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INCIDENCE OF ADVERSE EVENTS AFTER GREATER THAN 360 CUMULATIVE UNITS OF ONABOTULINUMTOXIN A GIVEN WITHIN A THREE MONTH TIME PERIOD

Hypothesis / aims of study
The manufacturer of onabotulinumtoxinA recommends no more than 360 cumulative units within a 3 month interval based on FDA trial data (1). High doses of onabotulinumtoxinA can potentially result in spread of toxin effect. Symptoms such as dysphagia and paralysis of respiratory muscles can be life-threatening (2). The aim of this study was to determine the occurrence of all adverse events, especially life-threatening adverse events, after the injection of a cumulative dose of more than 360 units onabotulinumtoxinA within a 3 month interval. We hypothesized that there would not be increased adverse events after injections exceeding dosage guidelines.

Study design, materials and methods
This is a retrospective cohort study of patients who received more than 360 units Botox within a 3 month interval, with at least one urologic indication for injection, between 1/1/2002 to 1/1/2013. The rate of any adverse event up to 8 days post-injection, and life-threatening adverse events up to 90 days post-injection was compared between injection sessions meeting the dosage guidelines and injection sessions exceeding the dosage guidelines.

Results
13 patients met study criteria. There were no adverse events after injection sessions falling within manufacturer recommended dosage guidelines. There were 6 adverse events out of a total of 135 (4.4%) injection sessions that exceeded manufacturer recommended dosage guidelines. These adverse events were minor and eventually resolved. There were no life-threatening adverse events in either group. See Table 1.

Interpretation of results
The adverse event rate after injections exceeding dosage guidelines was low. None of these adverse events were life-threatening. Limitations of this study include that most of the patients had multiple sclerosis (MS) thereby limiting the generalizability, potential omission of adverse events due to the retrospective nature of the study, and lack of testing for onabotulinumtoxinA antibodies over time, although this test is not readily available in laboratories.

Concluding message
High cumulative doses of onabotulinumtoxinA were tolerated in a retrospective cohort of patients undergoing injection for multiple indications. There were no life-threatening adverse events. Prospective studies are necessary to redefine the maximum cumulative dosage of onabotulinumtoxinA that can be safely administered within a certain time period.

Table 1: Patients who received > 360 units Botox within a 3 month interval

Patient	first procedure	Sex	Diagnosis	Indication for Botox	Sites Injected	Follow-Up Time (months)	Total # Procedures	Botox units injected within 3 months	Minor Adverse Events after >360 units within 3 months*
1	35	F	MS	NDO Spastic Extremities	Bladder Extremities	72	34	1200	2
2	51	F	MS	NDO Spastic Extremities Dystonia Gastroparesis	Bladder Extremities Neck Pylorus	72	32	900	2
3	49	F	MS	NDO Spastic Extremities	Bladder Extremities	64	32	1700	0
4	48	F	MS	NDO Spastic Extremities	Bladder Extremities	65	20	900	0
5	42	F	MS	DSD Spastic Extremities	EUS Extremities	25	9	500	0
6	34	F	MS	NDO DSD Spastic Extremities	Bladder EUS Extremities	49	9	600	0
7	45	F	MS	NDO Spastic Extremities	Bladder Extremities	108	5	500	1
8	60	F	MS	NDO Spastic Extremities	Bladder Extremities	6	2	500	1
9	53	M	Sarcoidosis	Idiopathic UUI Spastic Extremities	Bladder Extremities	66	18	1900	0
10	69	F	MS	NDO	Bladder	16	5	600	0
11	56	F	MS	NDO	Bladder	40	7	400	0
12	36	F	SCI	Idiopathic UUI	Bladder	31	6	400	0
13	44	M	MS	DSD Hypertonicity of pelvic floor	EUS Pelvic floor	93	18	500	0

References

1. Childers MK, Brashear A, Jozefczyk P, et al. Dose-dependent response to intramuscular botulinum toxin type A for upper-limb spasticity in patients after stroke. Arch Phys Med Rehabil. 2004. 85: 1063-9
2. Allergan: Botox: OnabotulinumtoxinA Full Prescribing Information. Irvine, CA, 2013

Disclosures

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