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CASE REPORT

BOTOX® delivery by iontophoresis

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Summary We report two patients with severe palmar hyperhidrosis who responded to BOTOX® delivered not by injection, the usual method of delivery, but by iontophoresis. The Botulinum molecule has been considered too large for delivery into the skin this way. However, other large peptides, both non-ionic and cationic, have been delivered successfully by this method, so we suspected that BOTOX® could in fact be iontophoresed. Our saline-controlled treatment of these two patients with a small iontophoresis unit (Iomed Phoresor II) allowed small volumes of standard BOTOX® dilutions to be used, and demonstrates that iontophoresis can indeed deliver BOTOX® successfully. This has important therapeutic potential for the large number of patients with focal hyperhidrosis. They may be spared painful injections, and in more severe cases, invasive surgery.

Key words: botulinum toxin A, hyperhidrosis, iontophoresis

Iontophoresis is a drug delivery system that uses a small external electric current to deliver water-soluble, charged drugs into the skin. Tap-water iontophoresis of palmoplantar hyperhidrosis has been routine for several decades,[1] and is made more effective when necessary by the addition of anticholinergic agents.[2]

BOTOX®, a brand name for Botulinum toxin type A manufactured by Allergan Inc., of Irvine, CA, U.S.A., is a di-chain polypeptide that produces a dose-dependent blockage of presynaptic acetylcholine release.[3] It is a safe and very effective treatment for focal hyperhidrosis, producing chemodenervation of eccrine sweat glands.[4] However, it usually requires regional anaesthesia for delivery to the palms and soles, and invariably causes a transient weakness of small hand muscles.[5] The anhidrotic effects of palmar BOTOX® last some 6 months.[6]

Our rationale for testing iontophoresis as a delivery system for BOTOX® was straightforward. The requirements for a drug to be delivered by iontophoresis include solubility in water, polarity and a suitable molecule size. The Botulinum toxin A complex is negative at neutral pH.[7] Large, cationic peptides such as calcitonin have been delivered successfully by this method,[8] and lignocaine hydrochloride and epinephrine are already available in a commercial preparation [Iontocaine® (IOMED, Inc., Salt Lake City, UT, U.S.A.) licensed for use by the U.S. Food and Drug Administration], for use with the Iomed Phoresor II appliance that we use as a research tool in our department. Iontocaine® absorption after delivery in this manner has been studied in human and animal subjects: no detectable plasma levels have been found even by sensitive immunoassay techniques.[9] For these reasons we suspected that BOTOX® could also be iontophoresed safely.

Our saline-controlled treatment of two patients demonstrates that iontophoretic delivery of BOTOX® can be achieved. As far as we are aware, this is the first documented report.

Case report

A 22-year-old female with severe palmar hyperhidrosis since puberty was referred for tap-water iontophoresis. She was treated with a 0·5% glycopyrronium bromide solution but her remission lasted only 2 days. Disappointed with this, but reluctant to consider selective sympathectomy,[10] the patient chose to have intradermal BOTOX® injections.

We administered BOTOX® injections under regional anaesthesia to our patient, and repeated the procedure on her right hand some weeks later. A 6-month remission was achieved, but then her sweating

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recurred rapidly. Her dislike of needles made her reluctant to have further injections, and so we considered trying to deliver BOTOX® by iontophoresis.

BOTOX® is a large and unstable protein, which is best used diluted—a 100-IU vial in 3 mL of unpreserved saline.[11] Conventional iontophoresis machines use plastic trays for immersion of palms or soles in tapwater or glycopyrolate solution. The iontophoresis unit (Iomed Phoresor II, model PM700) we used allowed us to test BOTOX® delivery in small volumes. It consists of a controlled DC source powered by a 9-V battery, an active drug-delivery electrode (anode) in a small, circular, plastic drug reservoir of radius 0·45 cm, covering an area of 0·64 cm^2, a grounding electrode for the untreated limb, and lead wires that connect the unit to the electrodes. It is used in our department to iontophorese 0·1% noradrenaline, where it induces blanching of the skin over 4 cm^2.

We administered 100 IU diluted in 3 mL of saline to seven sites on the patient's palm, approximately 3 cm apart, in 300-μL aliquots, and to two sites on the pulp of her index and third finger. Blanching of palmar skin was noted at each site, confirming that the dermis at least was being penetrated. Two sites were treated with 0·7 mA for 5 min, and subsequent sites were treated with 1·4 mA for the same duration.

The patient reported significant reduction in sweating of her treated palm and fingers after 48 h. This was maximal after 5 days. She also noted that the area treated with the lower current, along with her finger pulp, was not quite as dry as the other treated areas. She noticed no muscle weakness, confirmed by a normal thumb–index finger pinch test. This was sustained for 3 months, and she described her results as '70% as good as the injections'.

We treated the patient a second time, after her sweating recurred, but this time her other hand was treated with saline only, as a control. We iontophoresed 100 IU BOTOX® in 2 mL of saline to seven sites in her left palm in 300-μL aliquots, 3 cm apart, and saline only, similarly to her right palm. At the same time we also treated a second patient in the same manner; each site in both subjects received 15 mAmin. A starch–iodine test and gravimetry were performed for objective assessment pretreatment, and 2 weeks after treatment. Both patients and the assessor were blinded to the treatment.

Both patients reported a subjective reduction in sweating of their treated hands of about 70% within 72 h, which correlated well with starch–iodine (Fig. 1) and gravimetry measurements (Fig. 2). Gravimetry at

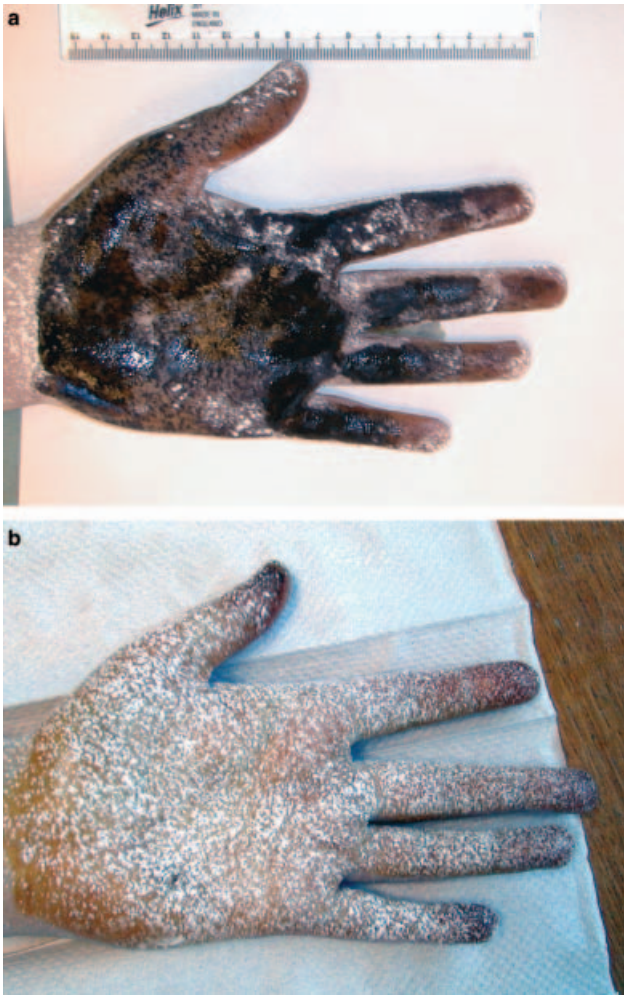

Figure 1. A starch–iodine test is used to delineate the hyperhidrotic area. This shows Patient 1's left palm (a) pre-, and (b) 2 weeks' post-BOTOX® iontophoresis.

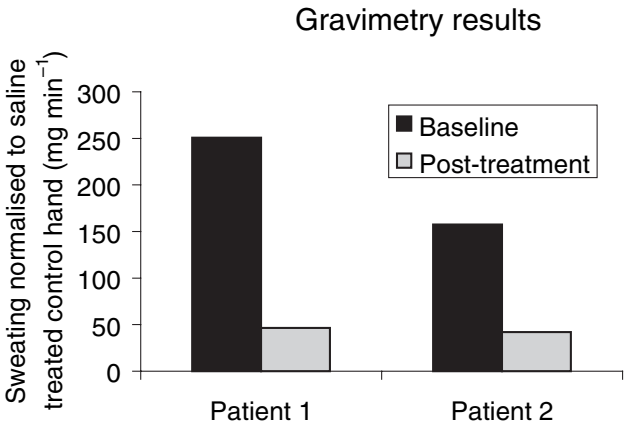

Figure 2. Paper gravimetry quantifies the amount of sweat produced. This gravimetry result for the BOTOX® -treated hand has been normalized to that of the saline-treated hand.

2 weeks showed a reduction in sweat rate of 81·1% in patient 1, and 73% in patient 2, normalized for interday variability using the control hand. There were no side-effects.

Discussion

Iontophoresis has also been known to deliver large nonionic hydrophilic compounds, at least in a rat model. As well as increasing solvent flow, the process actually appeared to increase pore size, and possibly induced new pore formation in the skin.[12] Sweat is produced by eccrine glands whose ducts open directly onto the skin surface,[13] and we believed that even the large BOTOX® protein (at 900 kDa) could be carried down these ducts.[14]

The amount of drug delivered by iontophoresis is directly proportional to the total electrical charge applied, which we express in milliampere minutes (mAmin). We anticipated that this simple formula could be manipulated to enhance the duration and potency of BOTOX® by iontophoresis. Twenty mAmin is our customary tap-water iontophoresis treatment time, so increasing towards this would seem reasonable.

Has it really worked for both our patients? Tap-water iontophoresis by itself can induce lasting remission of palmoplantar sweating, as we know,[15] but several treatments are required to produce that effect. Our first result, a sustained effect of 3 months after only one treatment, strongly suggests that BOTOX® was successfully delivered to our patient transdermally. Our more recent treatments appear to be confirming this. Our second patient, it is worth noting, was BOTOX®-naive. Perhaps water solubility is more important than molecule polarity or size, at least on the palms, where eccrine glands are heavily concentrated.

A double-blind trial of BOTOX® by iontophoresis is needed, using standard iontophoresis machines. Primary hyperhidrosis is a common problem, affecting approximately 2·8% of the population.[16] If further study shows that BOTOX® can be delivered by iontophoresis, a great many sufferers from palmoplantar hyperhidrosis will be spared painful injections, and in more severe cases, invasive surgery.

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