Evaluating botulinum toxin products for clinical use requires accurate, complete, and unbiased data

Modern clinical use of botulinum toxin (BoNT) by doctors requires evidence-based facts and data to support their work. In particular, these need to be unbiased and complete. Too often in the past, speculative statements have been used and repeated until injectors have come to believe they are solid facts. Yet no supporting data exist. Consequently, doctors have often been reluctant to change to or even try other products because of what they have been told. This has not been a good situation for either clinicians or patients. We have published about these “urban legends” and tried, on many occasions, to correct these inaccuracies (see, for example, 2,3).

Therefore the recent paper by Park and colleagues, claiming to be a review of a relatively new BoNT product used in blepharospasm, was disappointing at best.4 Many of the old and outdated claims about the properties of BoNT products have again been repeated. In 2011, this is an incorrect approach and borders on a marketing activity.

For example, the product data contained in their Table 14 has no references cited as to the sources of information, is inaccurate, and does not even take into consideration previous publications which have highlighted errors in such tabular data.1 We published last year a definitive work on the formulation composition of BoNT products in clinical use5 specifically to stop these errors. We have previously suggested that authors contact manufacturers of BoNT products before they publish such data, to ensure complete accuracy;1 all of this has apparently been ignored by Park and colleagues.

Data in error in their Table 1 include the manufacturer of Myobloc®/Neurobloc® (this should be US WorldMeds, who acquired Solstice in August 2010), “stabilization” of Xeomin® (also a freeze-dried product and not as cited), the vial size of Dysport® (also available as 300 units per vial in many countries, including the United States), the vial sizes of Botox® (also available as a 50 and 200 units per vial product in many countries), the so-called “complex sizes” for each product (none of which exist for the BoNT-A products in the actual vial)6 and storage after reconstitution of Myobloc® (this is already liquid product and not stable “for a few hours” after reconstitution – which simply does not happen!)

More important clinically, Park and colleagues have published a data line reporting “biological activity in relation to Botox®” in their Table 1,4 citing a ratio of 1:1 for Xeomin® and 3:1 for Dysport. This so-called “dose equivalence ratio” is probably the
most contentious issue about use of BoNT-A products and
should never be described so definitively. As the authors
will know, the regulatory authorities around the world have
required an insertion, in all BoNT-A product literature sup-
plied to clinicians worldwide, which clearly states that the
units of each product are specific to that product and are
not interchangeable. In particular, many clinicians would
strongly argue that any “ratio” between Dysport® and Botox®
units is more likely to be 2 or 2.5:1, respectively, and not as
cited in their table – different reviews of many data strongly
indicate this.

Xeomin® is stated as “being obtained from the same strain
of Clostridium botulinum as Botox®”. This is incorrect. The
statement is contradicted by a publication which specifically
looked at the subject7 and has been corrected in relation to
another recent publication comparing BoNT-A products
which reported the same error.8

One of the standard reasons always given why clinici-
ans should use Xeomin® is the reduced potential to raise
BoNT neutralizing antibodies in patients. This was, indeed,
the prime reason for initially developing the product.9
Often, the subject of how the other proteins of the BoNT-A
complex (the neurotoxin associated proteins – NAPs) may
have immunostimulating properties has been raised (see, for
example,10). However, this has never been demonstrated,
even experimentally in animals. Park and colleagues have
re-stated old data from flawed studies on this subject.11 They
have, unfortunately, dismissed careful and critical appraisal
of those studies by the leading expert in the field of BoNT
immunology, Professor Zouhair Atassi.10,12

There is currently no evidence that the removal of the
BoNT-A NAPs from Xeomin® has had any beneficial effects
on reducing BoNT-A neutralizing antibody formation in
patients. The current immunological status for the product is
carefully described in the current United States prescribing
information for Xeomin®—“the potential for antibody for-
mation has not been fully characterized”.11 Statements such
as “may reduce the risk markedly”4 are inappropriate in the
context of critically reviewing and assessing the properties
of a BoNT-A product for clinical use.

Indeed, Park and colleagues have cited a 17-year-old
reference that describes the levels of antibody formation
in patients treated with BoNT-A.14 These data originated
from use of “old” Botox®, that is the original version of
Botox® pre-1997, which was known to contain significant
levels of inactive BoNT.15 The inactive BoNT promoted
neutralizing antibody responses in patients treated with
high doses for conditions such as cervical dystonia, accord-
ing to the treatment regimens in use at that time (typically,
short intervals between injections, “booster” injections,
when effects were not apparent after short periods). For
modern clinical data dealing with blepharospasm, the
report of Bentivoglio and colleagues16 on a large group of
patients treated long term with BoNT reported only three
patients (2.3%) who likely had antibodies (but also not
determined by direct assay).

Indeed, one animal study which apparently found that
Xeomin® raised no neutralizing antibodies under conditions
where other BoNT-A products did, has been cited by Park
and colleagues, namely that of Blumel et al reported actually
in 2005.17 Unfortunately this was a poster at an international
conference. Careful assessment of those data showed that the
doses used of one product in the comparison were so high
that they killed several of the test animals. The study was
invalidated for comparative purposes.

One factor of product comparison that Park and
colleagues14 have used is the amount of BoNT protein that
would be injected for each product as used in therapy. This
is designated the “protein load” of the product, presented
as nanograms (ng) per vial.18 The basis of their argument
is that injecting patients with less BoNT protein per treat-
ment is a way of reducing the risk of antibody response.
However, they have repeated, yet again, incorrect data for
Dysport®. We have published several times over the last
8 years clearly describing the Dysport® historic data for
protein load over a 15-year period.19 No similar data have

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Table 1 Clinical studies reported on the use of Xeomin® for the treatment of blepharospasm

<table>
<thead>
<tr>
<th>Authors</th>
<th>Publication year</th>
<th>Patient number treated with Xeomin®</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roggenkamper et al21</td>
<td>2006</td>
<td>129</td>
<td>First published use study</td>
</tr>
<tr>
<td>Jankovic et al24</td>
<td>2009</td>
<td>–</td>
<td>Poster—pre-report of 2011 study publication25</td>
</tr>
<tr>
<td>Jankovic et al24</td>
<td>2009</td>
<td>–</td>
<td>Development of rating scale using earlier data23</td>
</tr>
<tr>
<td>Jankovic27</td>
<td>2009</td>
<td>–</td>
<td>Review of earlier data23</td>
</tr>
<tr>
<td>Jankovic et al21</td>
<td>2011</td>
<td>75</td>
<td>Second published use study</td>
</tr>
<tr>
<td>Wabbels et al21</td>
<td>2011</td>
<td>33</td>
<td>Third published use study</td>
</tr>
</tbody>
</table>

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ever been published for the other BoNT-A products. The correct figure is 4.35 ng of Dysport® per vial, not 12.5 ng as Park and colleagues have cited – from a reference related to Xeomin®.10

But, strangely, Park et al have not used and compared data on the Xeomin® protein load per vial that have recently been published.9 These new data, giving 0.44 ng per vial, significantly contradict those previously reported for Xeomin® of 0.6 ng per vial.10 True, these are very small amounts but they actually represent a significant difference as reported by the product manufacturer. These differences have recently been challenged but no satisfactory explanation has been provided in response.20 Which figure is correct? What is the long-term consistency of the product?

Park et al have discussed the clinical data available for the use of Xeomin® in blepharospasm. In fact, to my knowledge only six clinical papers on treatment of this condition with the product are listed in PubMed. Of these, one is a poster abstract, two repeat or re-analyse data from a previous study, leaving only three studies overall (Table 1). The study by Wabbels and co-workers21 was not referenced by Park et al,4 leaving only two studies with which to conduct their review. Over all studies, just 237 patients are reported in the literature as treated with the product since first licensure in 2005 (Table 1). Park et al have also included in their review use of the product in other conditions such as cervical dystonia. Given that cervical dystonia is a large-muscle condition which requires large doses of BoNT-A for efficacy, certainly in comparison with blepharospasm, the dissimilarity between the conditions seems to outweigh the use of the different data sets for the review of use in blepharospasm. Facial muscles, as treated in blepharospasm, have a fundamentally different distribution of BoNT target neuromuscular junctions compared with larger muscles of the body.22

The reader must make up their own mind as to whether the review appropriately deals with the subject in question. But issues, especially with accuracy of data cited, must also be taken into proper account.

Disclosure
The author declares no conflicts of interest.

References
