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High doses of onabotulinumtoxinA in post-stroke spasticity: a retrospective analysis

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Abstract We retrospectively evaluated the efficacy and safety of high doses of onabotulinumtoxinA (from 600 to 800 units) in 26 patients affected by upper and/or lower limb post-stroke spasticity. They were assessed before, 30 and 90 days after treatment. We observed a significant muscle tone reduction and a significant functional improvement (assessed with the Disability Assessment Scale). No adverse events were reported. In our retrospective analysis the treatment with high doses of onabotulinumtoxinA showed to be effective and safe.

Keywords Stroke · Spasticity · Botulinum toxin type A · OnabotulinumtoxinA · Higher doses

Introduction

Post-stroke spasticity (PSS) has been described as a relevant clinical problem in stroke survivors, as it can impair manual dexterity, mobility and balance, with a negative impact on independence (Martin et al. 2014).

OnabotulinumtoxinA has been proposed as a part of effective integrated treatment programme for the management of PSS (Brashear et al. 2002a, b; Wissel et al. 2009; Baker and Pereira 2013).

Clinical experience showed a good safety profile (Ghasemi et al. 2013) both in the short- (Naumann and Jankovic 2004) and in the long-term use (Naumann et al. 2006).

The optimal dose for onabotulinumtoxinA is determined by the patient's characteristics and by the treatment's goal but there is not a general consensus on maximum dose. Francisco (2004) suggested a dose up to 400–600 units (U) per session, whereas Wissel et al. (2009) remarked that it should not exceed 600 U. However, in clinical practice doses as high as 800 U are used by some practitioners, even if safety and efficacy of routine use of doses higher than 500 U still await further evidence (Francisco 2004).

The aim of our study was to retrospectively evaluate the efficacy and safety profile of higher doses of onabotulinumtoxinA (up to 800 U) in patients affected by upper and/or lower limb PSS.

Materials and methods

Patients

We retrospectively analysed data from 119 patients affected by upper and/or lower limb PSS who referred to the Physical and Rehabilitative Medicine Unit of University Hospital "Maggiore della Carità" in Novara (Italy) between July 2012 and April 2014.

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The inclusion criteria were: spasticity due to an ischemic or hemorrhagic stroke; time from stroke at least 6 months; total dose required of onabotulinumtoxinA ≥600 U; age >18 years. The exclusion criteria were: previous treatment with Botulinum Toxin Type A (BoNT-A) in the last 4 months; spasticity due to any other cause; presence of other concomitant neurological or neuromuscular diseases; dementia; concomitant therapy with myorelaxants (oral or intrathecal baclofen, benzodiazepines, tizanidine); previous treatment of PSS with phenol, alcohol injection or local surgery; presence of fixed contractures or muscular fibrosis at ultrasound evaluation that could have negatively influenced the treatment with onabotulinumtoxinA.

26 patients who fulfilled the inclusion criteria were included in this study; 93 patients were excluded due to treatment with other BoNT-A formulations (abobotulinumtoxinA, incobotulinumtoxinA) or doses of onabotulinumtoxinA <600 U.

Each patient and/or caregiver gave his/her written consent before the treatment.

Assessment

The same physician evaluated all the patients before treatment and 1 and 3 months after injections, as performed in clinical routine. Before treatment the patients, together with the treating physician, chose their primary therapeutic target between the four domains of the Disability Assessment Scale (DAS), i.e. dressing, limb position, pain and hygiene (Brashear et al. 2002a, b). At baseline and 30 and 90 days after treatment the functional impairment of the upper limb was evaluated with DAS (a four-point scale from 0 = no disability to 3 = severe disability), whereas changes in muscle tone were assessed with Modified Ashworth Scale (MAS) (a five-point scale from 0 = no increase in tone, to 4 = affected parts rigid in flexion or extension) (Brashear et al. 2002a, b; Bohannon and Smith 1987).

To evaluate the efficacy of the treatment, investigators, patients and their caregivers were asked to rate the patients' overall treatment tolerability (Global Assessment of Efficacy, GAE) in a four-point scale (from 1 = very good to 4 = poor) after a postinjection period of 30 and 90 days (Kaňovský et al. 2011).

In addition, a clinical examination was performed to evaluate the safety of the treatment and the presence of adverse events, which were assessed at each visit using a semi-quantitative scale (0, no adverse effects; 4, serious adverse effects) (Mancini et al. 2005).

Treatment

OnabotulinumtoxinA (Botox®, Allergan Inc., Irvine CA) was administered in 2 mL of 0.9 % dilution saline; the injections were performed under ultrasonographic guide by the same investigator. The clinicians planned target muscles, doses and number of injection sites for each muscle depending on spastic hypertonia grade and muscle size. After onabotulinumtoxinA injection, all patients participated in a 10 day-rehabilitation programme (electrical stimulation and stretching of injected muscles, strengthening exercise, gait training if applicable).

Statistical analysis

Since data were not normally distributed, according to Shapiro–Wilk test (data not shown), within-group comparisons were made using the Friedman test for repeated measures. In addition, Dunn's Multiple Comparison Test was performed to evaluate differences between single variable measurements (t1 vs t0, t2 vs t0 and t2 vs t1).

For statistical purpose, a MAS score "1" was considered as 1, a MAS score "1+" as 2, and so on until 5 (Biering-Sørensen et al. 2006). An alpha error level of 0.05 was chosen.

Statistical analysis was performed using GraphPad Prism 1.4 for Macintosh OS 10.6.

Results

The demographical and clinical characteristics of the 26 patients studied are represented in Table 1. Considering all the patients, 23 of them received the treatment at both upper and lower limb, whereas 3 patients were treated at lower limb only. 14 patients (53.8 %) were naive to treatment with onabotulinumtoxinA (8 previously treated with other BoNT-A formulations, 6 naive to any BoNT-A formulation for spasticity).

Muscles treated and relative doses are shown in Table 1.

Concerning the GAE, both 30 days (t1) and 90 days (t2) after injection patients, caregivers and clinicians rated the efficacy of treatment as "good" or "very good", except in one case where it was evaluated as "moderate" by clinicians. The complete results of GAE are represented in Table 2, together with the results of clinical evaluations with MAS and the principal target in DAS at baseline (t0), t1 and t2.

Spasticity after injections showed a significant reduction ($p < 0.0001$) considering MAS results at elbow/shoulder, wrist/finger, thigh and leg. We observed a significant reduction in muscle tone in all muscle groups both at t1 vs t0 and t2 vs t0, whereas no significant difference was seen at t2 vs t1 (Table 2). As primary therapeutic target in DAS evaluation, 18 patients (69.2 %) chose limb position, 4 patients (15.4 %) dressing, 3 patients (11.5 %) hygiene and

Table 1 Patients' demographical and clinical characteristics

Patients (*n*)	26
Total dose of onabotulinumtoxinA ≥700 U (*n*)	13
Age (years) mean ± SD	54.7 ± 11.6
Gender	
Female % (*n*)	50 (13)
Male % (*n*)	50 (13)
Time from stroke (months) mean ± SD	50 ± 48.8
Type of stroke	
Ischemic % (*n*)	57.7 (15)
Hemorrhagic % (*n*)	42.3 (11)
Type of hemiparesis	
Right % (*n*)	73.1 (19)
Left % (*n*)	26.9 (7)
Total dose of BoNT-A (U) mean ± SD	676.9 ± 86.3
Dose of BoNT-A pro kg (U) mean ± SD	9.6 ± 1.4
Total dose elbow/shoulder (U) mean ± SD	148.5 ± 58.6
Pectoralis major (U) mean ± SD	41.1 ± 11.7
Biceps brachii (U) mean ± SD	61.6 ± 16.2
Brachialis (U) mean ± SD	58.9 ± 15.7
Brachioradialis (U) mean ± SD	35 ± 22.6
Total dose wrist/finger (U) mean ± SD	165.2 ± 79.2
Flexor ulnaris carpi (U) mean ± SD	42.9 ± 14.7
Flexor radialis carpi (U) mean ± SD	45.4 ± 16.3
Flexor superficialis digitorum (U) mean ± SD	43.6 ± 22.4
Flexor profundus digitorum (U) mean ± SD	39.1 ± 16.6
Flexor longus pollicis (U) mean ± SD	23.4 ± 11.1
Flexor brevis pollicis (U) mean ± SD	21 ± 7.4
Adductor pollicis (U) mean ± SD	20 ± 0
Total dose thigh (U) mean ± SD	75.6 ± 21.3
Rectus femoris (U) mean ± SD	67.5 ± 17.1
Biceps femoris (U) mean ± SD	100 ± 0
Adductor longus/brevis/magnus (U) mean ± SD	100 ± 0
Total dose leg (U) mean ± SD	404.4 ± 112.4
Gastrocnemius medialis (U) mean ± SD	92 ± 17.3
Gastrocnemius lateralis (U) mean ± SD	92 ± 17.3
Soleus (U) mean ± SD	89.2 ± 19.8
Flexor hallucis longus (U) mean ± SD	41.6 ± 10.1
Flexor digitorum longus (U) mean ± SD	48.3 ± 11.2
Tibialis posterior (U) mean ± SD	72.9 ± 22
Tibialis anterior (U) mean ± SD	37.9 ± 9.9
Extensor hallucis longus (U) mean ± SD	40 ± 32.9
Muscles treated (*n*) mean ± SD	11.6 ± 2.3

Data are presented as mean ± standard deviation (SD) or percentage

1 patient (3.9 %) chose pain. Notably, a significant improvement in DAS principal target score has been observed at t1 vs t0 ($p < 0.001$) and t2 vs t0 ($p < 0.05$).

No adverse events were reported in patients' group (mean score 0).

Table 2 MAS, DAS and GAE evaluation at baseline (t0), 30 days (t1) and 90 days (t2)

	t0 ($n = 26$)	t1 ($n = 26$)	t2 ($n = 26$)
MAS elbow/shoulder			
Mean ± SD	3.5 ± 1	1.5 ± 0.5*	2 ± 0.8§
95 % CI	3.1–3.9	1.3–1.7	1.7–2.4
MAS wrist/finger			
Mean ± SD	3.6 ± 0.7	1.4 ± 0.5*	2.1 ± 0.7§
95 % CI	3.3–3.9	1.2–1.6	1.8–2.4
MAS thigh			
Mean ± SD	2.4 ± 0.7	0.9 ± 0.4*	1.3 ± 0.5^
95 % CI	1.8–3	0.6–1.2	0.9–1.6
MAS leg			
Mean ± SD	3.7 ± 0.7	1.5 ± 0.6*	2.1 ± 0.7§
95 % CI	3.4–4	1.2–1.7	1.8–2.4
DAS principal target			
Mean ± SD	2.3 ± 0.5	1.5 ± 0.6*	1.8 ± 0.7^
95 % CI	2.1–2.5	1.2–1.7	1.5–2
GAE patients			
Very good % (*n*)	–	65.4 (17)	61.5 (16)
Good % (*n*)		34.6 (9)	38.5 (10)
GAE caregivers			
Very good % (*n*)	–	57.7 (15)	69.2 (18)
Good % (*n*)		42.3 (11)	30.8 (8)
GAE clinicians			
Very good % (*n*)	–	69.2 (18)	69.2 (18)
Good % (*n*)		30.8 (8)	26.9 (7)
Moderate % (*n*)		0 (0)	3.9 (1)

Data are presented as mean ± standard deviation (SD) or percentage

* $p < 0.001$ t1 vs t0

§ $p < 0.001$ t2 vs t0

^ $p < 0.05$ t2 vs t0

Discussion

In our study, we observed a significant muscle tone reduction and clinical improvement with high doses of onabotulinumtoxinA, without any adverse events.

In recently published literature, the efficacy and safety of higher doses of incobotulinumtoxinA in PSS treatment has been described: Santamato et al. (2013) reported no adverse events in 25 patients with upper and lower limb PSS, evaluated 30 and 90 days after injections with doses up to 840 U; moreover, Invernizzi et al. (2014) evaluated changes in autonomic heart drive potentially induced by doses greater than 600 U, without meaningful alterations in linear and non linear Heart Rate Variability measures in 11 stroke survivors.

On the other hand, the current recommended dose of onabotulinumtoxinA is 400 U per session (Brin 1997) and, even if clinical experience suggests a maximum dose of

600 U (Francisco 2004; Wissel et al. 2009), there is no evidence of safety for doses greater than 500 U except for paediatric patients (Francisco 2004; Goldstein 2006).

Interestingly, Mancini et al. (2005) reported minor adverse effects (generalised weakness, weakness of the treated limb, flu-like syndrome and oedema; mean score 1.2) 4 weeks after administration of onabotulinumtoxinA in lower limb PSS, with a mean dose of 540 U. In addition, also Varghese-Kroll and Elovic (2009) presented a case report about contralateral weakness and fatigue after repeated high doses (800 and 500 U) of onabotulinumtoxinA for PSS.

In our study, the mean total dose of onabotulinumtoxinA was 676.9 ± 86.3 U, but we did not report any adverse event. A possible explanation might be the use of ultrasonography to identify target muscles; in fact, as reported by Henzel et al. (2010), ultrasound localization may improve accuracy of needle placement, avoiding injection into vascular structures and reducing the potential risk of systemic diffusion of BoNT-A. Moreover, this technique can improve clinical outcome both in upper and lower limb PSS (Picelli et al. 2014; Santamato et al. 2014).

To our knowledge, this is the first study showing the safety and the efficacy of PSS treatment with doses of onabotulinumtoxinA up to 800 U, higher than those typically used in clinical practice for PSS.

Nevertheless, we have to take into account that our paper suffers for the limitations of a retrospective study, as selection bias and observer bias. Besides that, the sample size is relatively small.

Further research is required to better identify the optimal dose of onabotulinumtoxinA to optimize clinical outcome and safety profile.

Conflict of interest Dr. Baricich, Dr. Cisari and Dr. Invernizzi received educational grants from Allergan, Ipsen and Merz. Dr. Santamato received educational grants from Merz.

Ethical standard All procedures performed in the study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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