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Consistent Biochemical Data are Essential for Comparability of Botulinum Toxin Type A Products

The recent article from Dr Frevert of Merz,[1] together with the accompanying commentary from Dr Sesardic of NIBSC,[2] makes a new contribution to the data available for clinical botulinum toxin type A (BoNT-A) products. However, in addition to the comments about the various technical aspects of the data provided by Dr Frevert, as described by Dr Sesardic,[2] one important and key factor about the BoNT-A products has not been mentioned. The units of each product are different, not interchangeable, and no fixed or established conversion ratio exists between them,[3-5] regardless of what clinical data are presented.

This means that any data trying to represent the biochemical characteristics of the products in relation to their potency units, and then comparing them with each other, is potentially misleading to the reader. The data included in the article, giving the amount of BoNT-A neurotoxin per 100 LD_{50} (median dose that is lethal to 50% of animals tested) units of potency, is therefore incorrect as a comparison.[1] It is inappropriate to provide such data as readers may draw erroneous (and potentially dangerous) conclusions without a detailed interpretation. Product comparisons based on these data should not be made. Dr Frevert has not informed the reader that the potency units of each product are specific to that product. Quite the contrary – he has attempted to show that 1 unit of Xeomin® is equivalent to 1 unit of Botox®, which is against the regulatory requirements for the products, as stated in their product characteristics.[4-5]

True, there is a new statement in the product characteristics for the Merz low-dose product Bocouture®,[6] which states ''Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency.'' However, immediately above this in the document is the standard statement (in bold) that reads ''**Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin.**''

Dr Frevert has also commented that all three of the main BoNT-A products are made from the same Hall strain of bacteria. In fact, there is no evidence yet published to support this. Quite the contrary – latest data indicate that the so-called Hall strains are different to each other.[7,8] As previously described, there are several so-called Hall strains and they are different.[7] The Allergan strain information is published[9] and the Ipsen and Merz strains have only been described as 'Hall strain', with no identification.[1,10]

As written several times before, certain data claimed for Dysport® (the size of the BoNT-A complex, for example), have never been published. The early reference from 1992 cited by Dr Frevert is incorrect for Dysport®. However, Dysport® is the only commercial BoNT-A product for which detailed biochemical characterization data have been published, notably on composition.[10] We have challenged colleagues in the other manufacturers to publish their own, similar data, but to date they have declined. This is somewhat extraordinary for products that have been available commercially, for many years.

Dr Frevert once again discusses BoNT-A complexes and their respective so-called 'sizes' for the products.[1] We have published about this misleading subject on several occasions.[11-13] From his own data, Dr Frevert has already demonstrated that the 'size' of the toxin complex is irrelevant to the biological actions.[14] Indeed, the very latest data from Merz,[15] published after Dr Frevert's article, appear to now clarify this subject. The BoNT-A neurotoxin molecules are free in the vial after reconstitution and not associated with the complex. These are the only data relevant to the discussion on the 'size' of the BoNT-A complex and use of the clinical products – the complex size itself appears to be irrelevant. BoNT scientists had expected this finding, but proof was needed; it now exists.

The purpose of Dr Frevert's article was to compare the neurotoxin content of each of the BoNT-A products in the vial.[1] A new figure has now appeared for Xeomin®, 0.44 ng per vial, as compared to the 0.6 ng previously published.[16] This finding is somewhat dismissed as a technical issue but, in reality, represents a 27% reduction. Could this be due to changes in the product since the data were first reported or the product first used (perhaps changes in batches of active component, for example, see Quarta[17] or other issues)? Whatever the cause, this significant difference is a product inconsistency that warranted further comment, representing an important aspect of the work to the clinicians – consistent product gives consistent clinical results.

Data comparing the characteristics of the various BoNT-A products and misleadingly comparing these to labeled units are not helping clinicians select products for use. Instead, detailed overall data, notably on history of product consistency, such as those previously published for Dysport®,[10] are important for clinicians and these are still awaited for the other BoNT-A products. Perhaps the time has also come to stop discussing BoNT-A complex 'sizes' in a clinical context unless and until data are produced that clearly demonstrate any relevance to clinical use? None now seem likely.

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Acknowledgments

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Author's Reply

The main focus of the letter to the editor by Dr Pickett[1] is the interchangeability of botulinum toxin A dosages between products, and therefore this answer will address this issue.

In contrast to the argument of Dr Pickett, it is justified to draw conclusions on botulinum toxin A products based on the potency. It is true that the units of each product are determined by dif-