

‘Similar To’ Is Not ‘Identical With’, and ‘Identical With’ Is Not ‘The Same As’

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Presently, we have a large number of botulinum neurotoxins (BoNTs) at our disposal, but in the western hemisphere these are limited almost exclusively to the botulinum toxin A preparations: Abo- (ABO), inco- (INCO), and onabotulinumtoxinA (ONA). Because these are biological preparations, they are never identical to each other, but they are, at most, similar to each other. Their efficacy has been well demonstrated in numerous studies and is undebated [1]. Since their introduction, new batches have repeatedly been made available, and the purity of ABO and ONA has essentially been improved upon. INCO is the most recent formulation and is free of complex proteins.

The paper by Frevert [2] in this issue addresses the question of comparability of the three medications, focusing mainly on the differential potency between the preparations and on the immunogenicity between them, giving special consideration to the complex neurotoxin accessory proteins (NAPs). It must be emphasized that the author of the publication and the manufacturer of INCO view the lack of these complex proteins as a major distinguishing factor and in fact an advantage to their preparation.

The author addresses the topic of complexing proteins in his abstract. Complexing proteins are not covalently bound to the core neurotoxin itself, but are considered a part of the active pharmacological ingredient. Furthermore, after injection of BoNT, complexing proteins are shortly separated from the neurotoxin due to a change in pH and other local environmental factors, thus antibodies against complexing

proteins should not inhibit neurotoxin activity. The author further describes differences between the three different products related to their immunogenicity. Until now, there has been no clinical evidence showing significant differences in immunogenicity between ABO, INCO, and ONA [3]. Furthermore, differences in assay sensitivity may lead to differences of measured immunogenicity rates, thus no direct comparison can be made today. Further studies encompassing long-term treatment are needed to assess differences of immunogenicity amongst BoNT products.

Frevert raises many important considerations relevant to BoNT therapy, although matters of potency require careful interpretation. For example, Frevert states that one study found equivalent potency across ONA and INCO [4], in an assay that in fact was developed by Dr. Frevert and is used by the company. However, the author fails to consider contrasting results by Hunt who established potency differences between the two products using two independent assays—an LD50 and also a SNAP-25 cleavage [5, 6]. The different results across these studies indicate underlying differences between products that are evident under some testing conditions but not others. A simple comparison of the potencies of the preparations based merely on different bioassays must be evaluated critically so as to avoid false interpretations and the consequent negative effects on patients. If such differential potencies are described, the regulatory requirements would have to be considered, as would any peculiarities of the individual methods.

In several places, the author claims that studies show “clinical equipotency” of ONA and INCO at a 1:1 dose ratio. This needs to be viewed in the light of several factors: (1) worldwide labeling clearly states that the units of one toxin are not interchangeable with another; (2) non-inferiority trial designs, as opposed to equivalence trial designs, do not establish biologic equivalency for efficacy

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and safety [7, 8]; and (3) product response profiling needs to be assessed at multiple doses and time points. For instance, a randomized equivalence study established that 30 units of INCO was as effective as 20 units of ONA for glabellar lines at the primary time point, but not at later time points due to a trend toward higher response rates with ONA [9]. Therefore, the dose-response profiles, and consequently the products, are not equivalent. In clinical practice, based on the registration trials [7, 8], a 1:1 ratio was assumed for blepharospasm and cervical dystonia, which does not establish scientific proof for equipotency. To date, we do not have a defined ratio for comparing ABO with INCO or ONA. Possibly, we have to define different ratios for different indications and doses.

The active pharmaceutical ingredients of ONA and ABO comprise BoNT, along with NAPS, which together make up the neurotoxin complex, whereas INCO includes only the neurotoxin protein. Based on pre-clinical and in vitro data, the author concludes that the NAPS confer an increased risk of immunogenicity and neutralizing antibodies. This repeated conclusion is an over-interpretation of pre-clinical and in vitro results without recognizing clinical data. The conclusion that NAPS increase the risk of neutralizing antibody formation is particularly conspicuous in the abstract, where it is presented as a well-supported fact without any caveat or critique. In fact, all three products are associated with very low rates of neutralizing antibodies and antibody-induced non-response in clinical studies and practice, inasmuch as the ‘protein burden’ can be taken as low-leveled for all three preparations [10]. At the moment we do not know whether INCO is free of the risk of reducing antibodies. This statement would have to be confirmed in relevant studies. There is no clinical evidence that NAPS are clinically relevant for inducing, activating, or increasing immunogenicity against BoNT. All evidence to date is pre-clinical (in vitro and bio assay in vivo in animals) [3].

The author writes that proteins protect the neurotoxin from acidic and proteolytic degradation in the digestive tract, and, in addition, they aid in stabilizing the neurotoxin from changes in temperature [11].

BoNT-A can be considered as an excellent therapy for dystonia and spasticity, with considerable advantages for our patients. For a good number of years we have had two different high-quality BoNT-A preparations available on the market, and the introduction of INCO meant significant

progress [12]. These medications are biological preparations. Thus, they perform their service per definition in a unique fashion, and are not easily exchangeable with each other. Any comparisons of such substances require a high degree of objectivity.

Conflict of interest The author is a consultant and speaker for all three manufacturers.

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