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Botulinum Toxin for an Overactive Bladder

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1. Introduction

Preparations of botulinum toxin (BoNT-A) have rapidly become established as a treatment option for detrusor overactivity (DO) and overactive bladder (OAB). DO can be neurogenic (NDO) (e.g. after spinal injury or multiple sclerosis) or idiopathic (IDO) (no obvious underlying cause). Although data were initially limited, several randomised controlled trials (RCTs) have been published in the last 3 years. However, the role of BoNT-A in treatment algorithms is yet to be fully established. This paper reviews the existing data, provides suggested guidance on the advice to give patients and initial dosing, and highlights where information is still lacking.

Generally, patients with OAB are initially treated with conservative measures (lifestyle changes, caffeine intake reduction, pelvic floor exercises and bladder drill), before introducing one of a range of the available anticholinergic medications (e.g. oxybutynin, tolterodine, solifenacin, trospium). Most clinicians will try two or more oral medications, before moving on to second-line treatments, which currently include implantable sacral nerve stimulators, or botulinum toxin. Guidelines from the National Institute for Health and Care Excellence¹ suggest that, following a multidisciplinary team review, BoNT-A could be considered for women with OAB caused by confirmed DO in whom conservative management, including pharmacological treatment, has been ineffective.

Botulinum toxin is administered via a cystoscope and injected into the detrusor from within, usually at 20–30 sites across the dome of the bladder, and usually sparing the trigone. It can be administered under local or general anaesthesia via rigid or flexible cystoscopy. Flexible cystoscopy and local anaesthesia is quick, easy and carries few risks.²

2. Mode of action and data from patients with NDO

BoNT-A blocks the presynaptic release of acetylcholine and causes full or partial paralysis and weakening of overactive muscle. Muscle injection of BoNT-A was first approved in 1989 to treat strabismus and subsequently found to be effective in treating various neurological disorders characterised by focal skeletal muscle hyperactivity. BoNT-A was first demonstrated to be effective when it was injected into the detrusor of patients with NDO, as a result of spinal cord injury.^{3,4} Since then, both small local observational studies and large pharmaceutical company sponsored multicentre RCTs have demonstrated significant efficacy in ameliorating NDO, reducing detrusor pressure, increasing bladder capacity, reducing episodes of incontinence and improving quality of life in patients with neurogenic incontinence. However, these improvements are usually offset by a degree of impaired bladder emptying.

It has been shown that the mechanism of action is more complicated than simple paralysis of the detrusor. As well as returning the expression of neuronal sensory receptors to normal levels in bladder biopsies taken from patients being effectively treated,⁵ the mechanism of action may also include a complex inhibitory effect on vesicular release of excitatory neurotransmitters and the axonal expression of other proteins. These are thought to be important in mediating the intrinsic or spinal reflexes thought to cause NDO.⁶ This suggests that the sensory afferent pathway is involved. An additional effect upon efferent (motor) pathways is probable because impairment or worsening of bladder emptying frequently occurs in patients with NDO,⁷ and IDO,⁸ although to a lesser extent.

The pivotal licensing study of the effect of onabotulinumtoxin A (onaBoNT-A) (Botox®, Allergan, Marlow, Bucks, UK) for NDO was published in 2011.⁷ It is now licensed for the treatment of NDO in the USA and most European countries, including the UK. There are alternative preparations of BoNT-A: abobotulinumtoxin A (aboBoNT-A) (Dysport®, Ipsen, Slough, UK), rimabotulinumtoxin B (rimaBoNT-A) (Myobloc®, Solstice Neurosciences, Louisville, KY, USA) and incobotulinum toxin A (incBoNT-A) (Xeomin®, Merz, Frankfurt, Germany). Essentially, these different preparations have the

same mode of action, but units of activity are not comparable. These alternative preparations are not yet licensed for NDO. OnaBoNT-A is now also licensed for the treatment of IDO and overactive bladder in the USA and most European countries, including the UK.

Initially onaBoNT-A was administered at 300 units for NDO, but there has been a move towards using 200 units in more recent trials. Cruz et al.⁷ randomised patients with multiple sclerosis or spinal injury to receive 200 or 300 units of onaBoNT-A or placebo. Both doses reduced weekly incontinence episode frequency within six weeks (-21.8 and -19.4 respectively) and urodynamic variables improved. The authors concluded that both doses were equally effective. Ginsberg et al.⁹ conducted a very similar RCT recruiting 416 patients and demonstrated similar improvements with a clear dose-response relationship for voiding dysfunction and concluded that 300 units had no clinical benefits over a dose of 200 units. The latter is now the usual starting dose for treatment of patients with NDO.

3. Data from patients with IDO

Numerous uncontrolled case series have reported the effects of BoNT-A in men and women with IDO and the results are broadly in agreement. Outcomes of these studies consistently demonstrate large improvements in OAB symptoms, such as urgency and frequency of urination, incontinence, use of continence pads and disease-specific quality of life outcome measures. However, there are only four RCT studies assessing the efficacy of BoNT-A as a treatment for IDO.

The first RCT compared the effect of 200 units of onaBoNT-A with placebo in a mixed-gender sample of 34 participants.¹⁰ Significant increases in bladder capacity (primary outcome) occurred in parallel with symptomatic improvement (secondary outcomes), which was maintained for 6 months by 16 patients treated with the active drug. The second RCT investigated the effects of 200 or 300 units of onaBoNT-A in comparison to placebo.¹¹ At 6 weeks, the treatment group (n = 15) showed a 57.5% reduction in the frequency of daily incontinence episodes, in contrast with a 9.3% increase over the same period among the placebo group (n = 7). However, there were no longer follow-up assessments of the participants; it is unclear whether these effects were maintained.

Brubaker et al.⁸ conducted an RCT on women only and showed that 72% (18/25 women) of the treated group who completed an additional diary reported a minimum of a 75% reduction in incontinence episodes. However, the trial was prematurely terminated due to a high incidence of asymptomatic urinary retention in the treatment group and was therefore underpowered. Tincello et al.¹² have recently completed the largest single-dose RCT comparing 200 units of onaBoNT-A to placebo in a group of 240 females over a 6-month period. There were significant improvements in voiding frequency, urgency episodes, leakage episodes and quality of life outcome measures. It was found that 31% of the treatment group became continent, compared to 12% of the control group. However, of those in the treatment group, one in six showed some voiding dysfunction during follow-up and approximately 30% were diagnosed with a urinary tract infection at some point during the study.

4. Data from patients with overactive bladder

OAB is the symptom syndrome including urgency, frequency, nocturia, with or without incontinence. OAB is associated with the urodynamic observation of DO. While the majority of the research on OAB symptoms is based on patients with a diagnosis of DO, recent studies have investigated subsets or entire groups of patients with OAB without urodynamic confirmation of DO.^{13,14} Rapp et al.¹³ evaluated 35 patients (men and women) treated with 300 units of onaBoNT-A. At 3 weeks, 60% reported 'slight' to 'complete' improvement and this effect was still evident at 6 months. There was no control group in this study. A small uncontrolled study of seven women treated with 300 units of onaBoNT-A (50–75 units injected into the urethral sphincter) showed reductions in frequency and nocturia, fewer pads used and a 20% increase in bladder capacity at three months.¹⁴ These studies have indicated that BoNT-A has a similar effect on OAB regardless of whether the patient has a confirmed diagnosis of DO.

There are two recent RCTs of botulinum toxin in OAB alone. A dose-ranging phase II randomised study¹⁵ compared doses of onaBoNT-A (50, 100, 150, 200 and 300 units) to placebo in a mixed-gender sample of 313 participants, of whom 272 completed the study. All doses of onaBoNT-A were superior to placebo in improving urgency and weekly incontinence episodes. However, there was a durable effect with doses of 100 units or more and it was suggested that a dose of 150 units was optimal as there appeared to be no obvious benefit from higher doses. Denys et al.¹⁶ reported a dose-ranging study (50, 100 or 150 units versus placebo) on 99 patients (mostly women), but this was stopped before recruiting the planned sample of 160. Both doses showed benefits in OAB symptom improvement. 65% and 56% of patients in the 100- or 150-unit dose groups respectively and 29% of the placebo group reported at least 50% improvement in symptoms; for 75% improvement these proportions were 42% in both groups. Differences in urgency and frequency episodes were significantly different from placebo in only the 150-unit group. 50% of patients achieved continence at 3 months with 150 units, compared to 55% of those in the 100-unit group and 15% in the placebo group. Urinary infection occurred in less than 10% of all treatment cases and urinary retention requiring catheterisation varied between 5–15%, the lowest level being in the 100-unit group.

Nitti et al.¹⁷ reported results from a large placebo-controlled RCT of 100 units of onaBoNT-A on 557 patients with OAB. At 3 months, treated patients had greater improvement in incontinence episodes than placebo (-2.65 versus -0.87, $P < 0.001$). 22.9% of treated patients became continent (6.5% of placebo patients). All other OAB symptom outcomes and health-related quality of life scores also improved. Urinary retention was experienced by 5% of subjects.

In view of these results, increasing numbers of clinicians are now treating patients with OAB symptoms alone with BoNT-A. However, currently there is no agreed consensus from all international guidance, partly because the evidence supporting this practice through RCTs has only become available very recently. Certainly, the majority of UK clinicians do not routinely use BoNT-A in women without a urodynamic diagnosis of DO at present.

5. Other indications for onaBoNT-A

Parkinson's disease is associated with an increase in urinary disturbance in up to 30% of patients and has traditionally been treated with anticholinergic drugs. However, the efficacy of this treatment has been shown to be poor. Early results have suggested that BoNT-A can be used in the management of bladder symptoms in Parkinson's disease by modifying the afferent nerve activity.¹⁸

BoNT-A injections were found to improve the possibility of having sexual intercourse and levator ani EMG hyperactivity in women diagnosed with vaginismus and improve the symptoms of bladder pain.¹⁹⁻²² However, RCT research of this treatment for such disorders is in its infancy.

6. Unanswered questions

For patients with NDO, the administered dose of onaBoNT-A has fallen as recent research has shown lower doses to be equally effective. The same is true for treatment of IDO where recent data from two trials^{15,16} suggest that 100 units may be as effective as 150 or 200 units, but with a lower rate of adverse events and a particularly low rate of urinary retention. It is not yet entirely clear whether this comes at a cost of more rapid return of symptoms away from a research environment. Thus, there is not a fully defined algorithm to recommend a starting dose, nor when or in whom a higher dose should be administered. There is very little data comparing different doses of the other preparations.

The majority of data published are from studies using onaBoNT-A. While there is no evidence to suggest alternative preparations of BoNT-A have a different effect profile, caution may be advised when extrapolating results from one preparation to another. Different preparations have units of activity which are not analogous so care must be taken to ensure equivalence is achieved and to our knowledge there is very scant data on rimabotulinumtoxin B (rimaBoNT-A) (Myobloc®) and incobotulinum toxin A (incBoNT-A) (Xeomin®).

Research into repeat BoNT-A injections suggests that there is no loss of treatment efficacy using this method, but data are limited. The optimal interval between injections is yet to be assessed, and it is currently unclear whether patients will require repeat injections for life or whether a proportion of patients will achieve cure after treatment. The optimal number of injection sites, depth of injection and whether it is necessary to avoid the trigone are also currently uncertain.

We do not know if any patient factors predict treatment success. It should be noted that some patients treated with the active drug in the studies above failed to obtain symptom relief, for reasons unknown. Given that there is as yet no evidence that BoNT-A is curative, some robust cost-effectiveness data are required to allow an assessment of the likely cost-benefit of single and repeated treatments in patients with IDO or OAB, particularly for those countries where health care is funded by central government rather than privately. To date, cost-effectiveness data are currently not available from randomised studies. A cost-consequence analysis of a cohort of patients with NDO or IDO suggested that onaBoNT-A was a viable option, with average moderate cost (£617) per year of symptom improvement.²³ Extrapolation of these findings suggested that onaBoNT-A would achieve a cost-effectiveness of £30,000 per Quality-Adjusted Life Year (QALY), which is generally regarded as the threshold for meaningful cost-benefit. However, until data are obtained from prospective randomised or cohort studies comparing BoNT-A with 'standard care', these figures must be regarded as preliminary data only.

7. Opinion

Current evidence suggests that BoNT-A may be effective for the symptomatic treatment of DO and OAB. Its use should however be reserved for patients who fail to improve with conservative treatment and medical management with two different anticholinergic drugs.

Most of the current evidence relates to onabotulinum toxin A (Botox®), with some data on abobotulinumtoxin A (Dysport®). Different preparations have units of activity which are not identical, so care must be taken to ensure equivalence is achieved and caution must be employed if using the other agents for which scant data are available.

The available data indicate that onaBoNT-A may provide significant relief from OAB symptoms and DO with a median duration of around 6 months. Patients should however be warned regarding adverse effects including urinary tract infections in up to one in six patients and voiding dysfunction (either total or partial) in up to 10% of women which is usually managed with self-catheterisation. Furthermore, it seems likely that the majority of patients who commence treatment with onaBoNT-A will require long-term repeat treatments, although a few may achieve 'cure'. In view of the lack of data on long-term outcomes after repeat treatment, there is currently no evidence demonstrating that this treatment is cost-effective compared to other treatments that may initially seem more expensive.

Treatment of IDO should be with 100 units of onaBoNT-A (or an equivalent dose of the other preparations). The lower dose appears to carry similar efficacy with lower rates of retention.

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