# LETTERS

## NOTES & COMMENTS

### Botox and Dysport: Is there a dose conversion ratio in dermatology and aesthetic medicine?

*To the Editor:* The use of botulinum neurotoxin A is the most frequent intervention in aesthetic medicine. Sales of the two main preparations—Botox (Allergan Inc, Irvine, CA) and Dysport (Ipsen Ltd, Slough, Berkshire, UK)—amounted to USD $1 billion in 2007, and the trend is still growing.

Even after 15 years of clinical use, the unit equivalence between these two main botulinum neurotoxin A products is still a matter of discussion. Because of the different excipients used to dilute the test toxins, the UK assay used to test Dysport is more sensitive than the US assay used for Botox, resulting in a different efficacy per unit in both formulations.[1-3] For the mouse assay used to standardize each batch of Dysport, the toxin is diluted in a phosphate buffer containing gelatine that stabilizes the toxin at low concentrations, whereas saline is used as the diluent for the Botox assay, which gives a loss of potency because of dilution artefacts. This was first shown by Hambleton and Pickett,[4] who measured different samples of Botox and Dysport using the two assays: a Botox unit was approximately 3 times more potent in the Dysport assay, and a Dysport unit was approximately 2.5 times less potent (activity declined to 39.7%) in the saline assay. In the Dysport assay, a unit of Botox was equivalent to 2.87 units of Dysport. In the saline assay, one Dysport unit was equivalent to a nominal 0.4 units of Botox, suggesting a potency ratio of 1:2.5.

The clinical literature on dose equivalence is extensive but confusing, and many published studies differ in rigor and validity. Ratios from 6:1 down to 1:1 can be found in the literature, but the more recently published literature suggests that one unit of Botox is equivalent to about two to four units of Dysport (ratio, 2:1 to 4:1). A recently published review[5] identified only four key papers[6-9] on head-to-head comparison of Botox and Dysport that are of sufficient quality to fulfill the criteria of evidence-based medicine. In these studies, unit ratios of 4:1 and 3:1 Dysport:Botox were tested in patients with blepharospasm or torticollis, and the joint conclusion was that 3:1 is more appropriate than 4:1, but that the two products are not equivalent at this ratio. In fact, the effect of Dysport was consistently marginally greater and longer lasting in two of these studies[7,8] that tested 3:1 and in a more recent double-blind controlled independent study at a ratio of 3:1 in axillary hyperhidrosis.[10] This suggests that even the ratio 3:1 may be too high.

In Germany, the manufacturers' recommended dose for the treatment of glabellar wrinkles is 50 U Dysport or 20 U Botox (ie, a dose ratio of 2.5:1). In Austria, both products are registered for the treatment of axillary hyperhidrosis, with an initial dose of 100 U Dysport or 50 U Botox (ie, a ratio of 2:1). Despite this, ratios of 4:1 or even higher are still accepted, and papers supporting higher ratios have been published recently[11]—although these are not head-to-head controlled trials.

Investigations in dermatology generate objective data with parameters that are more easily measured than those in indications such as dystonia or spasticity. Studies on anhidrotic action halos have shown equivalent halo size at a dose ratio between 2.5:1[12,13] and 2:1,[14] and larger halos after Dysport with a ratio of 3:1.[1] Although these latter studies have been variously interpreted, in particular with the claim that Dysport diffuses more than Botox, our own work suggests that this is a simple dose effect. At 3:1, the effects on forehead wrinkles and electromyographic activity were statistically significantly higher with Dysport than with Botox in a side-controlled, double-blind randomized study,[15] suggesting that the correct ratio is lower than 3:1.

We do not believe that there are different ratios for different indications, because the two products are not so different that different muscle groups would react differently. However, there may be variations which are caused by unfamiliarity with the optimal dilution for a given muscle group. The effect on glands (hyperhidrosis and hypersalivation) and smooth muscle (bladder) is longer lasting than on skeletal muscle, but this does not necessarily imply that the dose ratio between the two products is different. As stated at the beginning of the letter, the dose ratio is basically an artefact of different assay techniques.

Whatever the indication for the use of botulinum neurotoxin A, the maxim must be "as much as necessary but as little as possible" to avoid side effects caused by unbound toxin spreading away from the injection site. In our experience, the manufacturers' recommended doses for wrinkle treatment (ratio of 2.5:1) are adequate. Given that most studies have assumed and tested a higher ratio, further head-to-head studies with ratios of 2.5:1 or lower are justified. Physicians using both these

products for dermatologic indications should be aware of the problems with published conversion ratios to avoid overdosing with Dysport, particularly because much aesthetic use is "off-label." Only the indications of glabellar wrinkles and axillary hyperhidrosis are registered in most countries.

A correct unit conversion ratio is essential for safe and adequate treatment, but much of the literature is not free of commercial bias. Because the number of botulinum neurotoxin A treatments is constantly increasing, we think an independent, commercial-free statement on the current evidence is needed.

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## Conflict of interest?

*To the Editor:* I read with great interest the article[1] comparing various treatment modalities for nonmelanoma skin cancer in the July 2009 issue of the *Journal*. As a critical reader, I typically pay attention to the "financial disclosure" section listed for each article. In this article, no financial conflicts were declared.

According to the American Academy of Dermatology's recent position statement,[2] a conflict of interest is "a situation in which financial or other personal considerations have the potential to compromise or bias judgment and objectivity." The study concluded that Mohs surgery, along with electrodessication and curettage and simple excision, is one of the "most affordable options" for treating nonmelanoma skin cancer. The fact that both authors are Mohs surgeons gives them a potential significant financial conflict of interest (ie, both of them stand to gain financially from the treatment of skin cancers with the more expensive Mohs procedure—with potentially higher reimbursement for the clinician—rather than with a less expensive procedure, such as curettage and electrodessication or simple excision).

These facts do not detract from the merits of their study. Their article was well written and clear, and their conclusions appear solid. However, as a reader, it is concerning that the authors did not disclose this potential conflict of interest. It casts a shadow of doubt over the integrity of the paper and potentially