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Comparison of two different formulations of botulinum toxin A for the treatment of oesophageal achalasia

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SUMMARY

Background: Intrasphincteric injection of botulinum toxin has been reported as a safe and effective alternative treatment in oesophageal achalasia, especially in high-risk and elderly patients.

Aim: To compare two formulations of botulinum toxin in the management of achalasia.

Patients and methods: We randomly compared the efficacy and safety of 100 U of Botox (Allergan, Irvine, USA) and 250 U of Dysport (Ipsen, Milan, Italy), injected through a sclerotherapy needle at the level of the lower oesophageal sphincter, in 78 consecutive patients with achalasia. Symptom score, oesophageal manometry and 24 h pH-metry were recorded (before and 1 month after therapy). Symptom score was also obtained 6 months after treatment.

Results: One month after treatment, the effects of the toxin on symptoms and oesophageal tests were similar for both formulations. Lower oesophageal sphincter pressure decreased from 31 ± 12 to 18 ± 5 mmHg after Botox, and from 35 ± 9 to 18 ± 10 after Dysport. At the end of the follow-up period (6 months), symptom score decreased from 5 ± 1.2 to 1.2 ± 0.8 after Botox and from 5.2 ± 1.5 to 1.5 ± 1 after Dysport. Moreover, the percentages of patients who failed to respond to treatment (10% and 17.5%) and who relapsed during follow-up (12% and 24%) did not differ significantly. No patient complained of reflux symptoms after treatment, although abnormal acid exposure was documented in two subjects.

Conclusions: Both formulations of botulinum toxin have comparable efficacy in the treatment of oesophageal achalasia, for up to 6 months of follow-up.

INTRODUCTION

Achalasia is a primary oesophageal motor disorder characterized by absence of peristaltic activity and impaired relaxation of the lower oesophageal sphincter (LES).[1] Current therapeutic options include drug treatment (mainly calcium channel blockers and long-acting nitrates), pneumatic dilatation, surgical myotomy and, more recently, intrasphincteric injection of botulinum A toxin.[2] The latter has been reported to be an effective measure in this condition,[3] even in patients in whom previous myotomy or dilatation have failed.[4] The effect of the toxin is that of decreasing LES pressure, thereby allowing oesophageal emptying by gravity.

This approach has also been shown to display a long-term effect,[5] and in one study up to 75% of patients were in remission after 24 months of follow-up.[6] However, repeated injections of toxin were needed to

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achieve a stable effect on symptoms, and in the experience of other authors, the long-term results appear to be less satisfactory than those obtained by pneumatic dilatation.[7]

Although the exact role of botulinum toxin is still to be defined, there is widespread agreement that this approach is useful for patients who cannot undergo dilatation and who are not surgical candidates.[8] The use of botulinum toxin has been found to be remarkably safe; however, the possibility that it could induce oesophagogastric reflux has not yet been formally evaluated.

Two different formulations of botulinum toxin A are commercially available, but there are no studies comparing their efficacy in achalasia. The purpose of the present study was therefore to compare the efficacy and tolerability of the two botulinum toxin formulations in this condition; and also to verify the possible appearance of gastro-oesophageal reflux following this therapeutic approach.

PATIENTS AND METHODS

Seventy-eight achalasic patients (44 men, 34 women, age range 20–77 years) entered the study. All patients underwent clinical evaluation of oesophageal symptoms, upper gastrointestinal endoscopy, oesophageal manometry, and 24 h oesophageal pH-metry (50 patients).

A standard symptoms questionnaire concerning the presence of dysphagia, regurgitation and chest pain was given to all patients. A score of 0 to 3 was attributed to each symptom, depending on its occurrence: never, occasionally, more than once a week, or daily. Response to treatment was arbitrarily defined as a total score of < 3, while a score of > 3 was considered as treatment failure (or relapse).[9]

Oesophageal manometry was carried out according to a previously described technique,[9, 10] with the resting LES pressure measured by station pull-through and oesophageal body activity evaluated in response to at least 10 wet swallows (5 mL of water) administered 30 s apart.[11] pH-metry was carried out and analysed according to a standard procedure.[12]

Clinical, manometric and pH-metric evaluations were carried out at baseline and 1 month after the therapy. Thereafter, the patients were contacted monthly by telephone for up to 8 months, in order to assess symptom frequency and possible side-effects.

Botulinum toxin injection

Upper gastrointestinal endoscopy was carried out under conscious sedation with 10 mg intravenous diazepam. After identification of the LES area, 100 U of Botox (Allergan, Irvine, USA) or 250 U of Dysport (Ipsen, Milan, Italy) were injected according to a double-blind randomization list. The equivalency of the two doses was calculated according to literature data.[13, 14] Both botulinum toxin formulations were injected in eight aliquots of 0.5 mL each at two different sites (1 cm apart) of each LES quadrant. Patients were allowed to eat the same day and were closely monitored for 24 h for the presence of side-effects.

Ethical considerations

After careful explanation about the aims of the investigation, all patients gave informed consent, and the study was carried out in accordance with the local ethical guidelines and the recommendations of the Declaration of Helsinki.

Statistical analysis

Statistical analysis was carried out using Fisher's exact test and the Wilcoxon signed rank test, where appropriate. Values of $P < 0.05$ were chosen for rejection of the null hypothesis. Data are expressed as means ± s.d.

RESULTS

Table 1 shows the clinical variables in the two treatment groups before treatment. The only significant difference was age, which was significantly higher in the Dysport group.

Table 1. Baseline clinical variables in the two patient groups

	Botox	Dysport	*P*-value
No. of patients	38	40	N.S.
M/F	19/19	25/15	N.S.
Age (years)	48 ± 16	60 ± 17	0.01
Symptom duration (months)	21 ± 22	27 ± 32	N.S.
Weight loss (kg)	4.3 ± 5	4.3 ± 3.3	N.S.
Vigorous achalasia	6	10	N.S.
Symptom score	5 ± 1.2	5.2 ± 1.5	N.S.
LES pressure (mmHg)	31 ± 12	35 ± 9	N.S.
% pH < 4	0.4 ± 0.8	0.3 ± 0.6	N.S.

(Mean ± s.d.)

Table 2. Clinical and instrumental variables in the two achalasia groups after treatment

	Botox	Dysport	*P*-value
No. of failures	4/38 (10%)	7/40 (17.5%)	N.S.
LES pressure (mmHg)	18 ± 5	18 ± 10	N.S.
Symptom score	1.2 ± 0.8	1.5 ± 1	N.S.
% pH < 4	1.4 ± 1.9	0.3 ± 0.5	N.S.
Chest pain	2/38 (5.3%)	3/40 (7.5%)	N.S.
No. of relapses	4/34 (12%)	8/33 (24%)	N.S.
Follow-up (months)	6 ± 3	5.5 ± 3	N.S.

(Mean ± s.d.)

After botulinum toxin injection, 90% of the Botox group and 82.5% of the Dysport group had a symptomatic response (total score < 3) to the treatment. No differences were found between the two formulations with respect to clinical and instrumental variables (Table 2). Side-effects were reported by five patients (two in the Botox and three in the Dysport group), and consisted of mild chest pain of short duration following drug injection.

Basal pH-metric study did not reveal abnormal oesophageal acid exposure; after botulinum toxin injection no patient complained of reflux symptoms, and the average percentage of time with pH < 4 was within normal limits. However, in two patients (one in each group, who showed, respectively, % of pH < 4 of 5.8 and 6.2) an abnormal acid exposure was disclosed.

At the end of the follow-up period, symptom relapse was documented in 12% of Botox patients and 24% of Dysport patients (P = N.S.).

DISCUSSION

The present study, carried out in a relatively large group of patients, once again confirmed that intrasphincteric botulinum toxin injection, at least in the short to medium term, is a safe and effective therapeutic option for the treatment of oesophageal achalasia.

This study is the first to compare two equivalent doses of commercially available formulations of botulinum toxin, and showed that 100 U of Botox and 250 U of Dysport share similar therapeutic efficacy and tolerability in the treatment of achalasic patients. These effects were similar after both a month of treatment and at the end of the follow-up period (average about 6 months). The choice of the Dysport dose was based on literature data suggesting that 1 U of Botox is roughly equivalent to 3–4 U of Dysport. Because Dysport is supplied as packages containing 500 U, we chose a dose of 250 U for practical (i.e. economical) reasons, in that this choice would allow treatment of two patients with each package.

Another aim of the study was to evaluate whether a therapy that lowers LES pressure, although from an abnormal (pathological) level, might favour the occurrence of pathological acid reflux in the oesophagus. Although such an event is reported to occur in about 2% of achalasia patients after pneumatic dilatation,[15] no data are available on long-term follow-up. Moreover, a recent study claimed that 20/48 (41.6%) achalasic patients had pathological acid reflux before dilatation.[16] Further studies, however, documented that pathological acid reflux in achalasic patients before treatment is uncommon, and that the increased acidification in the oesophageal lumen may be due to fermentation of the ingesta.[17] Our own results also showed that this is a rare phenomenon, and it was documented in only 2/50 (4%) patients who, however, did not complain of acid-related symptoms.

After surgical myotomy, notwithstanding anti-reflux procedures, the percentage of oesophageal acid reflux is 15% by abdominal approach, 11% by thoracic approach, and 11% by laparoscopic approach.[2] In a few studies with a longer follow-up (10–20 years), these results also seem to worsen.[18–20]

From previous experience,[21] up to 20% of achalasic patients do not experience any benefit from botulinum toxin treatment. To date, the overall results cannot predict whether this is due to a resistance to botulinum toxin[22] or to some intrinsic characteristics of these patients that may be responsible for the lack of response.

In conclusion, both available formulations of botulinum toxin are potentially useful for treatment of achalasic patients. The trend towards less favourable results with Dysport could be due to the greater mean age in this group. However, in our experience older patients treated with botulinum toxin usually had better results than younger patients (V. Annese and G. Bassotti, unpublished data). It remains to be determined whether this approach is also effective in the long term, because such data on Dysport are not available. Moreover, when considering the combined failure and relapse rates, nearly 40% of patients in the Dysport group did not have a satisfactory outcome. This should be kept in mind, together with the unitary cost per patient, which in Italy is about US$350 for Botox and US$450 for Dysport.

Finally, the precise role of this approach is still being debated, as well as the cost-effectiveness in comparison to older, more traditional therapeutic approaches. This warrants further studies, in order to establish firm conclusions on the most effective approach to this not uncommon pathological condition.

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REFERENCES

1 Wong RKH, Maydonovitch CL. Achalasia. In: Castell DO, ed. The Esophagus. Boston: Little, Brown, 1995: 219–45.
2 Vaezi MF, Richter JE. Current therapies for achalasia. Comparison and efficacy. J Clin Gastroenterol 1998; 27: 21–35.
3 Pasricha PJ, Ravich WJ, Hendrix TR, Sostre S, Jones B, Kalloo AN. Botulinum toxin for the treatment of achalasia. N Engl J Med 1995; 322: 774–8.
4 Annese V, Basciani M, Lombardi G, *et al.* Perendoscopic injection of botulinum toxin is effective in achalasia after failure of myotomy or pneumatic dilatation. Gastrointest Endosc 1996; 44: 461–5.
5 Pasricha PJ, Rai R, Ravich WJ, Hendrix TR, Kalloo AN. Botulinum toxin for achalasia: long-term outcome and predictors of response. Gastroenterology 1996; 110: 1410–15.
6 Annese V, Basciani M, Borrelli O, Leandro G, Simone P, Andriulli A. Intrasphincteric injection of botulinum toxin is effective in long-term treatment of esophageal achalasia. Muscle Nerve 1998; 21: 1540–2.
7 Vaezi MF, Richter JE, Wilcox CM, *et al.* Botulinum toxin versus pneumatic dilatation in the treatment of achalasia: a randomised trial. Gut 1999; 44: 231–9.
8 Gordon JM, Eaker EY. Prospective study of esophageal botulinum toxin in high-risk patients. Am J Gastroenterol 1997; 92: 1812–17.
9 Annese V, Basciani M, Perri F, *et al.* Controlled trial of botulinum toxin injection versus placebo and pneumatic dilation in achalasia. Gastroenterology 1996; 111: 1418–24.
10 Bassotti G, Battaglia E, Debernardi V, *et al.* Esophageal dysfunction in scleroderma. Relationship with disease subsets. Arthritis Rheum 1997; 40: 2252–8.
11 Bassotti G, Fiorella S, Germani U, Roselli P, Battaglia E, Morelli A. The nutcracker esophagus: a late diagnostic yield notwithstanding chest pain and dysphagia. Dysphagia 1998; 13: 213–27.
12 Jamieson JR, Stein HJ, DeMeester TR, *et al.* Ambulatory 24 h esophageal pH monitoring: normal values, optimal thresholds, sensitivity, specificity and reproducibility. Am J Gastroenterol 1992; 87: 1071–5.
13 Jankovic J. Botulinum toxin in movement disorders. Curr Opin Neurol 1994; 7: 358–66.
14 Brin ME. Botulinum toxin: chemistry, pharmacology, toxicity, and immunology. Muscle Nerve 1997; 20(Suppl. 6): S146–68.
15 Reynolds JC, Parkman HP. Achalasia. Gastroenterol Clin North Am 1989; 18: 223–53.
16 Shoenut JP, Micflikier AB, Yaffe CS, Den-Boer B, Teskey JM. Reflux in untreated patients with achalasia. J Clin Gastroenterol 1995; 20: 6–11.
17 Benini L, Sembenini C, Castellani G, *et al.* Pathological esophageal acidification and pneumatic dilation in achalasic patients. Too much or not enough? Dig Dis Sci 1996; 41: 365–71.
18 Ellis FH, Watlins E, Gibb SP, Heatley GJ. Ten to 20-year clinical results after short esophagomyotomy without an antireflux procedure for esophageal achalasia. Eur J Cardiovasc Surg 1992; 6: 86–9.
19 Malthaner RA, Tood R, Miller L, Pearson FG. Long-term results in surgically managed esophageal achalasia. Ann Thorac Surg 1994; 58: 1343–6.
20 Mattioli S, Di Simone MP, Bassi F, *et al.* Surgery for esophageal achalasia. Long-term results with three different techniques. Hepatogastoenterology 1996; 43: 492–500.
21 Annese V, Bassotti G, Coccia G, *et al.*. Multicentre, dose-finding study of botulinum toxin for the therapy of esophageal achalasia. Gastroenterology 1998; 114: A713 (Abstract).
22 Jannkovic J, Schwartz KS. Clinical correlates of response to botulinum toxin injections. Arch Neurol 1991; 48: 1253–6.