BOTULINUM TOXIN AND NEUROPATHIC PAIN

Valeria Tugnoli
Neurophysiological Unit, Neuroscience/Rehabilitation Dpt, Ferrara, Italy

Palermo 11-13 marzo 2010
AGENDA

➢ BoNT and Pain ➔ Serendipitous Target

➢ Clinical application: muscle-related pain
➢ Clinical application: not muscle-related pain
    (nociceptive, neuropathic and rheumatologic pain)

➢ How do BoNT reduces pain
BoNT and Pain → Serendipitous Target

- Clinical application: muscle-related pain
- Clinical application: not muscle-related pain (nociceptive, neuropathic and rheumatologic pain)
- How do BoNT reduces pain
1) 2/3 pts affected by Cervical Dystonia (CD) \(\rightarrow\) **PAIN**

- 76-93% of Pain in CD has been reduced by BoNT, also if dystonic pattern didn’t change,
- **Different timing** (Tsui '85, Jancovic '91, Freund '03)

2) …..Patients treated for facial wrinkles
- ….. improved migraine headache (Binder '00)

3) Chronic anal fissure improvement before healing, long-lasting resolution of pain (Runfola et al. 2006)
AGENDA

- BoNT and Pain ➔ Serendipitous Target
  - Clinical application: muscle-related pain
  - Clinical application: not muscle-related pain (nociceptive, neuropathic and rheumatologic pain)
  - How do BoNT reduces pain
Muscle-related pain and BoNT

- **Dystonia** (Jankovic J ‘91, Costa J ‘06)
- **Spasticity** (Group SS M&N ‘97)
- **Chronic cervical pain** (Chesire PIN ‘94, Porta Pain’00, Wheeler Pain’01)
- **Anal fissures, Chronic Pelvic pain, Hemorrhoidectomy pain** (Gui ‘94, Zermann ‘00, Thomson ‘05, Abbott ‘06, Patti ‘06, Lai ‘07, Sinha ‘09, Apostolidis A’09)
- **“Whiplash” neck pain** (Freund Headache ‘00)
- **“Painless arms/moving fingers”** (Singer ’07)
- **Postoperative pain** (muscle spasms, adductor muscle contracture) (Adler ‘96, Racette ’98, Kern ‘03, Schofferman ’05, Cannard ‘05, Hamdy ‘07, Filipovic’09, Hamdy’09, Santamato ‘10)
- **Temporomandibular Dysfunction** (Berardelli ’94, Brin ’95,Nixdorf 2002)
Primary headache prophylactic treatment: Migraine, Chronic Daily and Tensive Headache (Silberstein ’01,’05,’06, Evers ’04,’06, Dodick ’05, Schulte-Mattler ’07, Relja ’07, Straube ’08, Burstein R’09)

Chronic Facial Pain (Borodic ’02), Acute angle glaucoma (Chien ’10), Aphthous ulcer (Yan’09)

Painful Neuropathies, CRPS (Argoff ’02, Bach.-Rojecky ’07, Knoderer ’07)

Trigeminal (Allam ’05, Piovesan ’05, Liu ’06), Occipital Neuralgia (Kapural ’07,Taylor’08)

Post-herpetic Neuralgia (Dykstra ’04, Schwartz ’04, Liu ’06, Ko ’07)

Notalgia paresthetica (Weinfled ’07), Thelalgia (Heigelshoven ’06),

Painful Keloid (Uyesugi ’10), SCI Allodynia (Jabbari ’03), Phantom Limb (Jin’09)

Interstizial Cystitis (Smith et al ’04, Namazi ’08)

Refractory joint pain (Monnier et al ’06, Mahowald ML et al’06, Singh ’06-’09, Monnier et al’07, Oskarsson et al’08, Singh’09, Mahowald’09), Plantar Fasciitis (Babcock et al ’05), Tennis Elbow (Lin ’10), Patellofemoral Pain S.

Stellate ganglion block for facial pain (Wilkinson ’06), and CRPS (Carroll’09)
An open study of botulinum-A toxin treatment of trigeminal neuralgia

Abstract—Thirteen subjects with trigeminal neuralgia were treated with botulinum-A neurotoxin (BoNT/A) in an open-label pilot study. After BoNT/A, visual analog scale score, surface area of pain, and therapeutic coefficient were reduced in all patients and for all branch trigeminal nerves studied. Therefore, BoNT/A is an efficient treatment. There were no major side effects. A placebo-controlled clinical trial is needed to confirm these findings.

E.J. Piovesan, MD; H.G. Teive, MD; P.A. Kowacs, MD; M.V. Della Coletta, MD; L.C. Werneck, MD, PhD; and S.D. Silberstein, MD, FACP

To the Editor →
Studio non controllato Effetto ipostenia....
Botulinum Toxin A Relieved Neuropathic Pain in a Case of Post-Herpetic Neuralgia

Hsu-Tang Liu, MD,*,‡ Shen-Kou Tsai, MD, PhD,*,‡ Ming-Chang Kao, MD,* and Jenkin S. Hu, MD*,§

- Paziente di 80 aa
- Da 1 mese bruciore, gnawing tightness pain, Allodinia T2-4
- Terapia farmacologica VAS 10→4 ma effetti collaterali
- Catetere epidurale con anestetico inefficace
- BoNT/A 100U → VAS 10 → 1 dopo 2 gg per 52 gg poi alla ripresa dolore gestibile con terapia farmacologica classica (amitriptilina e gabapentin)
- Effetto placebo??? Atipico l'andamento temporale

Poster 166
Treatment of Herpes Zoster With Botulinum Toxin Type A Injections: A Case Report. Dennis D. Dykstra, MD, PhD (Univ Minnesota, Minneapolis, MN); Paul J. Amundson, MD, e-mail: dykst001@umn.edu.

Poster 167
Subcutaneous Botulinum Toxin Type A in the Treatment of Postherpetic Neuralgia: A Case Series of 24 Patients. Brian Freund, MD (Crown Institute, Pickering, ON, Canada); Marvin Schwartz, DDS, e-mail: freund@crowninstitute.com.

POST-HERPETIC NEURALGIA AND TRIGEMINAL NEURALGIA PAIN IMPROVED WITH INTRADERMAL BOTULINUM TOXIN-A
G.D. Ko a,b,c, I. Finkelstein *c,d

Arch Phys Med Rehabil 2004
Pain Medicine 2006
Randomized, controlled study vs placebo

29 pts affected by post-herpetic neuralgia, painful neuropathy (trauma or surgery) since 6 months

VAS 3-10, area < 60cm²

Endpoints → 50% decrease of daily pain (BPI), previous 24 h pain, Allodinia area and intensity, pressure and thermic pains

40% high improvement; 7% mild improvement, 53% unchanged vs 7% placebo

Significant improvement of burning and paroxysmic pain and allodynia (unchanged deep pain, paresthesias)
Conclusions: This pilot study f(18pts) found that botulinum toxin type A significantly reduced diabetic neuropathic pain (3 cm VAS → 44% BoNT vs 0% placebo) and transiently improved sleep quality. Further large-scaled study is warranted.

We are skeptical of the benefits of BoNT/A in treating neuropathic pain. We also believe that Apfel’s accompanying editorial was too positive regarding this study involving only 18 patients…. BoNT/A has proven indications, but the drive to expand them is industry-driven and is reminiscent of the marketing strategy of Neurontin. Given its cost and mode of use, larger studies funded by unrelated sources should be pursued. (Torgovnick J et al, Neurology 2010)
Review

New indications for botulinum toxin in rheumatology

Guy Monnier*, Laurent Tatu, Fabrice Michel

- Rephreactory joint pain → improved in 55% knees-ankles, 71% shoulders (25-100U i.a., long duration 3-12 months)
- Active range of motion → increased 67% in flexion and 42% in abduction (Mahowald 2006)
- Safe treatment, no adverse events

- Controlled studies vs placebo are needed
<table>
<thead>
<tr>
<th>Disease</th>
<th>BoNT</th>
<th>Level Evidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical Dystonia</td>
<td>BoNT/a BoNT/B</td>
<td>1A</td>
<td></td>
</tr>
<tr>
<td>Pelvic Pain, Plantar Fasciitis, Temporomandibular pain</td>
<td>BoNT/A</td>
<td>1B</td>
<td></td>
</tr>
<tr>
<td>Piriformis syndrome, Whiplash</td>
<td>BoNT/A BoNT/B</td>
<td>1B</td>
<td></td>
</tr>
<tr>
<td>Neuropathic pain, Phantom limb</td>
<td>BoNT/A</td>
<td>1C</td>
<td></td>
</tr>
<tr>
<td>Myofascial pain, Chronic LBP</td>
<td>BoNT/A</td>
<td>2A</td>
<td>2B against MFP</td>
</tr>
<tr>
<td>CTS, Joint Pain, CRPS, Trigeminal Neuralgia, PHN, Neuroma, Brachial Plexopathy, Peripheral Neuropathy, MS</td>
<td>BoNT/A</td>
<td>1C 2C</td>
<td></td>
</tr>
</tbody>
</table>

Jeynes LC et al 2008
AGENDA

- BoNT and Pain ➔ Serendipitous Target

- Clinical application: muscle-related pain
- Clinical application: not muscle-related pain (nociceptive, neuropathic and rheumatologic pain)

- How do BoNT reduces pain
Blocco esocitosi
1-Dolore e BoNT animale

- **In vitro:** vescica ratto *(ATP)* (Smith Hannover 2002)
- **In vitro:** *sostanza P* dai Gangli dorsali di ratto stimolati con capsaicina (Purkiss 2000)
- **In vitro:** *Noradrenalina* in cellule PC12 (Shone 1992)
- **In vitro:** *CGRP* in gangli trigeminali (Durham 2004) e terminali autonomici vasodilatatori (Morris 2001)

- **In vivo:**...Modello Formalina zampa ratto *(glutamato)* (Cui ‘00, ‘02)
- **In vivo:**...Modello Dolore neuropatico ratto *(legatura L5-L6)* (Park et al 2006), Alloidinia topo *(legatura sciatico)* (Luvisetto et al ‘05,’07)
Botulinum Toxin A inhibits the inflammatory pain in rat *formalin model*. Cui et al. 2000

- BoNT A iniettato pianta via sottocutanea, poi formalina → licking
- Fase 1 → stimolazione diretta dei nocicettori e infiammazione
- Interfase quiescienza → modulazione centrale inibitoria del dolore
- Fase 2 → processi di sensibilizzazione centrale
- Two phase pain: dolore acuto, dolore infiammazione secondaria
- BoNT A causava una riduzione “licking”, solo con dosaggi alti fase 1, per tutti i dosaggi Fase 2 (dosaggi alti= effetti sistemici)
Mechanisms of the antinociceptive effect of subcutaneous BOTOX: inhibition of peripheral and central nociceptive processing
(Cui et al Hannover 2002)

✓ Modello ratto trattato con formalina zampa non varia soglia termica
✓ Diminuisce, con effetto dose-dipendente: 1) Release glutamato locale, 2) attività elettrica neuroni corna dorsali MS, 3) espressione spinale di C-fos (indicatore attività neuronale) lamina I-II (circuiti monosinaptici), lamina V-VI (circuiti polisinaptici)
✓ BoNT→invariato "early acute nociceptive (AN), diminuisce late tonic nociceptive (TN)" (FIG.1)
✓ Effetto persistente 12 gg (FIG.2)
Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A (Aoki KR ‘05)

- Possibile ingresso per “pinocitosi”
- Release di sostanze eccitatorie dalle fibre nocicettive (Glu, CGRP, Sost.P), e di sostanze attive pro-infiammatorie (BK, PG, HA, 5HT)
- Espressione dei recettori di superficie TRPV1

- Conclusione: infiammazione e sensibilizzazione nocicettori periferici e secondaria del processo di sensibilizzazione centrale
1. Azione analgesica delle BoNT dipende dal sierotipo
2. Azione analgesica delle BoNT dipende dalla modalità di somministrazione sc vs icv

3. BoNT/A inibisce Fase 2 sia sc che icv
4. BoNT/B inibisce fase 1 solo sc, determina iperalgesia nella interfase se icv. Quindi →

5. **BoNT/A blocca** neurotrasmettitori eccitatori durante la sensibilizzazione periferica e centrale, agisce sulla percezione del dolore, sulla vasodilatazione ed infiammazione (agisce su GLU, SostP, CGRP)

6. **BoNT/B blocca** neurotrasmettitori nocicettivi rilasciati dai terminali sensitivi primari, **blocco centrale della via discendente inibitrice GABA-mediata** (terminali GABA non hanno SNAP25 target della BoNT/A, hanno invece VAMP tagliata da BoNT/B)
Modello allodinia legatura sciatico) misura della forza applicabile prima della retrazione della zampa
Efficace solo se somministrata dopo chirurgia (da 50→80% guadagno 30%) 
Non efficace se pretrattato (-3gg)

Diverso dal modello formalina (più rapido 1-2h) e più “infiammatorio” BoNT somministrata dopo il danno (5-12gg) può interferire con fenomeni di sprouting e di cambiamenti fenotipici delle fibre A,
Analgesia dopo 1 g, stabile per 30 gg
BoNT didn’t impair the withdrawal nociceptive reflex
- Induced dose-dependent inhibition of carrageenan hyperalgesia (without modifying oedema), only when applied in the treated carrageenan site
- Induced dose-dependent inhibition of paclitaxel hyperalgesia in both sites (no systemic diffusion). It remains to be clarified how BoNT may affect proinflammatory cytokines cascade in DRG or spinal cord (synaptic plasticity or retrograde

Pharmacol Biochem Behav. 2009 Dec;94(2):234
Central origin of the antinociceptive action of botulinum toxin type A.
Bach-Rojecky L, Lacković Z
Botulinum Toxin type A reduces capsaicin-evoked pain and neurogenic vasodilatation in human skin

Valeria Tognoli a,b, Jay Guido Capone a,b, Roberto Eleopra a, Rocco Quatrale a, Mariachiara Sensi a, Ernesto Gastaldo a, Maria Rosaria Tola a, Pierangelo Geppetti b,c
BoNT/A →
the reduction of pain and flare
induced by capsaicin

(Tugnoli et al, 2007)
Subcutaneous Botulinum toxin type A reduces capsaicin-induced trigeminal pain and vasomotor reactions in human skin

Parisa Gazerani a,b, Natalia Spicina Pedersen c, Camilla Staahl a,c, Asbjørn Mohr Drewes a,c, Lars Arendt-Nielsen a,c
BoNT and Pain: effects on *Non Muscular-related* events

- Block of the PKC-induced surface expression of Vanilloid receptors TRPV1 (Morenilla-Palao ‘04)
- Inhibition of neuropeptide release from primary sensory neurons (Glu (Cui’00,’02), CGRP (Morris’01, Durham’04), Subst.P (Purkiss ’00), Norepinephrine (Shone’02), ATP (Smith Hannover ’02), Trigeminal Ganglia in vitro and in vivo (animals) models
- Reduction of peripheral sensitization (Formalin-pain models) and of the related central sensitization (c-Fos, Wells ’01)
- Different effects for BoNT/A and BoNT/B if administrated sc or ivc (Luvisetto ’06)
- Inhibition of Autonomic System and of Inflammatory cells (mastzellen)?
Regulated Exocytosis Contributes to Protein Kinase C Potentiation of Vanilloid Receptor Activity

Received for publication, October 21, 2003, and in revised form, March 22, 2004. Published, JBC Papers in Press, April 5, 2004, DOI 10.1074/jbc.M311151202

Cruz Morenilla-Palao, Rosa Planells-Cases, Nuria García-Sanz, and Antonio Ferrer-Montiel

A

Control

ACPD

pH

B

BoNT A

200 nA

4.4 min

C

Potentiation (x fold)

Control

BoNT A

p<0.05
BTX has both direct and indirect actions:

- **Direct:**
  - 1. inhibition of alpha and gamma-motor neurons;
  - 2. inhibition of release of local nociceptive neuropeptides/agents via vesicle-dependent exocytosis.

- **Indirect:**
  - 1. reduction in neurogenic inflammation;
  - 2. alterations within the autonomic nervous system resulting in changes to regional perfusion, as well as central changes affecting behavior and stress;
  - 3. alterations in sensory patterns within the central nervous system (CNS).

The effects of these actions are:
1. prevention of spasm and the subsequent sensitization and activation of nociceptors, and the recruitment of mechanoreceptors as nociceptors;
2. reduction in central sensitization and wind-up;
3. possible neuroplastic reorganization within CNS.
Is time to challenge this “ancient” chapter

Aoki KR ‘05

(Aoki KR ‘05)
Lectina da Erythrina cristagalli (ECL) binds Gal in nociceptive peripheral and central terminals

LHₜ/A-ECL → selectively blocks SNAP25 exocitosys in vitro DRG (SP, CGRP)

In vivo: C fibers drive decrease, without interfering with A-beta function

Long duration of the effect

Possible new drug for the selective use in neuropatic pain
Take Home message

- The “weight” of evidences for BoNT efficacy in painful conditions is growing but still debated
- It does appear that BoNT should be useful in selected patients but we don’t yet know what type of patients
- BoNT seems a promising and safe treatment for different kind of pain, but it must be further evaluated in wider populations and in controlled studies
- Different mechanisms other than cholinergic block do occur to justify BoNT analgesia
Review

- Aoki KR 2005
- Schulte –Mattler ’07
- Jancovic J J Neurol Neurosurg Psy 2004;75:951-957
- Monnier G et al Joint Bone Spine 2006;73:667-671
- Jeynes LC et al Pain Practice 2008;8:269