

What is the feasibility of switching to 200IU OnabotulinumtoxinA in patients with detrusor overactivity who have previously received 300IU?

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Introduction To assess the feasibility of converting from 300IU to 200IU OnabotulinumtoxinA in patients diagnosed with either idiopathic detrusor overactivity (IDO) or neurogenic detrusor overactivity (NDO).

Material and methods Retrospective case–notes review of patients who were converted from 300IU to 200IU OnabotulinumtoxinA. Subjective patient reported improvements at interview and bladder diary reported parameters of urgency, urgency incontinence, frequency and nocturia.

Results Forty–four patients had received 300IU OnabotulinumtoxinA and were switched to 200IU after July 2008, 28 for IDO and 16 for NDO. Thirty–seven patients reported ongoing improvement with 200IU OnabotulinumtoxinA, six patients had worsening in their symptoms since down–titrating to 200IU and one patient did not attend follow–up. Improvement in urgency and urgency incontinence episodes per day were 82% and 72%, respectively, in patients who received 200IU. Of the 44 patients, 39 continued to receive 200IU, four requested up–titration to 300IU (due to decreased effect) and one did not attend after the 1st treatment. After converting from 300IU to 200IU, additional three patients were started on CISC for de novo voiding difficulty.

Conclusions Seventy–nine percent of patients were satisfied with their symptoms after switching from 300IU to 200IU OnabotulinumtoxinA. Only 9% of patients (all with NDO) reverted back to receiving 300IU. This study showed similar efficacy and longevity in the majority of patients (90%) using 200IU in both NDO and IDO.

Key Words: idiopathic detrusor overactivity ◊ neurogenic detrusor overactivity
◊ OnabotulinumtoxinA ◊ Botox ◊ Dose ◊ incontinence

INTRODUCTION

The largest systematic review to date of the use of botulinum toxin for the management of both neurogenic and idiopathic detrusor overactivity (NDO and IDO) revealed that 300IU OnabotulinumtoxinA was the most commonly reported dose in the former and 200IU in the latter [1]. With the initial off–licence use of this therapy, well designed dosing studies were lacking and therefore, a dose of 300IU was commonly utilised in patients with proven detrusor overactivity. Subsequently, data emerged which showed the

efficacy of lower doses of OnabotulinumtoxinA for both NDO and IDO [2, 3]. We had been treating all patients with either NDO or IDO with 300IU in our institution. In light of the new evidence, a decision was made in July 2008 to switch all new patients to an initial dose of 200IU. We found no evidence in the literature describing the feasibility of down–titrating patients who had already received 300IU down to 200IU OnabotulinumtoxinA. Therefore our aim was to assess treatment efficacy and longevity after switching from 300IU to 200IU in patients with either NDO or IDO.

MATERIAL AND METHODS

All patients admitted prior to June 2008 with detrusor overactivity (DO) received 300IU OnabotulinumtoxinA at our institute. We audited this practice, which included 79 patients (Group A). All 79 patients were started on 300IU OnabotulinumtoxinA and had proven detrusor overactivity prior to injection. After July 2008, due to the emergence of new evidence, we down-titrated the administered dose to 200IU OnabotulinumtoxinA in all patients with DO. All patients were aware of the down-titration of the treatment. A retrospective notes review was performed for all patients (Group B) that had received 200IU after 300IU up to April 2011, to assess the efficacy and tolerability of dose reduction.

OnabotulinumtoxinA 100IU (Allergan, Irvine CA) was dissolved in 5 ml of normal saline, making a concentration of 20IU/ml. All patients were injected using a flexible cystoscope and an Olympus needle using intraurethral 2% Lidocaine hydrochloride gel anesthesia only. Injection volume was 0.5 ml resulting in 30 injections with 300IU and 20 injections with 200IU. We injected with evenly distributed intramural injections in the base and the posterolateral walls of the urinary bladder and spared the dome and trigone.

All patients received a prophylactic course of antibiotic; Ciprofloxacin 500 mg twice a day for three days is the preferred choice of antibiotic unless contraindicated. All patients were educated on the use of clean intermittent self-catheterization (CISC) prior to receiving the injections. All patients were taught to record symptoms such as

Table 1. The underlying reasons for which patients from group-A did not proceed to receive further OnabotulinumtoxinA therapy

Reason for stopping BTX	Number of patients	
	NDO	IDO
Insertion of suprapubic catheter	1	3
Treatment stopped due to lack of efficacy	2	9
Clam cystoplasty	1	3
Neuromodulation	1	0
TOT	0	1
Ileal conduit diversion	1	1
Symptom cure	0	1
Transurethral resection of prostate	0	1
Discharged back to district general hospital	3	2
Lost to follow up	1	3
Died of concurrent illness	1	0

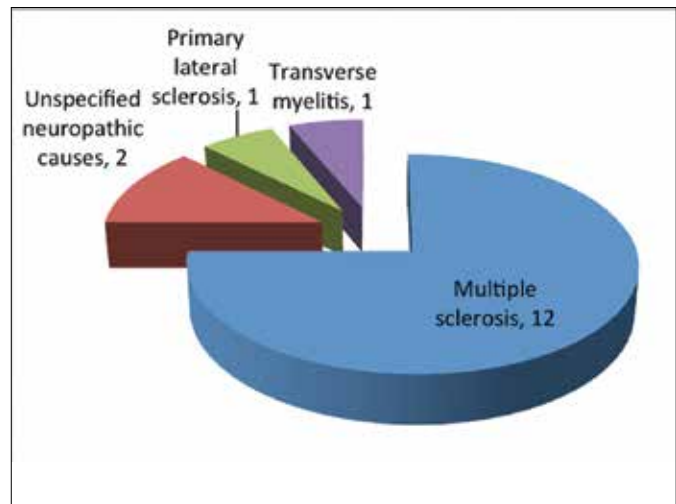


Figure 1. Underlying diagnoses in patients with NDO.

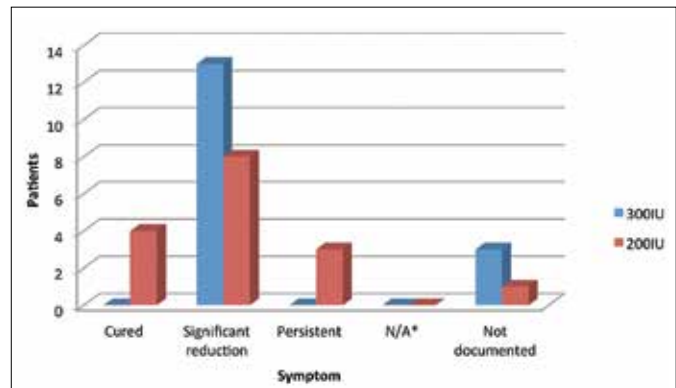


Figure 2. Subjective improvement in the urgency symptom in NDO patients while they were receiving 300IU and 200IU respectively.

frequency of voids, urgency episodes, and incontinence episodes in a voiding diary. All patients were scheduled for an initial review of symptoms six weeks after treatment.

All adverse events were recorded as reported by the patient. Urinary tract infections, which settled with antibiotic therapy ± microbiological evidence of bacteriuria were defined as appropriate urinary symptoms. Patients were instructed to telephone the continence specialist nurse when symptoms (frequency, urgency, and incontinence) returned and further injections were required. In order to assess overall perception of treatment satisfaction, at a three year follow up visit patients were also asked the following question: compared to previous injections, how much has this new dose changed your symptoms? Possible replies included: better than before, same as before, or worse than before. Patients were free to request up-titration to 300IU throughout the study.

RESULTS

From 79 patients in Group A, who started with 300IU OnabotulinumtoxinA injections, 44 patients went on to receive 200IU OnabotulinumtoxinA (36 female and 8 male). Of these, 16 patients had a diagnosis of NDO (Figure 1 shows the underlying neurological diagnoses) and 28 patients of IDO. Table 1 lists the reasons why 35 patients in Group A did not receive any further injections. Only one patient failed to attend follow-up after the first treatment.

Neurogenic detrusor overactivity

After switching NDO patients to 200IU, 15 (94%) patients continued to report symptomatic improvement. One patient reported deterioration of symptoms when receiving 200IU OnabotulinumtoxinA compared to 300IU. Four patients (all with NDO) reverted back to receiving OnabotulinumtoxinA 300IU with good effect and two patients had another 200IU of OnabotulinumtoxinA after five months and reported good efficacy.

The median longevity of efficacy was 4–5 months. Only one patient noticed shorter longevity of treatment with OnabotulinumtoxinA 200IU (3 months) compared to 300IU (5 months).

Reduction rates of daytime frequency and nocturia in patients receiving 200IU OnabotulinumtoxinA were 87.5% and 81.3% respectively *vs.* 75% and 75% in the same group of patients when they were receiving 300IU OnabotulinumtoxinA. Significant or complete improvement in urgency was reported by 81% and 75% of patients receiving 300IU and 200IU respectively (Figure 2).

At three year follow-up, 82% of NDO patients who had switched to the lower dose were happy with their symptomatic improvement and were keen to continue receiving 200IU OnabotulinumtoxinA. One patient chose to have neuromodulation because of the short efficacy of OnabotulinumtoxinA.

Idiopathic detrusor overactivity

After switching IDO patients to 200IU, 22 (79%) patients continued to report symptomatic improvement; five (18%) patients reported mild deterioration of their symptoms when they received 200IU OnabotulinumtoxinA, compared to their symptoms while they were receiving 300IU, and one patient did not attend follow-up.

The median longevity of efficacy was 6–7 months with both doses and only two patients noticed a shorter longevity of efficacy with 200IU (2 and 6 months) compared to 300IU (7 and 8 months).

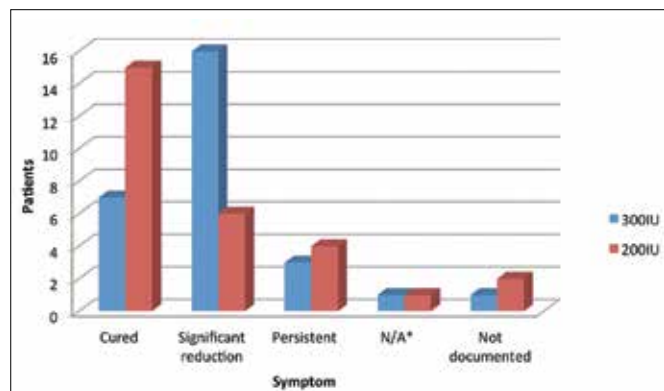


Figure 3. Subjective improvement in the urgency symptom in IDO patients while they were receiving 300IU and 200IU respectively.

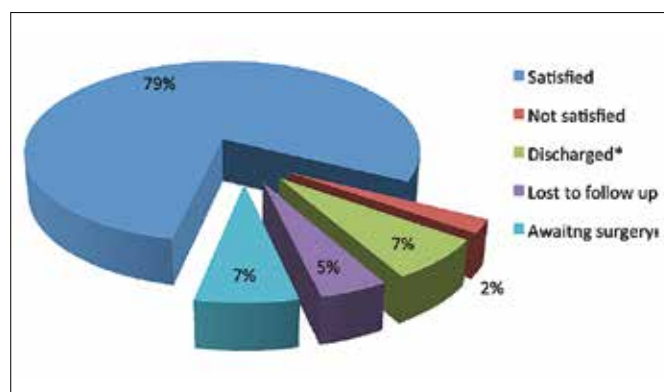


Figure 4. Outcome of treatment with OnabotulinumtoxinA 200IU after previous therapy with 300IU. *2 patients wished for no further treatments and 1 patient was unable to perform CISC. +3 patients wished to have neuromodulation.

Reduction rates of daytime frequency and nocturia in patients receiving 200IU OnabotulinumtoxinA were 50% and 64% respectively, compared to 60.7% and 71.4% respectively in the same group of patients when they had previously received 300IU OnabotulinumtoxinA.

The majority of IDO patients reported either a significant or complete improvement in their urgency symptoms while they were receiving OnabotulinumtoxinA 300IU (82.2%) and 200IU (75%) (Figure 3).

Three (7%) patients, all with IDO, had to commence intermittent self-catheterisation for *de novo* voiding difficulty after receiving OnabotulinumtoxinA 200IU. At three year follow-up, 75% of IDO patients who had switched to the lower dose were happy with their symptomatic improvement and were keen to continue receiving 200IU OnabotulinumtoxinA. Two patients chose to have neuromodulation because of the short efficacy of OnabotulinumtoxinA.

Twelve out of 44 patients (both groups A&B) developed symptoms of UTI, of which eight had positive urine culture. Rate of UTI's and other complications (including cough, suprapubic pain, and lethargy) were comparable between both groups (Table 2).

DISCUSSION

Neurogenic detrusor overactivity

To our knowledge, this cohort study is the first to evaluate the feasibility of switching patients with NDO from 300IU to 200IU OnabotulinumtoxinA in real life clinical practice and the first to assess the longevity of this treatment. A recent abstract presented at the 2012 EAU congress reported similar efficacy and quality of life improvements in 46 neurogenic patients with DO who switched from 300IU to 200IU [4]. No data on longevity was presented.

We found a similar subjective efficacy with OnabotulinumtoxinA 200IU among NDO patients when compared to 300IU, once an effective dose had been administered. The median longevity of treatment was similar at 4–5 months. This lower dose was effective in 79% with NDO. Confirmation of this finding is provided by a study reported in abstract form by Ginsberg et al., which has reported similar findings to ours in terms of longevity of treatment. They reported that the median time until repeated treatment was not different between 200IU and 300IU at 36.6 weeks and no significant differences were seen in the improvements over baseline in the bladder diary parameters [5]. However, in that study both groups of patients were exclusive and the patients were not switched to the lower dose.

More recently, dosing studies have been completed in patients with NDO. Cruz et al. have compared 200IU or 300IU OnabotulinumtoxinA against placebo [6]. By two weeks, both doses had led to significant improvements in urgency incontinence episodes per week in patients with multiple sclerosis and spinal cord injury. Although at two weeks the difference between urgency incontinence episodes was less than three per week (10%) in favour of 300IU, this was not deemed significant, and by 12 weeks there was no difference between the doses. Maximum cystometric capacity also increased by 150 ml in both groups. Median time until repeated treatment for both doses was 42 weeks compared to 16 weeks for placebo. In patients not routinely performing self-catheterisation, increases in post void residue were reported in 12, 30 and 42% of the placebo, 200IU and 300IU groups respectively. Only one serious, treatment related, adverse effect of muscular weakness was reported in a patient who received 300IU.

Table 2. Outcomes of injecting OnabotulinumtoxinA 300IU and 200IU in patients with NDO and IDO

Parameter	NDO: 300IU	NDO: 200IU	IDO: 300IU	IDO: 200IU
% patients with subjective efficacy	83.3%	93.7%	81.6%	78.5%
Median longevity	4–5 months	4–5 months	6–7 months	6–7 months
Need for catheter / CISC	93%	93%	42.9%	53.5%
UTI	23%	37.5%	26.5%	32.1%*
Other complications	10%	6.2%	6.1%	7.1%**

*Patients experienced UTI symptoms. Urinary cultures were available for all patients. **Abdominal pain (1 patient), cough (1patient) and lethargy (1 patient)

Similarly, Apostolidis et al. have assessed 50IU, 100IU and 200IU OnabotulinumtoxinA in NDO patients, randomised against placebo in 19, 21, 17 and 16 patients respectively [7]. All patients were given 30 injections. Significant symptomatic improvements compared to placebo were only seen in the 200IU group, however due to the low power of the study, significant differences in the use of the lower doses were not seen over 54 weeks.

One must remember that these studies have been performed in adults. In children a different formula of 10–12IU/kg is utilised. With this, Zeino et al. have shown good efficacy in children with meningomyelocele [8].

Idiopathic detrusor overactivity

Similarly to NDO, we did not find any clinical difference in the subjective efficacy among the IDO patients when they received OnabotulinumtoxinA at a dose of both 300IU and 200IU. The median longevity was 6–7 months in both groups. This lower dose was effective in 94% with IDO.

Interestingly, our study revealed an increase in the need of intermittent self-catheterisation among IDO patients when they were treated with OnabotulinumtoxinA 200IU. This was also noted in the Dmochowski study, where they reported the proportion of patients requiring intermittent catheterisation were 21% and 16% in the 200IU and 300IU groups respectively. However, we feel that this is not a significant finding in an underpowered retrospective study; since, in the Dmochowski study, a lower dose of OnabotulinumtoxinA was similarly efficacious with a lower retention rate. Our study is limited by the relatively small number of patients involved. The lack of randomisation of patients to different therapeutic

dose groups and lack of variation in the baseline demography of patients are also limiting factors.

The dose ranging study, by Dmochowski et al., has also reported significant improvements in frequency, incontinence, and quality of life (QoL) scores over placebo for 100IU, 150IU, 200IU and 300IU OnabotulinumtoxinA [9]. The dose–response curve revealed that doses greater than 150IU did not impart further significant symptomatic improvements. Fifty units were shown to lead to significant improvements in incontinence episodes but the proportion of patients who were completely dry was less than with higher doses.

Denys et al. have investigated even lower doses of OnabotulinumtoxinA (50IU, 100IU and 150IU) versus placebo in IDO patients with greater than three urgency or urgency incontinence episodes in a three day diary [10]. Reduction of urgency and/or urgency incontinence rates by 50% were 29%, 37%, 65% and 56% for the placebo, 50IU, 100IU and 150IU groups. Only three patients with a post–void residual volume over 200ml were reported in the 150IU group. Another study assessed lower doses by comparing 100IU and 150IU OnabotulinumtoxinA [11]. The authors report no significant differences between the doses and symptom reduction. Although the authors state that a greater number of incontinent patients became dry with 150IU, this was not deemed significant. The limitation of this sub–analysis was that there were only 12 patients in each sub–group.

Limitations of our study include its retrospective nature and the fact that it relies on the accuracy of past documentation. We also did not use a validated QoL assessment tool. In addition, there was a 1/3 reduc-

tion in the volume of injection and number of injection sites with 200IU. Data from guinea–pig bladders has shown 2IU dissolved in 20 ml led to increased cleaving of SNAP–25 compared to 2IU in 2 ml both given as single injections [12]. This study suggests that the volume of injection may affect toxin uptake. Although we did not find significant differences in outcomes, it must be recognised that the dose was not the only parameter altered in this study.

Furthermore, it has been suggested that injection of the trigone improves outcomes without adverse events [13, 14]. We spared the trigone due to earlier concerns regarding the possible occurrence of ureteric reflux if the trigone was injected. This was only later proven not to be the case [14]. We did inject into the detrusor. One study has shown no differences between intradetrusor and suburothelial injections, however the number of patients for each was only 15 and therefore limited information can be gained from this [15]. In real life clinical practice the depth of injection probably does not make a significant difference.

CONCLUSIONS

This study shows that down–titrating NDO and IDO patients treated with 300IU to 200IU OnabotulinumtoxinA leads, in 90% of cases, to similar efficacy with no apparent reduction in longevity of treatment. Patients with NDO may need up titrating back to 300IU.

Larger, multi–centre studies investigating effects of lower doses would support these observations. Although it has some weaknesses, to our knowledge this is the first study which explores the feasibility of dose down–titration in real life clinical practice

References

- Mangera A, Apostolidis A, Andersson KE, Dasgupta P, Giannantoni A, Roehrborn C, et al. An Updated Systematic Review and Statistical Comparison of Standardised Mean Outcomes for the Use of Botulinum Toxin in the Management of Lower Urinary Tract Disorders. *Eur Urol*. 2013 doi: 10.1016/j.eururo.2013.10.033 [Epub ahead of print].
- Schurch B, de Sèze M, Denys P, Chartier–Kastler E, Haab F, et al. Botulinum toxin type a is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6–month study. *J Urol*. 2005; 174: 196–200.
- Kuo HC. Urodynamic evidence of effectiveness of botulinum A toxin injection in treatment of detrusor overactivity refractory to anticholinergic agents. *Urology*. 2004; 63: 868–872.
- Hussain M, Helal M, Ocholor J, & Hamid R. Does dose reduction of Botulinum toxin–A affect quality of life in patients with multiple sclerosis? *Eur Urol*. 2012. Abstract: <http://www.uroweb.org/events/abstracts–online/?AID=37759>.
- Ginsberg D, Gousse A, Keppenne V, Sievert KD, Thompson C, Lam W, et al. Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. *J Urol*. 2012; 187: 2131–2139.
- Cruz F, Herschorn S, Aliotta P, Brin M, Thompson C, Lam W, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double–blind, placebo–controlled trial. *Eur Urol*. 2011; 60: 742–750.
- Apostolidis A, Thompson C, Yan X, & Mourad S. An exploratory, placebo–controlled, dose–response study of the efficacy and safety of onabotulinumtoxinA in spinal cord injury patients with urinary incontinence due to neurogenic detrusor overactivity. *World J Urol*. 2012; 31: 1469–1474.
- Zeino M, Becker T, Koen M, Berger C, & Riccabona M. Long–term follow–up after botulinum toxin A (BTX–A) injection into the detrusor for treatment of neurogenic

- detrusor hyperactivity in children. *Cent European J Urol.* 2012; 65: 156–161.
9. Dmochowski R, Chapple C, Nitti VW, Chancellor M, Everaert K, Thompson C, et al. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. *J Urol.* 2010; 184: 2416–2422.
10. Denys P, Le Normand L, Ghout I, Costa P, Chartier-Kastler E, Grise P, et al. Efficacy and safety of low doses of onabotulinumtoxinA for the treatment of refractory idiopathic overactive bladder: a multicentre, double-blind, randomised, placebo-controlled dose-ranging study. *Eur Urol.* 2012; 61: 520–529.
11. Cohen BL, Barboglio P, Rodriguez D, & Gousse AE. Preliminary results of a dose-finding study for botulinum toxin-A in patients with idiopathic overactive bladder: 100 versus 150 units. *Neurourol Urodyn.* 2009; 28: 205–208.
12. Coelho A, Cruz F, Cruz CD, & Avelino A. Spread of onabotulinum A after injection in the bladder wall. Experimental study in guinea-pig urinary bladder using the distribution of cleaved SNAP-25. *Eur Urol Suppl.* 2011; 10: 189–189.
13. Kuo HC. Bladder base/trigone injection is safe and as effective as bladder body injection of onabotulinumtoxinA for idiopathic detrusor overactivity refractory to antimuscarinics. *Neurourol Urodyn.* 2011; 30: 1242–1248.
14. Manecksha RP, Cullen IM, Ahmad S, McNeill G, Flynn R, McDermott TE, et al. Prospective Randomised Controlled Trial Comparing Trigone-Sparing versus Trigone-Including Intradetrusor Injection of AbobotulinumtoxinA for Refractory Idiopathic Detrusor Overactivity. *Eur Urol.* 2012; 2012; 61: 928–935.
15. Kuo HC. Comparison of effectiveness of detrusor, suburothelial and bladder base injections of botulinum toxin a for idiopathic detrusor overactivity. *J Urol.* 2007; 178: 1359–1363. ■