

Editorial

Botulinum Toxins for Analgesia

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In a landmark article in *Annals of Neurology*, Ranoux et al (1) have convincingly demonstrated that botulinum toxin type A (BTX-A) may provide direct analgesic effects in patients with focal chronic neuropathic pain independent of its effects on muscle tone. Ranoux and colleagues (1) appropriately point out that large-scale studies are needed to confirm the results and to determine whether BTX-A may also be effective in other forms of neuropathic pain. However, in spite of a relatively small number of patients, Dr. Murinson (2) accurately reports that Ranoux et al provide Class I evidence in support of an effective new approach to the treatment of focal neuropathic pain.

Preclinical evidence exists supporting the antinociceptive qualities of BTX-A (3). Subcutaneous (s.c.) BTX-A also inhibits inflammatory pain in the rat formalin model, and the present study examined whether this could be due to a direct action on sensory neurons (3). BTX-A (3.5-30 U/kg) was injected s.c. into the subplantar surface of the rat hind paw followed 1–5 days later by 50 mL of 5% formalin. Using microdialysis, it has been shown that BTX-A significantly inhibited formalin-induced glutamate release (peak inhibitions: 35%, 41%, and 45% with 3.4, 7, and 15 U/kg respectively) (3). BTX-A also dose dependently reduced the number of formalin-induced Fos-like immunoreactive cells in the dorsal horn of the spinal cord and significantly (15 and 30 U/kg) inhibited the excitation of wide dynamic range neurons of the dorsal horn in Phase II but not Phase I of the formalin response. These results indicate that s.c. BTX-A inhibits neurotransmitter release from primary sensory neurons in the rat formalin model (3). Through this mechanism, BTX-A inhibits peripheral sensitization in these models, which leads to an indirect reduction in central sensitization (3).

Early in the use of BTX-A for dystonia, some au-

thors noted that pain relief preceded muscle decontraction and exceeded what would have been expected solely as a consequence of muscle relaxation (3). These findings suggested that BTX-A might have analgesic properties independent of its myorelaxant action. Further information came from in vitro experiments demonstrating that BTX-A could inhibit neurogenic inflammation, a process that results from the sensitization of C-fiber nociceptors (4). The effects of BTX-A involved attenuation of the release of neurotransmitters including substance P (5,6), calcitonin gene-related peptide (7,8), and glutamate (9), and inhibition of vanilloid receptor activity (10). Consistent with these in vitro experiments, peripheral injections of BTX-A reduces nociceptive behaviors in animal models of inflammatory (9,11) and traumatic neuropathic pain (12-14).

The efficacy of BTX-A in neuropathic pain has been suggested only in small anecdotal case reports (15-18). In this study, Ranoux and colleagues investigated for the first time the potential direct analgesic effects of one-time BTX-A in the painful area in patients with focal neuropathic pain (e.g., posttraumatic/postoperative pain or postherpetic neuralgia)

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associated with allodynia using a double-blind, placebo-controlled parallel group design (1). The injections were performed intradermally to exclude effects on muscle tone (1).

Twenty-nine patients received a one-time intradermal administration of BTX-A (20 – 190 units) into the painful area. Outcome measures, evaluated at baseline, then at 4, 12, and 24 weeks, included average spontaneous pain intensity, quantified testing of thermal and mechanical perception and pain, allodynia to brushing (area, intensity), neuropathic symptoms, clinical global impression, and quality of life (1).

Treatment was administered by a neurologist not involved in the assessment. Aliquots of 100U/vial BTX-A were reconstituted with 4ml nonpreserved saline solution (0.9%) as recommended by the manufacturer (concentration of 5 units BTX-A/0.2 mL, and placebo consisted of an equal volume of saline [9% NaCl]). The injection of BTX-A or saline was performed according to a procedure adapted from that used for hyperhidrosis (19): BTX-A or placebo was injected intradermally into the skin 1.5 cm apart (0.2 mL, and thus 5 units of BTX-A per site) (1).

The primary outcome measure was self-reported average pain intensity from each morning's record in a diary concerning the last 24 hours using the 11-point numerical scale (0 = no pain; 10 = maximal pain imaginable) of the Brief Pain Inventory (1, 20).

Sensory deficits and pain were measured and assessed by the same investigator at baseline, and after 4 and 12 weeks, as in prior therapeutic trials (21,22). Brush-induced allodynia was evaluated by stroking the skin with a standardized brush (Sense-lab brush-0.5; Somedic AB, Horby, Sweden) and was considered as present if this evoked a clear sensation of pain. The intensity of allodynia (recorded on a 100mm visual analog scale) and its area (traced on a transparent paper, then digitized for measurement on Canvas 6.0 software) were measured. Mechanical sensations (detection thresholds to nonpainful stimuli) and pain thresholds were measured with calibrated von Frey hairs (0.06 – 300gm) (Somedic AB, Sweden). Thermal sensations and pain thresholds (in °C) were assessed with a Somedic thermotest (Somedic AB) by the method of limits, with baseline temperatures adjusted to the patient's skin temperature according to a procedure largely described

elsewhere (23). Measurements obtained in the area of maximal pain were compared with those of the homologous contralateral side (1).

Other secondary outcome measures (completed at baseline and follow-up visits) included a visual analog scale rating the average pain over the last 24 hours on a 100mm line; the neuropathic pain symptom inventory (24) rating the mean intensity of 10 neuropathic symptoms and their combination into 5 distinct dimensions during the last 24 hours on 11-point (0 – 10 points) numerical scales, the duration of spontaneous pain and number of pain paroxysms (assessed with the neuropathic pain symptom inventory on categorical scales), 6 of 7 items for pain interference of the Brief Pain Inventory (with the exclusion of the item "ability to walk" judged irrelevant here) rated from 0 (does not interfere) to 10 (complete interference), the Hospital Anxiety and Depression Scale (25) including 14 items scored as anxiety and depression scores (each on 21), subjective pain relief because of the treatment over the past week (from 0% [no pain relief] to 100% [maximal pain relief]), the patients' overall impression of change on a 7-point scale (from very much improved to very much worse), and the assessment of blindedness (1).

BTX-A treatment, relative to placebo, was associated with persistent effects on spontaneous pain intensity from 2 weeks after the injection to 14 weeks. These effects correlated with the preservation of thermal sensation at baseline ($p < 0.05$). BTX-A also improved allodynia to brush and decreased pain thresholds to cold, without affecting perception thresholds. There were sustained improvements in the proportion of responders (number needed to treat for 50% pain relief: 3.03 at 12 weeks), neuropathic symptoms, and general activity. Most patients reported pain during the injections, but there were no further local or systemic side effects (1).

Ranoux and colleagues concluded that BTX-A may induce direct analgesic effects in patients with chronic neuropathic pain independent of its effects on muscle tone (1). The treatment of postherpetic neuralgia and painful focal neuropathies with BTX-A offers several distinct benefits compared with existing treatment options, including that it is reasonably safe, effective, long-lasting, and potentially free from cognitive side effects (2).

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