Botulinum toxin type A: Another unlikely therapy for painful neuropathy

Sirs,

As readers will know, neuropathic pain – pain originating from damaged nerves rather than the tissues that they innervate – is a chronic, progressive, debilitating and burdensome condition for affected individuals and the healthcare services charged with their care. The condition is characterised by exaggerated responses to normally non-painful stimuli or persistent or paroxysmal pain in the absence of tissue damage (Baron, 2009).

There is no universally accepted classification of neuropathic pain – not least because multiple, relatively poorly-defined mechanisms, are often involved. Given the many questions surrounding the nature of painful neuropathy, it is no surprise that often we are unable to relieve its symptoms in our patients. The agents proposed for relief – reuptake-blocking antidepressants, calcium-modulating and sodium-blocking anticonvulsants, opioids, local anaesthetics or counterirritants, neurotoxins (such as capsaicin) – frequently yield disappointing results.

Now another candidate has thrown its hat in the ring of neuropathic pain relief: botulinum toxin type A. Will it offer new hope for those suffering from diabetic neuropathic pain? According to the authors of a small, randomised double-blind crossover trial published in *Neurology*, the answer is yes – or, at least positive enough to be sufficient for them to suggest that a larger scale study is warranted (Yuan et al, 2009).

The authors investigated the effects of low-dose intradermal botulinum toxin by injecting it in a grid pattern into the dorsum of the foot of a small group of people with diabetic neuropathic pain (n=18). Participants were followed for 12 weeks after botulinum toxin or placebo injection, then the treatment arms were crossed over and the method repeated. A significant reduction in visual analogue scale pain scores was seen at weeks 1, 2, 4, 8 and 12 in the botulinum toxin group as compared to the placebo group (P<0.05). One case of mild local skin infection at an injection site was reported and successfully treated with antibiotics.

Botulinum toxin is responsible for a reversible but remarkably prolonged proteolytic action that, by disabling acetylcholine exocytosis, results in deadly toxicity after ingestion or inhalation of nanogram amounts (Montecucco and Molgo, 2004). At low doses, the agent is widely exploited by the cosmetic industry to reduce frown lines and wrinkles (de Maio and Rzany, 2007).

In the field of neurology, the agent plays a role in the relief of spasticity associated with cerebral palsy, stroke, Parkinson's disease and multiple sclerosis (Tintner and Jankovic, 2001). Botulinum toxin has also been used to treat torticollis, focal dystonias and dyskinesias, as well as spasmodic dysphonia, blepharospasm and extra-ocular muscle tethering in thyroid eye disease – it has also been suggested that multiple injections of botulinum toxin into the muscles of the head and neck might treat migraine (Evers, 2003). For most of these indications – and many others besides – small studies using "hard methodology" to lend biological and statistical credence to soft endpoints tend to be the order of the day.

Intuitively, the mode of action of botulinum toxin in many of these indications involves reduction in muscle tone or, in the case of severe axillary hyperhidrosis, acetylcholine neurotransmission. But how is botulinum toxin supposed to work in the context of neuropathic pain?

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Antonucci F, Rossi C, Gianfranceschi L et al (2008) Long-distance retrograde effects of botulinum neurotoxin A. *J Neurosci* **28**: 3689–96

Baron R (2009) Neuropathic pain: a clinical perspective. *Handb Exp Pharmacol* **194**: 3–30

de Maio M, Rzany B (2007) *Botulinum Toxin in Aesthetic Medicine*. Springer-Verlag, Berlin

Evers S (2003) Is there a role for botulinum toxin in the treatment of migraine? *Curr Pain Headache Rep* **7**: 229–34

Foran PG, Mohammed N, Lisk GO et al (2003) Evaluation of the therapeutic usefulness of botulinum neurotoxin B, C1, E, and F compared with the long lasting type A. Basis for distinct durations of inhibition of exocytosis in central neurons. *J Biol Chem* **278**: 1363–71

Montecucco C, Molgo J (2004) Botulinal neurotoxins: revival of an old killer. *Curr Opin Pharmacol* **5**: 274–9

Tintner R, Jankovic J (2001) Focal dystonia: the role of Botulinum toxin. *Curr Neurol Neurosci Rep* **1**: 337–45

Yuan RY, Sheu JJ, Yu JM et al (2009) Botulinum toxin for diabetic neuropathic pain: a randomized double-blind crossover trial. *Neurology* **72**: 1473–8

After the toxin is endocytosed by nerve terminals and reaches the cytosol, it degrades SNARE proteins (soluble N-ethylmaleimide-sensitive fusion protein attachment proteins), which are essential for vesicle fusion and axonal release of acetylcholine – the neurotransmitter responsible for muscle contraction. In addition to its action on this classic neurotransmitter, botulinum toxin is also thought to impair the release of glutamate, substance P and calcitonin gene-related peptide, all of which are co-localised with acetylcholine and involved in neurogenic inflammation, nociception and central sensitisation of nociceptor nerve terminals (Foran et al, 2003).

Upregulation of sodium channels and receptors (e.g. alpha, vanilloid TRPV1 and menthol-sensitive TRPM8 receptors) have been associated with neuropathic pain and are believed to be responsive to the effects of botulinum toxin. Changes in muscle spindles altering sensory input affecting nociceptive transmission have also been adduced along with neuronal hyperexcitability and collateral damage of uninjured neurons by substances released from dying cells. Increased muscle, but also – somewhat curiously – tendon, joint, nerve and vessel "irritation" have been implicated in botulinum toxin-responsive neuropathic pain (Foran et al, 2003).

Added to this panoply of descriptive and self-fulfilling mechanisms are observations that pain reduction after the use of botulinum toxin in dystonia not only develops before the onset of muscle weakness, but also outlasts it and seems to be evident in muscle groups that have not been injected at all. The widespread paralysis in botulism, however, is a testament to botulinum toxin's astonishing potency as a neurotoxin, rather than its ability to migrate along nerves or penetrate the central nervous system, although retrograde neuronal transport from the muscle to the dorsal root and spinal cord that was thought not to occur, or be so slow that the toxin is inactivated before reaching the central nervous system, has fairly recently been demonstrated (Antonucci et al, 2008).

What then could be the mechanism by which an array of injections on the dorsum of the foot could relieve diabetic neuropathic pain that begins in the toes and spreads proximally like a stocking? Biological plausibility aside, a reduction in visual analogue pain scale scores in just eight of Yaun et al's (2009) 18 participants is not all that compelling.

So should the potential of botulinum toxin for the relief of neuropathic pain in diabetes be explored further? Given the limitations of current treatments, the answer is "perhaps". But there may not yet be sufficient grounds to warrant the diversion of resources from other studies. ■

Yours sincerely,
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