
Duration of efficacy increases with the repetition of botulinum toxin A injections in primary axillary hyperhidrosis: A study in 83 patients

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Background: Intradermal injections of botulinum toxin are effective but transitory in primary axillary hyperhidrosis. These injections are repeated when the symptoms recur. The reported duration of efficacy is variable, from 2 to 24 months, but it is unknown how the duration of efficacy changes when injections are repeated.

Objective: In this retrospective study, we aimed to evaluate changes in the duration of efficacy of botulinum toxin injections (Dysport, Ipsen, Boulogne-Billancourt, France) with the repetition of injections in patients with axillary hyperhidrosis.

Methods: From May 2001 to April 2012 inclusive, 83 patients were treated with a dose of 125 U per underarm. We compared the duration of effect of the first and last toxin injections.

Results: The median duration of efficacy for the first injection was 5.5 months, whereas that for the last injection was 8.5 months. The difference between these 2 durations is statistically significant ($P = .0002$).

Limitations: Although retrospective and based on the declarative, this work is the first to our knowledge to highlight this benefit of treatment and to evaluate botulinum toxin over such a long period (11 years).

Conclusion: There appears to be an increase in the duration of efficacy of botulinum toxin A injections with the repetition of injections in patients with primary axillary hyperhidrosis. The reasons for this effect may be linked to the mechanism of action of botulinum toxin, and may improve our understanding of its pharmacologic effects. (J Am Acad Dermatol 2013;69:960-4.)

Key words: axillary; botulinum toxin; duration of efficacy; hyperhidrosis; increase; repetition of injections.

Hyperhidrosis is excessive production of sweat. It affects 1% to 3% of the population, with a sex ratio of 1, and its prevalence is highest between the ages of 25 and 64 years.^{1,2} It can have major psychosocial repercussions for patients.³⁻⁶ It is mostly idiopathic (primary), but may be associated with an underlying disease. It is localized in 90% of cases,⁷ but it may also be generalized. The regions of the body most affected are the underarms, palms of hands, soles of the feet, forehead, and inguinal folds. Sweat is secreted and excreted by the eccrine sweat

glands, which are innervated by cholinergic fibers, paradoxically, via the sympathetic system. Options include topical medications (most commonly aluminum chloride), iontophoresis, botulinum toxin injections, systemic medications (including glycopyrrolate and clonidine), and surgery.⁸ Endoscopic thoracic sympathectomy is one possibility for invasive treatment and frequently causes compensatory hyperhidrosis.⁹⁻¹¹ Most other reported complications are postoperative pain, pneumothorax, segmental atelectasis, and transient Horner syndrome.¹² It is

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also an expensive treatment. Intradermal injections of botulinum toxin are used as a second-line treatment and have been shown to be effective,¹³ by blocking the presynaptic release of acetylcholine. These injections are repeated when the symptoms recur. They have been reported to be effective for about 2 to 24 months,^{3,14-23} but nothing is known about the change in the duration of efficacy with repeated injections. The aim of this retrospective study was to evaluate the change in the duration of efficacy of botulinum toxin injections for axillary hyperhidrosis with the repetition of injections.

METHODS

We included all eligible patients followed up for primary axillary hyperhidrosis and seen between May 2001 and April 2012 in dermatology consultations at Le Mans

Hospital, France, for treatment with botulinum toxin.

All these patients had axillary hyperhidrosis detected by Minor test.²⁴ In this test, 2 g of iodine and 4 g of potassium iodide in alcohol to 100 mL is painted over the skin area. After it has dried, a fine starch powder is applied. Sweat causes the color to turn dark blue. The result is measured over 5 minutes at room temperature and at rest. In all cases the iodine-starch test made it very easy to identify the location of excessive sweating in the axillary skin. All the patients had experienced treatment failure for first-line treatment with antiperspirants based on aluminum salts with concentration at 20%, with major psychosocial repercussions. All had a Hyperhidrosis Disease Severity Scale (HDSS) score of more than 2/4, indicating severe hyperhidrosis and that sweating interfered with activities of daily living. It is a disease-specific scale for hyperhidrosis that provides a qualitative measure of the severity of the patient's condition based on how it affects daily activities. A score of 1 corresponds to "my underarm sweating is never noticeable and never interferes with my daily activities"; a score of 2 corresponds to "my underarm sweating is tolerable but sometimes interferes with my daily activities"; a score of 3 corresponds to "my underarm sweating is barely tolerable and frequently interferes with my daily activities"; and a score of 4 corresponds to "my underarm sweating is intolerable and always interferes with my daily activities." The validity and reliability of the HDSS were proved, and the

use of this scale is recommended by the Canadian Hyperhidrosis Advisory Committee.¹³

The exclusion criteria were myasthenia and pregnancy. All patients underwent a pretreatment evaluation consisting of a clinical examination, objective excessive sweating, with criteria of primary hyperhidrosis (focal, visible, excessive sweating of at least 6 months' duration without apparent cause with at least 2 of the following characteristics: bilateral and relatively symmetric, impairs daily activities, frequency of at least 1 episode/wk, age of onset <25 years, positive family history, cessation of focal sweating during sleep).²⁵ An evaluation, including a clinical examination, thyroid palpation, and determinations of glycemia and thyroid-stimulating hormone, was carried out to exclude cases of secondary hyperhidrosis.

All patients were treated with a first injection of botulinum toxin A (Dysport, Ipsen, Boulogne-Billancourt, France), at a dose of 125 U per underarm. The botulinum toxin (250 U) was diluted in 1.25 U of saline and delivered with a syringe fitted with a 30-G needle. In total, 12 to 13 intradermal injections of 0.05 mL of Dysport (Ipsen) (10 U), separated by a distance of 1 to 2 cm, were carried out for each underarm (about 120-130 U/underarm). Subsequent sessions were performed at the patient's request, when the symptoms recurred with a moderate discomfort (HDSS score >2/4) with a positive Minor test result. The HDSS and Minor test scores were evaluated at each visit. During these successive sessions, the duration of efficacy of the previous injection was evaluated by asking the patients how long it took for the symptoms to recur.

We compared the median duration of efficacy of the first and the last injections of botulinum toxin. We determined median values rather than means, because the median is considered much more reliable than the mean for analyses of time intervals, which are generally asymmetrically distributed. Indeed, the presence of an extreme value for a single individual has a considerable effect on the mean, but little or no effect on the median.

We used the nonparametric Wilcoxon matched pairs test to compare the durations of efficacy between the first and last injections, with a significance threshold of 5%. Statistical analyses were carried out with R software.²⁶

CAPSULE SUMMARY

- Injections of botulinum toxin are effective but transitory in primary axillary hyperhidrosis.
- We report a significant increase in the duration of efficacy of botulinum toxin with the repetition of injections.
- This finding provides additional evidence about long-term effectiveness. Patients can expect a decreased need for injection sessions over time.

RESULTS

We included 83 patients, 57 women and 26 men, aged from 18 to 73 years, between May 2001 and April 2012. The median duration of efficacy was 5.5 months for the first injection and 8.5 months for the last injection (Fig 1). The difference between these 2 values was statistically significant ($P = .0002$, Wilcoxon matched pair tests). The patients underwent a mean of 4 injection sessions: 65% of the patients had 2 to 4 injection sessions, 34% had 5 to 10 injection sessions, and 1 patient had 17 injection sessions. One patient had only 2 injection sessions. The mean duration of follow-up was 2.73 years, with a range of 3 months to 9 years. Overall, 5% of the patients were followed up for less than 1 year, 29% were followed up for more than 4 years, and 4% of these patients were followed up for 9 years. The minimum and maximum values for the duration of efficacy of the first injection were 3 weeks and 18 months, respectively. The minimum and maximum values for the duration of efficacy of the last injection were 3 weeks and 48 months, respectively. None of the patients reported major adverse effects, such as compensatory sweating, myalgia, itching, or headaches, in particular.

DISCUSSION

To our knowledge, this study is the first to suggest an increase in the duration of efficacy of botulinum injections with the repetition of injections.

Botulinum toxin A is produced by the anaerobic bacterium *Clostridium botulinum*, which causes botulism.²⁷ In hyperhidrosis, intradermal injections of botulinum toxin block the exocytosis of acetylcholine by the presynaptic membrane of the cholinergic neuron, thereby decreasing sweat production.^{14,28,29} We have 3 drugs with botulinum toxin A: Botox (Allergan, Courbevoie, France), Dysport (Ipsen, Boulogne-Billancourt, France), Xeomin (Merz Pharma, Maisons-Laffitte, France). The ration of efficacy of Dysport (Ipsen) and Botox (Allergan) is half to one-fourth, depending on the site of injection.³⁰ Many studies have demonstrated the efficacy and safety of this treatment for primary axillary hyperhidrosis,^{15-20,31,32} and reported patients satisfaction with this treatment is higher than that for other treatments.³ This treatment improves the quality of life of the patient,^{3,33,34} which is often impaired because of major socioprofessional repercussions of the condition. Complications are rare and not very severe: headaches, myalgia, itching and, more rarely, compensatory sweating in a zone not previously affected.^{19,21} This last adverse effect, which occurs frequently after sympathectomy (50%-80% of patients),⁹⁻¹¹ has rarely been reported

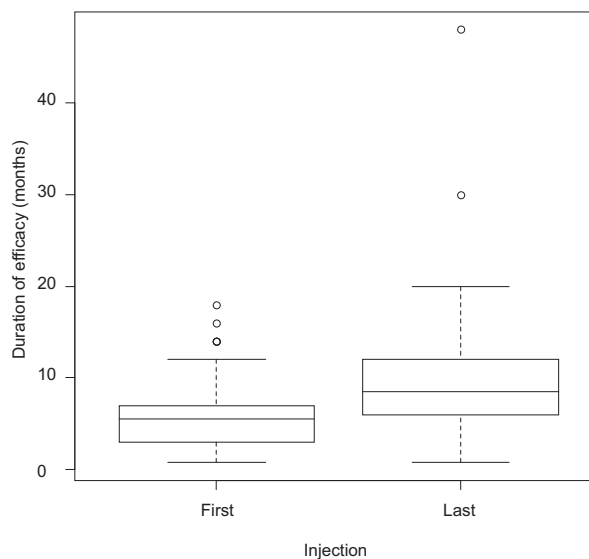


Fig 1. Box and whisker plots of duration of efficacy of first and last injections. **Bold line** indicates median duration of efficacy, **horizontal lines** indicate quartiles, **upper and lower horizontal lines** represent maximum and minimum, and **points** indicate extreme values.

after injections of botulinum toxin A (5% of patients in the study by Naumann and Lowe³² with Botox [Allergan]).

The reported duration of efficacy varies between the many studies, from 2 to 24 months.^{3,14-23} In 1 study, it was suggested that the dose of toxin injected was related to the duration of efficacy: in 47 patients followed up for 29 months, Wollina et al³⁵ demonstrated that the duration of action was longer for a higher dose of botulinum toxin (200 U of Botox [Allergan] per underarm), but the comparison was made with published data rather than with a paired group. This hypothesis had already been put forward by Karamfilov et al³⁶ in a study demonstrating that safety levels were similar for high and low doses of botulinum toxin (Botox, Allergan).

The repetition of the injections does not lead to a decrease in efficacy,³³ as confirmed by Schnider et al²¹ in a study of 61 patients treated for axillary or palm hyperhidrosis, with a dose of 400 mU of Dysport (Ipsen) used in cases of axillary hyperhidrosis. The patients were followed up for a maximum of 3 years. Reinjection was never performed earlier than 3 months after the previous treatment, to prevent the formation of neutralizing antibodies. The median time interval between the sets of injections was 34 weeks. In 8 patients who received 3 injections, subjective evaluation after the first, second, and third injections revealed no significant difference in subjective efficacy ($P = .68$) and no difference in the duration of efficacy ($P = .69$).

A difference in the duration of efficacy was not demonstrated in this study maybe because the duration of follow-up was shorter.

It has been suggested that neutralizing antibodies may be produced after repeated injections of botulinum toxin. Indeed, as this toxin is of bacterial origin, the hypothesis of antibody development is physiologically plausible. The factors potentially favoring antibody development are a high dose at each treatment session, the total cumulative dose, a short interval between consecutive injection sessions, and a protein formulation of the toxin.³⁷ In a study of 207 patients, only 1 possible case of seroconversion, with the formation of neutralizing antibodies, was noted, and the efficacy of injections of Botox (Allergan) was conserved.³² In our study, on a large number of patients with a long follow-up period, we did not check for the formation of antibodies, but the increase in the duration of efficacy with repeated injections is not consistent with a hypothetical neutralizing activity because of antibodies. When the botulinum toxin blocks the synapse at the motor plate, it destroys one of the proteins required for the fusion of synaptic vesicles with the membrane. This leads to degeneration of the motor axon terminal. This terminal gradually grows back, accounting for the transient nature of the effect of the botulinum toxin.³⁸ We can explain the increase of duration efficacy with the repetition of injections by a slowing of regrowth of axon terminal.

CONCLUSION

There appears to be an increase in the duration of efficacy of botulinum toxin A against primary axillary hyperhidrosis with the repetition of injections. This is supported by a statistically significant increase in the duration of efficacy with the repetition of injections from a retrospective review of 83 patients with primary axillary hyperhidrosis seen between May 2001 and April 2012 in dermatology consultations at Le Mans Hospital, France. It is the only study to have evaluated botulinum toxin over such a long period (11 years). The value of this treatment is supported by this study, which also confirms the absence of adverse effects in the long term.

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