Est-il licite de changer de toxine quand l'une n'est pas efficace?

Pr Philippe Marque

To Switch or not to switch ?

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Conflit d'intéret

- Consultant et symposium :
  - Allergan
  - Dysport
  - Xeomin

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Echec 1

- L'objectif n'est pas atteint mais la spasticité des muscles injectés a diminué :
  - Tardieu : 3 ->2
- Les objectifs étaient-ils compris et acceptés par le patient?
- Les objectifs étaient-ils atteignables par le patient?
  - SMART

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Echec 2

- La toxine a-t-elle été injectée au bon endroit?
  - Expérience de l'injecteur
  - Technique de repérage

- Si besoin de vériier : IRM
  - Hypersingal diffus en T2

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Malgré tout

To switch from Botox to Dysport in children with CP, a real world, dose conversion, cost-effectiveness study

Kristina Tedroff [a,c,*], *Gustaf Befrits* [d], *Carl Johan Tedroff* [c], *Stefan Gantelius* [b,c]

J Neurol (2016) 263:1188–1194
DOI 10.1007/s00415-016-8136-x

ORIGINAL COMMUNICATION

Botulinum toxin treatment failures in cervical dystonia: causes, management, and outcomes

H. A. Jinnah[1] · Emily Goodmann[2] · Ami R. Rosen[2] · Marian Evatt[2,3] · Alan Freeman[2] · Stewart Factor[2]

SWITCH FROM ABOBOTULINUMTOXINA (DYSPORT®) TO INCOBOTULINUMTOXINA (XEOMIN®) BOTULINUM TOXIN FORMULATION: A REVIEW OF 257 CASES

Donald G. Grosset, MD, Elaine G. Tyrrell, MPhil and Katherine A. Grosset, MD

From the Institute of Neurological Sciences, Southern General Hospital, Glasgow, UK

Journal of Neural Transmission (2018) 125:1481–1486
https://doi.org/10.1007/s00702-018-1911-3

NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - ORIGINAL ARTICLE

Antibody-induced failure of botulinum toxin therapy: re-start with low-antigenicity drugs offers a new treatment opportunity

Dirk Dressler[1] · Lizhen Pan[1,2] · Fereshte Adib Saberi[1]

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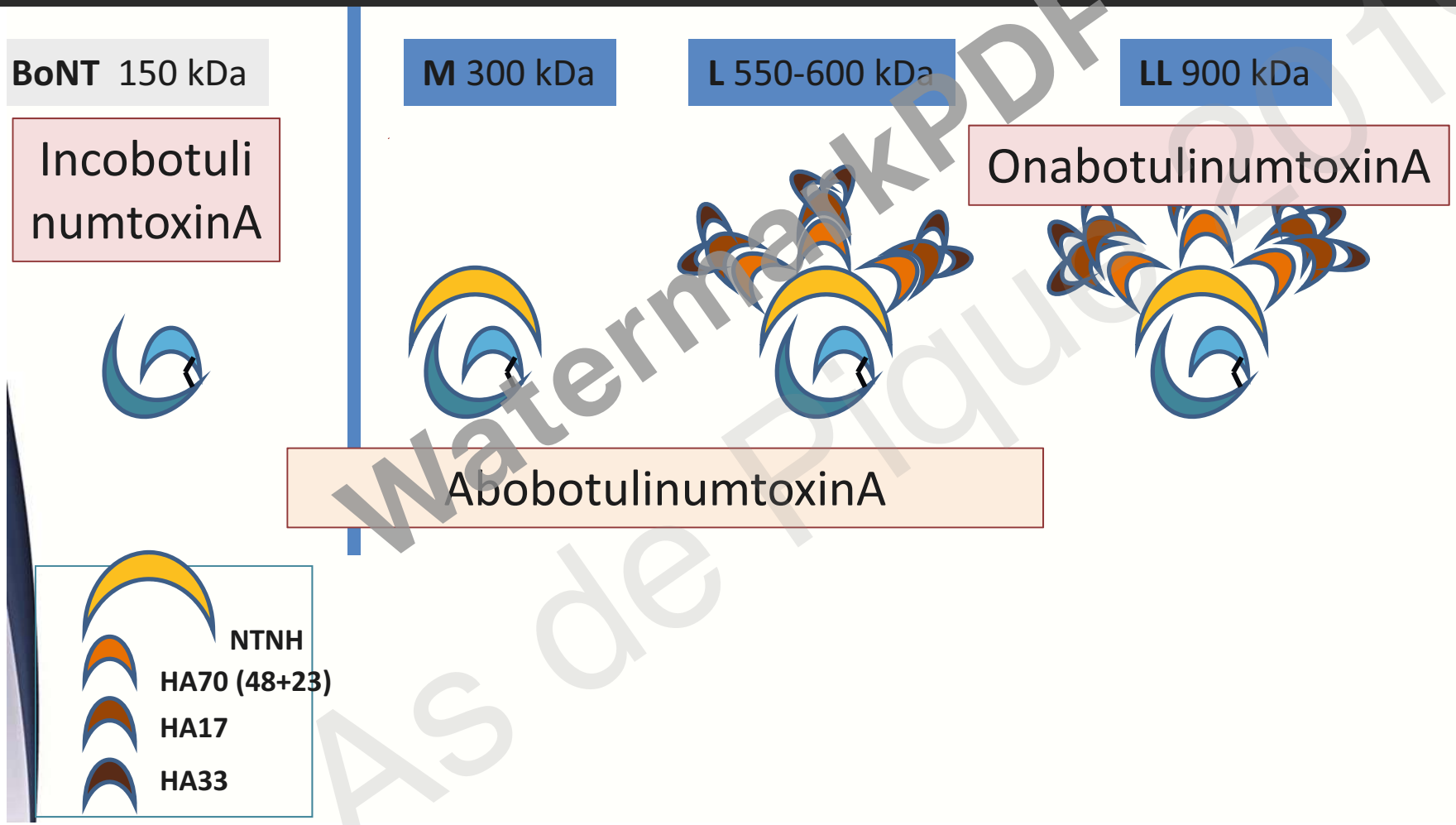
D'après B Poulain

Complexe protéique en fonction formulation



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D'après B Poulain

Le complexe protéique a peu d'importance

Complexe protéique Toxine

- **Stable à pH acide < 6,25**
- **Dissociation complète si pH>7**
- **En moins d'1 mn**
- *DasGupta et al., 1966 ; Eisele et al., Toxicon. 2011; Gu et al., Science 2012*

acidic pH

physiological pH

Seul la neurotoxine agit sur les terminaisons nerveuses
Les 3 toxines A contiennent la même neurotoxine Sous type A1

(Botox ®(OnabotulinumA): Zhang et al, 2003; Xeomin ®(IncobotulinumA): Bigalke, 2009; Dysport ®(AbobotulinumA): Panjwani et al, 2008)

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Des observations…

Parkinsonism and Related Disorders 21 (2015) 663–664

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Letter to the Editor

Secondary treatment failure in cervical dystonia after treatment with inco- and abobotulinumtoxinA

Keywords:
Cervical dystonia
IncobotulinumtoxinA
Secondary treatment failure

Journal of the Neurological Sciences 350 (2015) 110–111

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Letter to the Editor

Secondary antibody-induced treatment failure under therapy with incobotulinumtoxinA (Xeomin®) in a patient with segmental dystonia pretreated with abobotulinumtoxinA (Dysport®)

2012, performed as previously described in [3], again did not show evidence for nAbs. In February 2014, a third MDA was initiated due to the continuously insufficient response to incobotulinumtoxinA. After serum for this MDA was taken, treatment was again switched

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Malgré tout

Received: 8 November 2016 | Accepted: 27 February 2017
DOI: 10.1002/nau.23291

ORIGINAL CLINICAL ARTICLE

WILEY Neurourology Urodynamics ICS SUFU

Switch to Abobotulinum toxin A may be useful in the treatment of neurogenic detrusor overactivity when intradetrusor injections of Onabotulinum toxin A failed

Florie Bottet[1] | Benoit Peyronnet[2] | Romain Boissier[3] | Bénédicte Reiss[4] | Jean G. Previnaire[5] | Andrea Manunta[2] | Jacques Kerdraon[6] | Alain Ruffion[7] | Loïc Lenormand[8] | Brigitte Perrouin Verbe[4] | Sarah Gaillet[3] | Xavier Gamé[9] | Gilles Karsenty[3] | Groupe d'Etude de Neuro-Urologie de Langue Française (GENULF) and the committee of NeuroUrology of the French Association of Urology (AFU)

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INTERNATIONAL JOURNAL OF UROLOGY
International Journal of Urology (2015) **22**, 1160–1165 doi: 10.1111/iju.12950

Original Article: Clinical Investigation

Failure of botulinum toxin injection for neurogenic detrusor overactivity: Switch of toxin versus second injection of the same toxin

Benoit Peyronnet,[1,2] Evelyne Castel-Lacanal,[3] Andréa Manunta,[2] Mathieu Roumiguié,[1] Philippe Marque,[3] Pascal Rischmann[1] and Xavier Gamé[1]

[1]Department of Urology, CHU Rangueil, Toulouse, [2]Department of Urology, CHU Rennes, Rennes, and [3]Department of Physical Medicine, CHU Rangueil, Toulouse, France

Eficacité et Dose?

- Détrusor différent muscle strié spastique
  - Durée d'efficacité
- Equivalence probablement différente en fonction du type de muscle

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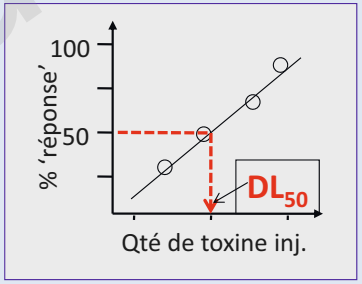
D'après B Poulain

Dose L 50

- Injection intrapéritonéale
- Recette différente d'une formulation à l'autre :
  - Abobotulinum : gelatine; Hambleton et al 1994
  - Incobotulinum : Albumin; Dressler et al, 2012
  - Onabotulin : saline solution; Hunt et Clark, 2009
- Conditions biologiques d'élevage spécifiques à chaque formulation

Test de létalité chez la souris (mouse LD50 assay)



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D'après B poulain

Des formulations différentes

Name of toxin or neurotoxin	Name of product	Toxin or Neurotoxin load /vial	*Relative Neurotoxin load by ELISA*[4]	MW	Excipients		Bio assay	Units/ pack.
					HSA (µg)	Other		
OnabotulinumA	Botox®	~5 ng[1]	*0.73 ng*	900 kDa Complex (but see 5)	500	NaCl	mLD50 without added proteins	100 AU
	Vistabel®	2.5 ng	*ND*		250			50 AU
AbobotulinumA	Dysport®	4.3[illegible] ng[2]	*3.24 ng*	Unknown((but see 4, 5)	125	Lactose	mLD50 with added proteins (gelatin)	500 SU
	Azzalure®	1.1 ng	*ND*		125			125 SU
IncobotulinumA	Xeomin®	0.6 ng[3]	*0.44 ng*	150 kDa Neuro-toxin	1000	Sucrose	mLD50 without added proteins	100 U
	Bocouture ®	0.3 ng	*ND*		1000			50 U

(1) www.Allergan.com (2010); (2) Panjwani et al (2008) The TBJ 1:153-166;
(3) Jost et al (2007) Drugs 67:669-683; (4). Frevert, Drugs R D, 2010, 10(2)
(4) (5) Eisele et al., 2011, Toxicon 57:555-565.

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D'après B Poulain

Le processus de purification/formulation donne lieu à un mélange de neurotoxine(active) et d'apotoxine (inactive)

- L'apotoxine contribue à la charge protéique mais pas à l'activité biologique
- La mention pondérale n'est donc pas suffisante
- C'est l'activité biologique qui doit être évalué

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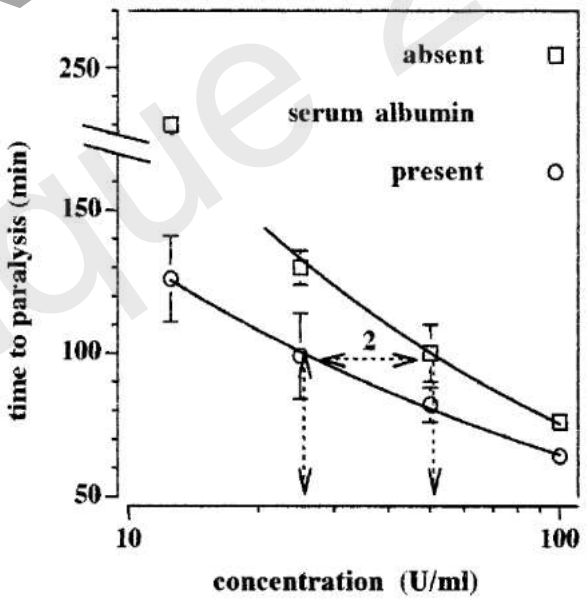
D'après B poulain

Rôle de l'albumine

L 'augmentation de l'albumine dans les formulations améliore l'efficacité:

- Réduction de l'absorption non spécifique
- Meilleure récupération de la neurotoxine contenu dans le flacon



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Introduction

gic diseases constitute 28% of the global disease burden and are d to rise worldwide with the ageing of human populations. There is d to develop new molecular systems that can deliver drugs ally into neurons. Neuronal drug delivery must rely on agents that cognize neurons with high specificity and affinity. Here we introduce l technology that utilizes duplicated botulinum binding domains, g neuronal targeting surpassing native botulinum neurotoxins.

Methods

ngineered binding domains of botulinum neurotoxins by attaching peptides and combined them to produce duplicated botulinum ructs. This resulted in high-affinity binding agents that can deliver ing agents and large therapeutic enzymes into neuronal cytosol**.

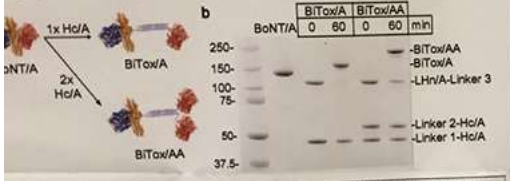

Figure 1 a. Schematic showing the structures of BoNT/A, BiTox/A and BiTox/AA with duplicated receptor-binding domain Hc/A. **b.** Coomassie-stained SDS-PAGE showing native BoNT/A and the formation of BiTox/A and BiTox/AA.

e also used recombinant fusion to create a single-molecule version of a uplicated botulinum neurotoxin type C (BoNT-2xHc/C), as a proof of oncept for one-step production of duplicated botulinum neurotoxin olecules.

Figure 2 Structural diagram (left) and SDS-PAGE (right) showing the difference between BoNT/C and the novel BoNT-2xHc/C.

These agents were tested in differentiated human SiMa neuroblastoma cells for potency, using the proteolytic domain of botulinum neurotoxin type A and an immunoblotting assay to detect levels of its cleaved target, synaptosomal-associated protein (SNAP)-25.

As Botulinum type C has been found to induce apoptosis in differentiated neuroblastoma[1], Deep Blue cell viability assay was used to determine the level of cell death in cells treated with BoNT/C and our double-binding variant.

Finally, as BiTox/A has previously been found to reduce mechanical sensitivity in the Spared Nerve Injury (SNI) model of neuropathic pain in rats, while causing reduced paralysis compared to BoNT/A[2], rats were treated with either 2ng of BiTox/A or BiTox/AA 5 days after SNI surgery, and their mechanical sensitivity was measured by Von Frey Apparatus.

**Patent number: WO2018109447A1 / GB201621111D0

Results

BiTox/AA cleaved SNAP-25 at lower concentrations than both the single binding domain equivalent BiTox/A and native Botulinum toxin type A (BoNT/A), and has a faster onset of cleavage.

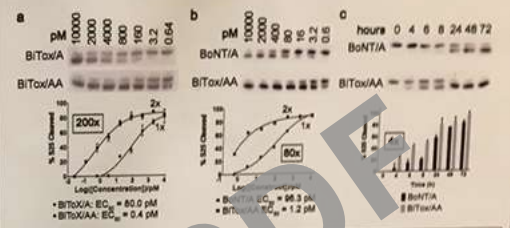

Figure 3 Immunoblots showing proportion of cellular SNAP-25 cleaved in differentiated neuroblastoma cells following application of BoNT/A variants. Lower graph represents quantification of the immunosignals, n=3 **a.** Titration comparing BiTox/A and BiTox/AA after 65h **b.** Titration comparing native BoNT/A with BiTox/AA after 65h **c.** Time course of SNAP-25 cleavage after application of 2nM BoNT/A or 2nM BiTox/AA.

Cleavage of SNAP-25 by BoNT-2xHc/C was also more potent and had a faster onset time than the native Toxin equivalent, BoNT/C, and a higher degree of cell death was caused by the double-binding variant.

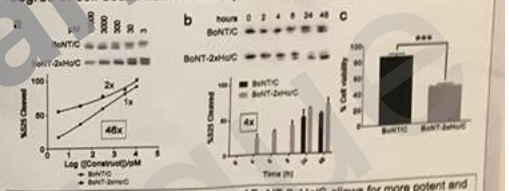

Figure 4 The additional binding domain of BoNT-2xHc/C allows for more potent and faster entry into differentiated SiMa neuroblastoma cells. **a +b.** Immunoblot showing proportion of cellular SNAP-25 following application of BoNT-2xHc/C and BoNT/C variants. Lower graph represents quantification of the immunosignals, n=3 **a.** Shows cleavage after 65h, **b** shows cleavage at 3nM concentration. **c.** Viability of differentiated SiMa neuroblastoma cells after 65h incubation with BoNT/C variants, normalised to cells treated with vehicle buffer, n=3. Significance determined using unpaired t-test. ***=<0.001.

BiTox/AA also caused reduced mechanical sensitivity in SNI model rats compared to BiTox/A, while still showing no signs of paralysis at the dose used.

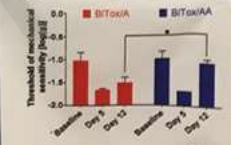

Figure 5 Mechanical sensitivity of SNI rats treated with BiTox/A and BiTox/AA. Graph shows baseline measurement (before surgery), Day 5 (after surgery, before injection of BiTox) and Day 12 (after surgery and injection of BiTox). Significance determined using one-way ANOVA, *=< 0.05

Ongoing Work

BiTox/AA is currently being trialed in other pain models, including migraine model, and we are testing the possibility of using these molecules to deliver other, non-clostridial, enzymes into neuronal cytosol.

Bibliography

[1]Rust et al. Oncotarget. 2016 May 31; 7(22): 33220–33228
[2] Mangione et al. Pain. 2016 May; 157(5): 1045–1055.

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Poster 2019

Mon Gégé…..
Belote
Rebelote
et dix de der…..

MERCI ……

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