ORIGINAL ARTICLE

Dispensing profile of botulinum toxin for treating spasticity: Brazilian national data

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ABSTRACT

The physiatrists specialized in treating spasticity were brought together for a panel discussion about the use of botulinum toxin (BT) in the public system in different states of Brazil. The data analyzed during the discussion of Datasus demonstrate a low-demand profile of the product dispensed by the Unified Health System (SUS), with heterogeneity in the distribution of TB in the Brazilian states. This scenario seems to be set up mainly for lack of a properly planned public policy, such as lack of unification and standardization of distribution centers, the lack or inadequacy of TB compensation proceeding to treatment centers, in a standardized manner by SUS and shortage of trained doctors to do it together with the lack of qualified multidisciplinary rehabilitation centers. The use of botulinum toxin for therapeutic purposes in Brazil began in the 90s, to treat dystonia and spasticity. It is currently employed in different clinical conditions; however, despite growing demand and indications over the years, there are few reports or publications on its use and benefit to patients served by the Unified Health System (SUS). To address this issue, in May 2015, in São Paulo, physiatrists from different states of Brazil met and discussed the relevance of botulinum toxin in treating spasticity.

Keywords: Botulinum Toxins, Muscle Spasticity/rehabilitation, Public Health Policy, Brazil

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Spasticity and adults and children

Spasticity is a clinical manifestation resulting from higher motor neuron lesion present in central nervous system diseases such as stroke, spinal cord injury, cerebral palsy, brain injury, neurodegenerative diseases, tumors, infectious and inflammatory processes, among others.[1]

The change caused by muscle spasticity prevents an adequate movement width that can lead to shortening of muscle or tendon fibers, causing contracture in joint structures, which can generate fixed deformities.[2] These changes may cause movement limitation, increasing the risk for developing pressure ulcers, as well as painful conditions and varying degrees of inability to perform activities of daily living (ADLs) such as hygiene, feeding, locomotion, clothing, and for the activities of everyday life (AVP) such as study, work and domestic activities.[3,4]

In addition to these changes, there is an impact on the mental, socio-cultural and economic, aspect, with great damage in the patient's quality of life and his family.[5,6] Considering that there is no single treatment for patients with spasticity, they must be inserted into a rehabilitation program. The objectives of this treatment are the pursuit of functional improvement, prevention of deformities by facilitating the use of orthotics and rehabilitation equipment (such as wheelchairs, parapódio, walker, cane etc.), prevention and treatment of pain, easing of care and management of the patient by the caregiver. There is evidence that the treatment of patients with spasticity should be introduced as early as possible and continued control over the progress of their disability.[7-10]

The assessment of patient with spasticity requires clinical knowledge of the installed disability and of waste and potential capabilities. Thus, the work of the medical expert to define the diagnosis, treatment plan and to coordinate the rehabilitation team is required.

The team may consist of doctor specialized in rehabilitation and other medical specialties, physical therapist, occupational therapist, speech therapist, psychologist, nurse, prosthetist-orthotic technician, social worker, nutritionist, physical educator and pedagogue.

The therapeutic modalities should be prescribed according to the diagnosis and prognosis of the patient, in accordance with their aspirations and their families in a planned manner, with defined goals and individual goals. Patients should be reviewed periodically and goals redefined as their evolution.

According to ordinance SAS/MS Nº. 377 (11/10/2009), the reference center for spasticity must be linked to a physical medicine and rehabilitation service (physiatry) accredited by the Unified Health System (SUS).When impossible, this must be linked to institutions of excellence in medical education, accredited by SUS, with a multidisciplinary team made up of specialized medicine (physiatry, neurology, neurosurgery or orthopedics) with experience in clinical and functional assessment of spasticity, occupational therapist and physiotherapist.[11]

The use of type A (TAB) Botulinum toxin (TB) has proven to be useful in the control of muscle tone, improvement of joint range of passive and active motion, reducing associated painful conditions, reducing the use of pain and anti-spastic medications, preventing muscle contractures and joint deformities, facilitating the use of orthoses, as well as being able to reduce the need for corrective surgical procedures.[12,13]

Several studies have linked the use of TAB with functional patient gains such as improved gait (walking), balance, manual and bimanual ability to perform ADLs and AVPs. Another benefit of using TAB is the facilitation of care and patient handling with higher motor dysfunction (greater degree of immobility) by the caregiver. Importantly, the use of TAB for treating spasticity has a positive impact on the quality of life of patient and caregiver.[1,14,15]

Nowadays, with increasing urban violence and traffic accidents, chronic diseases and the improvement of medical support, there is an increasing number of patients with central nervous system and spasticity injury requiring rehabilitation treatment, being a public health problem. For proper treatment of prisoners, some shortcomings in the management of these patients are identified:

- Lack of rehabilitation content as a compulsory subject in the curriculum in undergraduate medicine courses.
- Unawareness of health professionals regarding rehabilitation.
- Lack of care line of patients with spasticity, from acute to ambulatory monitoring.
- Lack of referral centers for spasticity.
- Lack of referral centers for physical medicine and rehabilitation.
- Few professional experts in rehabilitation.

These factors lead to delayed access to rehabilitation treatment, with a consequent increase in complications associated with spasticity, thus bringing a large socioeconomic impact. Therefore, it is emphasized the need for a government policy to provide more training for health professionals and the dissemination of rehabilitation specialized centers.

Botulinum toxin

Botulinum toxin (BT) is a protein complex produced by a type of bacterium called *Clostridium Botulinum*. There are seven serotypes of toxins classified from A to G. All serotypes can cause botulism, which is a life-threatening condition involving a symmetrical flaccid paralysis, autonomic dysfunction and respiratory impairment.[1]

The clinical syndrome of botulism has been described in detail in 1820 when Justinus Kerner published his observations about the poisoning from sausage (sausage poisoning). He correctly established the hypothesis that this syndrome could be caused by a biological poisoning which interrupts nerve conduction. Although unable to isolate the toxin sensed, it would be possible to use it for therapeutic purposes.

BT acts by blocking the release of acetylcholine in cholinergic terminals, blocking transmission at the neuromuscular junction and producing paralysis and autonomic changes.[16]

Applied intramuscularly, BT causes a local and temporary paralysis, suggesting that besides the muscle relaxation effect, it leads to blockage of sensory transmission and consequent analgesic effect. Each serotype has a different activity time, being type A (TAB) the longest, with its effects lasting for three to four months.

TAB has been used clinically for the first time in 1977 to treat strabismus. From that moment, it was used to treat various conditions including dystonia, spasticity, tremor, achalasia, migraine, overactive bladder, hyperhidrosis, drooling and hyperkinetic facial lines.

There are several TAB preparations in the world market, the most studied: Dysport (Ipsen), Botox® (Allergan) and Xeomin® (Merz Pharmaceuticals); however, Prosigne® and

Botulift® (Amgen) are also available in the Brazilian market. The strength of each product is different and doses are not interchangeable.

Adverse effects of TAB post-application are usually mild to moderate and transient. Local reactions such as erythema, rash, edema and local pain were reported. The spread of TAB to adjacent tissues can cause weakness in the neighboring muscles and autonomic disorders; for example, injections in the cervical region can result in xerostomy and dysphagia. Effects such as fatigue, malaise and flu-like symptoms are related to systemic dissemination of TAB. There are occasional reports in literature of muscle weakness away from application site and even cases of botulism like syndrome.

Use of botulinum toxin in treating spasticity

The use of phenol in the treatment of focal spasticity became a therapeutic use in our environment in the early 1970s.[17]

Phenol mechanism of action was demyelination; therefore, had limited use to the nerves with predominantly fibers motor, since they could bring dysesthesia side effect in mixed nerves or with sensory component.

It was used mainly in the obturator nerve to control canine hip adduction and chest and musculocutaneous nerve to reduce the adduction spasticity of shoulder and elbow flexor. Due to these limitations, its use was not widespread.TAB as a treatment for spasticity allows the effective control of this dysfunction in all muscle groups, but the limitations on maximum recommended therapeutic doses should be taken into account.

The advent of TAB has not made phenol obsolete as treatment resource. The combined use (TAB and phenol) can simultaneously handle a larger number of muscles that interfere with the functional capacity with effective results without side effects caused by injuries in the sensory nerves or doses higher than the therapeutic safety range of TAB.[18,19]

Use of TAB in physiatry in Brazil

In 1995, the first results with the use of TAB in spasticity were presented at the Brazilian Congress of Cerebral Palsy.

At the congress of the Asociación Médica Latino Americana de Rehabilitación (AMLAR) in São Paulo, in 1997, the first workshop was organized that established the concepts of the use of TAB such as a facilitator resource in the rehabilitation of spastic patients with an interdisciplinary focus. The main services in Brazil and throughout Latin America were represented at this meeting, thus forming a milestone in the spread of therapy by TAB.

The Brazilian Association of Physical Medicine and Rehabilitation promoted in 2001 the National Consensus on Spasticity, which was updated in 2004 and revised in 2014 (pending publication), as part of the design of Diagnostic and Treatment Guidelines of the Brazilian Medical Association (AMA).[20]

Ordinance GM/MS Nº. 1318 of 2002 regulates the supply of TAB for units of the states within the exceptional medication dispensing program.[11]

From the federal regulation in 2002, specialized services have been organized and installed in a singular manner in several states of Brazil according to their peculiarities.

Thus, each state has its own distribution flow chart of this medication. There is great heterogeneity in the distribution of the drug in different states of Brazil, with main concentration in the states of São Paulo, Minas Gerais and Santa Catarina (Table 1).

There has been a clear preponderance of use of 500 U TAB regarding 100 U TAB held for each year of assessment (Table 2).

There has been a clear preponderance of use of 500 U TAB regarding 100 U TAB held for each year of assessment. Despite the categorization of TAB as a biological product by the National Health Surveillance Agency (Anvisa), from the publication of the Ordinance of the Ministry of Health in December 2013, the federal government has centralized the purchase and exclusive distribution of a single supplier of 100 U TAB.[21]

There has been a great heterogeneity in the distribution of TAB in the Brazilian states, with the highest concentration in the states of São Paulo, Minas Gerais and Santa Catarina, but that does not correlate at all with the population size of each state and the distribution of doctors; for example, the state of Rio de Janeiro has a consumption markedly lower than that in the states of Santa Catarina and Goiás.

It can be assumed that this scenario is justified by several factors:

- Lack of unification and standardization of the distribution centers, as there is logistics facilitation at the places where the medication is dispensed to the applicator center, allowing better planning of treatment and proper medication storage, ensuring greater safety of the procedure.
- No compensation procedure to treatment centers in a standardized manner in the Unified Health System (SUS) table. This situation makes the procedure unattractive to health managers, who show no interest in expanding existing centers or implementing new centers.
- Few doctors trained to perform the procedure and lack of qualified rehabilitation centers (medium and high complexity) in most of the country for multidisciplinary treatment as recommended by the Clinical Protocol and Therapeutic Guidelines: Spasticity (Figure 1).
- Ordinance SAS/MS Nº. 377 of November 10, 2009.[11]

It is observed that the number of patients treated with TAB in Brazil in this historic series (2009 to 2014), from 4500 to 8000 patients per year, although rising, is far short of the estimated patients who potentially need such treatment. For example, considering only the incidence of cerebrovascular accident (CVA) in Brazil, about 210 thousand cases a year, at least 100,000 of these cases are potential candidates who would benefit from treatment with TAB.

By analyzing the distribution of the number of bottles per patient, it is noted that during this historic series increased consumption of 500 U TAB (Table 3) and decreased 100U TAB (Table 4). The average number of TAB vials applied by the patient, despite having oscillations over the years evaluated, it is still above the recommended in the medical literature.

Table 1. Number of patients treated with Botulinum toxin per State

Period	MAT '09 (Nov 08 - Oct 09)		MAT '10 (Nov 09 - Oct 10)		MAT '11 (Nov 10 - Oct 11)		MAT '12 (Nov 11 - Oct 12)		MAT '13 (Nov 12 - Oct 13)		MAT '14 (Nov 13 - Oct 14)	
Toxin	500 U TOXIN	100 U TOXIN	500 U TOXIN	100 U TOXIN	500 U TOXIN	100 U TOXIN	500 U TOXIN	100 U TOXIN	500 U TOXIN	100 U TOXIN	500 U TOXIN	100 U TOXIN
AC	16	95	34	23	0	27	16	6	29	23	29	2
AL	137	83	129	30	105	27	78	68	86	87	213	109
AM	68	74	86	48	126	87	144	129	140	157	112	187
AP	0	8	0	0	1	3	0	8	3	1	2	4
BA	405	140	717	219	501	353	608	310	309	419	4	85
CE	90	374	162	326	37	539	9	572	5	532	126	597
DF	76	189	128	205	129	189	129	224	200	243	220	282
ES	137	350	373	261	292	407	189	577	314	557	589	248
GO	237	370	314	327	393	417	609	354	745	440	783	566
MA	0	62	0	73	22	81	23	111	20	141	38	152
MG	831	584	989	511	1.414	585	1.747	622	2.103	704	2.480	796
MS	104	169	79	146	62	147	70	100	219	166	195	116
MT	116	44	235	44	238	39	291	31	285	86	270	70
PA	61	98	70	95	29	180	96	197	107	192	87	188
PB	349	54	342	151	320	168	380	134	328	144	335	180
PE	193	343	267	397	347	326	510	318	847	158	716	134
PI	126	56	119	90	90	163	34	208	71	153	81	165
PR	111	158	364	284	463	363	594	332	789	409	712	519
RJ	148	377	234	124	306	665	249	635	482	469	701	182
RN	2	286	0	283	0	319	25	203	78	325	179	310
RO	42	49	83	54	173	54	181	48	151	63	184	81
RS	5	871	5	899	1	988	7	1.037	9	955	37	1.035
SC	310	1.050	763	47	924	497	1.284	602	1.119	507	1.264	797
SE	7	113	15	119	42	104	45	83	92	61	55	82
SP	4.653	1.321	4.788	1.179	5.201	1.304	5.658	1.251	6.332	994	6.488	1.023
TO	1	20	1	26	2	27	6	15	22	24	12	19
RR	0	0	4	0	2	1	0	0	0	0	2	0
BRAZIL	8.224	7.336	10.298	5.961	11.214	8.058	12.982	8.172	14.881	8.007	15.910	7.926
Total Market Unique patients (500 Tox + 100 Tox)	14.911		15.512		18.505		20.263		21.977		22.872	

Data source: DATASUS/Consultation period: January 2008 to October 2014.
Note about the concept of UNIQUE PATIENTS: Values mentioned below are the number of unique patients under treatment in the selected period. Although the patient does not come to the base for more than once, he/she will be counted only once per variable. The same patient can discontinue more than one medication in a closed period; because of that, the sum of patients per product should not match the Total Market. The same happens when there is open information per State; the sum for many times does not match the Total Brazil because the patient can move to another address and discontinue the medication in another State or Municipality.

Table 2. Number of patients treated with Botulinum toxin in Brazil per disease

Diagnosis group	Toxin	MAT '09 (Nov 08 - Oct 09)	MAT '10 (Nov 09 - Oct 10)	MAT '11 (Nov 10 - Oct 11)	MAT '12 (Nov 11 - Oct 12)	MAT '13 (Nov 12 - Oct 13)	MAT '14 (Nov 13 - Oct 14)
Dystonia	500 U Toxin	4.639	5.555	5.616	5.739	5.267	5.177
	100 U Toxin	4.418	3.823	4.882	4.910	4.870	4.754
Cerebral palsy	500 U Toxin	1.641	1.972	2.223	2.999	3.565	4.044
	100 U Toxin	1.236	981	1.550	1.529	1.498	1.44
Spasticity	500 U Toxin	2.524	3.370	3.671	4.414	5.662	6.604
	100 U Toxin	2.009	1.474	1.931	1.895	1.629	1.541
Others	500 U Toxin	10	270	329	450	560	602
	100 U Toxin	18	43	109	142	202	385
Total Brazil Unique patients	500 U Toxin	8.224	10.298	11.214	12.982	14.881	15.910
	100 U Toxin	7.336	5.961	8.058	8.172	8.007	7.926
Total Market Unique patients	100 U Toxin + 500 U Toxin	14.911	15.512	18.505	20.623	21.977	22.872

Data source: DATASUS/Consultation period: January 2008 to October 2014.

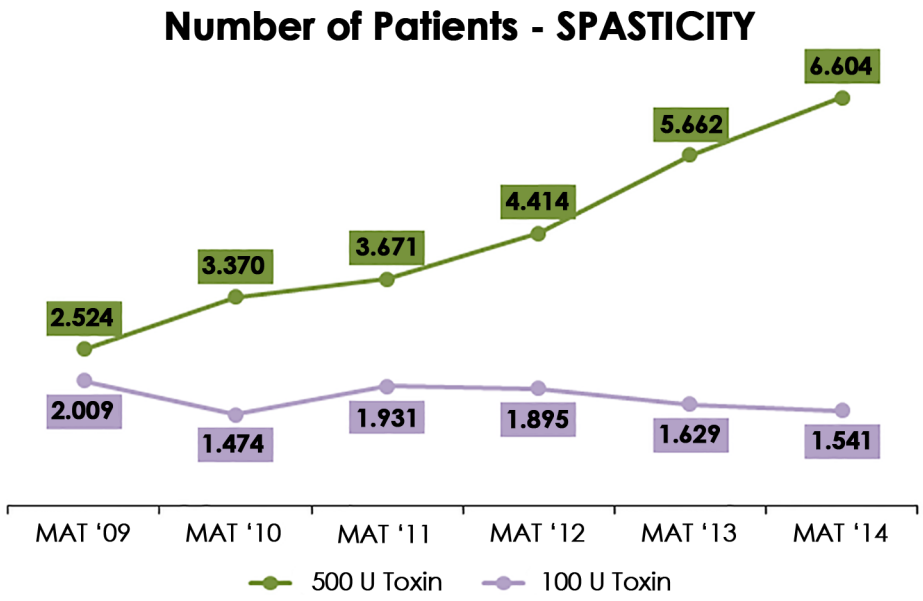

Figure 1. Number of patients - Spasticity

Perspective

After days of analysis and discussion about the dispensation profile of Botulinum toxin by SUS, it seemed evident that a planned specific public policy could alleviate the imbalance observed in Datasus;

- Unification and standardization of the distribution centers, as there is logistics facilitation in the places where the medication is dispensed to the applicator center, allowing better treatment planning and proper medication storage, ensuring greater safety of the procedure.
- No compensation procedure to treatment centers in a standardized manner in the Unified Health System (SUS) table. This situation makes the procedure unattractive to health managers, who show no interest in expanding existing centers or implementing new centers.

Table 3. Number of treated patients versus number of used vials 500 U Toxin

Diagnosis group	Variable	MAT '09 (Nov 08 - Oct 09)	MAT '10 (Nov 09 - Oct 10)	MAT '11 (Nov 10 - Oct 11)	MAT '12 (Nov 11 - Oct 12)	MAT '13 (Nov 12 - Oct 13)	MAT '14 (Nov 13 - Oct 14)
Dystonia	Nº. patients treated	4.639	5.555	5.616	5.739	5.627	5.177
	Nº. used vials	10.890	13.801	16.036	14.455	13.998	13.708
Cerebral palsy	Nº. patients treated	1.641	1.972	2.223	2.999	3.565	4.044
	Nº. used vials	3.686	5.389	8.532	7.473	8.293	10.509
Spasticity	Nº. patients treated	2.524	3.370	3.671	4.414	5.662	6.604
	Nº. used vials	9.391	12.565	17.114	14.607	19.527	25.075
Others	Nº. patients treated	10	270	329	450	560	602
	Nº. used vials	30	383	787	742	1.100	1.052
Total	Nº. patients treated	8.814	11.167	11.839	13.602	15.414	16.427
	Nº. used vials	23.997	32.138	42.469	37.277	42.918	50.344
	Quantity of vials/patient	2.7	2.9	3.6	2.7	2.8	3.1

Data source: DATASUS/Consultation period: January 2008 to October 2014.

Table 4. Number of treated patients versus number of used vials (100U toxin)

Diagnosis group	Variable	MAT '09 (Nov 08 - Oct 09)	MAT '10 (Nov 09 - Oct 10)	MAT '11 (Nov 10 - Oct 11)	MAT '12 (Nov 11 - Oct 12)	MAT '13 (Nov 12 - Oct 13)	MAT '14 (Nov 13 - Oct 14)
Dystonia	Nº. patients treated	4.418	3.823	4.882	4.910	4.870	4.754
	Nº. used vials	16.256	9.110	13.046	12.370	11.957	12.537
Cerebral palsy	Nº. patients treated	1.236	981	1.550	1.529	1.498	1.440
	Nº. used vials	6.437	3.143	6.243	5.999	5.621	4.527
Spasticity	Nº. patients treated	2.009	1.474	1.931	1.895	1.629	1.541
	Nº. used vials	17.720	5.285	11.676	10.159	8.513	7.388
Others	Nº. patients treated	18	43	109	142	202	385
	Nº. used vials	49	77	164	252	380	701
Total	Nº. patients treated	7.681	6.321	8.472	8.476	8.199	8.120
	Nº. used vials	40.462	17.615	31.129	28.780	26.471	25.153
	Quantity of vials/patient	5.3	2.8	3.7	3.4	3.2	3.1

Data source: DATASUS/Consultation period: January 2008 to October 2014.

- Train doctors to perform the procedure and increase accredited rehabilitation centers (medium and high complexity) in most of the country, for multidisciplinary treatment as recommended by Clinical Protocol and Therapeutic Guidelines: Spasticity. Ordinance SAS/MS Nº. 377 of November 10, 2009.[11]

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