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Observational Study

Low Prevalence of Botulinum Toxin-A Adverse Effects: Good Safety Profile or Underreporting?

Abstract

Introduction: The incidence of botulinum toxin type A (BoNT-A) injections related adverse effects (AE) is relatively high in literature. Many of injections are carried out yearly in our Physical and Rehabilitation Medicine (PRM) unit, however only 4 adverse effects have been reported since 2010.

The aim of this single-center prospective observational study was to determine the reasons to explain the large difference in the prevalence of AE reported in the literature and in our PRM unit, and to take measures to improve AE reporting.

Method: Patients suffering from limb spasticity were monitored between May and August 2015. Four to six weeks after intramuscular BoNT-A injection, patients were contacted by a pharmacist and questioned about any AE experienced. A survey was also performed to explore the reporting of adverse effects among the physicians injecting BoNT-A.

Results: Twenty-seven patients were included in the study. Thirteen patients (44%) reported 23 AE that occurred between 4 and 6 weeks after injection. Two of them were major effects and all resolved spontaneously. Physicians reported having noted AE following BoNT-A injection in the medical files, without declaring them. **Conclusion.** The results of this study confirm that BoNT-A related AE are under-reported. Information and training are required to raise physician awareness and increase AE reporting. This will improve management of its tolerance and efficacy.

Abreviation

AE: Adverse Effect; ANSM: Agence Nationale de Sécurité des Médicaments et des Produits de Santé – National; Agency for Drug Safety and Health Products; BoNT-A: Toxine Botulinique de type A; CP: Cerebral Palsy; CVA: Cerebrovascular Accident; EMG: Electromyogram; MS: Multiple Sclerosis; PMR: Physical and Rehabilitation Medicine; SCI: Spinal Cord Injury; SmPC: Summary of Product Characteristics; TBI: Traumatic Brain Injury

Introduction

Intramuscular Botulinum toxin type A (BoNT-A) injections are a common treatment for the reduction of spasticity in the upper and lower limbs of patients with neurological disorders [1,2]. Currently in France, 3 products containing BoNT-A as an active substance are available: Botox[®] (OnabotulinumtoxinA) [3], Dysport[®] (AbobotulinumtoxinA) [4] and Xeomin[®] (IncobotulinumtoxinA) [5]. These neurotoxins differ by their

composition, and more particularly by the presence or not of adjuvant protein, which modifies their molecular weight. The weight of the toxin complex affects retention in the target muscles and systemic migration. Clinically, these properties can have advantages or disadvantages, depending on the size of the target muscle and the desired effect [6]. BoNT-A injections are associated with certain adverse effects (AE). An AE is defined as an adverse reaction (harmful and unintended reactions resulting from authorized use at normal doses), misuse (intentional and inappropriate use of improper drug marketing authorization or best practice recommendations), overdose, abuse or a drug error [7].

In July 2006, the Pharmacovigilance Inspectors Working Group, established by the European Medicines Agency with the remit to focus on harmonisation and coordination of Pharmacovigilance related activities at the European Union level, evaluated the risks of adverse effects related to the diffusion of each BoNT-A product remotely from the injection site [8]. Following this evaluation, warnings regarding undesirable

effects stated in the summary of product characteristics (SmPC) were reinforced, leading to a newsletter addressed to all health professionals concerned in June 2007 [9].

In February 2011, the ANSM (Agence Nationale de Sécurité des Médicaments et al. des Produits de Santé – National Agency for Drug Safety and Health Products) published a European Risk Management plan for toxins which required, in complement of the lawful requirements of Pharmacovigilance, strengthening of pharmacovigilance and the establishment of tools to minimize risks [8].

In 2011, the report “Recommandations de Bonne Pratique: traitements médicamenteux de la spasticité” (Good Practice Guidelines: drug treatments for spasticity) included several observations regarding BoNT-A related AE, along with recommendations to limit AE and contribute to the good use of these products [10].

Around 2,000 BoNT-A-injection per year are carried out in our physical and rehabilitation medicine (PRM) unit for the symptomatic treatment of upper and/or lower limb spasticity in adults. Only 4 BoNT-A related AE had been reported by physicians in our PRM unit since 2010. This contrasts greatly with the incidence of BoNT-A related AE reported in the literature [11-15]. Over the same period, 157 adverse effects reports were recorded in the national pharmacovigilance database. The aim of this study was to determine the reason for the large difference between rates of AE reported in the literature and in our PRM unit. We hypothesized that AE were under-reported and carried out a prospective observational study to accurately assess the incidence of BoNT-A-related AE, with the larger aim to put measures in place to improve their detection and declaration to the Pharmacovigilance center.

Material and Methods

We conducted a single-center prospective observational study consisting in monitoring AE observed after intramuscular BoNT-A injections in adult patients with upper and/or lower limb spasticity in our PRM unit between May and August 2015. Patients with central neurological injury who were prescribed BoNT-A injection in muscles (lower and upper limbs) could be included. There were no inclusion or exclusion criteria other than no opposition to participate. To assess the safety and incidence of BoNT-A related AE, a self-questionnaire was given to all patients who agreed to participate. The patient's questionnaire contained a list of potential AE grouped into: general, musculoskeletal, respiratory, digestive and urinary disorders and visual disturbances, in addition to a free text field. Patients were asked to record any AE experienced within 4 to 6 weeks after injection, with the date of onset and the outcome of the AE. This range was chosen since adverse effects generally occur within the first 3 weeks after injection and last for 3 to 4 weeks [16,17]. Patients were then contacted by a pharmacist to collect all safety data. In parallel, a clinician self-questionnaire was given to the 8 physicians involved in BoNT-A injections. This one asked questions regarding the number of years of experience in toxin injection, the type of BoNT-A products used, the average number of BoNT-A

injections performed, the number of AE observed following injections, and any difficulties in reporting AE.

The study, including the information letter and questionnaires, was submitted for information to the French Ethical Committee Paris XI (14 april 2015) and was declared to the Commission National pour l'Informatique et des Libertés (CNIL n° n°1852551).

Results

Patient's characteristics and outcome after 4-6 weeks follow-up are detailed in table 1. Among 293 patients who were injected between May and August 2015, 27 were included and followed-up during 6 weeks (9.2%; 27/293). The median age of patients was 52 years (mean age 50.6 +/- 14.5 years), the gender ratio was 0.8 (12 men and 15 women; 12/15). Fifteen patients had cerebrovascular accidents, 7 had spinal cord injury, 2 had cerebral palsy, 2 had traumatic brain injury and 1 had multiple sclerosis. The goal of treatment was to improve function for 24 patients (89%), prefect orthopedic deformities for 10 (37%) and reduce pain for 1 (4%). Thirteen (48%) patients were injected with Botox®, 4 (15%) with Dysport® and 10 (37%) with Xeomin® with respective mean dose per patient of 552 ± 299 U Allergan, 568 ± 349 U Speywood and 400 ± 248 U DL50. Four patients received doses of Botox® and 10 of Xeomin® that were higher than the maximum recommended dose according

Table 1: Patient's characteristics and outcome after 4-6 weeks of follow-up (N=27)
CVA: cerebrovascular accident SCI: spinal cord injury CP: cerebral palsy MS: multiple sclerosis TBI: traumatic brain injury.

Clinical and demographic characteristics	value
Median age of patients	52 years
Mean age of patients +/- SD	50,6 +/- 14.5years
Gender (M/F)	12 male / 15 female
Pathologies of patients	15 (56%) CVA: 7 (26%) SCI: 2 (7%) CP: 1 MS: 1 TBI: 1 other
Products injected	
- OnabotulinumtoxinA	13 (48%)
- AbobotulinumtoxinA	4 (15%)
- IncobotulinumtoxinA	10 (37%)
Median dose injected	
- OnabotulinumtoxinA	500U Allergan
- AbobotulinumtoxinA	500U Speywood
- IncobotulinumtoxinA	400U DL50
Mean dose injected	
- OnabotulinumtoxinA +/- SD	552 +/- 299U Allergan
- AbobotulinumtoxinA +/- SD	568 +/- 349U Speywood
- IncobotulinumtoxinA +/- SD	529 +/- 248U DL50
Injection site	
- Lower limb	11
- Upper limb	3
- Lower limb + upper limb	13
Number of adverse effects	23
Number of patients reporting adverse effects	
(OnabotulinumtoxinA/AbobotulinumtoxinA / IncobotulinumtoxinA)	13 (48%)

to the European consensus table on the use of BoNT-A for the treatment of adult spasticity [16]. Eleven patients were injected in the lower limbs, 3 others in the upper limbs and 13 both in the lower and upper limbs. Xeomin® was administered in the lower limbs of 9 patients, which is an off-label use.

Forty eight percent (13/27) of patients reported 23 AE. Eleven of these occurred in 7 patients treated with Botox® (out of 13 patients injected with this product), 1 occurred in 1 patient treated with Dysport® (out of 4 patients injected with this product) and 11 occurred in 5 patients treated with Xeomin® (out of 11 patients injected with this product). All AE occurred between 4 and 6 weeks after injection. No unexpected adverse effects occurred and the majority of the effects were reversible. Most of reported AE concerned general (10/23) and musculoskeletal (8/23) disorders. In 1 patient, diffusion of the toxin was suspected and therefore he underwent electromyogram. No AE were reported to the pharmacovigilance centre during the study period by the physicians.

Six of the 8 physicians involved in BoNT-A injections responded to the questionnaire. 4 had more than 10 years' experience in the practice of BoNT-A injections and 2 had less than 5 years' experience.

All of them used the 3 BoNT-A products in routine medical practice. They each carried out 10 to 30 BoNT-A injections per month and declared having already noted AE following injection in patients' medical records. Three physicians reported that more AE occurred especially with one of the 3, but did not specify which one. Concerning AE reporting, 1 physician declared having encountered no serious or unexpected adverse effects, 1 specified some difficulties in determining whether the AE was expected or not, and had no knowledge of the pharmacovigilance system, 1 found the procedure too constraining and the 3 others did not answer the question.

Discussion

During our study period, 23 AE were reported by patients while none were declared to the pharmacovigilance centre, which confirms that AE are under reported in our PRM unit. Because of the small number of patients included in this work, we cannot compare the rate of AE with that reported in the SmPC or in literature [18]. Although BoNT-A products are usually well tolerated, AE observed in this study are similar to those already described in literature including musculoskeletal, respiratory, as well as visual disturbances [11-15].

The results of the physician's questionnaires provide some explanations for this under-reporting. Physicians may lack training and information regarding how to recognize and determine an AE, as well as how to report it. Reporting procedures for AE are considered too complicated. The AE reported by the patients confirm previous reports in the literature, namely that they occur during the first 3 weeks after injection and improve spontaneously within a few days or weeks [8]. Reporting AE is essential to allow monitoring, evaluation, management and prefection of drug-related risks. Since generalized muscle weakness and blurred vision are considered as serious AE, they

were reported to the pharmacovigilance center after the end of the study by the pharmacist.

Both expected and unexpected AE should be reported, as well as their severity, and any other factor that health professionals consider relevant to report. With regard to BoNT-A-related AE, it is also necessary to distinguish adverse effects related to the product from those related to the injection technique. The results of this study suggest that clinicians require information regarding the regulatory aspects of pharmacovigilance, as well as how to determine, monitor and declare AE. However, the physicians involved in the study were all experienced and well aware of BoNT-A related adverse effects described in the product SmPCs, as well as how to manage them. Therefore they deal with any AE within their clinical practice and do not necessarily feel the need to report them (other than noting them in the patient's medical records). In addition, the diagnosis of AE related to BoNT-A injection is based on symptoms and their spontaneous resolution, often based only on patient report. For example, a fall is classed as an AE, however it may not be related to the BoNT-A injection. To be sure that the AE is actually due to the BoNT-A injection, a single fibre EMG should be carried out during the time of the AE as well as after its resolution. If the AE is BoNT-A related, the jitter will be abnormal during the AE and will normalize afterwards. In the present study, single fibre EMG was carried out for only one patient (with generalized muscle weakness) therefore this is the only AE that can definitely be attributed to BoNT-A injection. The other AEs (except perhaps the eye watering) likely relate to the BoNT-A injection, however this cannot be stated with certainty.

To improve the declaration of BoNT-A related AE, several measures have been put into place by meetings with physicians in the PMR unit to highlight the importance of reporting AE and by adding an AE section (check boxes) on the injection report that is completed during the post-injection assessment consultation. This consultation is systematically scheduled between 6 to 8 weeks after injection. The AE section includes effects related to the remote diffusion of BoNT-A from the injection site, such as generalized muscle weakness, impaired vision, difficulty swallowing etc. If a box is checked, a copy of the injection report is faxed to the local pharmacovigilance correspondent.

Conclusion

The results of this study highlight the lack of reporting adverse effects by clinicians and demonstrate the need to raise awareness and to improve the reporting of AE. Patients are important partners for the identification of AE, which may or may not be linked to these drugs. Reporting of AE is essential to improve drug tolerance and efficacy. Further studies should investigate the declaration of AE relating to BoNT-A injections for other indications (such as muscle spasticity in children and detrusor hyperactivity in adults). It is also important to remind clinicians to carry out complementary examinations to confirm that the AE is truly related to the diffusion of BoNT-A. The results of this study led to increased cooperation between the physicians, pharmacists and nursing staff regarding 138 pharmacovigilance for BoNT-A. We plan to develop tools to

facilitate reporting of adverse effects, as well as to increase the use of existing traceability documents. A study on the effectiveness of these 140 measures will be carried out shortly.

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