Novel treatment (new drug/intervention; established drug/procedure in new situation)

Jaundice following intravesical botulinum toxin – a previously unreported complication

R R Marri,¹ S J Bromage,¹ A Darmalingum,¹ C Calvert,² G Banait,² D A Jones,¹ S Islam¹¹ Department of Urology, Royal Blackburn Hospital, Blackburn, Burnley, Lancashire, UK² Department of Gastroenterology, Royal Blackburn Hospital, Blackburn, Burnley, Lancashire, UK

Correspondence to R R Marri, marrireddy@yahoo.com

Summary

A 59-year-old woman presented 5 days after her third instillation of intravesical botulinum toxin with right upper quadrant pain and jaundice. Blood tests demonstrated deranged liver function tests. An abdominal ultrasound, radiograph, magnetic resonance cholangiopancreatography, serum hepatitis screen, immunoglobulins and autoantibody testing were normal. An ultrasound-guided liver biopsy was performed. The histological appearances were those of chronic active/lobular hepatitis. Following treatment with steroids, her jaundice improved over a period of about 3 weeks. Her serum liver function tests returned to normal in 3 months. The steroids were discontinued once her liver function tests normalised. The patient had no further recurrence of jaundice and serum liver function tests have been within normal limits after 6 months follow-up.

BACKGROUND

Botulinum toxin (BTX) was first used in urology 20 years ago for treating detrusor external sphincter dyssynergia. Although currently unlicensed for intravesical injection in the United Kingdom, it is a widely accepted treatment for detrusor overactivity.¹ It has also been used for various other medical and cosmetic procedures.² There is limited data regarding the safety profile of BTX. To the best of our knowledge, there have been no reports of jaundice following administration of BTX to any part of the body. We present a case of jaundice following intravesical BTX injection. We also review the literature regarding the use of intravesical BTX for detrusor overactivity and its safety profile.

CASE PRESENTATION

A 59-year-old woman presented 5 days after her third instillation of intravesical BTX-A (Botox; Allergan, Irving, California, USA) with a 2-day history of spasmodic right upper quadrant pain and jaundice. She was complaining of nausea, vomiting, pale loose stools and dark urine. Mild icterus was noted on examination. The patient denied taking any regular medications as well as any known drug allergies. She was a non-smoker and had minimal weekly alcohol intake (<5 units per week). Following a diagnosis of urodynamically proven detrusor overactivity, she had undergone two previous intravesical BTX-A instillations. All three procedures were performed under general anaesthetic using a rigid cystoscope. Each treatment consisted of intradetrusor injection of 200 IU of BTX-A (mixed with 20 ml of 0.9% saline) into 20 sites in the bladder sparing the trigone (10 IU per site). On each occasion, fentanyl and propofol were used as the anaesthetic agents and the patient also received 1.2 g of prophylactic co-amoxycylav intravenously at induction. She had previously undergone surgical procedures (appendicectomy, cystocoele repair, hysteroscopy with polypectomy) using identical anaesthetic agents with no subsequent problems.

On direct questioning, the patient admitted to having had similar episodes, though much less severe, after both previous treatments with intravesical BTX-A. Following her first BTX-A treatment, she had experienced abdominal pain and vomiting lasting 1 day, which settled spontaneously without requiring medical attention. Similarly, 2 days following her second dose of BTX-A, she presented to accident and emergency with right upper quadrant pain and vomiting. Routine blood tests, including liver function tests, were normal at that time, as was the abdominal ultrasound. The patient was discharged with a suspected diagnosis of biliary colic despite the lack of biliary calculi on ultrasound. She made a full recovery from this episode over a week.

INVESTIGATIONS

Urine dipstick and subsequent urine culture and microscopy were within normal limits. Blood tests demonstrated deranged liver function tests with elevated levels of serum bilirubin, alanine aminotransferase and alkaline phosphatase (figure 1). An abdominal ultrasound and radiograph were reported as normal. Magnetic resonance cholangiopancreatography demonstrated no evidence of obstruction. A serum hepatitis screen (hepatitis A immunoglobulin M (IgM), hepatitis B surface antigen, hepatitis B core antibody and hepatitis C antibody) and immunoglobulins (IgG, IgA and IgM) were within normal limits. Autoantibody testing (antinuclear antibody, antimitochondrial antibody, antineutrophil cytoplasmic antibody, anti-smooth muscle antibody) revealed no autoantibodies. In the absence of a clear aetiology for the persistent jaundice, a needle core ultrasound-guided liver biopsy was performed. The histology showed mild hepatocellular steatosis of predominantly macrovesicular type with a spotty chronic lobulitis and foci of apoptosis. There was focal chronic interface hepatitis, but no evidence of cirrhosis, dysplasia or neoplasia. In conclusion, the appearances were those of chronic active/lobular hepatitis (Ludwig/Batts grade 2,

Figure 1 Serum liver function test following the third instillation of intravesical BTX-A (normal range).

stage 1–2). The aetiological possibilities for these appearances include viral hepatitis, autoimmune hepatitis, a drug reaction and non-alcoholic steatohepatitis (NASH) due to obesity.

DIFFERENTIAL DIAGNOSIS

In this patient, the jaundice and abnormal hepatic function may have been related to intravesical treatment with BTX-A. The mechanism for this, however, is unclear. Other likely causes of jaundice were ruled out, as were reactions to other agents, such as anaesthetic agents that had been administered with no problems in the past. Co-amoxiclav is one of the most frequently implicated causes of drug-induced hepatotoxicity.³ O'Donohue *et al* reviewed 22 patients with co-amoxiclav-induced jaundice (oral administration in 21 and intravenous in 1). The mean duration of treatment with the antibiotic was 7 days (range 3–21 days). Liver biopsy in these patients showed lymphocytic infiltration of portal tracts and perivenular bilirubinostasis.⁴ Neither of these histological features was seen in our patient. It can be argued that jaundice could have resulted due to an idiosyncratic reaction to co-amoxiclav. But the patient had had oral co-amoxiclav in the past without any adverse reactions. Considering previous uneventful treatment with co-amoxiclav and the histopathological features, we feel that co-amoxiclav is unlikely to be the causative agent. Autoimmune hepatitis also seems unlikely as her autoantibodies were negative. Given the patient's obesity and steroid-related hyperglycaemia, NASH could explain some of the histopathological changes noted on biopsy.

OUTCOME AND FOLLOW-UP

Following treatment with steroids, her jaundice improved over a period of about 3 weeks. Her serum liver function tests were regularly monitored and returned to within normal limits in 3 months. The steroids were discontinued once her liver function tests normalised. While on steroids her blood glucose levels were elevated subsequently normalising after withdrawal. There was no relapse of jaundice (clinical or biochemical) after discontinuing the steroids.

DISCUSSION

BTX-A is being increasingly utilised in the management of neuropathic and idiopathic detrusor overactivity refractory to other forms of medical treatment. A number of studies have confirmed its clinical efficacy.¹ It has also been used for various other specialised medical and cosmetic procedures like cervical dystonia, blepharospasm, facial spasms and aesthetic treatment of glabellar frown lines.² However, there is a comparative dearth of data regarding the safety profile of intravesical BTX. Dmochowski and Sand² reviewed 53 studies involving the use of BTX-A in the overactive bladder and reported high postvoid residuals requiring intermittent self-catheterisation, transient muscle weakness and dose-related hyposthenia as the main side effects. None of the studies reported any major systemic adverse effects. Awsare and Jones⁵ have reported paraplegia following intravesical BTX injection. There have been no reports of jaundice following administration of BTX to any part of the body.

The fact that the patient experienced similar, but less severe side effects following each instillation of BTX-A, suggests a similar mechanism of action on each occasion. Each episode she experienced seemed to be worse than the previous one, suggesting a possible element of sensitisation. Antibody production following intradetrusor injection of BTX-A has been reported.⁶ This patient's jaundice could possibly have been caused by a similar mechanism of action. Corticosteroids have no proven benefit in drug-induced hepatotoxicity but they may have a role in treating patients with hypersensitivity reactions. This could possibly explain the improvement in this patient's liver function tests following the initiation of steroids.

Only 20% of patients presenting with acute liver failure due to drug-induced liver injury survive with supportive care.³ This case report highlights the need to consider the possibility of hepatotoxicity in symptomatic patients presenting to hospital after BTX injections given intravesically or to any part of the body.

Learning points

- ▶ Non-obstructive jaundice may be a possible side effect of BTX injections.
- ▶ The possibility of hepatotoxicity needs to be considered in symptomatic patients presenting to hospital after BTX injections.
- ▶ Further research into the safety profile of BTX is needed.
- ▶ With the increasing usage of BTX in different specialities, we propose that future studies should incorporate monitoring of liver function tests following BTX treatment.

Competing interests None.

Patient consent Obtained.

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