

Brief Reports

High-dose Botulinum Toxin Therapy: Safety, Benefit, and Endurance of Efficacy

Shannon Y. Chiu*, Bhavana Patel, Matthew R. Burns, Joseph Legacy, Aparna Wagle Shukla, Adolfo Ramirez-Zamora, Wissam Deeb & Irene A. Malaty

Department of Neurology, Fixel Institute for Neurological Diseases, University of Florida, Gainesville, FL, USA

Abstract

Background: Botulinum neurotoxin therapy (BoNT) is a powerful tool for treating many neurologic disorders. The U.S. Food and Drug Administration (FDA)-approved maximum onabotulinum toxin A (OnaA) dose is 400 units (U) per visit, but higher doses are commonly necessary, particularly when treating multiple body regions.

Methods: We collected demographics, OnaA dose, body regions injected and indications, patient-reported efficacy via 7-point Clinical Global Impression Scale (CGIS), and duration of benefit.

Results: Sixty-eight patients were identified receiving OnaA >400 U/session. Dystonia (n = 44) and spasticity (n = 24) were the most common indications for high-dose OnaA. Mean duration of benefit was 9 weeks (standard deviation [SD] 3). More than 70% of patients self-reported “very much improved” or “much improved” at 6 month, 1 year, and last visit. No serious adverse effects were reported.

Discussion: The majority of patients tolerated >400 U OnaA with continued benefit. OnaA doses >400 U may be safe and effective in appropriate patients.

Keywords: Botulinum toxin, onabotulinum toxin A, dystonia, spasticity

Citation: Chiu SY, Patel B, Burns MR, Legacy J, Wagle Shukla A, Ramirez-Zamora A, et al. High-dose botulinum toxin therapy: Safety, benefit, and endurance of efficacy. Tremor Other Hyperkinet Mov. 2020; 10. doi: 10.7916/tohm.v0.749

*To whom correspondence should be addressed. E-mail: Shannon.chiu@neurology.ufl.edu

Editor: Elan D. Louis, Yale University, USA

Received: November 23, 2019; **Accepted:** January 15, 2020; **Published:** February 27, 2020

Copyright: © 2020 Chiu et al. This is an open-access article distributed under the terms of the Creative Commons Attribution–Noncommercial–No Derivatives License, which permits the user to copy, distribute, and transmit the work provided that the original authors and source are credited; that no commercial use is made of the work; and that the work is not altered or transformed.

Funding: None.

Financial Disclosures: None.

Conflicts of Interest: The authors report no conflicts of interest.

Ethics Statement: This study was reviewed by the authors’ institutional ethics committee and was considered exempted from further review.

Introduction

Botulinum neurotoxin therapy (BoNT) is an effective treatment for numerous movement disorders involving muscle overactivity. According to the latest American Academy of Neurology (AAN) guidelines, onabotulinum toxin A (OnaA) is a treatment option for the management of blepharospasm (level B), cervical dystonia (level B), upper and lower limb spasticity (level A), and chronic migraine (level A)¹; additional applications have also included focal limb dystonia, hemifacial spasm, laryngeal dystonia, neurogenic detrusor overactivity, strabismus, and glabellar lines.^{2,3}

Currently, the U.S. Food and Drug Administration (FDA)-approved maximum dose of OnaA is 400 units (U) within a 3-month interval, which is based on the parameters of early, sentinel trials.^{4–6} There is a potential risk of spread of the toxin, as adverse effects can be localized or generalized.

Symptoms of adverse reactions include muscle weakness, diplopia, ptosis, dysphagia, and breathing difficulties.³ Repetitive injections of OnaA may also increase the risk of developing neutralizing antibodies, although their effect(s) on causing partial or secondary treatment failure is complex.⁷ However, in general, the treatment is well tolerated.^{1–3}

Compared to the selected population studies in early trials, numerous patients require doses greater than 400U due to (1) severity and distribution of symptoms or (2) multiple co-occurring indications for OnaA injections (e.g., patients with post-stroke spasticity affecting both upper and lower limbs). Due to the current FDA labeling constraints of maximum OnaA 400 U within a 3-month interval, treatment is often limited or delayed because of insurance limitations. This risks severe detriment to patients’ quality of life and unnecessary suffering.

In clinical practice, higher doses of OnaA are frequently used. We aimed to evaluate safety, benefit, and efficacy of patients receiving OnaA >400 U per visit. We hypothesized that higher OnaA doses would be well-tolerated and effective and provide lasting benefit.

Methods

This is a retrospective database review using the Institutional Review Board-approved INFORM database at the University of Florida Norman Fixel Institute for Neurological Diseases. We included patients who consented to participate in the INFORM database and were treated with OnaA between 2009 and 2017. While there are currently 4 U.S. FDA-approved preparations of BoNT (serotypes A and B), the toxins have different approved clinical indications, and doses are non-equivalent for conversion. Thus, to allow for consistent comparison, we included only those patients who received OnaA, which has the broadest application. Patients were excluded if they had no follow-up after first visit with OnaA >400 U. Fellowship-trained movement disorder neurologists administered the BoNT injections and recorded clinical indications, benefits, adverse effects, the total units of BoNT injected per treatment session or additional interventions.

For each patient treated with OnaA >400 U per visit, we collected demographics, therapeutic indication(s), OnaA dose, body regions injected, patient-perceived efficacy using the 7-point Clinical Global Impression Scale (CGIS), and patient-perceived number of weeks of benefit. CGIS reports symptoms as very much improved, much improved, minimally improved, unchanged, minimally worse, much worse, or very much worse, compared to baseline (without BoNT).

Safety was determined by reported side effects at the first follow-up. We assessed long-term outcomes at 6 months, 12 months, and last follow-up in the database.

We described categorical variables as counts and percentages. Ordinal variables were displayed as medians, and continuous variables were displayed as means and standard deviations.

Results

Clinical and demographic characteristics

Of the 68 patients included in the study who received OnaA >400 U per session, 43 (63%) were females. Mean age was 60 years ±15. The majority of patients were Caucasian (n = 59, 87%). Most patients were initiated on OnaA below 400 U per session (n = 61, 90%), prior to dose escalation >400 U. Of the seven patients who received OnaA >400 U at their first visit in our tertiary center, five were already receiving OnaA at outside institutions; we identified two patients, naïve to BoNT, who were initiated on OnaA >400 U (n = 1 generalized dystonia, n = 1 spastic paraparesis). At first visit >400 U in our cohort, mean total dose was 501 U ± 46 (range 425–800). Mean duration of follow-up was 23 months +/- 20 (range 3–86). Table 1 summarizes the demographic data.

Dystonia (n = 44) and spasticity (n = 24) were the most common indications for patients receiving OnaA >400 U (Table 1). Some patients with dystonia were also injected for migraine or sialorrhea. The majority of patients received injections in more than one body region; seven patients (10%) received BoNT in one distal limb only. For patients with dystonia, the most common underlying etiologies included primary

Table 1. Patient Demographics and Clinical Indications

Patient Demographics		Clinical Indications for BoNT	
Female sex, n (%)	43 (63)	Dystonia patients (n = 44)^a	
Age, mean (SD)	60 (15)	Cervical dystonia	31
Education, mean (SD)	14 (3)	Upper extremity dystonia	14
Mean duration of follow-up, months (SD)	23 (20)	Lower extremity dystonia	14
Patients receiving DBS after BoNT, n (%)	9 (13)	Jaw opening/closing dystonia ^b	7
		Blepharospasm ^b	6
		Truncal dystonia	2
		Other indications ^b : migraine	3
		sialorrhea	3
		Spasticity patients (n = 24)	
		Focal upper extremity spasticity only	9
		Focal lower extremity spasticity only	7
		Combined	8

Abbreviations: BoNT, Botulinum Neurotoxin Therapy; DBS, Deep Brain Stimulation; SD, Standard Deviation.

^a24 patients had primary/generalized dystonia and received injections for multiple body regions.

^bSome patients with dystonia had additional indications for BoNT, such as chronic migraine, sialorrhea, blepharospasm, and oromandibular dystonia.

dystonia, idiopathic Parkinson's disease, or atypical parkinsonian syndrome. For patients with spasticity, common etiologies included stroke, traumatic brain injury, and cerebral palsy.

Patient-reported efficacy, duration of benefit, and side effects

The reported duration of benefit among all patients after first treatment >400 Units was 8.8 weeks \pm 3.1. At the first follow-up visit, 47 patients (69%) reported overall good benefit by CGIS (17 rated "very much improved" and 30 rated "much improved"), while 14 rated "minimally improved," 2 rated "no change," and 1 rated "minimally worse." More than 70% of patients self-reported "very much improved" or "much improved" at 6 month, 1 year, and last visit. No patient reported "much or very much worse" at any time point.

Ten patients (15%) reported adverse effects (AEs) at the first follow-up, of which three had more than 1 AE. Table 2 summarizes reported AEs after the first OnaA >400 U. With longer follow-up, 13 patients (19%) reported AEs at 1 year, and seven patients (10%) reported AEs at the last follow-up. The most common AE reported was bruising. We did not observe severe dysphagia or major AEs requiring hospitalization or additional interventions.

At the last visit, nine patients (13%) received a dose less than 400U due to lack of benefit (n = 2), AEs (n = 2), fewer indications treated (n = 2), benefit from interval deep brain stimulation (n = 2), and insurance barrier (n = 1). One patient switched toxin preparation for unclear reasons. Thirty-eight patients discontinued injections at our center; reasons included lost to follow-up/moved (n = 18), death/hospice (n = 7), and, least commonly, AEs (n = 1). Table 2 lists reasons for discontinuation.

Discussion

In this retrospective study, we found that most patients receiving OnaA >400 U in a single session had good benefit and tolerated higher doses without any serious AEs (receiving doses of up to 800 U). The

majority of patients continued to report good benefit after last exposure to high-dose OnaA (longest follow-up was 86 months).

The U.S. FDA currently approves a maximum dose of 400 U for OnaA, although guidelines in Europe allow for doses up to 600 U of OnaA (at least in treatment of adult spasticity).⁸ Several small case series have reported on the use of higher OnaA doses for certain indications, namely spasticity (e.g., post-stroke)⁹⁻¹³ and neurogenic detrusor overactivity.¹⁴ In a randomized double-blind dose-finding study, post-stroke patients with symptomatic spasticity showed greater and more prolonged response with higher doses (mean 540 U \pm 124) than those receiving lower doses (mean 167 U \pm 31).⁹ More recently in a prospective, multicenter dose-titration study, escalating incobotulinum toxin A (which doses similarly to OnaA) from 400 U to 800 U in patients with spasticity did not compromise safety or tolerability; enabled treatment in a greater number of muscles/spasticity patterns; and was associated with increased treatment efficacy, improved muscle tone, and goal attainment.¹² Surveys of international experts and patients have highlighted the desire for greater flexibility in treatment protocols than currently approved.¹³ To our knowledge, our study is the first to evaluate the efficacy and safety of high doses of OnaA across a wide range of indications and etiologies.

There are several limitations to this study. The full description of response may be further understood by having condition-specific scales to build on the CGIS, but using this allowed for an exploratory investigation across multiple indications treated. The retrospective design also may limit full characterization of side effects documented in the medical record, as well as all doses used in selected muscles (i.e., not feasible in this study given wide range of indications and body regions injected). All patients were specifically asked about dysphagia, weakness, and common side effects by completing a pre-injection form as part of routine practice. It is notable that no serious, systemic, or life-threatening AEs were documented at any time. Systemic side effects, such as flu-like symptoms, iatrogenic botulism, and encephalopathy, are uncommon,

Table 2. Adverse Effects and Reasons for Discontinuing BoNT

Adverse effects reported after first therapy of OnaA > 400 U^a		Reasons for patients discontinuing BoNT	
Headache	1	Lost to follow-up	13
Bruising	3	Passed away or transferred to hospice	7
Dysphagia	2	Lack of benefit	6
Muscle weakness	3	Moved away	5
Head drop	3	Other ^b	3
Flu-like symptoms	2	Insurance barriers	2
		Side effects	1
		Received DBS	1

Abbreviations: BoNT, Botulinum Neurotoxin Therapy; DBS, Deep Brain Stimulation; OnaA, Onabotulinum Toxin A.
^aThree patients reported more than 1 AE, Adverse effect.
^bOther reasons included functional movement disorder; transportation difficulties; patient no longer needed BoNT.

with variably reported prevalence of 2–20% and unknown mechanism¹⁵; thus, it remains unclear whether systemic adverse effects would be more common with higher dosage. As we excluded patients without follow-up after initial exposure to OnaA >400 U (n = 7), it is conceivable that rates of adverse effects and efficacy may be slightly higher or lower, respectively, than reported. Furthermore, this small sample of excluded patients (n = 7) reduced our sample size at longer follow-ups (i.e., missing data from subsequent 6-month and 12-month follow-ups). As detailed in Table 2, these included patients that discontinued injections at our center, including “snow birds” who seasonally live in Florida. Referral bias may also affect our study population, as patients receiving care at a tertiary care center may have more severe disease requiring higher OnaA doses than commonly necessary. It is also worth mentioning that in this setting, there may be a high level of experience and expertise that allows for safe delivery of higher doses, especially given risk of associated toxin spread to unintended muscles based on injection technique. Generalizability, therefore, may depend on similar experience level of injectors. Finally, we were unable to assess for the risk of antibody formation objectively (e.g., via enzyme-linked immunosorbent assay [ELISA]), given our retrospective design. However, the fact that most of our patients tolerated OnaA >400 U with continued benefit would argue against the development of partial/secondary treatment failure, which one might expect with any clinically significant antibody formation.

Future directions would include a comparison between our cohort and patients receiving OnaA <400 U, injected for similar indications. Longer follow-up will be needed to assess the clinical response at 10 years and beyond.

In conclusion, this study suggests that OnaA dosage >400 U in a single session can be safely administered, is efficacious, and has lasting benefit for multiple indications. This is important as literature is limited in addressing higher dose requirements in some patients. Our results highlight the need to reconsider the maximum dose administered per single treatment of OnaA in order to best serve patients' individual needs along with discussion with payors regarding coverage. Ongoing research is needed to confirm our findings and validate the role of higher doses of OnaA to improve patients' functional outcome.

Acknowledgments

The authors thank the patients who participated in the study and the general support of the Parkinson Foundation, Tyler's Hope for a Dystonia Cure, Smallwood Foundation, Harry T. Mangurian Jr. Foundation, and the Barbara Padgett Dein professorship.

References

1. Simpson DM, Hallett M, Ashman EJ, Comella CL, Green MW, Gronseth GS, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2016;86(19):1818–1826. doi: 10.1212/WNL.0000000000002560

2. Simpson DM, Blitzer A, Brashear A, Comella C, Dubinsky R, Hallett M, et al. Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008;70(19):1699–1706. doi: 10.1212/01.wnl.0000311389.26145.95

3. Botox® (onabotulinumtoxinA). Prescribing Information. Irvine, CA: Allergan, Inc., 2019. Available from: <https://media.allergan.com/actavis/actavis/media/allergan-pdf-documents/product-prescribing/20190620-BOTOX-100-and-200-Units-v3-0USPI1145-v2-0MG1145.pdf> [cited 11 February 2020].

4. Brin MF. Dosing, administration, and a treatment algorithm for use of botulinum toxin A for adult-onset spasticity. *Muscle Nerve Suppl* 1997;6:S208–S220. doi: 10.1002/(SICI)1097-4598(1997)6+<208::AID-MUS15>3.0.CO;2-1

5. Simpson DM, Alexander DN, O'Brien CF, Tagliati M, Aswad AS, Leon JM, et al. Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. *Neurology* 1996;46(5):1306–1310. doi: 10.1212/WNL.46.5.1306

6. Childers MK, Brashear A, Jozefczyk P, Reding M, Alexander D, Good D, et al. Dose-dependent response to intramuscular botulinum toxin type A for upper-limb spasticity in patients after a stroke. *Arch Phys Med Rehabil* 2004;85(7):1063–1069. doi: 10.1016/j.apmr.2003.10.015

7. Albrecht P, Jansen A, Lee J-I, Moll M, Ringelstein M, Rosenthal D, et al. High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy. *Neurology* 2019;92(1):e48–e54. doi: 10.1212/WNL.0000000000006688

8. Wissel J, Ward AB, Erztgaard P, Bensmail D, Hecht MJ, Lejeune TM, et al. European consensus table on the use of botulinum toxin type A in adult spasticity. *J Rehabil Med* 2009;41(1):13–25. doi: 10.2340/16501977-0303

9. Mancini F, Sandrini G, Moglia A, Nappi G, Pacchetti C. A randomised, double-blind, dose-ranging study to evaluate efficacy and safety of three doses of botulinum toxin type A (Botox) for the treatment of spastic foot. *Neurol Sci* 2005;26(1):26–31. doi: 10.1007/s10072-005-0378-9

10. Baricich A, Grana E, Carda S, Santamato A, Cisari C, Invernizzi M. High doses of onabotulinum toxin A in post-stroke spasticity: a retrospective analysis. *J Neural Transm (Vienna)* 2015;122(9):1283–1287. doi: 10.1007/s00702-015-1384-6

11. Baricich A, Picelli A, Santamato A, Carda S, de Sire A, Smania N, et al. Safety profile of high-dose botulinum toxin type A in post-stroke spasticity treatment. *Clin Drug Investig* 2018;38(11):991–1000. doi: 10.1007/s40261-018-0701-x

12. Wissel J, Bensmail D, Ferreira JJ, Molteni F, Satkunam L, Moraleda S, et al. Safety and efficacy of incobotulinum toxin A doses up to 800 U in limb spasticity the TOWER study. *Neurology* 2017;88(14):1321–1328. doi: 10.1212/WNL.0000000000003789

13. Wissel J. Towards flexible and tailored botulinum neurotoxin dosing regimens for focal dystonia and spasticity – Insights from recent studies. *Toxicon* 2018;147:100–106. doi: 10.1016/j.toxicon.2018.01.018

14. Nuanthaisong U, Abraham N, Goldman HB. Incidence of adverse events after high doses of onabotulinum toxin A for multiple indications. *Urology* 2014;84(5):1044–1048. doi: 10.1016/j.urology.2014.07.046

15. Baizabal-Carvallo JF, Jankovic J, Pappert E. Flu-like symptoms following botulinum toxin therapy. *Toxicon* 2011;58(1):1–7. doi: 10.1016/j.toxicon.2011.04.019