RECOMMENDATION

Guidelines for practical usage of botulinum toxin type A (BoNTA) for refractory idiopathic overactive bladder management: Translation of French recommendations

Recommandations pour l’utilisation de la toxine botulinique de type A (Botox®) dans l’hyperactivité vésicale réfractaire idiopathique


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Summary
Objective. — Provide guidelines for practical usage of botulinum toxin type A (BoNTA) for refractory idiopathic overactive bladder management.

Patients and methods. — Guidelines using formalized consensus guidelines method. These guidelines have been validated by a group of 13 experts quoting proposals, subsequently reviewed by an independent group of experts.

Results. — In the case of patients with urinary tract infection, it must be treated and injection postponed. Before proposing an injection, it is recommended to ensure the feasibility and acceptability of self-catheterisation by patient. The injection can be performed after local anesthesia of the bladder and urethra (lidocaine), supplemented where necessary by nitrous oxide inhalation and sometimes under general anesthesia. Injection is performed in the operating room or endoscopy suite. The bladder should not be too filled (increased risk of perforation). Treatment should be applied in 10 to 20 injections of 0.5 to 1 mL homogeneously distributed in the bladder at a distance from the urethral orifices. It is not recommended to leave a urinary catheter in place except in cases of severe hematuria. The patient should be monitored until resumption of micturition. After the first injection, an appointment must be scheduled within 3 months (micturition diary, uroflowmetry, measurement of residual urine and urine culture). Performance of self-catheterisation should be questioned in the case of a symptomatic post-void residual and/or a residue > 200 mL. A new injection may be considered when the clinical benefit of the previous injection diminishes (between 6 and 9 months). A period of three months must elapse between each injection.

Conclusions. — Implementation of these guidelines may promote best practice usage of BoNTA with optimal risk/benefit ratio.

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Résumé
Objectifs. — Définir des recommandations pour l’utilisation pratique de la toxine botulinique de type A (BoNTA) dans l’hyperactivité vésicale réfractaire idiopathique (HAVRI).

Méthode. — Élaboration de recommandations de bonne pratique par consensus formalisé, validées par un groupe de 13 experts puis par un groupe de lecture indépendant.

Résultats. — En cas d’infection urinaire, celle-ci doit être traitée et l’injection reportée. Avant l’injection, il est recommandé de s’assurer de la faisabilité et de l’acceptabilité de l’autosondage. L’injection peut être réalisée après une anesthésie locale urétrovésicale (lidocaïne), éventuellement complétée par l’inhalation de protoxyde d’azote et parfois sous anesthésie générale. L’injection sera réalisée au bloc opératoire ou en salle d’endoscopie. La vessie ne doit pas être trop remplie (risque de perforation). Le traitement doit être appliqué en 10 à 20 injections de 0,5 à 1 mL réparti de manière homogène dans la vessie en restant à distance des méats urétéraux. Il n’est pas recommandé de laisser en place une sonde vésicale sauf en cas d’hématurie importante. Le patient doit être surveillé jusqu’à la reprise mictionnelle. Une note d’information sur les effets indésirables éventuels doit lui être remise à sa sortie.
Introduction

Since the first time the botulinum toxin A was used, almost 25 years ago, on the striated sphincter of the urethra to treat detrusor-sphincter dysynergia [1], the use of botulinum toxin has been progressively extended to numerous areas of urology. Several major publications have allowed its application in neurogenic detrusor overactivity to be validated [2,3], and this toxin has now become a component of the therapeutic algorithm used in the management of neurological bladders [4].

New indications, such as the non-neurological refractory overactive bladder, have been studied [5]. This pathology represents a diagnostic and therapeutic challenge. It is a functional pathology which is non-life-threatening and has no influence on renal prognosis, but which can lead to profound changes in the patient’s quality of life. Currently, the therapeutic methods used for its treatment do not allow this condition to be fully managed.

The efficacy of drug treatments is inconsistent, and these can lead to side effects, which hinder observance of the treatment [6]. Behavioural therapy and rehabilitation are also first line treatments, whose efficacy is unfortunately inconsistent. Among possible second line treatments, percutaneous posterior tibial nerve stimulation can be a suitable choice in terms of benefit-risk ratio [7]. Sacral neuromodulation, which is more invasive, is a validated form of treatment. It calls for the use of a preliminary effectiveness test, prior to permanent implantation. Good long-term results have been demonstrated, although this is an expensive treatment and can have undesirable effects, sometimes requiring reoperation. The use of more complex surgical techniques (enterocystoplasty) is currently rare, in the case of non-neurological detrusor overactivity, as a consequence of the morbidity and inconsistent long-term outcome associated with its use.

Currently, numerous publications have reported on the usefulness and efficacy of BoNTA for this indication [8–10]. Contrary to neurological patients, treatments involving the intradetrusor injection of BoNTA are confronted by the difficulty of ensuring voiding which is reliable, efficient, spontaneous, and non-deleterious (renal protection and risk of infection).

Although the efficacy and safety of botulinum toxin A have been validated by major evidence-based publications (randomized placebo control studies), practical information for its use cannot be based on a strong consensus. Moreover, these studies are often disparate, in terms of their inclusion or exclusion criteria (men and/or women, different definitions for the clinical criteria of OAB, presence or absence of detrusor overactivity, different definitions for the refractory nature of the symptoms) and in the injection technique (high dosage – 200 to 300 IU — or low dosage – 100 to 150 IU, number of injections, injection sites, dilution of the toxin, submucosal or detrusor injections). In France, drug marketing approval for BoNTA is currently limited to cases of neurogenic detrusor overactivity. The encouraging results described in the literature have led BoNTA to be used by expert centres in the scope of a research protocol, as a last resort therapy for non-neurological bladder overactivity. A request for an extension of the French drug marketing approval (AAM) has been submitted, and an expert group has prepared a set of recommendations for the use of BoNTA, in order to govern medical practices should this request be granted.

Patients and method

As a result of the absence or the inadequacy of literature with a high level of evidence, dealing specifically with questions related to the practical use of botulinum toxin for this indication, it was not possible to prepare good practice recommendations using the method for clinical practice recommendations (CPR). It was thus necessary to use the method for formalised consensus recommendations (FCR). This method has the advantage of identifying the degree of agreement, disagreement, or indecision between experts, on several independently submitted propositions. The corresponding procedure was that published in 2010 by the French National Authority for Health (HAS) [11]. The first step was to draft a list of proposed recommendations, based on the critical analysis of a summary of accessible bibliographic data and the discussion of current practices.

A systematic review of the literature was carried out on Pubmed using the following keywords: “botulinum toxin” and “bladder overactivity”, or “idiopathic detrusor overactivity”, or “non-neurological”. Twenty-five papers were retained out of a total of 417 papers revealed by the bibliographic search, which was limited to papers published in English or French.

The analysis of these papers was focussed on the proposed indications, the criteria for primary and secondary efficacy, the technical protocols used for the injections, and the reported side effects. Only those publications dealing with onabotulinum toxin A (Botox®) were retained.

The rating and evaluation group comprised 13 members hailing from different specialities (urology, gynaecology-obstetrics, or physical and rehabilitation medicine), all of...
whom deal with the treatment of bladder overactivity. These experts had not participated in the initial elaboration of the voted proposals. The initial version of the recommendations was electronically submitted for a first round of ratings. Each member of the group was required to rate each proposal with a grade ranging from 1 to 9, with 1 corresponding to a totally inappropriate proposal, 9 corresponding to a totally appropriate proposal, and 5 corresponding to an undecided opinion.

Following the analysis and summary of the responses, the group met in order to validate the recommendations. A recommendation was accepted in the case of strong group approval (median rating greater than or equal to 7, and ratings lying in the range between 7 and 9). The group was then invited to provide details of the reasoning behind the inappropriate and uncertain proposals, and following this discussion each member was given the opportunity to modify his/her rating.

Following this meeting, any modifications to the proposals, or the potential withdrawal of some proposals, could be decided upon.

This questionnaire was then submitted for a second round of ratings requiring a certain degree of tolerance, so that the systematic rejection of any proposals by one expert could not block the proposal selection process.

The rating group then met a second time, in order to establish a consensus of recommendations, with proposals having the option of being classed as appropriate, uncertain or inappropriate.

An initial version of the recommendations was thus established. This was submitted for evaluation to a reading group comprising 30 participating urologists, gynaecologists and specialists in physical and rehabilitation medicine. Sixteen members (53%) of the reading group replied. These members gave their opinion on the content and form of the initial version of the recommendations, in particular concerning their acceptability, applicability and clarity. An analysis and synthesis of these responses was compiled by the project leader, who drafted any necessary modifications. These minor modifications concerned mainly the comments added to the recommendations. The final text was then validated.

Results

Indications and contraindications

A Botox® injection can be used for idiopathic bladder overactivity which has developed over a period of at least six months.

As a general rule, Botox® is not a first line treatment for idiopathic bladder overactivity, except when there is a contraindication for a first line pharmacological treatment.

The failure of an anticholinergic treatment is defined by the absence of any significant efficacy, with at least two pharmacological agents taken orally at the dosage recommended by the French AWM, for a period of three months, or by the interruption of treatment due to adverse effects.

Botox® injections are contraindicated during pregnancy, breastfeeding, in the case of myasthenia gravis or an amino-glycoside treatment.

An evaluation period of at least 6 months for idiopathic bladder overactivity was retained, in order to be certain of dealing with the context of a chronic, but not a subacute or acute pathology.

As a consequence of the invasive nature of an intradetrusor Botox® injection, and the availability of first line pharmacological or rehabilitative treatments, the botulinum toxin injection remains a second line treatment.

The criteria retained to determine the failure of first line treatments vary widely in the literature. Very often, this is related to the failure of one or sometimes several anticholinergics, or sometimes the failure of anticholinergics and physical rehabilitation or behavioural methods. The recommendation adopts the notion of failure of at least two orally administered pharmacological agents, in order to test drugs having different availabilities or modes of action.

In order to account for the practical constraints of consultations, a period of at least three months of treatment was required, although periods of one to two months are frequently encountered in the literature.

Evaluation prior to injection

Before proposing a Botox® injection, confirmation of the idiopathic nature of an overactive bladder requires any possible urological, gynaecological, neurological or psychogenic cause to be eliminated by means of a full clinical assessment, uroflowmetry evaluation, cytopathological testing of the urine, and ultrasound imagery of the urinary tract combined with a measurement of the post-void residual and endoscopy of the bladder.

It is recommended to establish a voiding diary before initiating a treatment involving Botox® injections.

Full exploration of the bladder-sphincter function by means of a urodynamic evaluation, including exploration of the voiding phase, is recommended prior to carrying out Botox® injections.

The search for the cause of bladder overactivity is an indispensable prerequisite. Indeed, the discovery of a uro-gynaecological or neuro-psychogenic aetiology requires prior treatment of the cause, before envisaging any possible symptomatic treatment.

The purpose of a voiding calendar is to determine the frequency and volume of daytime and night-time urination, the number of episodes of urge incontinence with or without leakage, and the daily volume of urine.

Concerning the role of a urodynamic evaluation prior to making intradetrusor injections of Botox®, no consensus was reached. Most experts recommended its systematic use. Some experts preferred to limit exploration of the bladder-sphincter function to a urodynamic evaluation, including exploration of the voiding stage in at-risk patients (subjects over 65 years in age, males, with a history of pelvic surgery or sacral neuromodulation failure, mixed urinary incontinence, flowmeter abnormalities, or the presence of a significant post-voiding residual).

Urinary tract infection and antibioprophylaxis

In the case of a positive cytopathological examination of the urine, a Botox® injection should not be carried out. In
the case of a urinary tract infection, this must be treated and the injection postponed.

Current knowledge does not allow any conclusion to be made concerning the usefulness of an antibiotic prophylaxis carried out prior to a Botox® injection. In a neurological patient, the legal terms of use recommend the administration of an antibiotic for 1 to 3 days prior to treatment (at least two days in the case of asymptomatic bacterial colonisation), on the day of treatment, and 1 to 3 days following treatment (at least two days in the case of asymptomatic bacterial colonisation). These recommendations cannot be extended to the case of non-neurological patients, who have quite different bacteriological urine profiles.

In published studies, injection protocols have, or have not included an antibiotic prophylactic treatment (with differing product, dosage and duration modalities). Although the rate of urinary tract infections appears to be significantly higher, following a Botox® injection, than in the case of a placebo, this appears to be more closely related to the Botox® injection dosage, to the existence of a post-voiding residual, or to the absence of a clear definition of a urinary tract infection in the studies, than to the use of, or the modalities of the antibiotic prophylaxis. However, until now no study has provided a specific response to this question.

Anticoagulants and antiplatelet drugs

It is not recommended to make a Botox® injection in a patient treated with oral anticoagulants.

The approach to be taken with respect to antiplatelet agents is defined by the good practice recommendation of the French National Authority for Health (HAS), related to the importance of taking thrombotic and haemorrhagic risks into account during a urological endoscopic procedure in a coronary patient (June 2012) [12].

It is always advisable to compare the thrombotic risk associated with the withdrawal or modification of an antiplatelet treatment, with the haemorrhagic risk associated with the injection.

The haemorrhagic risk with a Botox® injection can be likened to that of a bladder biopsy.

In the case of a major thrombotic risk, it is recommended to delay the procedure, or to maintain the treatment using acetylsalicylic acid and to stop the administration of clopidogrel 5 days beforehand (or of prasugrel 7 days beforehand).

In the case of a minor thrombotic risk, when acetylsalicylic acid monotherapy is used, this must be stopped 3 days beforehand.

In the case of a clopidogrel monotherapy, this is to be stopped 5 days beforehand or possibly replaced by acetylsalicylic acid.

In the absence of any active bleeding, resumption of an antiplatelet agent treatment must be initiated as soon as possible, if possible the same day as the injection.

Feasibility and acceptance of self-catheterisation

Before proposing a Botox® injection, it is recommended to verify the feasibility and acceptability of self-catheterisation.

According to major evidence-based study publications, the rate at which self-catheterisation is adopted, following an intradetrusor injection of Botox®, decreases with the injected dose, leading to self-catheterisation rates greater than 40% at 300 units (Botox®), of the order of 30% at 200 units (Botox®), and lying in the range between 7% and 11% at 100 units (Botox®) [2,9,13].

These findings make it necessary to correctly inform the treated patients, to confirm the acceptability of this risk and to verify their ability to implement this gesture. A pp-test can be used to verify the patient’s aptitude [14].

The recommended dose is that having the best benefit-risk ratio, i.e. 100 units (Botox®).

Anaesthetic procedures

The Botox® injection can be carried out following local urethrosvesical anaesthesia using lidocaine, possibly supplemented by the inhalation of nitrous oxide.

This involves instilling a solution of two vials of 2% lidocaine without adrenaline in 30 mL of 14 per 1000 bicarbonate, supplemented by the instillation of one vial of lidocaine gel in the urethra.

The injection of Botox® can sometimes be carried out under general anaesthesia, depending on the patient’s pain perception threshold.

Most published studies make use of local anaesthesia involving, at varying degrees, intravesical and intrarectal lidocaine, sometimes associated with sedation. Some protocols make use of general anaesthesia, which is however difficult to accept for this functional pathology, when low pain perception thresholds have been reported under local anaesthesia.

Practical methods for carrying out injections

Immediately prior to making a Botox® injection, it is recommended to carry out an endoscopic exploration of the bladder, to verify its normality.

The injection is carried out in an operating room or an endoscopy room by a practitioner trained in this technique, using a rigid or a flexible cystoscope, whilst respecting the usual aseptic precautions.

The recommended irrigation fluid is an isotonic solution of sodium chloride.

The needle must be suitable for this application.

The bladder must not be too full, at the risk of making its lining thinner, leading to perforation.

The needle must penetrate the detrusor, without transfixing it.

The treatment must be applied using at least 10 to 20 injections of 0.5 to 1 mL, which are uniformly distributed over the bladder, whilst remaining at a good distance from the urethral meatus.

The last injection must be made with 0.5 or 1 mL of physiological saline, to ensure that the foreseen dose is correctly delivered, despite the dead space of the needle. The injection protocols used in the main published studies [8–10,13,15–20] report the use of 0.5 to 1 mL unit injections containing 5 to 10 units of botulinum toxin (Botox®).

It is not recommended to leave a urinary catheter in place, except in the case of major hematuria.
Studies comparing submucosal and intradetrusor injections do not appear to show any significant differences, even though this distinction appears rather artificial [21,22]. In fact, there is no accurate method for controlling the depth of injection, since this depends on the thickness of the bladder wall, the extent of its fibrosis, the degree of bladder filling, the type of needle used, and the pressure applied by the operator.

Injections in the region of the trigone do not appear to induce any vesicoureteral reflux. However, they do not appear to be efficient, nor to induce less post-operative residual, than injections uniformly distributed over the mobile part of the bladder [23,24].

Precautions for use

As soon as it has been prepared in the needle, the solution must be used immediately.

Disposable equipment must be stored in appropriate containers prior to incineration.

Surfaces contaminated by the botulinum toxin solution must be cleaned with an absorbent cloth soaked in a sodium hypochlorite solution (bleach).

In the case of an accidental projection into the eye, it is recommended to rinse the eye abundantly with water.

In the case of accidental projection onto the skin, it is recommended to apply a sodium hypochlorite solution, followed by abundant rinsing with water.

Post-operative follow-up

The patient must be monitored until urinary recovery. An information leaflet must be handed to the patient after the injection, and this must in particular indicate that in the case of burning micturition, fever, difficulties with urination, or an abundance of blood in the urine, the patient must consult without delay.

After the first injection, a consultation must be foreseen within a period of three months following the injection, in order to evaluate the treatment’s efficacy. This evaluation must include a urinary diary, flowmeter analysis, a measurement of the post-void residual, and a cytobacteriological examination of the patient’s urine.

A post-void residual which is greater than 200 mL and/or symptomatic must be accompanied by discussion of the use of self-catheterisation.

A renewed injection can be envisaged when the clinical benefit of the preceding injection wears off (typically after a period of 6 to 9 months).

In all cases, a delay of three months must be respected between each injection.

A delay of two weeks is indicated by major evidence-based studies, until maximum efficacy is achieved.

A decision to initiate self-catheterisation should take complete analysis of the clinical situation, together with the voiding catalogue and flowmeter analysis, into account.

Apart from the absolute value of the post-void residual, the ratio between the residual and the bladder capacity, the possible need for abdominal thrust, and the clinical tolerance expressed by the patient must be taken into account.

In the case of a lack of efficacy following injection, a 50 unit stepwise increase in BoNTA (Botox®) dosage can be envisaged, by evaluating the benefit-risk ratio for the patient.

The notion of dosage adjustment during injection is based on data found in the literature. Dowson et al. propose an increase in dosage in the case of insufficient efficacy, and a reduction in dosage in the case of a significant residual volume [25].

Conclusion

The literature provides data with a high level of evidence in terms of the efficacy/tolerance profile of the botulinum toxin A (onabotulinum toxin A/Botox®), allowing the botulinum toxin to be included in the therapeutic algorithm for the refractory idiopathic overactive bladder.

These recommendations provide a summary of current data found in the literature and expert practice concerning its methods of use.

Their aim is to harmonise practices, to assist the practitioner with his/her therapeutic options, to guide diagnostic evaluations and the treatment and monitoring of patients, and to limit the risks associated with incorrect usage of this medication.

Disclosure of interest

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Botulinum toxin type A (BoNTA)