Botulinum toxin A for refractory OAB and idiopathic urinary retention: can phenotyping improve outcome for patients: ICI-RS 2019?

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Abstract

Aims

Botulinum toxin A (BTX-A) is a well-established treatment for refractory idiopathic overactive bladder (OAB). It has also been used with short-term success in treating idiopathic urinary retention. However, efficacy and complication rates are variable and predicting those likely to benefit most from treatment would enable personalisation of therapy and optimisation of outcomes. At the ICI-RS meeting in 2019 a Think Tank addressed the question of how we can improve the way we phenotype patients undergoing BTX-A treatment.

Methods

The Think Tank conducted a literature review and expert consensus meeting focussing on how advances in basic science research of the mechanism of action of BTX-A, as well as assessment of psychological comorbidity, can be translated into clinical practice to improve patient selection for therapy.

Results

Idiopathic OAB and idiopathic urinary retention are heterogenous conditions encompassing several phenotypes with multiple potential pathophysiological mechanisms. Animal models have demonstrated a CNS mechanism of action of intravesically-injected BTX-A and this has been confirmed in human functional MRI studies, but whether this tool can be used to predict outcome from treatment remains to be determined. Phenotyping based on psychological comorbidity using validated screening tools should be studied as a way to potentially optimise patient selection for therapy.

Conclusions

Advances in basic science research into the mechanism of action of BTX-A have improved our understanding of the pathophysiology of OAB and may lead to novel ways to phenotype patients. Psychological assessment is another way in which phenotyping may be improved. Areas for further research are proposed.

1 Introduction

The efficacy of intravesical Botulinum Toxin-A (BTX-A) to treat idiopathic overactive bladder (OAB) has been proven in several large, long-term prospective and randomised studies, and is recommended by international guidelines after failure of oral pharmacotherapy (1, 2). Intra-sphincteric injection of BTX-A to treat idiopathic urinary retention in women is less well-studied but small trials have demonstrated good short-term success (3, 4). However, there is variability in efficacy, duration of response, and adverse event rates (urinary retention and UTI) between patients and predictors of poor response or adverse events have not been well-defined. Understanding which patients are likely to experience the greatest efficacy, or those that are likely to develop adverse events, would enable personalisation of therapy and optimisation of outcomes. Common methods to phenotype patients include pathophysiological mechanisms of disease, clinical, radiological and urodynamic factors, but none have been shown to consistently predict outcome of therapy to date. Improving our knowledge of the mechanism of action of BTX-A may provide insight into alternative ways to optimise patient selection for treatment. Furthermore, assessment of psychological comorbidity has been shown to be beneficial in assessing patients undergoing sacral neuromodulation, but its role in optimising patient selection for BTX-A treatment remains to be studied.

2 Materials and Methods

At the International Consultation on Incontinence-Research Society (ICI-RS) meeting in 2019, a Think Tank was convened to answer the question 'Botulinum toxin A for refractory OAB and idiopathic urinary retention: can phenotyping improve outcome for patients?'. We briefly summarised current approaches to phenotyping patients by way of background and then focussed on the following questions to understand whether these alternative approaches to phenotyping could improve outcomes:

1. Can recent advances in the basic science research of the mechanism of action of BTX-A be translated into clinical practice to phenotype patients and improve patient selection for therapy?
2. What is the role of psychological comorbidity in phenotyping patients and can this be used to optimise outcomes of therapy?

The pertinent literature on the mechanism of action of BTX-A was reviewed through PubMed searches and served as the basis for discussion. Areas for future research were then proposed and these are summarised at the end of this paper.

2.1 Phenotypes of idiopathic OAB

It has been suggested that 'idiopathic OAB' is a heterogenous condition encompassing several phenotypes with multiple potential pathophysiological mechanisms, and there is emerging evidence that the same is true for 'idiopathic urinary retention' (5, 6). Identification of these underlying subtypes in clinical practice may allow tailoring of BTX-A treatment. Several clinical phenotypes have been suggested based upon underlying pathophysiology. These theoretical phenotypes are discussed below but further research is required into how these subtypes can be identified clinically, and whether this stratification can improve treatment selection or outcome.

2.1.2 Urodynamic parameters - Presence or absence of detrusor overactivity

The presence or absence of detrusor overactivity (DO) on urodynamics has been used to phenotype patients with OAB, with different underlying pathophysiological mechanisms suggested based on this (6). Evidence for the clinical relevance of this in terms of optimising outcomes from therapy was the focus of an earlier Think Tank and so has not been discussed in detail here (7). The symptoms of OAB may originate from different anatomical locations within the urogenital tracts, each with slightly different clinical phenotypes.

Myogenic OAB is a subtype thought to be related to denervation-related myogenic dysfunction resulting in abnormal electric coupling of smooth muscle cells, propagation of this electrical activity, and coordinated detrusor contraction resulting in increased bladder pressure (DO). This non-micturition activity is distinct from overactive parasympathetic-based micturition activity which may also lead to OAB. Urgency incontinence may be more prevalent in this subtype.

Urotheliogenic OAB is thought to result from urothelial/suburothelial dysfunction resulting in increased afferent sensory activity and urinary frequency/urgency (with a lower rate of urgency incontinence), which may not exhibit DO (e.g. 'sensory urgency') (8).

Urethrogenic OAB is thought to arise from activation of the urethrovesical reflex with urine entering the proximal urethra. DO may not be demonstrated, but on close questioning patients may describe urgency incontinence when moving from a sitting to standing position or on stress manoeuvres (8).

Neurogenic OAB arises from the brain or brainstem due to abnormalities in central processing of urgency and voluntary voiding, with specific areas associated with DO or non-DO related urgency (9).

It has been postulated that different treatments may be more effectively-targeted to these individual phenotypes, potentially improving outcomes (6). However, the limited clinical evidence that exists suggests that the urodynamic finding of DO does not alter outcomes for BTX-A (10), although this may be related to the limitations of standard urodynamics in diagnosing DO (11).

2.1.2 Clinical factors

Several clinical factors have been studied as methods of sub-classifying patients with OAB symptoms to optimise selection of appropriate therapy. The presence of cardiac comorbidity and metabolic syndrome (12), hypo-oestrogenism (13), concomitant functional gastrointestinal disorders (14) and autonomic nervous system dysfunction (15) have all been associated with OAB symptoms and targeting these underlying comorbid conditions may improve overall outcomes from therapy. However, whether treating underlying comorbidities will improve the overall response to BTX-A, and whether these patients should be treated with different doses/forms of BTX, remains to be studied. The role of the urinary microbiome in generating OAB symptoms has been studied in recent years and may predict response to treatment (16, 17).

2.2 Phenotypes of idiopathic urinary retention

Idiopathic urinary retention is also a heterogenous condition with different pathophysiological mechanisms resulting in inability to void. A high-tone non-relaxing urethral sphincter may be demonstrated on urethral pressure profilometry or sphincter electromyography, or retention may occur in the absence of this finding. In some women, pelvic floor dysfunction may be the underlying cause, and co-existence of comorbid conditions (functional neurological symptoms, chronic pain, chronic intestinal pseudo-obstruction, opiate use, psychological disorders) may also indicate different phenotypes of this condition (18).

3 Can recent advances in understanding the mechanism of action of BTX-A translate into improved patient selection for therapy?

Improving our understanding of the underlying mechanism of action of BTX-A may enable optimisation of patient selection for therapy and possibly technique or mode of administration.

3.1 Basic science developments

Basic science developments have focussed on whether there is a central neural effect of BTX-A injected into the bladder.

3.1.1 Is there a central desensitisation effect of BTX-A?

The proposed mechanism of action of BTX-A in earlier literature involved the hypothesis of a central desensitisation effect (19, 20) as experiments in animal models of either chronic bladder inflammation or chronic spinal cord injury, in which BTX-A had been delivered intravesically, had found evidence of a central inhibitory effect reflected mainly by the reduced expression of c-fos positive cells in the L6-S1 spinal cord segments where bladder afferents are known to project in animals (21, 22). In the chronic SCI rat model, increased c-fos expression was noted in association with urodynamically-recorded DO. Following BTX-A instillation, the decrease in DO correlated with significant decreases in c-fos levels at the L6-S1 region (22). In another animal model of inflammation-induced bladder overactivity, intravesical BTX-A application had 'restoring' effects on bladder intercontraction intervals and contraction amplitude in parallel with decreases in histological inflammation and the expression of COX-2 and EP4 receptors in both the bladder and the L6-S1 segments of the spinal cord (23).

Further evidence for a central desensitisation effect comes from porcine models, where the use of a retrograde tracer revealed that bladder injections of BTX-A were followed by significant decreases of neuropeptides and neurotransmitters involved in bladder function, such as substance P (SP), calcitonin gene-related peptide (CGRP) and nNOS, in bladder projecting neurons from the dorsal root ganglia (DRG) (24). In a similar porcine model, BTX-A bladder injections appeared to induce changes in subpopulations of noradrenergic retrogradely labelled bladder-projecting neurons from sympathetic chain ganglia, which were positive for a number of markers involved in bladder function (neuropeptide Y, vasoactive intestinal polypeptide, galanin, somatostatin, enkephalin, neuronal NOS) (25). Finally, a short report in normal rats also suggested changes in the L6-S1 spinal cord segments and respective DRG of genes associated with bladder function (sensory, cholinergic and sympathetic) following bladder injection of clinically significant doses of BTX-A (26).

3.1.2 Could these changes be the result of a direct action of the toxin?

A wealth of evidence from animal experiments as early as 4 decades ago has documented that BTX-A injected in peripheral/skeletal muscles may be accompanied by central functional, electrophysiological and neurotransmitter/growth factor expression changes (27) (28) (29) (30) attributed to retrograde axonal transport of the toxin to the spinal cord and DRG (31) (32) (33) (34) (35) .

The BTX-A receptor SV2A has been found to be abundantly expressed in cultured human DRG neurons (36), and treatment of such neurons with BTX-A resulted in loss of neurites, accumulation of cytoplasmic vesicles, reduction of membrane receptors (such as TRPV1), and altered functional responses which were dose-dependent. The evidence to-date for a bladder-to-CNS axonal transport of BTX-A to support the hypothesis of a direct action in the CNS following bladder injection of BTX-A is scarce. A single experiment in normal rats showed significant accumulation of the toxin in the DRG and, to a lesser degree, in the spinal cord following bladder injection (26), providing proof-of-

concept for retrograde transport of the toxin from the bladder to the central nervous system (CNS). The reverse has also been demonstrated, with another animal experiment demonstrating anterograde transport of the toxin from the CNS to the bladder with intrathecal administration of BTX-A resulting in cleavage of SNAP25 in nerve fibres in the bladder (37).

However, since experiments to-date have not yet demonstrated cleaved SNAP-25 in the spinal cord, DRG or areas of the CNS above the spinal cord, the possible central desensitization effect of bladder BTX-A injection cannot be attributed with certainty to a direct effect of the toxin, and needs to be explored in further studies. In addition, the contribution of this CNS intoxication to the net effect of the toxin is unknown, and future research is needed to examine in parallel and in time-sequence the changes in the CNS and the bladder. Nevertheless, the clinical significance of a possible CNS intoxication is yet unknown; in the proof-of-concept experiment by *Papagiannopoulou et al* the doses used were significantly higher (relatively) compared to those applied in humans (26), and only 0.01% of the injected dose of BTX-A reached the DRG.

3.1.3 Changes in higher centres following peripheral BTX-A injection

Electrophysiological and ultrastructural experiments in cats injected in the lateral rectus muscle could demonstrate functional (synaptic and discharge characteristics) and ultrastructural changes in brainstem motor neurons (38) (39). A recent prospective observational imaging study used brain functional MRI (fMRI) in parallel with urodynamics in patients with multiple sclerosis (MS) who received intradetrusor injection of onabotulinumtoxinA to investigate post-BTX changes in brain centres associated with LUT control. Interestingly, the authors found significant changes in MS patients compared to a control population, including increased activation in most brain regions associated with sensation and processing of urinary urgency as well as decreased activation in regions (amygdala and parahippocampal area) where fear and anxiety, possibly associated with urgency incontinence, are processed (40).

3.2 Translational aspects

The discovery of a central mechanism of action of BTX-A injected into the bladder could have clinical implications for the selection of patients for therapy and possibly for mode of administration of BTX-A.

3.2.1 The role of functional MRI

The use of fMRI to assess central pathophysiological mechanisms in patients with idiopathic OAB has been increasingly studied in recent years. A cross-sectional study of 24 female patients with normal bladder function and 16 with urgency incontinence used fMRI and resting-state functional connectivity MRI (rs-fcMRI) to identify differences in brain functional architecture between the groups (41). Significant differences in brain activation in 18 brain regions were found between control patients and those with urgency incontinence, including areas involved in attention, decision-making and primary motor and sensory functions. Multivariate pattern analysis (MVPA) of connectivity data was found to be able to predict the presence of urgency incontinence (sensitivity 89%, specificity 83%) and disease severity. Findings from this study suggest that central mechanisms involved in urgency incontinence are related to 2 processes – the level of activity in specific brain regions, and the way these regions functionally interact. Although fMRI has limitations and does not distinguish cause or effect, this provides preliminary evidence that fMRI may be a promising tool to improve our understanding of bladder pathophysiology and to phenotype patients.

A recent study of patients with neurogenic DO secondary to MS undergoing intravesical BTX-A treatment has demonstrated the potential of fMRI to phenotype patients and optimise therapy based upon baseline activation patterns (40), but whether this tool can also be used to predict outcome from BTX-A treatment for idiopathic OAB remains to be determined.

3.2.2 Alternative modes of administration

The finding of a central sensitisation effect of BTX-A from animal studies may enable optimisation of the sensory effects of therapy whilst minimising motor effects (and therefore possibly improving urgency whilst reducing urinary retention rates). Alternative drug delivery techniques are being investigated in animal and human studies, such as intravesical delivery of BTX-A a) via electromotive-drug administration, b) following bladder treatment with protamine sulphate, c) following low-energy shock-wave treatment of the bladder, d) BTX-A mixed with dimethyl sulfoxide (DMSO), e) BTX-A encapsulated in liposomes (lipotoxin) or f) conjugated with cationic peptides and g) complexed with thermosensitive hydrogel (42). The 'lipotoxin' has been trialled in a double-blind randomised-controlled trial, albeit with short-term follow-up, with significant improvements in frequency and urgency and no increased risk of urinary retention compared to placebo (43). Although urodynamic variables were not investigated, a preliminary animal study of liposome-encapsulated BTX-A revealed a significant reduction in inter-contraction interval with no effect on voiding detrusor contraction strength, suggesting an afferent effect without significant efferent effect (44). The optimal number of injection points and location of injections remains to be studied. The clinical effect of this, and other, modes of administration in comparison to injection requires further evaluation, and to determine whether certain phenotypes would respond better to these different administration techniques is an interesting area for future research.

4 Phenotyping patients based on psychological comorbidity

There is a large and growing literature documenting psychological co-morbidities in patients with OAB and idiopathic urinary retention. There is an association between affective disorders, especially anxiety and depression, and OAB (45, 46). Furthermore, OAB has a significant impact on psychosocial wellbeing and is associated with poorer quality-of-life (47, 48). Although a bidirectional association between LUTS and anxiety and/or depression has been proposed the precise relationship between OAB and affective disorders is yet to be established (49). Few other psychological or psychiatric co-morbidities have been reported although studies have shown an association between OAB and functional somatic syndromes e.g. Irritable Bowel Syndrome (IBS) and functional dyspepsia (14, 50).

Reports of the association between psychological co-morbidities and idiopathic urinary retention can be traced back to the historical literature on 'psychogenic urinary retention'. This older literature documented a variety of predisposing and precipitating factors including major stressful life-events. In a study of 37 patients with urinary retention, with no organic basis, most of whom reported some medical or psychological trauma preceding the retention, the authors note that the 'most striking characteristics of these women were their multiple somatic complaints and their history of numerous surgical procedures' (51). Although the reported diagnoses (such as 'hysteria') do not correspond to current psychiatric terminology, the authors' conclusions are clear: in these cases, surgical intervention is contraindicated 'because this is basically an emotional problem' (51). The term 'psychogenic' is no longer used since Fowler and colleagues reported abnormal sphincter electromyogram findings in 72% of the 48 women they examined, which suggested a biologic basis for the urinary retention (52). Somatic co-morbidities, including functional neurological symptoms have been reported in patients with Fowler's syndrome (18). Furthermore, higher rates of bladder

dysfunction have been observed in survivors of sexual abuse in adulthood or childhood (53, 54) and these patients might have Post-Traumatic Stress Disorder (PTSD) or Complex PTSD (55).

4.1 Can psychological phenotyping improve outcomes in patients undergoing treatment with BTX-A?

Phenotyping according to different types, or severity, of psychological comorbidity in patients who have failed treatment with BTX-A may provide another method by which patient selection for therapy, and therefore outcomes, could be optimised. However, studies in this area are sparse. In a study of the causes of failed intrasphincteric BTX-A for voiding dysfunction, the causes of failed treatment in 23 patients included psychological difficulties (inhibition of voiding) in 2 patients, although this was not assessed in more detail (56).

In the related field of chronic pelvic pain, psychological aspects are integral to the recommended approach to clinical phenotyping (UPOINT system) with evidence of improved outcomes using this approach (57). Whether this approach would improve outcomes in patients with OAB and idiopathic urinary retention remains to be studied.

4.2 How can psychological comorbidity be assessed clinically?

A screening tool helps identify which patients should be referred for further assessment by a mental health professional. Comprehensive assessment will include: history of the presenting problem, previous psychiatric history, developmental history, social history, current life situation, specific stressors and social support, personality and coping mechanisms. The next step is a collaboratively developed 'case formulation' i.e. a hypothesis about the causes, predisposing, precipitating and perpetuating or maintaining influences on a person's psychological, interpersonal and behavioural problems (58).

4.2.1 The search for brief, validated psychometric screening tools

Hundreds of tests to measure psychological, cognitive, behavioural and emotional co-morbidities are available with data reported on their psychometric properties e.g. validity, reliability, sensitivity and specificity, and used in a range of patient populations and contexts. In a previous review, the 14-item Hospital Depression and Anxiety Scale (HADS) was found to perform well in assessing the symptom severity of anxiety disorders and depression in somatic, psychiatric and primary care patients and in the general population (59).

Studies have demonstrated that briefer tools have comparable measurement properties to longer versions. The Patient Health Questionnaire (PHQ) is a self-administered version of the PRIME-MD diagnostic instrument for common mental disorders. The PHQ-9 is the 9-item depression module (60) and the GAD-7 is the 7-item anxiety scale (61). The PHQ-9 and the GAD-7 are used widely in the UK, since they are two of the outcome measures used by the Improving Access to Psychological Therapies (IAPT) programme which began in 2008 and has transformed treatment of adult anxiety disorders and depression in England with over 900,000 people now accessing IAPT services each year. IAPT services provide evidence-based treatments for people with anxiety and depression, implementing National Institute of Clinical Excellence (NICE) guidelines. Even briefer screening scales have been developed e.g. the two-item GAD-2 which screens for Generalised Anxiety Disorder (60) and the two-item PHQ-2 screen for depression (62). The use of standardised and validated instruments in this way may enable improved phenotyping of patients with OAB and, if proven to have prognostic value, may lead to improved patient selection for BTX-A therapy.

5 Research proposals

- Animal and human studies to assess whether central changes following BTX-A injections are directly induced by toxin transport or produced indirectly via neural plasticity
- Animal and human studies to assess whether the prolonged effect of BTX-A in the bladder could be explained by such central changes
- Brain fMRI and novel functional cerebral imaging to phenotype patients
- Brain fMRI to assess effect of BTX-A and ability to be used as a predictive tool for success
- Further research into alternative BTX-A delivery techniques and their mechanisms of action in comparison to the injection technique
- Studies of alternative drug delivery techniques to assess whether they are more effective (or associated with fewer complications) for different phenotypes, or severity, of OAB
- Brief screening for psychological symptoms to phenotype patients with OAB and idiopathic urinary retention who are being considered for BTX-A
- Further research to determine the optimum brief screening tools

6 Conclusions

It is increasingly recognised that OAB and idiopathic urinary retention are heterogenous conditions with multiple potential underlying pathophysiological mechanisms resulting in similar clinical symptoms. Several phenotypes have been described, the commonest based upon the urodynamic finding of DO, but require further study into their utility in improving patient selection for therapy and optimising outcome from BTX-A treatment. Although less commonly used to treat idiopathic urinary retention, further understanding of the mechanism of action of BTX-A may optimise its use for this indication in the future. Advances in basic science research into the mechanism of action of BTX-A have improved our understanding of the pathophysiology of OAB and may lead to novel ways to phenotype patients. The finding from animal studies of a central sensitisation effect of BTX-A may be studied clinically with fMRI and there is some preliminary evidence that there are central changes in fMRI patterns following intravesical BTX-A treatment. Whether this tool can lead to better patient selection for therapy remains to be studied. Psychological assessment is another way in which phenotyping can be improved and further study will determine whether this will be useful in predicting treatment failure.

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