Exceeding the maximum recommended dose of onabotulinumtoxinA in urologic patients

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Introduction: *Although onabotulinumtoxinA (BTX) is commonly utilized by multiple specialists, it is unclear how often or reasons why patients receive more than the recommended maximum dose. The goal of this study was to determine if excess BTX use occurs in urologic practice.*

Materials and methods: *This retrospective cohort identified patients who underwent intravesical BTX between 01/2013-12/2017 at an academic hospital. All BTX administrations for any indication were identified. Excess BTX was defined as receiving greater than the current recommended maximum dosage of 400 units within 3 months.*

Results: *A total of 361 patient received intravesical BTX. These patients underwent 755 procedures using BTX, 673(89.1%) intravesical and 82(10.9%) non-urologic. Other site injections occurred in 14 patients, and 7 (50.0%) of these patients had at least one instance of excess. In these 7 patients, there were a total of 15 instances of excess use from either a single injection (3 instances) or a subsequent injection within 3 months (12 instances). No excess use occurred in patients who received only intravesical BTX. Discordance was noted between the administered dose, pharmacy dispensing information (46.9%), and nursing medication administration record (MAR) (54.3%). All dosages matched in only 39.2% procedures.*

Conclusions: *Although excess BTX use is overall infrequent in urologic practice, it is common in our patients prescribed the drug by non-urologic providers (50%). Pharmacy dispensing and nursing MAR information are unreliable in determining the actual administered dose. This highlights the need for providers to further discuss BTX use with patients and the need for improved tracking of BTX administration and communication across specialties.*

Key Words: overactive bladder, neurogenic bladder, onabotulinumtoxinA, urinary bladder

Introduction

OnabotulinumtoxinA (BTX) is a neuromuscular blocking agent commonly used by urologists for the treatment of overactive bladder (OAB) and neurogenic detrusor overactivity (DO).[1-3] Because the drug functions by inhibiting pre-synaptic acetylcholine release resulting in muscle paralysis, it is also commonly used by medical professionals in other specialties for various clinical indications, including blepharospasms, cervical dystonia, chronic migraines, severe axillary hyperhidrosis, strabismus, and facial lines.[4,5] Only one prior study has investigated patients in urology practice who received > 360 units of BTX in a 3 month period with no adverse events.[6] However, it is unclear how often and for what reasons our urology patients currently receive more than the recommended maximum dosage of 400 units across the multitude of indications for which the drug is used.

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Materials and methods

The study was approved by the institutional review board (IRB#STUDY00142049). We retrospectively identified all patients undergoing intravesical BTX injection between 01/2013-12/2017 at an academic medical center. Data were collected from the electronic medical record using an i2b2 based interface query tool, Healthcare Enterprise Repository for Ontological Narration (HERON).[7,8] CPT codes as well as pharmacy dispensing and nursing medication administration record (MAR) information were utilized to identify all other administrations of BTX in our cohort, Table 1. To ensure all administrations of BTX were identified, we also cross-referenced the data obtained electronically from the hospital's SQL database with the query software Crystal Reports (SAP Software Solutions). HERON and SQL data were both reviewed, and a formal chart review was completed to obtain reconciled administration dosages from the physician procedure note. We considered the procedure or operative note to be the correct dose administered. Excess administration was defined as receiving greater than the manufacturer's current recommended maximum dosage of 400 units within 3 months.[4] Descriptive data analysis was completed in SAS Studio.

TABLE 1. **All queried CPT codes with possible onabotulinumtoxinA use**

CPT code	Description of procedure
31513	Laryngoscopy, indirect (separate procedure); with vocal cord injection
31570	Laryngoscopy, direct, with injection into vocal cord(s), therapeutic
31571	Laryngoscopy, direct, with injection into vocal cord(s), therapeutic; with operating microscope
43201	Esophagoscopy, rigid or flexible; with directed submucosal injection(s), any substance
43236	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with directed submucosal injection(s), any substance
52287	Cystourethroscopy with injection(s) for chemodenervation of bladder
53899	Unlisted procedure, urinary system
64611	Chemodenervation of parotid and submandibular salivary glands, bilateral
64612	Chemodenervation of muscle(s); muscle(s) innervated by facial nerve (e.g., blepharospasm, hemifacial spasm)
64613	Chemodenervation of muscle(s); neck muscle(s) (e.g., for spasmodic torticollis, spasmodic dysphonia)
64614	Chemodenervation of muscle(s); extremity(s) and/or trunk muscle(s) (e.g., for dystonia, cerebral palsy, multiple sclerosis)
64615	Chemodenervation of muscle(s); muscle(s) innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (eg, for chronic migraine)
64616	Chemodenervation of muscle(s); neck muscle(s), excluding muscles of the larynx, unilateral (e.g., for cervical dystonia, spasmodic torticollis)
64617	Chemodenervation of muscle(s); larynx, unilateral, percutaneous (e.g., for spasmodic dysphonia), includes guidance by needle electromyography, when performed
64640	Destruction by neurolytic agent; other peripheral nerve or branch
64642	Chemodenervation of one extremity (1-4 muscles)
64643	Chemodenervation of one extremity (each additional muscle)
64644	Chemodenervation of one extremity (5 or more muscles)
64645	Chemodenervation of one extremity (each additional muscle)
64646	Chemodenervation of trunk muscles (1-5 muscles)
64647	Chemodenervation of trunk muscles (6 or more muscles)
64650	Chemodenervation of eccrine glands; both axilla
64653	Other area (hyperhidrosis)
67345	Chemodenervation of extraocular muscle

TABLE 2. **Injections of onabotulinumtoxinA outside the bladder**

	Number of procedures (n = 82)	%
Anatomic location		
Department of Neurology	48	(58.5%)
Department of Physical Medicine and Rehabilitation	34	(41.5%)
Indication for procedure		
Spasticity	32	(39.0%)
Chronic migraine	28	(34.1%)
Blepharospasm	18	(22.0%)
Dystonia	4	(4.8%)

Results

A total of 361 patients received intravesical BTX injection during the study period. The average age was 60.2 ± 15.6 years, 274 (75.9%) were female, and 304 (84.2%) were Caucasian. Intravesical administration was performed primarily by a urologist (327 patients, 90.6%) and less frequently by a urogynecologist (34 patients, 9.42%). Administered dose ranged from 100 to 300 units per procedure for indications including urgency, frequency, urge urinary incontinence, OAB, DO, and neurogenic DO.

This patient cohort underwent a total of 755 procedures using BTX. Of these, 673 (89.1%) were intravesical, an average of 1.86 ± 1.46 intravesical injections per patient. The other 82 procedures (10.9%) involved injection at other anatomic sites, Table 2. These other site injections occurred in 14 patients (3.88% of the total patient population).

Of the 14 patients who were administered BTX by multiple providers and departments, 7 (50.0%) patients encountered at least one instance of excess use. No excess use occurred in patients administered only intravesical BTX. In the 7 patients with excess use, there were 15 total instances. Excess BTX from a single procedure with administration of > 400 units occurred in 2 patients in 3 total instances. For example, one patient received 600 units during an injection procedure for the treatment of spasticity. The other 12 instances of excess use occurred in 6 patients and were the result a subsequent injection within 3 months. Of note, there were no adverse events identified in any of the 7 patients who received > 400 units at one time or within the 3 month window.

Of the 755 procedures, pharmacy dispensing information was discordant with the operative report in 354 cases (46.9%). On review of nursing MAR, 410 of 755 (54.3%) procedures had mismatched dosage

TABLE 3. **All queried CPT codes with possible onabotulinumtoxinA use**

	Number of instances (n = 354)	%
Reason for pharmacy dispensing mismatch		
Need to add multiple vials/doses to get final amount given	199	(56.2%)
No record of dispensed dosage	62	(17.5%)
Partial disposal of dispensed dose intraoperatively	49	(13.8%)
Alternative amount recorded	44	(12.4%)
	Number of instances (n = 410)	**%**
Reason for medication administration record mismatch		
No record of onabotulinumtoxinA dosage administered	283	(58.0%)
Zero units recorded although alternative amount given	113	(27.6%)
Partial disposal of dispensed dose intraoperatively not recorded	9	(2.19%)
Incorrect dosage recorded for unknown reason	7	(1.7%)
Multiple MAR entries must be added to obtain final dosage given	1	(0.24%)

data. The operative report, pharmacy dispensing information, and nursing MAR all matched in only 296 (39.2%) of the 755 procedures. The specific reasons for discordance are noted within Table 3. Of note, some procedures had multiple reasons for discordant dosage recording.

Limitations

This retrospective review may underestimate the actual number of instances of BTX excess use. We were only able to capture medication administration at our institution. If patients received the drug at an outside facility or clinic, it was not captured within our database. Additional instances of excess use may have been missed if they occurred due to administrations in the three months before or after our retrospective review window.

The overuse of BTX across all medical specialties is likely higher than that reported in our patient population, specifically in those who undergo procedures with total dosages that approach or exceed 400 units in a single procedure. Examples of such procedures which we have identified in our chart review most commonly include multi-site injections for limb spasticity. Further studies are needed to better define overuse of BTX in all patient populations receiving the drug as well as to investigate preventative measures to decrease instances of overuse.

Our study only evaluated the use of BTX. We did not investigate other neurotoxin agents such as abobotulinumtoxinA (Dysport) or incobotulinumtoxinA (Xeomin). Although the toxin in these different agents are the same, their alternative protein packaging limits our ability to compare and convert dosages between them directly. Serotype B botulinumtoxin, rimabotulinumtoxinB (Myobloc/NeuroBloc), usage was also not investigated in this study due to similar difficulties in dosage comparison and conversions.

Discussion and conclusion

Although excess administration of BTX is rare in our urology patient population as a whole, it is very common in our patients who received the drug from multiple providers for different indications, occurring in 50% of such patients. However, patients who received more than the current recommended dose did not experience any adverse events related to higher doses of BTX. These findings raise the question of whether patients can safely tolerate higher doses. The management of neurogenic bladder disease has been revolutionized with the addition of BTX. If the maximum recommended dose is increased, there is potentially additional opportunity to avoid urinary diversion for these patients, especially when they are also receiving BTX for other indications. Further studies are needed to investigate potential adverse effects after administration of larger doses at individual or multiple injection sites.

Pharmacy dispensing and nursing MAR information are unreliable in determining the dosage of BTX administered. The operative report should be utilized to identify the actual dosage given. Further studies are needed to determine methods for the tracking of BTX drug administration, such as a national tracking database for the drugs administration. This would improve communication between providers across the multitude of medical and surgical specialties who utilize BTX for multiple different clinical indications.

Importantly, these findings also emphasize a possible area for improvement in patient education. Healthcare providers should discuss with patients the importance of disclosing past or future BTX procedures to their physicians. It is unclear if patients currently understand the dosage limits of BTX which currently apply to all sites of injection within a 3-month timeframe. Additional patient education may help to prevent excess administration of the drug when administered by multiple providers in the future. □

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