



Platinum Priority – Editorial and Reply from Authors
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Finding the Correct Starting Dose for OnabotulinumtoxinA

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The article by Denys and colleagues in this edition of the journal reports the results of a multicentre double-blind randomised placebo-controlled dose-ranging study using onabotulinumtoxinA (ObTA) (Botox; Allergan Inc., Irvine, CA, USA) at doses of 50, 100, and 150 international units (IU) in patients with refractory idiopathic detrusor overactivity (IDO) and overactive bladder (OAB) [1]. This paper tackles the important issue of which dose at the lower end of the dose range is most appropriate for the management of patients with IDO/OAB. ObTA is commonly used at present in a number of centres on an off-label basis for the treatment of IDO/OAB. The evidence base for the use of this therapy is currently being accrued and was recently the subject of a consensus report [2]. More recently, an update on this therapy has been published in a comprehensive meta-analysis [3]. It is very clear from the existing literature that although four previous randomised controlled trials have been conducted, three of them have been based on small patient numbers.

Brubaker and colleagues reported a randomised trial using a dose of 200 IU of ObTA and 2:1 randomisation [4]. A total of 43 female subjects were randomised, including 28 on active drug and 15 on placebo. The study was placed on clinical hold after these subjects were randomised due to higher than expected rates of increased postvoiding residual (PVR) and associated symptoms of urinary tract infection (UTI). Sixty percent of the women who received the active treatment had a positive clinical response, based on patients' global impression of improvement score.

The authors defined retention as ≥ 200 ml. UTI was noted to occur at a rate higher than expected and was associated with increased PVR requiring intermittent self-catheterisation [4]. It is not clear whether the diagnosis of UTI was symptomatic or objective, although culture tests were

taken at a 2-mo visit. The overall conclusion was that the median duration of effect was almost 1 yr. The authors felt that the principal cause of UTI was the use of clean intermittent self-catheterisation. The authors' major concern was impaired bladder emptying in $>40\%$ of their patients and that was diagnosed in 75% only because of routine urine residual measurement.

At around the same time, Sahai and colleagues reported on a trial using 200 IU of onabotulinum toxin in a similar cohort of patients but that included both men and women [5]. A total of 34 patients were randomised, 16 to ObTA and 18 to placebo. Once again, the authors found the active agent to be efficacious in improving quality of life in patients. There was also improvement in other symptoms, objective parameters, and urodynamic measurements. Their study did not highlight particular problems with retention or UTI, in contrast with the study by Brubaker et al. [4]. In addition, some of the patients continued on anticholinergic therapy during the study period [5].

A third study was reported in 2009 by Flynn and colleagues [6]. This study evaluated the use of 200 and 300 IU of ObTA. The authors demonstrated significant improvements in both subjective and objective parameters compared to placebo, with a significant increase in PVR from a baseline of 25 ml to 107 ml with no significant change in the placebo group. It is of note that the patients were instructed to begin intermittent self-catheterisation if the PVR was >100 ml.

The authors of the paper remained blinded at the time of writing to the dose of ObTA used [6]. The small numbers of patients and the two doses used need to be borne in mind when interpreting the data. Four patients who received ObTA developed residuals >300 ml over a 6-wk time frame. Having stated that the paper was blinded to the dose used, it is noted in the discussion section that one patient who

developed catheterisation at 3 wk received 200 U of botulinum toxin. UTIs are not mentioned as a specific problem in this study. The study clearly demonstrates a reduction in urgency incontinence.

The results of a large phase 2 placebo-controlled randomised, dose-ranging study were recently published [7]. In this study, 313 patients, both male and female, with IDO and urinary urgency incontinence were randomised to placebo (44 patients), 50 IU of ObTA (57 patients), 100 IU of ObTA (54 patients), 150 IU of ObTA (48 patients), 200 IU of ObTA (58 patients), and 300 IU of ObTA (86 patients). Improvements were seen in incontinence and frequency episodes as well as in the Kings Health Questionnaire. A dose of 50 IU was shown to lead to a significant reduction of urgency incontinence episodes over placebo; however, the proportion of patients who were completely dry in the 50-IU group was significantly lower than the other treatment groups.

The proportion of patients requiring intermittent catheterisation were 0%, 5%, 11%, 20%, 21%, and 16% in the placebo, 50-IU, 100-IU, 150-IU, 200-IU, and 300-IU groups, respectively [7]. There were parabolic curves for both efficacy and PVR, suggesting that once a certain threshold dose is reached, further efficacy is not gained and voiding dysfunction appears to increase. From this study it can be concluded that the best ratio of clinical efficacy to voiding dysfunction can be achieved with a dose of between 100 and 150 IU. The results of further well-powered studies are awaited, but the conclusion appears to be that much higher doses of ObTA (300 IU) were used initially in clinical practice following the initial reports [8].

There was a further finding of interest in the study by Dmochowski et al, who also utilised standard urodynamics at baseline in all patients [9]. It was clearly demonstrated that there was improvement in urodynamic parameters that mirrored clinical improvement following the injection of ObTA. A key finding, however, was that there was no difference in outcome between those with or without baseline IDO on pressure/flow urodynamic testing, although all patients treated had significant symptoms suggestive of refractory OAB. Another interesting finding was the presence of a placebo response with saline, even in this group of refractory patients suffering with OAB who had failed to respond to anticholinergic therapy; however, the placebo response was significantly less than that seen with active treatment.

The experience from this pivotal phase 2 study emphasised two key issues associated with studying the use of ObTA therapy. First is the lack of any consensus among clinicians working in the field over what represents *clinically relevant retention* and what represents a *significantly raised PVR volume*. A clinical rule of thumb in functional urology (which has no evidence base but which I feel is appropriate and has traditionally been accepted) is that a raised PVR should be considered to be >40% of the functional capacity (ie, volume voided plus residual equals functional capacity). Further work is necessary to investigate and evaluate this issue in the future. Second, there is enormous difficulty in defining what represents a *clinically*

significant urinary infection. Most patients are treated with prophylactic perioperative antibiotic therapy. It must be borne in mind that this therapy involves multiple injections into the bladder and, not surprisingly because of the intervention, will result in storage symptoms that mimic a urinary infection.

Further consideration of the appropriate dose of ObTA at the lower end of the therapeutic range is clearly topical while the results of the phase 3 trial data are awaited. Review of the literature reveals a study that compared 100 IU and 150 IU of ObTA [10]. The limitation of this study is that there were only 12 patients in each subgroup; with no significant differences between the doses in symptom reduction, a greater number of incontinent patients became dry with 150 IU, and this was not deemed significant.

The article reported in this edition of the journal adds to the available literature base by reporting a fifth randomised placebo-controlled study utilising ObTA in the management of IDO/OAB. Ninety-nine patients were included in the analysis based on a history of OAB and with urodynamically confirmed IDO and were randomised to treatment with 50, 100, or 150 IU of ObTA. This study is important because it is the second to look specifically at the exact dose at the lower end of the dose range, where, clearly, in contemporary practice, one should consider starting therapy for IDO/OAB. Patients were followed up for 6 mo in this study. The authors concluded that 50 IU clearly demonstrated a lower symptom improvement than 100 IU and 150 IU. Objective parameters were similarly improved at both 100 and 150 IU, but this was only statistically significant versus placebo at the 150-IU dose. Objective urodynamic measurements showed a close relationship to dose with a trend towards a dose response between 100 and 150 IU.

The current evidence would suggest with ObTA that doses within the range of 100–150 IU should be considered as the optimum starting point for therapy. However, as noted with antimuscarinic therapy for IDO/OAB, there is the potential need for dose titration in some patients. Significant efficacy with improved balance between efficacy and safety can be achieved with lower doses of ObTA than was previously recognised, but definitive conclusions await the results of the ongoing phase 3 study programme. It is important to recognise that all botulinum toxin A preparations are unique in terms of dosing, efficacy, and safety, and at present, there are limited data with any agents apart from ObTA. Furthermore, it is not possible to accurately extrapolate from the results of one agent to another based on our current evidence base.

Conflicts of interest: The author is an advisor and researcher for Astellas, Allergan, Pfizer, and Recordati.

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Reply from Authors re: Christopher R. Chapple. Finding the Correct Starting Dose for OnabotulinumtoxinA. *Eur Urol* 2012;61:530–2

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The editorial comment submitted by Chapple [1] is of great value, and we thank him for this. OnabotulinumtoxinA (ObTA) seems destined to become one of the new treatments for non-neurogenic (idiopathic) refractory overactive bladder (OAB). The risks and benefits are clearly demonstrated through the results of our work [2] and through the recent studies described by Chapple that focus on finding the optimal dosage, with a clear trend to reducing the dose in comparison with patients with neurogenic detrusor overactivity (NDO) [3–5]. The issue of defining clinically significant residual urine and urinary tract infection (UTI) has not been solved at this time.

The development of new minimally invasive treatments with specific modes of action allows us to question whether we are able to select the best treatment for the best patient. Over the last 30 yr, because the only available treatments were anticholinergic drugs, OAB has been defined as an association of symptoms and the target for these drugs. In this way, we failed to emphasize the fact that the OAB patient population is clearly heterogeneous (male and female, young and aged, premenopausal and postmenopausal, with or without stress incontinence, with or without previous pelvic

surgery, with and without detrusor overactivity [DO]). Most clinical studies have tried to control these potential biases by selecting patients without urinary retention, with no urodynamic signs of obstruction, and so forth, but this approach does not reflect routine clinical practice and represents a real risk of misuse. New treatments such as ObTA for refractory OAB requires more comprehension of mode of action and pathophysiology as well as better selection of patients for an improved risk–benefit balance—a matter of importance in such a large population of patients.

NDO treatment with ObTA (Botox, Allergan), which is now licensed in most countries, should be a good demonstration that trying to incorporate this population into one group (NDO) fails to reflect the differences in terms of pathophysiology, symptoms, patient expectations, and risk of side effects. The differences observed between multiple sclerosis and spinal cord injury patients in terms of efficacy, placebo effect, and side effects perfectly illustrate this risk [6]. Moreover, the lack of evidence in stroke, dementia, or Parkinson's disease, despite frequently observed NDO in these populations, requires caution with the use of ObTA in those patients when indicated.

Based on the results from our study [2] and on the other double-blind placebo-controlled studies [6–9], we help determine a minimally efficient dose of 100 U ObTA as a second-line treatment for refractory OAB. Urinary retention, clean intermittent catheterization, and UTI risk seems to be dose dependent. These issues point to the need for a reduction of the dose used compared to that for neurogenic patients, but there are still unresolved questions. A recent article from the London group reported that in cases of detrusor oversensibility, 100 U of Botox failed to improve symptoms [9]. Confoundingly, in a recent phase 2 study, it seems that patients with or without DO may have the same benefit in term of symptom improvement [7]. Because of the relatively small numbers of patients in each group in all

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