

Future trends in botulinum toxin drug development

*Dirk Dressler**

*Egberto Reis Barbosa***

Botulinum toxin (BT) has now been used for more than 20 years with remarkable success to treat numerous disorders caused by muscle or exocrine gland hyperactivity (Scott, 1980; Moore and Naumann, 2003). Its use in pain disorders is currently being explored. Cosmetic use of BT is exploding, so that a new industry with annual revenues of well over one billion US dollars has emerged. However, we are still using more or less the original BT drugs. Is there no drug development?

The first type A BT was registered by the Oculinum Company and Allergan in 1989 as Botox. From 1998 to 1999 an improved version was introduced (Jankovic et al, 2003). A second type A BT was first registered in 1991 as Dysport (manufacturer: Ipsen) and has not been changed since then. In 2000 the first BT type B drug was licensed in USA by Elan Company as Myobloc/NeuroBloc. However, after its introduction it soon became clear that type B drugs have substantially different affinities to the motor and the autonomic nervous system (Dressler and Benecke, 2003) and, hence, patients with motor disorders treated with BT type B experience frequently autonomic adverse effects. This, together with a high antigenicity (Dressler and Bigalke, 2004), has prevented wide-spread use of this drug except for some niche indications such as antibody-induced therapy failure (ATF).

Are we all happy with the BT drugs we have? Do we have unmet needs? Are there any perspectives for further development of BT drugs?

One of the biggest problems of BT drugs is their antigenicity. It is true that we have a very low ATF frequency in blepharospasm and in cervical dystonia. But what is the ATF frequency when BT is used in the

skin, a tissue with a particularly high immunocompetence? What is the ATF frequency in spasticity where we usually apply heavy doses of BT? We do not know yet. But most of all: fear of antibody-induced therapy failure restricts our treatment strategies considerably. No booster injections or top ups when a patient is started on BT therapy and the optimal injection scheme has not yet been found. No early re-treatments, when the symptomatology returns before the generally advised three months interval between injection series is over. No increased dosages in severe cases with wide-spread muscle involvement.

If we had BT drugs with improved antigenicity all this might become possible. What a dramatic step forward this would be. But, how can we get there? How can we reduce the antigenicity of BT drugs?

One way to achieve this is to lower the protein load of BT drugs. All BT drugs contain biologically active and biologically inactive botulinum neurotoxin. The specific biological activity (SBA) describes this relationship (Dressler and Hallett, 2006). Biologically inactive botulinum neurotoxin is useless for therapy, but it still acts as an antigen. With the new formulation of Allergan type A BT introduced in 1998-1999 the SBA was increased to 60 equivalent MU/ng botulinum neurotoxin. Consequently, reduced antigenicity was claimed (Jankovic et al, 2003). In comparison, the SBA of Dysport is 100 equivalent MU/ng botulinum neurotoxin and the SBA of Myobloc/NeuroBloc is 5 equivalent MU/ng botulinum neurotoxin (Dressler and Hallett, 2006). Recently, a novel type A drug (Xeomin), was introduced in Germany by the manufacturer Merz (Benecke et al, 2006). Its SBA is 167 equivalent MU/ng

*Department of Neurology, Rostock University, Rostock Germany

** Department of Neurology, São Paulo University Medical School

botulinum neurotoxin, the highest of all BT drugs (Dressler and Hallett, 2006).

Another option to decrease antigenicity might be the removal of the complexing BT proteins (Lee et al. 2006). This, too, was tried in German BT (Xeomin) . Whether this works clinically, is still an open question. Shielding of the antigenic epitopes of the botulinum neurotoxin molecule might be another way for the future. Most promising, however, seems to be the development of high affinity botulinum neurotoxins, which could lower the protein load dramatically. Research into this area is currently under its way.

Other unmet needs include transdermal BT applications for treatment of hyperhidrosis. BT drugs labelled with optical, ultrasound, or radioactive markers will help us to handle, to place and to follow up BT drugs more accurately and more safely. Ready to use solutions may be a good idea for BT type A drugs as well. Abolition of temperature restrictions eases handling considerably. If this is possible for the German BT, it should also be possible for other BT drugs.

Clearly, we are not at the end of BT drug development, but at the very beginning. Exciting times are ahead of us...

References

- Dressler D, Benecke R . Autonomic side effects of botulinum toxin type B treatment of cervical dystonia and hyperhidrosis. *Eur Neurol* 2003; 49:34-38.
- Dressler D, Bigalke H . Antibody-induced failure of botulinum toxin type B therapy in de novo patients. *Eur Neurol* 2004; 52:132-135.
- Dressler D, Hallett M () Immunological aspects of Botox, Dysport, and NeuroBloc/MyoBloc. *Eur J Neurol* 2006; 13 (Suppl 1):11-15.
- Jankovic J, Vuong KD, Ahsan J. Comparison of efficacy and immunogenicity of original versus current botulinum toxin in cervical dystonia. *Neurology* 2003; 60:1186-1188.
- Lee JC, Yokota K, Arimitsu H, Hwang HJ, Sakaguchi Y, Cui J, Takeshi K, Watanabe T, Ohyama T, Oguma K. Production of anti-neurotoxin antibody is enhanced by two subcomponents, HA1 and HA3b, of Clostridium botulinum type B 16S toxin-haemagglutinin. *Microbiology* 2005; 151:3739-3747.
- Moore P, Naumann M. Handbook of Botulinum Toxin Treatment. 2nd Edition. Malden (MA, USA): Blackwell Science: 2003.
- Scott AB . Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *J Pediatr Ophthalmol Strabismus* 1980;17:21-25.

Correspondence addresses:

Dirk Dressler, MD, PhD
Associate Professor of Neurology
Department of Neurology
Rostock University
Gehlsheimer Str. 20 / D-18147 Rostock / Germany

Tel. +49-381-494-9541
Fax +49-381-494-9632
e-mail: dirk.dressler@med.uni-rostock.de
Egberto Reis Barbosa
Rua Sergipe 401, sala 311. São Paulo CEP: 012 43 – 906
Tels: (011) 32141457 / (011) 32552500
e-mail: egbertob@8415.com.br