Cervical dystonia

Respective potencies of Botox and Dysport: a double blind, randomised, crossover study in cervical dystonia

W Poewe

Clinically appropriate conversion factor may be less than three

The issue of apparently different potencies of the two available formulations of botulinum toxin type A—Dysport and Botox—has continued to perplex clinicians for more than a decade. Empirically chosen doses expressed in mouse units in different series and different indications reported in the literature seemed to differ by factors of three to six.[1 2] To date only two randomised controlled studies have tried to answer the question of what the correct conversion factor yielding bioequivalence should be. One was conducted in previously untreated patients with blepharospasm or hemifacial spasm and found a bioequivalence ratio of Botox to Dysport of 1:4 with duration of effect as the primary outcome variable.[3] The second comparative trial randomly assigned patients with cervical dystonia previously treated with Botox to receive either their clinically defined individual dose of Botox or three times that dose as Dysport units[4] and found similar effect size, duration of effect, and rates of adverse events. In the paper by Ranoux *et al* (this issue pp 459–462)[5] of this issue, results of another double blind randomised study comparing efficacy and safety of the type A preparations seem to suggest that the clinically appropriate conversion factor may be less than three.

Fifty four patients with cervical dystonia and a satisfactory response to two consecutive injections of Botox at the same dose into identical muscles received three successive treatments of either their usually effective dose of Botox or three or four times that dose of Dysport. Treatments were given in randomised order using identical volumes of injection and muscle patterns. The effect size as assessed by changes in Tsui scores and Toronto Western spasmodic torticollis rating scale (TWSTRS) pain scores was significantly greater with both Dysport treatments and duration of effect was also longer. Threefold or fourfold doses of Dysport produced similar effect sizes but duration tended to be increased with the fourfold dose. Side effects were significantly more frequent with both Dysport doses than with Botox but again not significantly different between the two Dysport doses (17.6% of patients treated with Botox, and 33% and 36% of patients treated with Dysport 1:3 and 1:4, respectively).

In summary, the authors suggest that even lower conversion ratios be used than 3:1 for Dysport to Botox. Should it then be 1:2.5 or even 1:2? If so, should we be using lower doses of Dysport or higher doses of Botox to achieve this? With only three randomised trials available differing in design, target population, and results, it is impossible to give a conclusive answer to this question. For the time being clinicians may be best advised to use the following landmarks for their dosing decisions when treating patients with dystonia. Firstly, the equivalence ratio of Dysport to Botox should not be greater than 3:1 according to the majority of available comparative clinical studies. Secondly, for cervical dystonia, the indication studied by Ranoux *et al*, a double blind dose ranging study has shown that Dysport doses needed for a satisfactory response are greater than 250 units and that doses greater than 500 units are associated with clear increases in adverse event frequency and severity.

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Author's affiliation
W Poewe, Universitätsklinik für Neurologie, Universität Innsbruck, Anichstraße 35, A-6020 Innsbruck, Austria

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Correspondence to: Dr W Poewe; Werner.Poewe@uibk.ac.at

REFERENCES

1 **Durif F**. Clinical bioequivalence of the current commercial preparations of botulinum toxin. *Eur J Neurol* 1995;**2**:17–8.
2 **Marion MH**, Sheehy M, Sangla S, *et al*. Dose standardisation of botulinum toxin. *J Neurol Neurosurg Psychiatry* 1995;**59**:102–3.
3 **Sampaio C**, Ferreira JJ, Simoes F, *et al*. DYSBOT: a single-blind, randomized parallel study to determine whether any differences can be detected in the efficacy and tolerability of two formulations of botulinum toxin type A—Dysport and Botox—assuming a ratio of 4:1. *Mov Disord* 1997;**12**:1013–8.
4 **Odergren T**, Hjaltason H, Kaakkola S, *et al*. A double blind, randomised, parallel group study to investigate the dose equivalence of Dysport and Botox in the treatment of cervical dystonia. *J Neurol Neurosurg Psychiatry* 1998;**64**:6–12.
5 **Ranoux D**, Gury C, Fondarai J, *et al*; Respective potencies of Botox and Dysport: a double blind, randomised, cross over study in cervical dystonia. *J Neurol Neurosurg Psychiatry* 2002;**72**:459–62.

Rehabilitation

Intensity of rehabilitation: some answers and more questions?

P Langhorne

No benefits to intensive rehabilitation in the long term

For many years rehabilitation researchers have pondered whether the observed recovery of patients from stroke occurs at the optimum natural recovery rate or may be further enhanced by rehabilitation interventions, in particular by increasing the intensity of rehabilitation input. A carefully conducted randomised trial by Kwakkel *et al*[1] indicated that increasing the intensity of physical training after middle cerebral artery stroke brought about improvements in the recovery during the first 6 months. When the additional training was focused on the upper limb improvements in dexterity were observed; when the lower limb was targeted walking ability and Barthel activities of daily living (ADL) scores improved. In their follow up paper (Kwakkel *et al* this issue pp 473–479)[2] they address the question of whether these benefits continue in the longer term. This follow up paper indicates that there were no significant differences between the treatment groups at one year after randomisation, an observation that appears to confirm previous similar trials.[3 4]

Why did the early benefits of intensive training disappear at a later stage? The first possibility is that there were differences in treatment after the intervention period ended but this appears unlikely. None of the patient groups received much rehabilitation input after six months. The second possibility is that the treatment group suffered a decline in function after their intensive treatment was removed. This also appears unlikely, as it is not supported by the longitudinal data. A third possibility is that the control group continued to improve until their function matched that of the intervention groups. On balance, this seems the most compelling explanation.

An additional observation was that patients who were noted to have made an incomplete functional recovery at 6 months showed the largest subsequent changes (including both improvement and deterioration) in impairments and disability. This observation is probably not an artefact of the measures used and does indicate that there is potentially a subgroup of patients in whom increased therapy could be targeted at a later stage.

The main message appears to be that increasing the intensity of upper and lower limb training for selected patients after a stroke can speed up recovery but the longer term effects are uncertain. It remains to be established whether we can identify patients who are exceptions to this general rule and would benefit from later intervention to optimise their recovery.

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Author's affiliation
P Langhorne, Academic Section of Geriatric Medicine, 3rd Floor, Centre Block, Royal Infirmary, Glasgow G4 0SF, UK

Correspondence to: Dr P Langhorne; p.langhorne@clinmed.gla.ac.uk

REFERENCES

1 **Kwakkel G**, Wagenaar RC, Twisk JWR, *et al.* Intensity of leg and arm training after primary middle-cerebral-artery stroke: a randomised trial. *Lancet* 1999;**354**:191–6.
2 **Kwakkel G**, Kollen BJ, Wagenaar RC. Long term effects of intensity of upper and lower limb training after stroke: a randomised trial. *J Neurol Nurosurg Psychiatry* 2002;**72**:473–9.
3 **Sivenius J**, Pyorala K, Heinonen OP, *et al.* The significance of intensity of rehabilitation after stroke. *Stroke* 1985;**16**:928–31.
4 **Sunderland A**, Fletcher D, Bradley L, *et al.* Enhanced physical therapy for arm function after stroke: a one year follow up study. *J Neurol Neurosurg Psychiatry* 1994;**57**:856–8.

Headache and hypertension

Headache and hypertension: refuting the myth

D Friedman

Why does the hypertension headache myth persist?

Patients often tell their physicians, "I know when my blood pressure is high because I get a headache". The relation of headache to hypertension has been debated in the medical literature for almost a century. Janeway observed it in a large clinical study of hypertensive patients (systolic blood pressure > 160 mm Hg) in 1913.[1] He described the "typical" hypertensive headache as non-migrainous, present upon awakening and resolving during the morning. However, his illustrative case histories are somewhat misleading because they all had malignant hypertension and systolic pressures > 230 mm Hg. Additionally, one patient was likely in analgesic rebound.

There are several reasons why the "hypertension headache" misperception persists: hypertension may be an epiphenomenon of acute pain, headache is associated with hypertensive encephalopathy as a manifestation of increased intracranial pressure, and headache is a side effect of some antihypertensive treatments. Conversely, many of the antihypertensive medications are also effective for headache prevention, so the risk of concurrent headache may be low unless the influence of treatment is considered.

The Physicians' Health Study prospectively examined 22 701 American male physicians aged 40–84 years, who were randomly assigned to receive daily aspirin, β carotene, both agents, or placebo.[2] Analysis of various risk factors for cerebrovascular disease found no difference in the percentage of patients with a history of hypertension between the migraine and the non-migraine groups. Additionally, no difference in risk factors was found between physicians with non-migrainous headaches and those with no headaches.

The paper by Hagen *et al* (this issue pp 463–466)[3] lends definitive clarity to the issue. In their prospective study spanning 13 years of 22 685 adults in Nord-Trøndelag County, Norway, patients' blood pressure was measured interictally and they provided information regarding headaches and the use of pain relieving medications. Patients were subdivided into those with migrainous and those with non-migrainous headache based on modified International Headache Society criteria for migraine. Contrary to popular belief, high systolic blood pressure at baseline was associated with low headache prevalence 11 years later. This was not related to antihypertensive medication treatment. A similar effect was observed in women with migraine.

Their study is relevant because it is a cross sectional study of a large unselected population. Hypertension is more common in men but women have a higher incidence of headaches. Both women (10 698) and men (11 987) participated in HUNT-1 and HUNT-2 (Nord-Trøndelag Health Survey), supporting the conclusions in both sexes. Generalisation of the results was addressed by the authors in other reports.[4] Race and geographic region contribute to variations in the prevalence of headache and hypertension. Participants in the HUNT studies were a homogeneous white population. Thus, the applicability of the results to other populations, such as African Americans, who have a higher prevalence of hypertension, is uncertain.

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Authors' affiliations
D Friedman, Department of Neurology, University Hospital, 750 E Adams Street, Syracuse, New York 13210, USA

Correspondence to: Dr D Friedman; friedmad@upstate.edu

REFERENCES

1 **Janeway TC**. A clinical study of hypertensive cardiovascular disease. *Arch Intern Med* 1913;**12**:755–98.
2 **Buring JE**, Hebert P, Romero J, *et al.* Migraine and subsequent risk of stroke in the Physicians' Health Study. *Arch Neurol* 1995;**52**:129–34.
3 **Hagen K**, Strovmer LJ, Vatten L, *et al.* Blood pressure and risk of headache: a prospective study of 22 685 adults in Norway. *J Neurol Neurosurg Psychiatry* 2002;**72**:463–6.
4 **Hagen K**, Zwart JA, Vatten L, *et al.* Prevalence of migraine and non-migrainous headache: head-HUNT, a large population study. *Cephalalgia* 2000;**30**:900–6.