The goal of this work is to present our results of the intradermic infiltration with botulinum toxin in patients with Frey syndrome. Sixteen hemifaces in 15 patients were studied. Gustatory stimulation was evoked by sucking on a slice of lemon while measurements were done on both hemifaces, with the normal side being used as a control. Skin temperature and color (erythema) were measured with a digital surface thermometer and a skin chromameter, respectively. Sweat quantity and surface were measured by using the previously described blotting paper and iodine-sublimated paper histogram methods, respectively. Testing was repeated 2 weeks after skin infiltration with botulinum toxin (dilution of 50 U/mL). The interinjection distances were 1 cm, and 0.1 mL (5 U) was infiltrated at each injection site. Frey syndrome complaints disappeared in all patients. Small residual amounts of sweat were measurable. The difference in sweat quantity before and after botulinum toxin infiltration was significant in every patient (P < 0.001). Skin temperature and color measurement gave inconclusive results. In conclusion, Frey syndrome treatment with botulinum toxin is an efficient and well-tolerated technique. Further work should address the optimal injection parameters.

Frey syndrome occurs several months to a few years after parotid surgery and is characterized by facial sweating and flushing during meals. Although this syndrome has come to bear Lucie Frey’s name, it was first reported by Baillarger in 1853 and not by Duphenix, as commonly cited. A series of arguments, reviewed elsewhere, favor the so-called aberrant regeneration theory as the physiopathologic explanation. The aberrant regeneration supposes that the parasympathetic fibers, which normally innervate the parotid gland after losing their parotid targets during parotidectomy, regenerate to innervate the facial skin vessels and sweat glands. The normal function of the parotid parasympathetic fibers is to increase salivary secretion during eating, and therefore their activation after aberrant regeneration produces a stimulation of the new targets during meals, resulting in a local vasodilatation (gustatory flushing) and localized sweating (gustatory sweating). What is rarely realized is that in order for this aberrant regeneration to occur, the sympathetic fibers to facial skin vessels and sweat glands have to be damaged. This is a frequent event after either parotid surgery or penetrating parotid trauma but may also occur after cervical sympathectomy. Among symptomatic patients, about half judge their symptoms as “important or embarrassing.” For these patients, different treatments have been attempted with limited success. These treatments can be classified into the following groups: (1) section of some portion of the efferent arc, such as the auriculotemporal nerve, the intracranial portion of the glossopharyngeal nerve, or the tympanic plexus in the so-called tympanic neurectomy; (2) radiotherapy; (3) local topical anticholinergics; and (4) reoperation and placement of an interposition barrier. All these techniques are either inefficient in the long run or have potential side effects that are worse than the symptoms they are supposed to treat. Therefore explanation and reassurance is commonly considered as the most adequate treatment for Frey syndrome.

Recently, several studies have described a new method for the treatment of Frey syndrome—the local infiltration of botulinum toxin in the involved skin. Botulinum toxin can be viewed as an anticholinergic, and this treatment is effective because the (normal sympathetic and regenerated parasympathetic) synapses on
cutaneous vessels and sweat glands are cholinergic, contrary to other sympathetic postganglionic synapses. Actually, the presence of an identical neurotransmitter (between the normal skin sympathetic innervation and the regenerating parotid parasympathetic fibers) is another requirement for an aberrant regeneration to occur.

We report our experience with this technique and the use of newly described methods for the evaluation of facial gustatory sweating.

**METHODS AND MATERIAL**

Sixteen symptomatic Frey syndrome hemifaces in 15 patients (one patient with bilateral Frey syndrome) were included in the study. The principal complaint was intense sweating during eating. This sweating was present during each meal in 12 patients. In addition to gustatory sweating, 4 patients also noted a localized flushing during meals, which was never described as disturbing.

Gustatory stimulation was evoked when the patient sucked...
on a slice of lemon. The lemon slice was placed in the mouth, and the patient was asked to gently suck on the slice without undue chewing. Measures were performed in a specially air-conditioned room (22°C ± 1°C, 25% ± 5% humidity) after 5 minutes of acclimatization of the patient. Most data were collected at the same time of the day (9-12 AM). Four parameters (skin temperature and color, sweating quantity, and surface) were measured during this gustatory stimulation on each hemiface, with the controlateral side being used as a control. Measures were taken on the day of the botulinum toxin infiltration and repeated 2 weeks later. Statistical comparison of the measures taken before and after botulinum toxin injection was performed with the bilateral Student t test by using the statistical algorithms of the SPSS 7.5 software (SPSS Inc, Chicago, IL).

The skin temperature was measured by using a digital contact thermometer (Digital Termometer TTX 1096; Ebro Electronic GmbH, Ingolstadt, Germany). The skin erythema was assessed with a digital chromameter (Minolta CR 300).

Sweat quantity and sweat surface were measured with the blotting paper (BP) and the iodine-sublimated paper histogram (ISPH) methods, respectively. Each method used a custom stencil (Fig 1, A) that was adapted to the rather complicated topology of the lateral facial area. In both methods the stencil was applied on both sides of the face during a gustatory stimulation for a duration of 1 minute. Technical details have been previously reported, as well as a calibration with known quantities of NaCl.28 Briefly, the BP technique is a quantitative measure of the amount of sweat generated by
measuring the weight change in a BP before and after the absorption of the sweat. The ISPH method is a modification of the classical Minor test. Regular office paper sheets, which naturally contain various amounts of starch, have been sublimated with iodine, taking on an amber color. Wetting this paper results in a localized color change from amber to blue, corresponding to the reduction of starch by water, which is similar to color changes of the Minor iodine-starch mixture. The colored paper sheet was scanned in an 8-bit grayscale mode, and the digital image was subjected to a histogram algorithm. Because the stencils were scanned in an 8-bit mode, the available range of darkness is from 0 to 256 (X-axis, Fig 1B). A threshold was applied to eliminate the clear amber tones of the stencil background (value 147; Fig 1B). The remaining histogram data were divided into 3 bins of equal width, corresponding to increasing darkness. The darkest bin (No. 1; Fig 1B and C) corresponds to paper zones in which the starch is supposed to be totally reduced by the applied water (sweat), and only the surface of this darkest bin was taken into account to evaluate the wet surface.

After mapping the surface involved by Frey syndrome with the ISPH stencils, botulinum toxin (5 U per 0.1 mL) was injected intradermally with a 30-gauge needle. Injection sites were about 1 cm apart, and each received about 0.1 mL (5 U) of botulinum toxin. We also asked patients to evaluate the pain of injection by using a 10-cm visual analogous scale.

RESULTS

Subjectively, facial sweating and flushing during meals disappeared in all patients after botulinum toxin injection. The pain of the intradermal injection was evaluated as 2.5 ± 1.2 on a scale from 0 to 10.

The total doses used for each patient varied from 0.3 to 1.5 mL or 15 to 75 U. No secondary side effects were reported by the patients or noticed by the investigators.

The results for skin temperature and color were not conclusive; that is, there was not a clear difference before and after injection with botulinum toxin. For the patients presenting a gustatory flushing, there was a decrease of the erythema after botulinum toxin injection, although the difference was not significant.

Representative data obtained by using the ISPH technique for an individual patient are shown before (Fig 1) and after (Fig 2) botulinum toxin injection. The results for the sweat surface and sweat quantity are shown in Fig 3. The quantity of sweat as measured with the BP technique was significantly decreased after botulinum toxin injection ($P < 0.05$). In addition, the surface of sweating as measured by the ISPH method was significantly decreased by the botulinum toxin infiltration ($P < 0.001$)

DISCUSSION

About 40% of patients undergoing parotidectomy will be disturbed by the symptoms of Frey syndrome. So far, the available treatments have either been of temporary benefit or are associated with potential side effects that are more important than the symptoms to be treated. The treatment of Frey syndrome with botulinum toxin injection, following a suggestion of Drobik and Laskawi, appears an attractive option.
The action of botulinum toxins is that of highly specific endopeptidases that cleave 3 different proteins (synaptosome-associated protein, synaptobrevin, and syntaxin) involved in the fusion of exocytosis vesicles with the cell membrane. The action of botulinum toxin type A is on synaptosome-associated protein. Although this action could occur in any cell, the extremely high specificity for cholinergic synapses is due to specific membrane proteins found only in the presynaptic endings of cholinergic synapses. After binding, the toxin is internalized by endocytosis and liberated in the presynaptic cytosol. By blocking the exocytosis mechanism of the presynaptic terminal, the release of acetylcholine is inhibited. The synapse remains intact but is nonfunctional, and for neuromuscular junctions, this results in muscle paralysis. The recovery of neuromuscular function is due to collateral sprouting from the same or other axons and the formation of new synapses.

Numerous advantages can be cited for the use of botulinum toxin for the treatment of Frey syndrome. The substance is relatively well known and has been used for a variety of pathologies in the last 20 years with few side effects. Its use is rather simple in the office setting, avoiding complicated procedures in the operating room. The only disadvantages are the pain associated with the needle sticking and the associated reluctance of some patients to be stuck, especially on the face. The pain associated with the needle injection was evaluated by our patients to be minimal (2 of 10 on an analog visual pain scale), a result found also in other studies. Whether the use of local anaesthetic cream (EMLA, Astra, Sweden) will increase patient’s acceptance of this mode of treatment remains to be seen.

There were no facial paralysis side effects of the botulinum toxin injection, as reported by others. It is difficult to understand how a strictly intradermal injection can result in the paralysis of facial nerve branches. Also, the membrane receptors responsible for the cholinergic specificity of botulinum toxins are located only in the presynaptic terminals and not in nerve fiber trunks. Therefore the most plausible explanation of these rare and partial temporary paresis is an injection deep to the dermis and diffusion to facial motor end plates.

Before a widespread acceptance of this mode of treatment, the technical aspects in terms of botulinum toxin dilution, interinjection distances, doses per injection site, and maximal doses per patient should be determined. There seems to be an agreement on the 10-mm interinjection distance and on an injection dose of 0.1 mL. The 10-mm interinjection distance is supported by the data of Shaari and Sanders for neuromuscular junctions: injections 10 mm away from the motor end plate band of the rat tibialis anterior muscle are ineffective in inducing paralysis. In the same experimental system, increasing the dose and volume of botulinum toxin resulted in increased paralysis. A 20-fold increase in the dose doubled the paralysis; however, little gain was achieved with injection doses above 5 U. As far as volume is concerned, a 100-fold increase in volume was necessary to double the paralysis. Studies on human sweat glands partially support these data.

Small volumes of concentrated botulinum toxin have the advantage of minimizing the diffusion and possible side effects. However, if side effects do occur, they would be more disabling because of the higher concentration. We used a concentration of 50 U/mL, with the idea that a smaller volume of injection will produce less discomfort and be more efficacious. This is probably necessary in zones with intense facial gustatory sweating (dark zone in Fig 1, A). However, others have obtained good results with a lower dilution (25 U/mL), and this dosage might be advantageous in patients who have a large surface of gustatory sweating.

The follow-up of our patient population is shorter than 1 year (median, 3 months), and therefore we can only speculate about the duration of the effect. In a recent publication, Laskawi et al have found that the effect of botulinum toxin on gustatory sweating is rather long lasting, with an average delay to recurrence of 15 months.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of patients</th>
<th>Botulinum dilution</th>
<th>Interinjection distance</th>
<th>Dose per injection (mL)</th>
<th>Dose per patient (U)</th>
<th>Maximal dose used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bjerkhoel and Trobbe</td>
<td>1997</td>
<td>14</td>
<td>25 U/mL</td>
<td>1 cm</td>
<td>0.1</td>
<td>38 ± 12</td>
<td>62.5</td>
</tr>
<tr>
<td>Naumann et al</td>
<td>1997</td>
<td>45</td>
<td>20 U/mL</td>
<td>1.5 cm</td>
<td>0.05-0.1</td>
<td>21 ± 14</td>
<td>72</td>
</tr>
<tr>
<td>Laccourreye et al</td>
<td>1998</td>
<td>12</td>
<td>25 U/mL</td>
<td>1 cm</td>
<td>0.1</td>
<td>65</td>
<td>88</td>
</tr>
<tr>
<td>Laskawi et al</td>
<td>1998</td>
<td>19</td>
<td>25 U/mL</td>
<td>2 cm</td>
<td>0.1</td>
<td>31</td>
<td>100</td>
</tr>
<tr>
<td>Dulguerov</td>
<td>1998</td>
<td>16</td>
<td>50 U/mL</td>
<td>1 cm</td>
<td>0.1</td>
<td>41 ± 22</td>
<td>75</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of the botulinum toxin type A dilution and doses in publication on Frey syndrome treatment with botulinum toxin
We have the impression that the new methods that were developed for the evaluation of gustatory sweating (and especially the ISPH method) are invaluable for deciding the zones to treat and the amount of botulinum toxin that should be injected. Although the Minor test provides indispensable topographic information, it is cumbersome to use and poorly tolerated by patients.

CONCLUSION

1. The treatment of Frey syndrome by intradermal injection of botulinum toxin type A appears simple, effective, reliable, and fast and is devoid of major side effects.
2. Further work is required to determine the minimal dose per injection, the maximal interinjection distance, and the long-term duration of the effect.
3. The ISPH and the BP techniques are accurate, objective, and topographic methods to localize Frey syndrome and evaluate the response to treatment.

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REFERENCES