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Letter to the editor

Venous thrombosis after botulinum therapy in lower limb: A case report and literature review

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Dear Editor

Intramuscular administration of botulinum neurotoxin type A (BoNT-A) is used in neurological disorders [1] such as spasticity or segmental dystonia. Its main mechanism of action is inhibition of acetylcholine release from presynaptic nerve terminals, leading to a decrease in muscular tone and reduction in abnormal muscular contractions [2,3]. BoNT-A adverse drug reactions (ADRs) are mainly "non-serious" and transitory. They occur in about 30% of patients. Serious ADRs, including death, have been rarely described. The most common ADRs are injection-site pain, muscle weakness, dizziness, botulism-like symptoms leading to dysphagia, dysphonia, and, less frequently, flu-like symptoms, dry mouth, rash, dry eye, ptosis or strabismus [1]. We report here for the first time and discuss a case of lower-limb vein thrombosis following BoNT-A injection for ankle and foot dystonia.

First, we describe a case report observed during our clinical practice. The causality was assessed by using the World Health Organization (WHO) method [4,5]. This is a validated combined assessment taking into account the clinical and pharmacological aspects of the case report and the quantity of documentation (i.e., previous case reports). Using this scale, each report is classified as "certain" "likely", "possible", "unlikely" or "unclassified". [4,5] Second, we performed a literature review using the following search algorithm in MEDLINE via PubMed: (onabotulinum OR incobotulinum OR abobotulinum OR botulinum neurotoxin) AND (thrombosis OR deep venous thrombosis OR phlebitis OR clot). Third, we investigated similar reports registered in the WHO pharmacovigilance database (VigiBase) [5]. The present study started from the inception of VigiBase and ended at 01/02/2019, with no geographical restriction. Research was performed with "Botulinium toxin type A "as "suspected" and "substance". Reported reactions (ADRs) belonged to Medical Dictionary for Regulatory Activities Terminology (MedDRA) terms: "Thrombosis", "Vessel puncture site thrombosis", "Peripheral embolism and thrombosis".

A 67-year-old woman with right-calf muscle spasticity and posterior tibial dystonia secondary to cerebral palsy caused by neonatal anoxia received 250 U of onabotulinum (Botox®): 200 U into calf muscles and 50 U into the posterior tibial muscle. She had no previous cardiovascular history and her medications included long-term oral baclofen (30 mg/day) plus paroxetine (20 mg/day). Botulinum toxin A 200 UI was diluted in 4 mL isotonic saline and botulinum toxin A 50 U in 1 mL isotonic saline, resulting in 5 U per 0.1 mL for each one. The woman received a total of 8 injections, 6 into the triceps surae muscle and 2 into the posterior tibial muscle. She had never previously received BoNT-A injection. There was no immediate ADR. Three days later, she had an unusual pain in the right leg with edema. Venous ultrasound revealed a right soleus vein thrombosis. The thrombophilia profile was negative. Other causes of thrombophlebitis were excluded, and apixaban 5 mg twice daily was introduced. Clinical symptoms disappeared after 2 weeks. The patient's condition was largely improved: she was able to perform daily living activities, including walking.

We found only 3 other reports of thrombosis after botulinum toxin injection. The first was published in 1995 and described an injection of BoNT-A in the striated anal sphincter [6]. The second report was hemorrhoid thrombosis in a patient receiving botulinum toxin for anal fissures [7]. The final report described axillary vein thrombosis after BoNT-A in a context of hyperhidrosis in a 32-year-old patient without any thromboembolic risk. The patient received enoxaparin (1 mg/kg/day) for 15 days, with complete resolution of symptomatology [8]. Our literature search revealed 2 other embolic ADRs (i.e., pseudo-temporal aneurysms after BoNT-A). One of these two ADRs was believed to be due to a technical error at the time of injection. The mechanism of the other ADR was unclear [9]. VigiBase contained 28 reports of thrombotic venous embolism (TVE) (17 with Botox®, 5 with Botox Cosmetic®, 1 with Xeomin® and 5 with a drug of unknown name). The cases occurred in 15 women and 11 men (2 other patients with unknown sex). The mean age was 54.5 years. Indications for BoNT-A were spasticity ($N = 9$ patients), dystonia ($N = 3$), neurological bladder ($N = 2$), rectal dyschesia ($N = 1$), dystonia ($N = 1$) and stiff man syndrome ($N = 1$). Other indications were unknown in the 5 other patients. Before injection, only 3 of these 28 patients received anticoagulants for prior TVE: 2 with rivaroxaban and 1 with apixaban. The delay of occurrence was described in only 7 reports: 48 hours to 2 months after BoNT-A.

In this letter, we describe the occurrence of an unlabelled ADR with BoNT-A injection. The mechanism by which BoNT-A could be related to deep vein thromboses remains unclear and deserves more thorough evaluation. One of the possible explanations could be a direct effect on vascular smooth muscles, relief of calf muscle hypertonia, or decreased mobility [6]. The occurrence of venous thrombosis 72 hours after BoNT-A injection suggests a

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chronologic link because this period matches the beginning of neurotoxin effectiveness. This patient exhibited no other thromboembolic etiology (trauma, inflammation, bacterial infection, varicose veins, cancer, other drugs etc.). Causality assessment was "plausible" according to the WHO method [4,5]. There are some controversies about the vascular effects of BoNT-A. Laboratory studies of flap viability, vasomotor properties and tissue perfusion have shown improvement in tissue perfusion in ischemic models and vessel diameter after BoNT-A injection. Several animal studies have shown a vasodilating action of botulinum toxin as well as its preventive effect on thrombosis [10].

This is the first report of a lower-limb TVE after BoNT-A. More generally, thromboembolic ADRs with BoNT-A injection are not described in US Food and Drug Administration and European Medicines Agency summaries. Physicians should be aware of this "serious" and "very rare" ADR. They should also inform patients of this possible thrombotic risk.

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Contributions

CT treated the patient and reported the ADR to the Toulouse University PharmacoVigilance Center. MM and FM analyzed the data and wrote the paper. All authors approved the final version of the manuscript.

Disclosure of interest

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