TECHNOLOGY ASSESSMENT STATUS EVALUATION

BOTULINUM TOXIN THERAPY IN GASTROINTESTINAL ENDOSCOPY

NOVEMBER, 1996

INTRODUCTION

In order to promote the appropriate use of new or emerging endoscopic technologies which impact on endoscopic practice, the ASGE Technology Assessment Committee has developed a series of Status Evaluation papers. By this process, relevant information about these technologies may be presented to practicing physicians for the education and care of their patients. In many cases, data from randomized controlled trials is lacking and only preliminary clinical studies are available. Practitioners should continue to monitor the medical literature for subsequent data about the efficacy, safety and socioeconomic aspects of these technologies.

BACKGROUND

Botulinum toxin type A is one of three toxins produced by Clostridium botulinum responsible for botulism in humans. The 150,000 MW neurotoxin binds irreversibly to presynaptic cholinergic nerve endings and inhibits acetylcholine release [1]. This blockade leads to an accelerated loss of junctional acetylcholine receptors, and ultimately results in functional denervation of the affected muscle. This effect is used clinically by injection of the toxin into specific muscles. The toxin is obtained for clinical use by acidification and centrifugation of bacterial cultures, and subsequent purification [2].

Injection of botulinum toxin has been used successfully to treat ophthalmologic and neuromuscular disorders including strabismus, nystagmus, blepharospasm, orofacial dyskinesia, cervical dystonia (spasmodic torticollis), laryngeal dystonia (spasmodic dysphonia), hemifacial spasm, and task-specific dystonias such as writers' cramp. The lack of durable response is a limiting factor, with a mean duration of response lasting from 7-19 weeks [2]. Patients may respond to repeat injections, but patients become refractory due to immunologic resistance to the toxin [3].

Achalasia is a motility disorder of the esophagus whose principal features are a variable loss of esophageal peristalsis and failure of relaxation of the lower esophageal sphincter (LES), thought to result from a loss of inhibitory nerves and unopposed stimulation of the smooth muscle by acetylcholine and other mediators. Botulinum toxin has been shown in vitro to interfere with cholinergic signaling in the myenteric nervous system, and thus to affect smooth muscle. Animal studies demonstrating a significant decrease in LES pressure after botulinum toxin injection led to clinical trials investigating its efficacy for the treatment of achalasia [4,5].

TECHNICAL CONSIDERATIONS

The lyophilized toxin is packaged in 100 U vials and is reconstituted using sterile non-preserved saline. Dilution should be performed gently, avoiding bubbling and shaking, to prevent denaturation of the toxin. The reconstituted preparation should be injected within four hours, and refrigerated until use. The lower esophageal sphincter is visualized endoscopically by identification of the sphincteric rosette, typically seen at the squamocolumnar junction. With the intent of intramuscular injection, a 5mm injector needle is used to infiltrate at least 20 units of

botulinum toxin (20 U/ml) into each quadrant for a total of 80 units. The optimal dose is currently unknown. Whether the addition of EUS to guide injection will increase or prolong response to therapy is also unknown.

INDICATIONS

Botulinum toxin injection is not FDA-approved for any gastrointestinal disorders. Studies support the use of botulinum toxin for achalasia[5-8], with anecdotal reports of its use in anal fissure [9,10], sphincter of Oddi dysfunction[11], "pseudoachalasia"[12], and Chagas' disease [13].

EFFICACY

Initial symptomatic response rates of 70-90% have been reported for patients with achalasia. Approximately two-thirds of patients will remain in remission at 6 months after a single treatment with a [6-8] median duration of remission of 468 days. Patients who relapse will often respond to subsequent injections. Older age and the presence of vigorous achalasia may predict a better response to injection [7]. In addition, thirteen preliminary reports comprising the experience of botulinum toxin injection in 244 patients have been presented [14-26]. Initial response rates were 60-100%, with 3 month efficacy rates of 55-80% after a single injection. No serious side effects have been documented.

Healing of chronic anal fissure after botulinum toxin injection of the external anal sphincter occurred in 70-83%, without the incontinence associated with surgical treatment [9,10]. There are limited data to make conclusions regarding efficacy in the setting of SOD, "pseudoachalasia" or Chagas' disease.

SAFETY DATA

Botulinum toxin has been used in thousands of patients with ocular and spastic muscle disorders at varying doses without serious reactions [2]. No significant morbidity or mortality has been reported with the use of botulinum toxin injection for achalasia. Botulinum toxin injection adds little incremental risk to that associated with upper gastrointestinal endoscopy. Adverse reactions include diffuse skin rash and transient chest pain or heartburn.

There has been no reported hypersensitivity to the agent. The effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or drugs known to interfere with neuromuscular transmission, e.g. paralytic agents. Teratogenicity of botulinum toxin is not known. However, in clinical trials of botulinum toxin several pregnant women have received the drug without adverse effect on the fetus. The LD50 of botulinum toxin is 40U/kg body weight when given intravenously or intramuscularly [2]. The entire contents of a 100 U vial is below the estimated dose for systemic toxicity in humans weighing 6kg or greater (Package insert, Allergan, Irvine, CA).

FINANCIAL CONSIDERATIONS

The average wholesale price of a 100 U vial is $382. There is no CPT code for botulinum toxin injection.

COMPARISON TO AVAILABLE TECHNOLOGIES

Currently, standard therapy for achalasia involves either surgical myotomy or pneumatic dilatation. Surgical myotomy is associated with a long-term response rate of 80-95%, and requires a hospital stay of approximately seven to ten days [27-29]. Laparoscopic myotomy may decrease hospital stay and convalescence.[30] Pneumatic dilatation is associated with a 65-90% response rate, and may be performed on an outpatient basis. The main complication of perforation occurs in less than 5% of cases [27,29,31]. There are no published randomized controlled trials comparing botulinum toxin injection with alternative therapies.

CONCLUSIONS

Botulinum toxin injection for achalasia is a promising technique, due to its minimally invasive nature, ease of use, and lack of morbidity. The significant relapse rate and need for repeat injection may limit its preferential use compared to conventional therapy. Prospective data comparing cost-effectiveness and long-term response with conventional therapy for achalasia are needed.

REFERENCES

1. Simpson LL. The origin, structure, and pharmacologic activity of botulinum toxin. Pharmacol Rev 1981;33:155-88.

2. Jankovic J, Brin MF. Therapeutic uses of botulinum toxin. N Engl J Med 1991;324:1186-94.

3. Borodic G, Johnson E, Goodnough M, Schantz E. Botulinum toxin therapy, immunologic resistance, and problems with available materials. Neurology 1996;46:26-9.

4. Pasricha PJ, Ravich WJ, Kalloo AN. Effects of intrasphincteric botulinum toxin on the lower esophageal sphincter in piglets. Gastroenterology 1993;105:1045-9.

5. Pasricha PJ, Ravich WJ, Hendrix TR, Sostre S, Jones B, Kalloo AN. Treatment of achalasia with intrasphincteric injection of botulinum toxin: A pilot trial. Ann Intern Med 1994;121:590-1.

6. Pasricha PJ, Ravich WJ, Hendrix TR, Sostre S, Jones B, Kalloo AN. Intrasphincteric botulinum toxin for the treatment of achalasia. N Engl J Med 1995;322:774-8.

7. 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.

8. Fishman VM, Parkman HP, Schiano TD, et al. Symptomatic improvement in achalasia after botulinum toxin injection of the lower esophageal sphincter. Am J Gastroenterol 1996;91:1724-30.

9. Jost WH, Schimrigk K. Therapy of anal fissure using botulin toxin. Dis Colon Rectum 1994;37:1321-4.

10. Gui D, Cassetta E, Anastasio G, et al. Botulinum toxin for chronic anal fissure. Lancet 1994;344:1127-8.

11. Pasricha PJ, Miskovsky EP, Kalloo AN. Intrasphincteric injection of botulinum toxin for suspected sphincter of Oddi dysfunction. Gut 1994;35:1319-21.

12. Vallera RA, Brazer SR. Botulinum toxin for suspected pseudoachalasia. Am J Gastroenterol 1995;90:1319-21.

13. Ferrari AP Jr, Siqueira ES, Brant CQ. Treatment of achalasia in Chagas' disease with botulinum toxin. N Engl J Med 1995;332:824-5.

14. Schroeder P, Slaughter R, Turbey C, et al. Treatment of achalasia: botulinum toxin versus pneumatic dilatation. Am J Gastroenterol 1995;90:1571.

15. Waterfall WE, Tougas G, Fachnie B, Chauhan U. Clinical and manometric response to botulinum toxin (Botox) used as primary treatment for achalasia. Gastroenterology 1995;108:A255.

16. Annese V, Perri F, Napolitano G, et al. Botulinum toxin for achalasia: a placebo-controlled trial with follow-up of six months. Gastroenterology 1995;108:A563.

17. Jin HO, Potter GD, Shah AN, et al. Effect of intrasphincteric injection of botulinum toxin on esophageal motility in achalasia. Gastroenterology 1995;108:A123

18. Bansal R, Koshy S, Scheiman JM, Barnett JL, Nostrant TT. Interim analysis of a randomized trial of Witzel pneumatic dilation vs intrasphincteric injection of botulinum toxin (BOTOX) for achalasia. Gastroenterology 1996;110:A56

19. CuilliÅre C, DucrottÄ P, Zerbib F, et al. Achalasia: outcome of patients treated by intrasphincteric injection of botulinum toxin (BT). Gastroenterology 1996;110:A86.

20. Eaker EY, Gordon JM. Esophageal botulinum toxin injection in high risk achalasia patients: a prospective trial. Gastroenterology 1996;110:A99.

21. Greaves RRSH, Mulcahy HE, Patchett SE, et al.Botulinum toxin in the treatment of achalasia: a promise unfulfilled. Gastroenterology 1996;110:A123.

22. Kozarek RA, Gelfand MD, Patterson DJ, et al. Prospective trial of 50 vs 100 IU of Type A botulinum toxin for idiopathic achalasia. Gastroenterology 1996;110:A162

23. Gaudric M, Guimbaud R, Chaussade S, et al. Pneumatic dilatation (PD) versus intrasphincteric botulinum toxin (BT) in the treatment of achalasia: preliminary results of a controlled study. Gastroenterology 1996;110:A667.

24. Boyce HW, Robinson BE, Jones J. Botulinum toxin (BoTox) therapy for classic and variant achalasia: results in 59 patients. Gastrointest Endosc 1996;43:292.

25. Kotfila R, Camp R, Willits N, Trudeau W. Transendocopic injection of botulinum toxin should be the initial therapy for achalasia. Gastrointest Endosc 1996;43:298.

26. Fiorini AB, Corti R, Valero JL, Bai JC, Boerr L. Botulinum toxin for achalasia: Results of a controlled trial with a follow-up of twelve months. Gastrointest Endosc 1996;43:335.

27. Ferguson MK. Achalasia: Current evaluation and therapy. Ann Thorac Surg 1991;52:336-42.

28. Csendes A, Braghetto I, Henriquez A,Cortes C. Late results of a prospective randomised study comparing forceful dilatation and oesophagomyotomy in patients with achalasia. Gut 1989;30:299-304.

29. Richter JE. Achalasia: Whether the knife or balloon? Not such a difficult question. Am J Gastroenterol 1991;86:810-11.

30. Ancona E, Anselmino M, Zaninotta G, et al. Esophageal achalasia: Laparoscopic versus conventional open Heller-Dor operation. Am J Surg 1995;170:265-70.

31. Barkin JS, Guelrud M, Reiner DK, Goldberg RI, Phillips RS. Forceful balloon dilation: an outpatient procedure for achalasia. Gastrointest Endosc 1990;36:123-6.

Prepared by:
Technology Assessment Committee
DL Carr-Locke, MD, Chair
M. Stanley Branch, MD
William J. Byrne, MD
Mitchell I. Conn, MD
Karen Laing, RN, CGRN
Douglas B. Nelson, MD
Bret T. Petersen, MD
Eduard Phillips, MD
Irving Waxman, MD

For reprints please contact:
American Society for Gastrointestinal Endoscopy
13 Elm Street
Manchester, MA 01944