DGI075

USE OF BOTULINUM TOXIN TYPE A IN POLAND: SYSTEMATIC REVIEW AND QUESTIONNAIRE SURVEY

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BACKGROUND:

In Poland, botulinum toxin type A is reimbursed for two indications: "Treatment of focal dystonias and hemifacial spasm" and "Treatment of spasticity in cerebral palsy". Three different botulinum toxin type A products are approved for use in these indications (including Botox® and Dysport®).
However, each of these products is a unique biologic agent, differing significantly in chemical structure, potency, migration beyond the site of administration, efficacy, and safety profile. For these reasons, attempting to define a fixed dose conversion ratio is inappropriate[1-10].

OBJECTIVE:

The purpose of the systematic review and questionnaire survey was to assess the relative doses used in clinical practice of two different brands of botulinum toxin type A, (Dysport® (DYS) and Botox® (BTX)) in the treatment of focal dystonias (FD), hemifacial spasm (HS) and juvenile cerebral palsy (JCP).

METHODS:

A systematic review of studies comparing Dysport® to Botox® was carried out in accordance with guidelines from the Cochrane collaboration and Polish Agency for Health Technology Assessment. Databases used were Pubmed, Embase, Cochrane and clinicaltrial.gov and searches were carried out for the period between 8th September and 15th December 2011. Search terms included *botulinum toxin type A, dystonic disorders, blepharospasm, hemifacial spasm and cerebral palsy.*
Studies were selected for inclusion based on a pre-defined PICOS scheme [Table 1].

Table 1
PICOS used for Systematic Literature Review

Patients	Intervention	Comparator	Outcome	Study Design
Patients with focal dystonias or hemifacial spasm	Botulinum toxin type A - **Botox®**	Botulinum toxin type A - **Dysport®*****	Duration of the effect, *Tsui* scale, TWSTRS pain scale, pain associated with cervical dystonia, adverse effects	RCT*
Patients with lower limb spasticity in cerebral palsy			Gross Motor Function Measure (GMFM), Ashwort/Ashwort modified scale (MAS), passive ankle mobility, gait pattern evaluation, the rate of energy consumption during walking, adverse effects	

* Other, non RCT study designs were also considered for additional analysis
**Placebo (PL) was also considered for indirect pairwise comparison in case of lack of trials directly comparing BTX and DYS

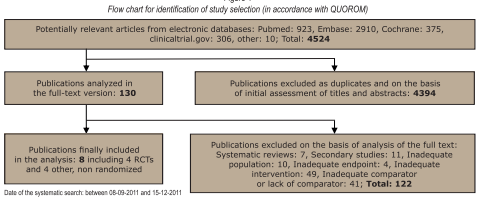
All decisions regarding the inclusion/exclusion criteria of studies involved at least two independent reviewers, with discrepancies resolved by a third reviewer. The reference lists of identified articles were then examined for additional publications. Calculations were performed using the StatsDirect® 2.6.8 statistical package.
In parallel, an electronic questionnaire survey was carried out in February 2012 involving eleven Polish doctors (6 neurologists, 2 rehabilitation specialists and 3 orthopaedic surgeons) consisting of 15 questions concerning the doses of BTX and DYS used in various indications.

RESULTS:

Focal dystonias (FD) and hemifacial (HS) spasm population

Out of 4,524 publications screened, 130 were analysed in full-text version, of which 8 (4 RCTs and 4 non randomized)[11-18] met the criteria for inclusion [Figure 1].

Figure 1
Flow chart for identification of study selection (in accordance with QUOROM)



Date of the systematic search: between 08-09-2011 and 15-12-2011

Results from Non-Randomized Studies:

Two RCTs involving patients with blepharospasm and hemifacial spasm assumed that 1.00 unit of BTX was equivalent to 4.00 units of DYS[11,14]. These studies did not show statistically significant differences between the interventions for any endpoints[11,14] [Table 2].

Two other RCTs compared BTX to DYS in the treatment of patients with spasmodic torticollis. Again, both assumed that 1.00 unit of BTX was equivalent to 4.00 units of DYS. One study found that DYS treated patients experienced significantly superior improvements in the Tsui and TWSTRS scores[12]. Statistical significance was not reached in the other study[13] [Table 2].

Table 2
Included RCT trials characteristics and results

Study	Indication	RCT design	Number of patients	Follow up	Estimated dose equivalence (Botox:Dysport)	Outcomes	Results
Nüßgens 1997[11]	Blepharospasm	Crossover	212	-	1:4	Duration of effect	**Efficacy** - No difference **Adverse effects** - Favored BTX
Ranoux 2002[12]	Cervical dystonia, spasmodic torticolis	Crossover	54	1 month	1:3 and 1:4	Tsui score TWSTRS pain score duration of action	**Efficacy** - Favored DYS **Adverse effects** - Favored BTX
Odergren 1998[13]		Parallel-group	73	12 weeks	1:3	Tsui score	No difference
Sampaio 1997[14]	Blepharospasm, hemifacial spasm	Parallel-group	91 (blepharospasm and hemifacial spasm)	1 month	Estimated dose equivalence (BTX:DYS) = 1:4	Duration of effects, number of boosters needed, latency of effect	The analysis favored the statistical and clinical equivalence of the two preparations at this ratio

Results from Non-Randomized Studies:

One non-randomized study assumed that 1.00 unit of BTX was equivalent to 4.00 units of DYS in blepharospasm and 5.00 units of DYS in cervical dystonia[18]. This study demonstrated greater improvements with BTX, based on duration of effect and TWSTRS score. However, another non-randomized study assumed that 1.00 unit of BTX was equivalent to 4.50 units of DYS in blepharospasm and found that DYS was associated with a longer treatment effect [Table 3]. This illustrates the potential danger of trying to define a fixed dose ratio.

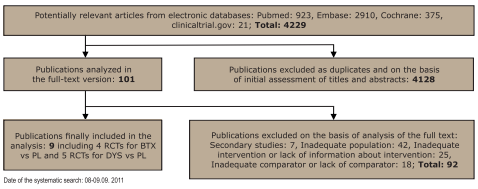
Table 3
Included non randomized trials characteristics and results

Study	Type of study	Indication	Number of patients	Follow up	Estimated dose equivalence (BTX:DYS)	Outcomes	Results
Kollewe 2010[15]	observational	Hemifacial spasm	97	12 years	1:2.56	Duration of effect based	No difference
Bentivoglio 2009[16]	retrospective	Blepharospasm	128	15 years	1:4.5	Severity of blepharospasm (Fahn & Burke dystonia scale) Duration of clinical effects	**Efficacy** - Favored DYS **Adverse effects** - Favored BTX
Mohammadi 2009[17]	retrospective	Cervical dystonia, spasmotic torticolis	207	6.7 ± 3.5 years	1:3	Duration of effect latency to response, side effects	No difference
Bihari 2005[18]	Cross-over (non randomized)	Blepharospasm, cervical dystonia, hemifacial spasm	48	12 weeks	1:4 in blepharospasm 1:5 in cervical dystonia and HFS	Duration of effect, Jankovic scale, severity score (blepharospasm), TWSTRS score (cervical dystonia)	**Efficacy** - In favor of DYS **Adverse effects** - Favored BTX

Lower limb spasticity in cerebral palsy

Out of 4229 publications screened, 101 were analysed in full-text version, and 9 (4 RCTs for BTX vs. PL and 5 RCTs for DYS vs. PL)[19-27] met the criteria for inclusion [Figure 2].

Figure 2
Flow chart for identification of study selection (in accordance with QUOROM)



Date of the systematic search: 08-09.09. 2011

No studies directly comparing BTX to DYS were found. Indirect statistical analyses of BTX vs. DYS were not carried out, due to heterogeneity across studies in endpoints, methodology, dosage and observation period[27].

Electronic questionnaire survey

Eleven Polish doctors completed a questionnaire which captured data from 101 of their patients. Mean age of patients included in the survery with FD, HS and JCP was 58.3, 54.7 and 8.9 years respectively. Of the 101 patients included, the percentage classified as having each of these conditions was 59.5%, 45% and 40.7% respectively (adds to over 100% due to some patients being classified as both FD and HS). DYS dosage ranged widely both within and across indications, with mean dose ratios 4.18 - 4.78 times those for Botox in FD and HS and 2.41 - 3.18 times those for Botox in JCP.

DISCUSSION:

Comparison of results across clinical trials is limited by differences in methodology and quality. Our review found that assumed dose equivalence between DYS and BTX varied between studies as did the efficacy results, thus confirming that available data do not provide support for a fixed conversion ratio between DYS and BTX. In addition, the electronic questionnaire survey found a wide range of dose ratios being used in clinical practice within a single country (Poland). These findings are consistent with the REAL DOSE study, where dose ratios varied depending on country, patient and condition treated[28] [Figure 3, Figure 4 and Figure 5].

Figure 3
Mean dose ratio by country (DYS:BTX)[28]

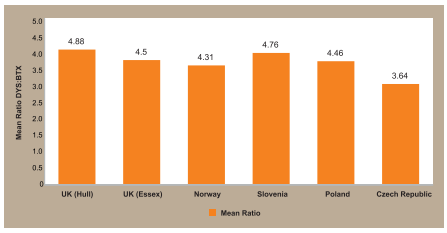


Figure 4
Number of patients being treated at dose ratio (DYS:BTX)[28]

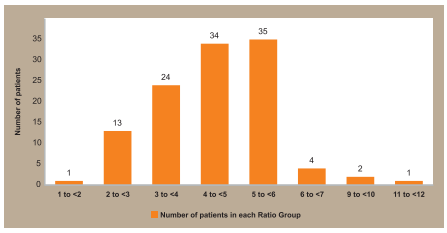
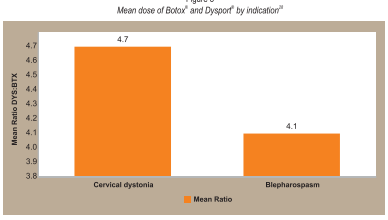


Figure 5
Mean dose of Botox® and Dysport® by indication[28]



CONCLUSIONS:

BOTOX® and Dysport® are not interchangeable. Treatment is individualized according to patient needs, experience and physician preference. The doses used in Poland are consistent with the results of the REAL DOSE study[28].

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