

Intrasphincteric injection of botulinum toxin for suspected sphincter of Oddi dysfunction

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Abstract

Botulinum toxin is a potent inhibitor of the release of acetylcholine from nerve endings. It has previously been shown that it can effectively reduce lower oesophageal sphincter pressures both in animals and humans with achalasia. This study examined the hypothesis that locally injected botulinum toxin could also reduce sphincter of Oddi pressure in patients with sphincter of Oddi dysfunction. Two patients with postcholecystectomy pain syndrome were diagnosed with sphincter of Oddi dysfunction (by biliary manometry in one patient and by hepatobiliary scanning criteria in the other). Botulinum toxin was injected into the sphincter of Oddi, by a sclerotherapy needle passed through a duodenoscope. In the first patient, intrasphincteric injection of botulinum toxin reduced sphincter pressure by about 50%, an effect that was sustained for at least four months. In the second patient, intrasphincteric injection caused about a 50% improvement in bile flow, with normalisation of scintigraphy. Neither patient showed any sustained improvement in pain despite these objective findings. Both patients eventually had endoscopic sphincterotomy, which also did not result in symptomatic improvement in either patient. No side effects were seen. Intrasphincteric botulinum toxin is a simple and effective means of lowering sphincter of Oddi pressure. This technique has potential for being useful clinically.

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Sphincter of Oddi dysfunction is a disorder that may be associated with a variety of pancreatobiliary syndromes, of which the commonest is possibly recurrent upper abdominal pain in the setting of a previous cholecystectomy. The disorder is characterised by various abnormal patterns of sphincter motility that supposedly result in a comparative obstruction to bile flow.¹ Despite some progress in the past five years, sphincter of Oddi dysfunction continues to be a clinical controversy.² It is difficult to diagnose without performing sphincter of Oddi manometry, a procedure that is potentially risky and not widely available. Yet, an accurate diagnosis is essential for successful treatment. To date, the only effective treatment for this condition has been sphincterotomy, which carries a significant risk of complications and thus cannot be recommended empirically.

Botulinum toxin is a potent inhibitor of the release of acetylcholine from nerve endings and

this property has been used effectively to treat patients with a variety of conditions associated with skeletal muscle spasm. More recently, we have shown that botulinum toxin can also be used successfully to treat smooth muscle disorders such as achalasia.³ We now report the first use of botulinum toxin in two patients with sphincter of Oddi dysfunction and suggest how the appropriate use of this agent may provide a new approach to this difficult clinical problem.

Patients and methods

BILIARY MANOMETRY

Endoscopic sphincter manometry was performed at the time of endoscopic retrograde cholangiopancreatography (ERCP) in a station pull through fashion using a standard triple lumen sphincter of Oddi manometry catheter with an outer diameter of 1.7 mm. The catheter lumen was perfused with distilled water at a rate of 0.25 ml/min by a pneumohydraulic capillary infusion system (Arndorfer Medical Specialties Inc, Greendale, Wisconsin). Pressures within the catheter were transmitted to external transducers and recorded by a 4 channel polygraph (Dynograph Recorder R611, Beckman Instruments, Palo Alto, California). Duodenal pressures were recorded simultaneously by means of a separate catheter taped to the outside of the endoscope.

BILIARY SCINTIGRAPHY

Hepatobiliary scanning was performed after a three hour fast. The patient received 0.02 µg/kg of cholecystokinin in a three minute infusion. Fifteen minutes later, 185 MBq of technetium-99m (^{99m}Tc)-DSIDA (disofenin) was given intravenously. Both static and dynamic images were obtained for the next 60 minutes. Counts were obtained from two regions of interest: the right lobe of the liver and the common bile duct. As previously described, a numeric score (range 0 to 12) was assigned to each scan, based on several parameters.⁴ According to this system, a score of 5 or more denotes sphincter of Oddi dysfunction, 'normal' scores being 0-4. In a prospective blinded study, the degree of correlation between this scintigraphic score and manometrically defined sphincter of Oddi dysfunction was shown to be 100%.⁴

INTRASPINCTERIC INJECTION OF BOTULINUM TOXIN

Botulinum toxin (Oculinum, Allergan), reconstituted in an appropriate volume of isotonic saline, was injected by a 5 mm sclerotherapy

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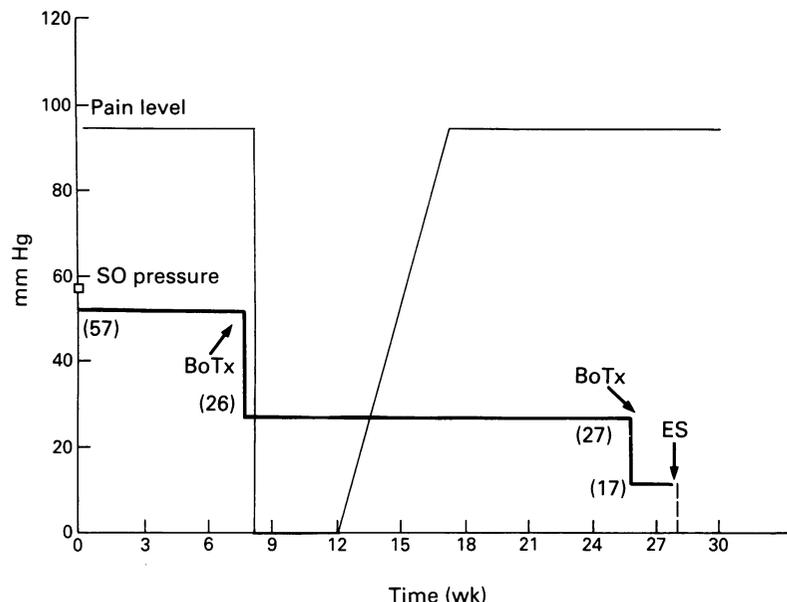


Figure 1: Clinical and manometric response to botulinum toxin injection (BoTx) and endoscopic sphincterotomy. This is a schematic depiction of the pain level (---) and sphincter of Oddi pressures (—) in relation to various interventions in the first case. Botulinum toxin (BoTx) injection is shown by the arrows and sphincter of Oddi (SO) pressures as determined manometrically are shown in parentheses. Note that the initial clinical response to BoTx injection was short lived, despite persistent low pressures. Pain intensity was unchanged despite a second injection of BoTx and endoscopic sphincterotomy (ES).

thrombocytopenia, the risk of sphincterotomy in this patient was considered to be increased. After extensive discussions with the patient, 20 units of botulinum toxin were injected into the sphincter. After one week, manometry was repeated and when interpreted by a blinded observer, showed that the basal sphincter of Oddi pressure had decreased to 26 mm Hg, a reduction of about 50%. Although the patient noted an initial improvement in her pain, her symptoms had returned to baseline in about two months. Follow up manometry done four months later showed a sphincter of Oddi pressure of 27 mm Hg. After a second injection (40 U) of botulinum toxin, a further decline in sphincter of Oddi pressure to 17 mm Hg was seen when measured three weeks later. No clinical improvement was seen either after the second injection or after a subsequent endoscopic sphincterotomy. No side effects were seen. Figure 1 summarises this patient's clinical and manometric data.

Case report 2

A 45 year old white woman presented with an 18 month history of right upper quadrant pain, which persisted despite a cholecystectomy. An ERCP was normal but biliary manometry could not be performed because of technical problems. Biliary scintigraphy, however, showed a considerably delayed bile flow with a scintigraphic score of 7, a figure that we have previously shown to be invariably associated with abnormally increased sphincter of Oddi pressure.⁴ Botulinum toxin (80 U) was then injected into the sphincter of Oddi as previously described. Biliary scintigraphy after one week showed improvement in common bile duct emptying at 60 minutes. Bile duct clearance increased from 30.8 to 44.8%, representing a nearly 50% improvement in biliary flow (Fig 2). Scintigraphic criteria normalised with a score of 1. There was no clinical improvement, however, in response to either the injection or a subsequent sphincterotomy. No side effects were seen.

needle in four aliquots of 0.25 ml each along the length of the intraduodenal segment of the sphincter (in the general direction of a conventional sphincterotomy).

Informed consent was obtained from both patients.

Results

CASE REPORT 1

A 43 year old white women with cryptogenic cirrhosis and a past history of cholecystectomy, presented with chronic intermittent right upper quadrant pain with radiation to the back. Poor liver excretory function invalidated the results of biliary scintigraphy in this particular patient. An ERCP did not show any significant lesions. Biliary manometry showed a raised sphincter of Oddi pressure of 57 mm Hg (normal <40 mm Hg). Because of a prolonged prothrombin time and comparative

Discussion

Recurrent postcholecystectomy pain is a common clinical problem, affecting 10% or more patients undergoing cholecystectomy every year.^{5,6} Sphincter of Oddi dysfunction has been implicated in the aetiology of 10–20% of these cases.⁵ Such dysfunction can result from a true stenosis or secondary to spasm of the sphincter. In most cases, sphincter of Oddi dysfunction continues to present problems, both in terms of diagnosis as well as treatment. Although muscle spasm is thought to play a significant part in these cases, the response to conventional smooth muscle relaxants such as nitrates and calcium channel antagonists has been disappointing.^{1,7,8}

Sphincterotomy is considered to be the most effective treatment for patients with sphincter of Oddi dysfunction.⁹ Unfortunately, there are major risks with this procedure such as pancreatitis and bleeding.¹⁰ This makes it

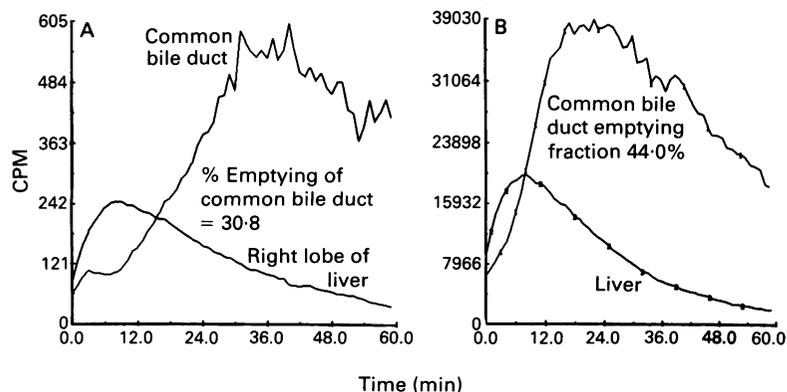


Figure 2: Scintigraphic improvement in bile flow after botulinum toxin (BoTx) injection. Bile emptying from the right lobe of the liver and common bile duct in the second patient are shown before (baseline) (A) and one week after (B) intrasphincteric BoTx injection. Note the considerable improvement in common bile duct emptying after treatment.

necessary for the endoscopist to firmly establish the diagnosis of sphincter of Oddi dysfunction before considering sphincterotomy. At present, the only reliable way to do this is by biliary manometry, a procedure that is difficult to perform, and associated with considerable discomfort to the patient as well as a significant risk of pancreatitis of its own.¹¹ A further and potentially more confounding problem is that even if manometric evidence of sphincter of Oddi dysfunction is obtained, it does not always prove that it is the cause of the patient's pain.² This is not surprising, as sphincter of Oddi dysfunction may be associated with a variety of other painful disorders associated with bowel dysmotility, such as gastroparesis, oesophageal motility disorders etc.¹

On the basis of our preliminary report, intrasphincteric botulinum toxin injection seems to be a promising method to lower sphincter of Oddi pressure, with several advantages over conventional treatment. It is a simple technique that can be carried out at the time of the initial diagnostic ERCP, has little or no systemic side effects at the doses used, maintains a constant effect, and is comparatively long lasting. The rationale behind the use of botulinum toxin in this condition is based on the assumption that cholinergic influences play an important part in the maintenance of sphincter tone.¹²⁻¹⁷ Botulinum toxin blocks the release of acetylcholine from nerve endings in both skeletal¹⁸ and smooth muscle systems.¹⁹ In this report, we have shown that a single injection of botulinum toxin reduced basal sphincter of Oddi pressure by about 50%, an effect that seemed to last several months (case report 1). Further, this effect is physiologically significant as it was shown to improve bile flow (case report 2).

This effect of botulinum toxin has the potential for being clinically useful in two ways. Firstly, intrasphincteric injection of botulinum toxin (followed by scintigraphic improvement in bile flow) may serve as a useful and simple therapeutic trial to select patients whose pain is caused by sphincter of Oddi dysfunction. Sphincterotomy may therefore be avoided in those patients whose pain does not respond to

botulinum toxin injection (such as the two patients in this report). Secondly, if longterm efficacy is established, botulinum toxin may prove to be a viable and potentially safer therapeutic alternative to sphincterotomy in patients whose pain is truly secondary to sphincter dysfunction. The validity of both these attractive hypotheses needs to be tested by further prospective studies, which are being carried out at our institution.

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