoscopy was performed. BT was injected through a sclerotherapy needle (TW IV 6 c, length 6 mm, diameter 0.7 mm, ABS, St Dié, France) into the four quadrants of the LOS (20 U/ml saline, total dose 80 U). To rinse the residual volume from the needle (0.5 ml), an additional injection of 1 ml of saline was performed after each BT injection. The patient was allowed to eat on the following day.

FOLLOW UP VISITS

Visits were systematically scheduled at two weeks and two and six months after BT injection (fig 1). In patients who showed no (or insufficient) improvement two weeks after the first injection, as well as in those whose symptoms recurred during the six month follow up, a second injection was proposed (using the same procedure). If symptoms recurred after the second injection, patients were withdrawn and considered to be failures.

CLINICAL ASSESSMENT

Symptomatic response was evaluated using a modified score according to Eckardt *et al*,³ which was the sum of the individual scores for dysphagia, regurgitation, and chest pain (table 1). An adjectival scale of therapeutic efficacy was also proposed to patients who chose between "excellent", "good", "tolerable", and "bad", according to their own perceptions.

In addition to undergoing immediate follow up after injections, patients were questioned about the occurrence of potential side effects from the injections, especially fever, symptoms of gastro-oesophageal reflux, and chest pain.

ADDITIONAL PROCEDURES

Two weeks and two months following injection, LOS pressure was manometrically measured, and 24 hour pH monitoring was performed. In addition, in two centres, the isotopic oesophageal emptying fraction was determined for solids and liquids (fig 1).

Oesophageal pH monitoring

Twenty four hour pH monitoring was conducted according to the usual procedures of each centre. After nasal introduction, the electrode was placed 5 cm above the LOS, which had been previously located by manometry. Oesophageal acid exposure was expressed as the percentage of total time below pH 4, with a cut-off value 4.2% above pH 4 as the upper limit of normality.

Figure 1: Trial design.

TABLE 1 Grading score for the evaluation of clinical symptoms in patients with achalasia (from Eckardt *et al*)³

Score	Dysphagia	Retrosternal pain	Regurgitation
0	None	None	None
1	Occasional	Occasional	Occasional
2	Daily	Daily	Daily
3	Each meal	Each meal	Each meal

Oesophageal scintigraphy

This was performed in two centres after an overnight fast. With the patient seated in front of the gamma camera, imaging was done from the oropharynx to the cardia in anterior projection. The patient was first given 10 ml saline containing 300 μ Ci of technetium-99m labelled sulphocolloid p.o., after which the liquid emptying fraction was measured after one and eight minutes. The patient then swallowed 1 g of pate radiolabelled with 1 mCi of ^{99m}Tc , after which the solid emptying fraction was measured after one and eight minutes.

STATISTICS

The primary end point – that is, the percentage of patients still in clinical improvement at six months, was analysed on an intention to treat (ITT) basis. Patients were classified into three

TABLE 2 Baseline characteristics of 55 patients with achalasia treated with intrasphincteric injection of botulinum toxin

Age (y) median (range)	53 (19–78)
Sex (M/F)	28/27
Previous pneumatic dilatation	
No of patients (%)	18 (33)
Median of dilatations (range)	1 (1–12)
Symptoms	
Dysphagia (%)	55 (100)
Regurgitation (%)	46 (83)
Chest pain (%)	32 (58)
Prior duration of symptoms (months) mean (SD)	39 (47)
Mean symptom score (SD)	5.1 (1.8)
Clinical status	
Weight (kg) mean (SD)	66.5 (14.0)
No of patients with weight loss >1 kg (%)	37 (67)
Weight loss† (kg) mean (range)	8.8 (1–27)
Oesophageal function	
Lower sphincter pressure (mm Hg) mean (SD)	27 (12)
Amplitude of waves (mm Hg) mean (SD)	37 (33)
Vigorous achalasia/classic achalasia (n/n)	22/33
Mean fractional emptying of solids at 1 min (SD)*	41 (31)%
Mean fractional emptying of liquids at 1 min (SD)*	39 (30)%
No of patients with abnormal acid exposure (%)	2/42 (5%)
Oesophageal diameter (cm) mean (SD)	4.4 (1.5)

†In 33 patients.

*In 15 patients.

TABLE 3 Results of intrasphincteric injection of botulinum toxin on symptoms at week 2 and months 2 and 6

	Baseline	Week 2	Month 2	Month 6
<i>Intention to treat analysis (n=55)</i>				
Clinical improvement		75	69	60
Failure		25	31	40
Subjective score (%) ^a				
Excellent – good		73	71	58
Tolerable – bad		27	29	42
<i>Per protocol analysis</i>		(n=55)	(n=53)	(n=51)
Clinical improvement		75	72	65
Failure		25	28	35
Subjective score (%) ^a				
Excellent – good		73	74	63
Tolerable – bad		27	26	37
Mean symptom score (SD)	(n=55)	(n=55)	(n=49)	(n=40)
Dysphagia	2.6 (0.6)	1.0 (1.0)***	1.0 (1.0)***	1.1 (1.0)***
Pain	1.0 (1.0)	0.5 (0.7)***	0.5 (0.7)***	0.4 (0.8)***
Regurgitation	1.5 (1.1)	0.4 (0.6)***	0.3 (0.5)***	0.5 (0.7)***
Total score	5.1 (1.8)	2.0 (1.6)***	1.7 (1.8)***	1.9 (2.0)***

n: Number of patients taken into account for statistical analysis. Non-parametric variance analysis for repeated measures was calculated with the number of subjects available at six months (per protocol analysis).

^a Subjective score was calculated by classifying patients lost to follow up and failure as bad results. ***p<0.001.

categories (clinical improvement, failure, or relapse). *Clinical improvement* was defined as a score ≤ 3 , *relapse* as a score > 3 and/or the need to perform an additional injection, and *failure* as a lack of improvement or a relapse after two injections. In ITT, patients lost to follow up were considered failures. Estimation of remission after a single injection of BT was determined by an actuarial method dividing the whole time range into 15 day periods.

Changes observed after BT injection (symptom score, manometric parameters, acid exposure, and scintigraphic data) were also evaluated on a per protocol basis by non-parametric analysis of variance for repeated measures.

Data are expressed as mean (SD) or median when appropriate. A search for factors predictive of therapeutic response was carried out using univariate analysis: Student's *t* test was used for normally distributed quantitative variables (age, LOS pressure, diameter of oesophagus); the Mann-Whitney test for non-normally distributed quantitative variables (duration of symptoms, weight loss, initial symptom score, magnitude of waves of oesophageal body contraction); and the χ^2 test for binary qualitative variables (sex, previous pneumatic dilatation). In addition, an attempt was made to identify outcome predictors. Relationships were examined between clinical improvement and the results of functional investigations (LOS pressure, scintigraphy of liquids and solids at one and eight minutes). Spearman correlation coefficients were calculated between each of these variables and time, and then compared with the Spearman correlation coefficient calculated between symptom score and time. A *p* value <0.01 was considered significant given the multiplicity of tests used on the same data (Bonferroni correction).

Results

PATIENT CHARACTERISTICS AT INCLUSION

Fifty five consecutive patients were enrolled by 12 centres between October 1994 and May 1995 (28 men, 27 women; mean age 53 years, range 19–78). Table 2 presents the main patient characteristics. Oesophageal pH monitoring was performed in 42 patients before BT. Median oesophageal acid exposure was 0.7 (1.8)% (range 0.0–10.9%). Two patients had abnormal acid exposure. Oesophageal scintigraphy was performed in 15 patients.

Upper gastrointestinal endoscopy detected no relevant abnormalities except food-salivary stasis in 24/55 patients (43.6%).

THERAPEUTIC RESULTS

No serious adverse effects were reported after the 73 injections (18 patients received two sets of injections). Sixteen patients (22%) had transient (<48 hours) mild chest or epigastric pain after injection, 13 of whom had reported retrosternal pains before injection. As four patients were lost to follow up, 51/55 patients (93%) completed the six month study. Table 3

presents the clinical results. Patients with an initial weight loss showed a significant weight increase (4.2 (3.0) kg, $n=23$) at six months. The median delay for symptomatic improvement was two days (range 1–30). Among patients who had improvement after BT, 46% were improved 24 hours after injection.

At week 2, 41 patients showed clinical improvement (74.5%). Among the 14 patients with failure, three were excluded from the trial and 11 received a second injection before month 2. Two of these 11 patients showed clinical improvement at month 6. At month 2, 38 patients showed clinical improvement (69%), nine had relapse (16%), and eight had failure (15%). Among the 41 patients showing clinical improvement at week 2, seven received a second injection between months 2 and 6; four of these seven patients showed clinical improvement at month 6. At month 6, 33 patients (27 with one injection) showed clinical improvement (60%), five had a relapse (9%), and 17 had failure (31%) (four were lost to follow up). The probability of clinical improvement at six months after one BT injection was 52% (fig 2). Overall, scores at month 6 were ≤ 2 in 31 patients, ≤ 1 in 22 patients, and null in eight patients.

Six of the 18 patients (33%) who received a second injection achieved sustained clinical improvement at month 6.

There were no significant differences between the seven centres which had five or more patients. The clinical improvement rate at month 6 ranged from 50% to 80%.

CHANGES IN OESOPHAGEAL FUNCTION (table 4)

In all patients but one, manometry showed the persistence of complete oesophageal aperistalsis (fig 3 shows changes in LOS pressure).

Among the 29 patients who had pH monitoring at two months, abnormal oesophageal acid exposure was recorded in only one (percentage of time less than pH 4: 0% at inclusion, 6.4% at two weeks, and 8.4% at two months), and there were no symptoms of gastro-oesophageal reflux disease.

There was a statistically significant improvement in scintigraphic parameters (fig 4).

OUTCOME PREDICTORS

Therapeutic response was not significantly affected by age, sex ($p=0.51$), previous pneumatic dilatation ($p=0.48$), prior duration of symptoms, initial weight loss, initial score, initial LOS pressure, diameter of oesophagus, or amplitude of oesophageal contractions (table 5). These findings remained valid even when the five patients who had just relapsed at six months were considered as responders, in which case the trend towards an age difference between responders (56.0 (14.7) years, $n=38$) and non-responders (47.6 (13.7) years, $n=17$, $p=0.053$) was strengthened. Clinical improvement at six months was more frequently observed in patients with vigorous achalasia (15/22; 68.2%) than in those with classic achalasia (18/33; 54.5%), but the

Figure 2: Probability of clinical improvement after a single intrasphincteric injection of botulinum toxin (actuarial method).

difference was not statistically significant (table 5).

Only Spearman correlation coefficients for scintigraphy of liquids at one minute ($p=0.369$, $n=49$) and for symptom score ($p=-0.565$, $n=51$) were not significantly different ($p>0.05$, absolute value). The other coefficients were significantly different, indicating that the time course between symptom score and the studied parameter was different.

Discussion

The results of the present study show that intrasphincteric injection of BT is a safe procedure, resulting in clinical improvement in 60% of patients with achalasia at six months. These results clearly confirm and extend those of Pasricha *et al.*^{8,9} Moreover, the lack of significantly different results between centres suggests that this therapeutic procedure is highly feasible for use in non-specialised centres.

The multicentre design of our study allowed us to enrol 55 consecutive patients within a relatively short period. With regard to age and disease characteristics, our study population was quite representative of achalasia and very similar to populations reported in other studies.^{3,4,21-23} Interestingly, the marked weight loss noticed in two thirds of our patients

Figure 3: Mean (SD) pressure of the lower oesophageal sphincter (LOS) at baseline and two weeks and two months after injection of botulinum toxin (***) $p<0.001$.

Figure 4: Mean (SD) percentage of liquid (A and B) and solid (C and D) isotopic meal emptied into the oesophageal region of interest at one (A and C) and eight minutes (B and D), at baseline and two weeks and two months after injection of botulinum toxin (n=15) (* p<0.05; ** p<0.01; *** p<0.001).

TABLE 4 Manometric, scintigraphic, and pH-metric data before and after intrasphincteric injection of botulinum toxin in patients with achalasia followed up at two weeks and two months

	Inclusion	2 Weeks	2 Months
Manometric data			
Lower oesophageal sphincter pressure (mm Hg) mean (SD)	(n=55) 26.8 (12.3)	(n=47) 18.9 (10.6)*	(n=39) 20.3 (9.2)*
Percentage of LOS relaxations (median (range))			
Complete (%)	0 (100)	0 (80)†	16 (80)†
Incomplete (%)	26 (100)	25 (100)†	29 (100)†
Absent (%)	52 (100)	50 (100)†	35 (100)**
Oesophageal scintigraphy (fractional emptying %) mean (SD)			
Liquids (n=15) 1 min	39 (30)	64 (23)*	68 (26)*
8 min	66 (26)	84 (15)**	79 (25)****
Solids (n=16) 1 min	41 (32)	52 (33)†	54 (32)****
8 min	79 (20)	83 (21)****	84 (21)***
Oesophageal pH monitoring† (median (range))			
Percentage of time under pH 4	(n=21) 0.1 (3.5)	(n=21) 0.2 (6.4)	(n=21) 0.2 (8.5)

n: Number of patients taken into account for statistical analysis.
*p<0.001; **p<0.01; ***p=0.02; ****p=0.03 (in comparison with "before treatment"); †not significantly different.

TABLE 5 Baseline characteristics (mean (SD)) of responders and non-responders at six month assessment

	Responders (n=33)	Non-responders (n=22)	p Value
Age (y)	55.9 (15.2)	49.6 (13.7)	0.125
Prior duration of symptoms (m)	40.9 (45.5)	37.1 (52.0)	0.915
Weight loss (kg)	5.2 (6.4)	7.0 (6.7)	0.324
Symptomatic score	4.9 (2.0)	5.5 (1.4)	0.183
Lower oesophageal sphincter pressure (mm Hg)	28.0 (12.5)	25.3 (12.1)	0.429
Oesophageal diameter (cm)	4.6 (1.4)	4.1 (1.3)	0.260
Amplitude of waves (mm Hg)	39.5 (34.2)	35.3 (32.0)	0.562
Vigorous achalasia/classic achalasia	15/18	7/15	0.311

(8.8 kg) probably reflects the severity of achalasia in this series.

BT injections (80 units) were well tolerated, with no occurrence of serious side effects. Minor side effects reported by 22% of the patients consisted of either transient retrosternal or epigastric pain. This figure compares well with the 30% of side effects reported both in the placebo group and the BT group in the trial conducted by Pasricha *et al.*⁸ Thus, these transient episodes of pain are more likely to be related to the injection itself than to any direct toxicity of BT. Moreover, among the 16 patients who reported minor side effects, 13 already had retrosternal pain before injection. Pathological acid exposure may be present in achalasia without any reflux symptoms.²⁴ However, in contrast to the results of other studies,^{25 26} a high incidence of abnormal acid reflux was not observed either before or after BT injections.

Individual symptoms as well as symptom scores were clearly improved at every time point, and mean weight gain (4.2 kg at six months) paralleled this therapeutic benefit. These results are once again close to those of Pasricha *et al* who found 64% of patients in remission at six months.^{8 9} Relief of symptoms occurred earlier and lasted longer than after BT injection in striated muscle,^{8 9 11 13} suggesting that smooth muscle has greater sensitivity.

Symptom relief was accompanied by a significant decrease in LOS pressure (for example a 31% drop at two months) after BT injection, although it remained above 20 mm Hg. It has not been determined whether an increase in BT dosage could result in a more marked effect on LOS pressure.²⁷ It is noteworthy however that a decrease in LOS pressure after pneumatic dilatation appears to be the best predictor of therapeutic response.³ Contrary to the findings of Pasricha *et al*⁹, in our series, the drop in LOS pressure after BT did not prove to be a reliable predictor of outcome.

It is also noteworthy that oesophageal emptying was markedly improved in many cases. In particular, the emptying of liquids (measured at one minute) was significantly correlated with symptom improvement.

Unlike Pasricha *et al*⁹, who observed better responses for patients over 50 years of age and for vigorous achalasia, we failed to detect any predictors of response to BT. Yet a trend was noted towards better responses in older patients and in those with vigorous achalasia. The fact that it fell short of statistical significance, especially for age, may reflect a type 2 error, even though a large number of patients was included in the study. More importantly, it should be emphasised that previous failure of pneumatic dilatation does not preclude response to BT. Therefore, these two techniques may actually broaden our therapeutic armamentarium rather than being competitive choices.

In conclusion, our series confirms that intrasphincteric injection of BT is a safe and highly feasible procedure which can easily be applied in non-specialised centres. The lack of significant side effects suggests that this treatment could be given on an outpatient basis, thereby reducing the cost of therapy. BT injection could be proposed as an initial treatment for patients with a high risk of complications with conventional procedures (pneumatic dilatation and surgery). Further studies are required to evaluate the potential for individualised treatment offered by higher BT doses in patients unresponsive to standard doses and to determine the as yet unknown long term effects of maintenance with repeated BT injections.

Despite the large number of patients required, multicentre controlled trials should be initiated now to compare BT with pneumatic dilatation and/or surgical treatment. In addition to the clinical improvement achieved, safety and duration of action as well as cost effectiveness are relevant end points in determining the most appropriate strategy. Moreover, the role of BT in patients who have failed to respond to pneumatic dilatation or surgery should be further evaluated.

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