Effect of botulinum toxin type A on idiopathic and neurogenic detrusor overactivity

Vpliv toksina botulina na idiopatski in nevrogeni čezmerno aktivni sečni mehur

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Ključne besede:
čezmerno aktivni sečni mehur, toksin botulin, inkontinenca urina, avtonomna disrefleksija, stroški zdravljenja

Key words:
Botulinum Toxin Type A; Urinary Bladder, Overactive; Urinary Bladder, Neurogenic; Autonomic Dysreflexia; Costs and Cost Analysis

Citirajte kot/Cite as:
Zdrav Vestn 2010; 79: 475–81

Prispelo: 18. feb. 2010,
Sprejeto: 13. apr. 2010

Izvleček

Izhodišča: Na našem oddelku kot standardno metodo uporabljamo od leta 2004 injiciranje toksina botulina tipa A v detruzor pri stanjih s čezmerno aktivnostjo sečnega mehurja, kadar odpove zdravljenje z antiholinergičnimi zdravili. Cilj je bil analizirati indikacije in učinkovitost ter razpravljati o varnosti in stroškovnem vidiku tega zdravljenja.

Metode: Retrospektivno smo analizirali 11 zaporednih bolnikov (8 z nevrogenim čezmerno aktivnim sečnim mehurjem in 3 z idiopatskim), zdravljenih med letoma 2004 in 2008. Vsi so bili ob vključitvi inkontinentni. Urodinamska preiskava je bila pri vseh opravljena pred injiciranjem toksina botulina in 16 tednov po njem. Odmerek je znašal 500 enot Dysporta v koncentraciji 25 enot/ml. Poseg je bil v večini primerov opravljen ambulantno v lokalni anesteziji.

Rezultati: Injiciranje toksina botulina v detruzor je olajšalo vse simptome čezmerno aktivnega sečnega mehurja in vplivalo na preučevane urodinamske parametre. Pri bolniku s tetraparezo je avtonomna disrefleksija, ki se je kazala kot pogosta hipertenzivna kriza med uriniranjem, izginila tretji dan po zdravljenju. Popolna kontinenca je bila dosežena pri 10/11 bolnikov (91 %), pri enem bolniku pa se je znižala stopnja inkontinence. Eden od bolnikov z idiopatskim čezmerno aktivnim sečnim mehurjem, ki je spontano uriniral pred zdravljenjem, je moral šesti dan po zdravljenju začeti s čisto redno samokateterizacijo. Zadovoljstvo vseh bolnikov, ki smo ga ocenjevali s 5-stopenjsko lestvico, se je povišalo od povprečno 1,2 pred zdravljenjem na povprečno 3,5 po zdravljenju ($p < 0{,}001$). 9/11 bolnikov (82 %) je bilo mnenja, da bi se za zdravljenje ponovno odločili ali bi ga ponovili, če bi ali ko bo učinek popustil. Zdravljenje čezmerno aktivnega sečnega mehurja z zdravilom Dysport v našem zdravstvenem sistemu ni dražje v primerjavi s peroralnimi antiholinergičnim zdravili, ki so na razpolago.

Zaključki: Toksin botulina tipa A nudi pomembno možnost zdravljenja bolnikov z neukrotljivimi simptomi čezmerno aktivnega sečnega mehurja ali bolnikov, ki ne prenašajo antiholinergičnih zdravil.

Summary

Objectives: Intra-detrusor botulinum toxin type A injection treatment for detrusor overactivity conditions, where anticholinergic medication fails, has been available as standard treatment in our institution since 2004. Efficacy, indications and pitfalls were assessed, and thoughts on safety and cost-related aspects of this treatment presented.

Methods: Retrospective study analyzed eleven consecutive patients (8 with neurogenic detrusor overactivity and 3 with idiopathic detrusor overactivity), treated between 2004 and 2008. All patients were incontinent. Complete urodynamic investigation was performed before and 16 weeks after treatment. Injections of 500U of Dysport in a concentration of 25 U/ml were per-

formed under local anesthesia as an outpatient procedure in most cases.

Results: Intra-detrusor botulinum injections alleviated all overactive bladder symptoms and improved urodynamic parameters. In a patient with tetraparesis, autonomic dysreflexia, associated with detrusor overactivity that manifested as hypertensive crisis during voiding, disappeared on the third day of treatment. Complete dryness was achieved in 10/11 patients (91 %) while incontinence grade in the remaining patient decreased . One of idiopathic patients who voided spontaneously before treatment had to start self catheterization sixth day after treatment. Satisfaction on a 5 point scale increased from 1,2 before treatment to 3,5 after treatment ($p < 0.001$). 9/11 patients (82 %) claimed that they would have treatment again when/if its effect diminished. In our health system, the treatment with Dysport is not more expensive compared to oral anticholinergic medications available.

Conclusions: Botulinum is a major treatment option in patients with intractable symptoms of overactive bladder or those unable to tolerate anticholinergic medications.

Introduction

Botulinum toxin produced by anaerobe gram – positive bacterium Clostridium botulinum is a neurotoxin causing food related poisoning called botulism. It was first isolated by Pierre Emile van Ermengen in 1897 and was quickly recognized as the most potent biological toxin known to man.[1] Botulinum toxin is licensed for the treatment of a number of striated muscle spasticity disorders. The mechanism of action of botulinum toxin was previously thought to be mediated only by blocking vesicular release of acetylcholine (Ach) at the neuromuscular junction. Recent evidence suggests much broader range of neurological effects on the lower urinary tract, on both afferent and efferent nerves, mediated by a variety of receptors and transmitters.[2] Therefore, in recent years, Botulinum toxin use for the treatment of lower urinary tract symptoms has been described. Most important among these are conditions characterized by detrusor overactivity.[3] The most common serotype of botulinum toxin in clinical use is botulinum toxin-A (BTX-A). There are quite a few formulations of BTX-A available for clinical use, most known being Dysport (Ipsen Ltd, Berkshire, UK) which is available throughout Europe and the United Kingdom, and Botox (Allergan, Irvin, CA, USA), which is most commonly used in the United States and quite frequently also in Europe. Although these products are of the same serotype, they have different dosage, efficacy and safety profiles. Therefore they should not be considered as generic equivalents. Based on clinical experience in humans, similar effect is expected from 1 IU (international unit) of Botox or 1.5–5 IU of Dysport.[4,5] In our country, although at present there are also others, at the beginning of this study period, only Dysport was widely available, therefore Dysport was used in our patients.

We included treatment with injections of Dysport into detrusor muscle for conditions characterized by detrusor overactivity into our standard armamentarium in 2004. The present retrospective study describes indications, observations and assesses efficacy of this treatment in our patients.

Patients and Methods

In a retrospective study, consecutive patients with detrusor overactivity resistant to anticholinergic medication and considered for BTX-A treatment between 2004 and 2008 were included. Anticholinergic treatment as monotherapy was used in all patients at baseline. The daily dosages used were tolterodine 4 mg or darifenacin 15 mg. All patients suffered from overactivity and incontinence. The primary indication for treatment with BTX-A was incontinence refractory to anticholinergics.

All patients had a complete urological evaluation before the treatment, including medical history, bladder diary for at last 48 hr, physical examination, urinalysis, urine culture and sensitivity, serum biochemistry, ultrasound of the upper urinary tract, urethro-cystoscopy, retrograde and voiding cysto-urethrography. A complete neurological history was taken and examination

performed during the initial assessment of each patient. No patient had urinary calculi or bladder tumor. There was no evidence of urinary tract infection at the time of treatment. Number of micturitions, voided volumes, incontinence episodes and number of pads used were recorded in bladder diaries. For urodynamic investigation, a Bonito urodynamic unit, Laborie, Canada, was used according to the guidelines of the International Continence Society (ICS).[6-8] Specifically, reflex volume was defined as the infused volume that induced the first hyperreflexive detrusor contraction during cystometric evaluation. Maximum cystometric bladder capacity corresponded to the volume at which involuntary voiding occurred or filling was stopped.

Standard exclusion criteria were used: diseases (amyotrophic lateral sclerosis, myasthenia gravis – due to risk of respiratory failure after BTX-A injections), pharmacological (amynoglycosides), bleeding disorders, pregnancy, breastfeeding, and urodynamic criterion (decrease in bladder compliance due to organic detrusor muscle changes or fibrosis).[9]

Eleven patients were selected for treatment according to the above criteria in the observed time period. Three patients suffered from idiopathic detrusor overactivity (IDO). Eight patients had neurogenic detrusor overactivity (NDO): four following spinal cord injury (neurological level L4, C6, Th7 and C7, respectively), one with multiple sclerosis, one with Parkinson's disease, one following spinal cord infarction (neurological level Th 3–5), and one with cerebral atrophy.

Of eleven patients in the program, until August 2008, 6 underwent one set of injections, 4 two sets and one patient had 4 sets of injections during five years. Present analysis focuses on short-term (four months) results in all patients after the first set of injections.

Bladder emptying by aseptic clean intermittent self catheterization (CISC) was practiced by three patients, two voided by triggering and used condom catheter, six patients voided spontaneously and needed pads for urine incontinence.

During baseline urodynamics and follow up special attention was given to reflex volume, maximum detrusor pressure during voiding, detrusor compliance, maximum cystometric bladder capacity and post void residual urine volume.

All patients were thoroughly informed about the procedure. Patients who did not need CISC were informed that this may be necessary following BTX-A detrusor injections. They needed sufficiently preserved cognition to understand the need for regular bladder emptying, either through spontaneous voiding or by CISC.

Operative technique

All patients except two were treated as outpatients. The procedure was carried out under antibiotic prophylaxis (oral ciprofloxacin 500 mg twice daily through five days). Lidocaine Jelly 2 % 30 g was applied to the urethra prior to treatment. Local anesthesia was obtained by the instillation of 20 ml Lidocaine 2 % saline solution into the bladder . The bladder was accessed using a rigid cystoscope. Dysport 500 IU powder was dissolved in 20 ml normal saline, so one ml contained 25 IU of BTX-A. It is attempted (as recommended by manufacturer) to mix BTX-A solutionc with as little agitation and foaming as possible. The posterior and lateral walls and the dome of the bladder were injected, sparing the trigone and anterior wall. There were between 20 and 40 different injection sites on each occasion. The injections were performed using a flexible injection needle (Tik Kobarid, Slovenia), pushed through the working channel of a 21F Storz cystoscope with Albarran lever.

Postoperative evaluation

The patients had a follow up in the second and sixteenth week after BTX-A injections. They kept a 48 hr urinary diary, underwent urine culture and ultrasound of the upper urinary tract. At sixteenth week they underwent a complete urodynamic investigation.

Patients were asked to reduce progressively anticholinergic medication within one week after the BTX-A injection procedure.

The outcome measures included assessment of overactive bladder symptoms (urge incontinence, urgency, frequency and nocturia), changes in urodynamic parameters such as maximum cystometric bladder capacity (MCC), reflex volume (RV), bladder compliance (BC), maximal detrusor pressure (p det max), maximal detrusor pressure at maximal flow (p det Qmax), maximal flow (Qmax) and post voided residual urine (PVR). Patients' satisfaction with the lower urinary tract function was assessed on a 5-point scale as follows: 1–very dissatisfied; 2–dissatisfied; 3–undecided; 4–satisfied; 5–very satisfied.[10]

Statistical analysis was performed with SPSS for Windows software. For parameters, which conformed to normal distribution, paired sample t-test was used. A P value of less than 0.05 was considered statistically significant.

Results

Eleven patients (seven men and four women), at a mean age of 53 years (25–79), with intractable detrusor overactivity symptoms and incontinence were treated with transurethral BTX-A injections into the detrusor muscle. Eight had NDO and three IDO. Overall complete symptom resolution was seen in nine patients and improvement in two. There was a significant decrease in overactive bladder symptoms and a significant improvement in urodynamic parameters. Specifically, we observed significant increases in maximal cystometric bladder capacity, bladder compliance, reflex volume and significant decreases in maximal detrusor pressure and maximal pressure at maximal flow. As expected, there was also a significant decrease in maximal flow rate and an increase in post void residual. Numerical results are presented in Table 1.

In a patient with spinal cord injury (C7) who presented with a clinically significant autonomic dysreflexia due to neurogenic bladder dysfunction, autonomic dysreflexia disappeared on the third day after BTX-A injections.

At sixteenth week post BTX-A injections, continence rate was 91 % (10/11). Nine patients were on CISC. One patient voided spontaneously and was completely dry. One patient voided spontaneously, reported a decrease in the degree of incontinence and used fewer pads compared to time before BTX-A injections. The last two patients discussed had IDO. One patient with IDO had to start using CISC, but due to the improvement in previously difficult symptoms, he did not complain about this.

Ten patients were able to discontinue anticholinergic medication. A patient with Parkinson's disease was maintained on the same pretreatment dose of anticholinergics because his bladder compliance was not sufficiently improved.

No injection-related complications or toxin-related systemic side effects (such as dysphagia, diplopia or paresis of the remote musculature) were observed in the studied patients. Also, during the first 16 weeks post injection in this series of patients, no symptomatic urinary tract infections occurred.

Patients' satisfaction with the function of the lower urinary tract changed significantly following BTX-A injections ($p < 0.001$). Before injections, most of the patients were very dissatisfied ($n = 10$) or dissatisfied ($n = 1$). Sixteen weeks following BTX-A injections most patients were satisfied ($n = 8$), one very satisfied ($n = 1$) and two undecided ($n = 2$). Nine patients said they would be willing to undergo a second BTX-A injection if/when the treatment effect diminishes. Detailed results of improvement in the quality of life score are also presented in Table 1.

Discussion

The mechanism of BTX-A action on the bladder and smooth muscle is at present still not fully understood. In the past it was assumed to be similar to its action on the skeletal muscle, where it interferes with presynaptic release of ACh in the motor endplate. This causes atrophy and histological changes which are visible at the beginning as well as after the end of effect, which occurs approximately after 3 months for a skeletal muscle. For smooth muscle, the effects last longer – up to a year and there is no atrophy or reduction in the number of mus-

Table 1: Results of the evaluation of urodynamic and clinical parameters before and after treatment with BTX-A injections into detrusor muscle for neurogenic or idiopathic detrusor overactivity, resistant to anticholinergic treatment.

Parameter	Before treatment		16-wk after treatment		p-value
	Mean (SE)	Median (range)	Mean (SE)	Median (range)	
Day time frequency (number)	13.4 (2.2)	12 (4–25)	4.9 (0,7)	4 (4–12)	< 0.001
Nicturia (episodes/night)	3.5 (0,6)	4 (0–6)	0.6 (0,2)	1 (0–2)	< 0.001
Incontinence (episodes/24h)	7.4 (2,0)	5 (3–24)	0.9 (0.8)	0 (0–9)	< 0.001
Urgency (episodes/24h)	8.2 (2,5)	6 (0–23)	1.3 (1.0)	0 (0–9)	< 0.001
Max bladder capacity (ml)	220 (32)	240(80–400)	490 (25)	470 (390–700)	< 0.001
Compliance (ml/cmH_2O)	27.5 (9.0)	18 (7–100)	64.6 (8.7)	70 (10–100)	0.004
Max det pressure (cm H_2O)	77 (11)	78 (40–150)	21 (6)	15 (4–60)	0.014
Pressure at max flow (cm H_2O)	51 (5)	54 (22–66)	23 (6)	24 (4–60)	< 0.001
Qmax (ml/sec)	15 (3)	13 (4–39)	2 (2)	0 (0–16)	< 0.001
Postvoid residual (ml)	100 (30)	100 (0–350)	440 (50)	500 (140–700)	< 0.001
Satisfaction (1–5)	1.2 (0,13)	1 (1–2)	3.5 (0,28)	4 (3–5)	< 0.001

cular fibers visible. An effect of BTX-A on the smooth muscle is however also inhibition of Ach release. ACh influences detrusor tonus directly or indirectly by afferent fibers and induction of micturition reflex. The effect of BTX-A is not limited to interference with ACh vesicles, it also interferes with other neurotransmitters, such as ATP and substance P and causes modification of the expression of purinogenic and capsaicin receptors. This is followed by central desensitization. All processes result in long-term inhibition of afferent and efferent mechanisms which represent a physiological basis for overactive bladder syndrome.[11,12]

Patients with NDO often suffer from recurrent urinary tract infections (UTI). With invasive procedure or in patients who did not need CISC before the procedure, dependence on CISC may hypothetically mean a higher risk for UTI. This is not the case. Studies actually proved the opposite – symptomatic UTI rate decreased during 6 months following BTX-A application. The decrease in the frequency of symptomatic UTI was correlated to an increase in bladder capacity and a decrease in detrusor pressure. Mere bacterial presence (colonization) was not a risk factor for symptomatic UTI.[13] Our observations were consistent with those findings: in the study period after BTX-A treatment we have not observed symptomatic UTI in our cohort of patients. In a tetraplegic patient in whom pyuria was documented on many occasions during a year before first BTX-A application, only occasional minimal bacteriuria and no pyuria were documented during a year after BTX-A treatment. A speculative explanation for the observed phenomenon , which requires further study, may be in permanent hypoxic condition of the wall of an overactive high-pressure low-capacity bladder, which may interfere with its ability to form protective layer and is therefore more susceptible to bacteria. Extending this hypothesis further, we sometimes see patients on CISC or even with permanent catheter, who still form bladder stones. Part of the explanation for this phenomenon may lie in permanent infection, which may perhaps be alleviated by the use of BTX-A.

Absence of systemic side effects in our trial is encouraging, as others have reported weakness and malaise, which may be severe.[14,15] Although our numbers are low and chance may be the reason for good results, we believe the most important reason for the safety of our approach was the dose of Dysport, which we limited to 500U,while side effects in other studies were reported for higher doses – 750U and 1000U.[3] Anoth-

er reason may be our selection of concentration and volume of injection (25 U/ml, up to 1 ml per injection site). Recently in a study on a skeletal muscle, volume of injection was shown to be related to spread of toxin to other muscles.[5] As for Botox, the optimum concentration suggested is 10 U/ml, while for Dysport it was reported as undetermined yet; according to our experience we believe we should stick with the present concentration (25 U/ml).[3]

At first, application of BTX-A injections was performed under general or spinal anesthesia. However, early in the development of the procedure it became clear this can be performed safely under local anesthesia.[16] Due to the risk of hypertonic crisis, some questioned its use in patients with autonomic dysreflexia, but others also reported no problems with local approach in this group of patients.[9]

This is in concordance with our experience, where there were no problems with procedures under local anesthesia. It should be emphasized that tetraplegic patients should also receive a full dose of local anesthetic, despite their lack of feeling and painless procedure, otherwise they may develop hypertensive crisis during the procedure.

Time for the evaluation of treatment success is an important issue. Our selection (16 weeks) is based on reports, which studied the expression of sensory receptors and showed their number to reach control levels 16 weeks after BTX-A application.[17] However, subjective as well as objective improvement is noted much earlier. In our patient with autonomic dysreflexia, this syndrome ceased already three days after treatment, which is in concordance with observations in other studies.[9] Further relevance of time span from injections to their effect is in correlation to the expected side effects, especially increase in residual urine and possible need for CISC. For oral anticholinergic drugs, effects are expected in 14 days after the onset of treatment, for 5-alpha reductase blocking drugs for prostate diseases first effects are expected in 3 months. Time from injections of BTX-A into the detrusor muscle for effect to set in was examined by a recent study using daily voiding dairy.[18] This study reported the first signs of effect after 3 days, when urgency (which is also the most disturbing symptom) started to decrease. After 5 days, urgency was reduced by 72 %. In our study, where the first formal evaluation was performed after 14 days, patients reported that their incontinence disappeared. The need for self-catheterization, however, became necessary earlier, approximately 5–6 days after treatment. The second most disturbing sign, nocturia, is alleviated later, after approximately 4 weeks. This correlates with micturition frequency during the day as at least part of the nocturia problem is also related to bladder overactivity and this part may be addressed with BTX-A treatment.

The question of cost-effectiveness of BTX-A treatment for bladder overactivity was raised on many occasions and recent consensus panel statement asked for reports on this issue.[3,19] In our opinion question is not an issue when treating NDO patients with a view of improving low bladder compliance and preserving the upper tract as this is significantly less invasive compared to bladder augmentation. However, in terms of the quality of life issues and incontinence aspects, especially in IDO patients, the question requires attention. In our health system, a price of 500U of Dysport (which is needed for treatment of a single patient for an average of 9 months) amounts to approximately 75 % of the price of 9-month treatment with anticholinergic drugs available (tolterodine, solifenacine, darifenacine). Their price is almost equal and older anticholinergics, which may be more cost-effective, are not available. Adding to this under-paid work of urologist and routine out-patient cystoscopy procedure (which is also necessary for patients on oral treatment to exclude treatable causes of disease), it seems BTX-A treatment for IDO compares very favorably to oral anticholinergic medication regimens.

The application of BTX-A injections into the detrusor muscle seems to be a relatively non-invasive outpatient procedure. It appears to be safe, reversible, effective, fast working and long lasting treatment for NDO and IDO with incontinence resistant to anticholinergic medication. Intra-detru-

sor BTX-A injections improve all overactive bladder symptoms, urodynamic parameters and quality of life. Moreover, in a patient with tetraparesis autonomic dysreflexia, associated with detrusor overactivity that manifested as a hypertensive crisis during voiding, disappeared after treatment.

The decrease in maximal detrusor pressure may, in NDO, prevent the development of vesico-renal reflux and damage of the upper urinary tract.

BTX-A will in the future represent a major treatment option in patients with intractable symptoms of overactive bladder or those unable to tolerate anticholinergic medications.

References

1. Harper M, Fowler CJ, Dasgupta P. Botulinum toxin and its applications in the lower urinary tract. BJU Int 2004; 93: 702–6.
2. Smith CP, Chancellor MB. Emerging role of botulinum toxin in the management of voiding dysfunction. J Urol 2004; 171: 2128–37.
3. Apostolidis A, Dasgupta P, Denys P, Elneil S, Fowler CJ, Giannantoni A, et al. Recommendations on the use of botulinum toxin in the treatment of lower urinary tract disorders and pelvic floor dysfunctions: a European consensus report. Eur Urol 2009; 55: 100–19.
4. Patel AK, Patterson JM, Chapple CR. Botulinum toxin injections for neurogenic and idiopathic detrusor overactivity: A critical analysis of results. Eur Urol 2006; 50: 684–709.
5. Wohlfarth K, Schwandt I, Wegner F, Jürgens T, Gelbrich G, Wagner A, et al. Biological activity of two botulinum toxin type A complexes (Dysport and Botox) in volunteers: a double-blind, randomized, dose-ranging study. J Neurol 2008; 255: 1932–9.
6. Bates P, Bradley WE, Glen E, Griffiths D, Melchior H, Rowan D, et al. The standardization of terminology of lower urinary tract function. J Urol 1979; 121: 551–4.
7. Blaivas JG, Awad SA, Bissada N, Khanna OP, Krane RJ, Wein AJ, et al. Urodynamic procedures: recommendations of the urodynamic society. I. Procedures that should be available for routine urologic practice. Neurourol Urodyn 1982; 1: 51–5.
8. Schäfer W, Abrams P, Liao L, Mattiasson A, Pesce F, Spangberg A, et al. Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. Neurourol Urodyn 2002; 21: 261–74.
9. Schurch B, Stohrer M, Kramer G, Schmid DM, Gaul G, Hauri D. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. J Urol 2000; 164: 692–7.
10. Ghalayini IF, Al-Ghazo MA. Intradetrusor injection of botulinum-A toxin in patients with idiopathic and neurogenic detrusor overactivity: urodynamic outcome and patient satisfaction. Neurourol Urodyn 2007; 26: 531–6.
11. Apostolidis A, Dasgupta P, Fowler CJ. Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. Eur Urol 2006; 49: 644–50.
12. Andersson KE, Yoshida M. Antimuscarinics and the overactive detrusor—which is the main mechanism of action? Eur Urol 2003; 43: 1–5.
13. Game X, Castel-Lacanal E, Bentaleb Y, et al. Botulinum toxin A detrusor injections in patients with neurogenic detrusor overactivity significantly decrease the incidence of symptomatic urinary tract infections. Eur Urol 2008; 53: 613–8.
14. Grosse J, Kramer G, Stohrer M. Success of repeat detrusor injections of botulinum a toxin in patients with severe neurogenic detrusor overactivity and incontinence Eur Urol. 2005; 47: 653–9.
15. Ruffion A, Capelle O, Paparel P, Leriche B, Leriche A, Grise P. What is the optimum dose of type A botulinum toxin for treating neurogenic bladder overactivity? BJU Int 2006; 97: 1030–4.
16. Del Popolo G, Filocamo MT, Li Marzi V, Macchiarella A, Cecconi F, Lombardi G, et al. Neurogenic detrusor overactivity treated with english botulinum toxin a: 8-year experience of one single centre. Eur Urol 2008; 53: 1013–19.
17. Apostolidis A, Popat R, Yiangou Y, Cockayne D, Ford AP, Davis JB, et al. Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. J Urol 2005; 174: 977–82.
18. Kalsi V, Apostolidis A, Gonzales G, Elneil S, Dasgupta P, Fowler CJ. Early effect on the overactive bladder symptoms following botulinum neurotoxin type A injections for detrusor overactivity. Eur Urol 2008; 54: 181–7.
19. Sangster P, Kalsi V. Health economics and intradetrusor injections of botulinum for the treatment of detrusor overactivity. BJU Int 2008; 102 Suppl 1: 17–9.