

# Treatment of Frey's Syndrome With Topical 2% Diphemanil Methylsulfate (Prantal®): A Double-Blind Evaluation of 15 Patients

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Fifteen patients with severe gustatory sweating after total parotidectomy and facial nerve preservation were asked to take part in a double-blind study.

All patients were alternatively treated with topically applied placebo and topically applied 2% diphemanil methylsulfate (an anticholinergic agent). A 10-day period was allowed between applications for return of symptoms. Two-percent diphemanil methylsulfate provided partial relief in 33.3% of patients and total relief in 40% of patients. Involvement of the hairy temporal line region with gustatory sweating was the main reason for failure. Duration of relief varied from 2 to 4 days. The only side effect was dryness of the mouth noted in two patients.

## INTRODUCTION

Localized gustatory sweating and flushing during mastication is a common complication after parotid surgery. This condition was first documented by Frey in 1923.<sup>1</sup> Several etiologies have been proposed to explain the phenomenon.<sup>2</sup> The aberrant regeneration theory is the most widely accepted. Multiple options are available for treatment. Administration of topical glycopyrolate to the involved skin area has been shown to reduce symptoms and be safe without secondary side effects.<sup>3,4</sup>

This present study was designed to confirm the beneficial effects of topical application of an anticholinergic agent in the treatment of Frey's syndrome. Glycopyrolate is no longer available in France; therefore, diphemanil methylsulfate (Prantal, Unicet Schering Laboratory, Kenilworth, NJ) was used. This

anticholinergic agent has been successfully used by dermatologists for treatment of hyperhidrosis of the palms and soles. It is available in 50-mg tablets or as a 2% cream, and can be obtained only in France, Italy, Australia, and New Zealand. A double-blind study using diphemanil methylsulfate versus a placebo in cases of severe Frey's syndrome after total parotidectomy was performed in order to assess its efficiency.

## MATERIALS AND METHODS

Fifteen patients who underwent a total parotidectomy with nerve preservation at the Laennec Hospital, University Paris from 1976 to 1986 were asked to take part in this preliminary study.

Patient ages ranged from 27 to 66 years. Nine men and six women were selected. All patients selected were free of contraindications for the use of systemic anticholinergic drugs (*i.e.*, diabetes mellitus, obstructive uropathy, glaucoma, thyroid, hepatic, renal, cardiovascular, or central nervous system disease). Women of child bearing age not using contraceptives and pregnant women were excluded. A pretherapeutic ophthalmological examination ruling out glaucoma was performed on every patient.

Patients included in the study had severe gustatory sweating that occurred during every meal and caused annoyance. The exact location was assessed and photographed using a preoperative Minor starch-iodine test. Inferior-superior and anterior-posterior axis of the involved skin varied from 9 to 14 cm and from 6 to 12 cm, respectively. Involvement of the temporal hairline region was noted in 73.3% (11/15) of the patients.

Placebo lotion was distilled water. Placebo cream was a water-soluble ointment base. Diphemanil methylsulfate is an anticholinergic agent with a pharmacologic formula of  $C_{21}H_{27}NO_4S$  and a molecular weight of 389.5. This agent is a quaternary ammonium compound that does not cross the blood-brain barrier. Diphemanil methylsulfate is manufactured under the trademark name of Prantal® as a 2% cream for topical application or as 50-mg tablets for systemic use. The 2% diphemanil methylsulfate cream was used for topical application, and our pharmacist compounded a 2% lotion out of the 50-mg tablets.

A double-blind study was designed. All patients were administered either 2% diphemanil methylsulfate or a placebo on day 1 and day 11 of the study. Cream was applied to the bare skin and lotion to the hairy temporal region. Topical applications to the involved skin area that included 1 cm of the noninvolved skin were performed by a

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nurse. Neither the physician nor the patient knew whether the placebo or diphemanil methylsulfate was being given at the time of application. A 10-day period between applications was allowed for return of symptoms. Patients were instructed to keep a daily record for 7 days of their subjective findings after each application.

## RESULTS

None of the 15 patients experienced relief with the placebo cream or lotion. Partial or complete relief was experienced by 73.3% (11/15) of the patients with 2% diphemanil methylsulfate cream. Relief was complete in six patients (40%), and partial in five (33.3%). Relief at the hairy temporal line with 2% diphemanil methylsulfate lotion was complete in 2 patients, partial in 5 patients, and 4 patients experienced no relief. Duration of relief varied from 2 to 4 days. No complications occurred with 2% diphemanil methylsulfate; however, two patients reported dryness of the mouth.

## DISCUSSION

Incidence of Frey's syndrome after parotid surgery varies from 5% to 59%.<sup>2</sup> Laage-Hellman, using the Minor starch-iodine test, reported this condition in 100% of his patients.<sup>5</sup> However, there is general agreement that no more than 10% of patients with Frey's syndrome have complaints. The aberrant regeneration theory is most widely accepted to explain this syndrome. During surgery, elevation of skin flaps interrupts sympathetic innervation to the sweat glands and subcutaneous vessels. Parotidectomy interrupts the postganglionic secretomotor parasympathic fibers to the parotid. Regenerating nerves from the otic ganglion course through the auriculotemporal nerve during the postoperative period. Regenerating fibers can no longer reach the parotid gland; instead, they reach the severed distal end of the sympathetic fibers to the sweat glands and subcutaneous vessels of the previously elevated skin flaps. During mastication, a new salivary reflex that stimulates the blood vessels and the sweat glands occurs. This reflex is made possible because postganglionic parasympathic nerve fibers and sympathetic nerve fibers share the same mediator: acetylcholine.

Various forms of treatment have been reported. Singleton and Cassisi reported a diminished incidence of Frey's syndrome when a thicker skin flap was elevated.<sup>6</sup> Preventive treatment at time of parotidectomy has been attempted. These procedures include either excision and ligature of the auriculotemporal nerve or placement of fascia lata, temporalis fascia, or free dermis fat transplant under the elevated skin.<sup>7-9</sup> Unfortunately, none of these techniques produced long-term beneficial results.

Various options are available in cases of symptomatic Frey's syndrome. Excision of involved skin might be useful in small localized areas.<sup>10</sup> Radiotherapy to the parotid gland, once advocated, has been abandoned because of the risk of radiation-induced cancer and

xerostomia. Various transplants have been used under the involved skin,<sup>8,9</sup> but this places the facial nerve at risk, especially if a total parotidectomy has been performed. Tympanic neurectomy, which disrupts the regenerative nerve fibers at the level of Jacobson's nerve, is a well-known procedure.<sup>11,12</sup> Parisier and coworkers, using tympanic neurectomy, reported complete relief in 38.5% of patients, partial relief in 23% of patients, and no change in 38.5%.<sup>12</sup> Associated section of the chorda tympani nerve has been advocated to improve results. This procedure has not attained complete success because it is presumed that other anastomotic connections between greater and lesser superficial petrosal nerves allow aberrant regeneration pathways.<sup>12,13</sup>

Medical therapy, in cases of gustatory sweating after parotid surgery, is based on the observation that transmission of the neural input to the sweat glands and subcutaneous vessels is cholinergic. Topical administration of anticholinergic drugs has been shown to be effective. Three-percent scopolamine cream and 2% glycopyrrolate cream have been reported to be beneficial.<sup>3,4,15</sup> Diphemanil methylsulfate is an anticholinergic agent that does not cross the blood-brain barrier and is routinely supplied as a cream. Topical administration of 2% diphemanil methylsulfate resulted in total relief in 40% of our 15 patients and partial relief in 33.3%.

The hairy temporal-line region was involved in gustatory sweating in 11 of 15 patients. Four patients experienced no relief with 2% diphemanil methylsulfate lotion, partial relief was seen in five patients, and total relief in two patients. These results indicate that involvement of the hairy temporal region is the main reason for topical anticholinergic agent failure. The results reported by May and McGuirt on five patients treated with 2% glycopyrrolate cream and lotion were confirmed.<sup>4</sup> We believe that distilled water did not permit good penetration of diphemanil methylsulfate through the hairy involved skin and, therefore, impaired the potential beneficial results of this anticholinergic agent. A new diphemanil methylsulfate lotion that includes agents that enhance skin penetration, such as propylene glycol and ethyl alcohol, is being studied to improve results in cases of hairy temporal region involvement.

## CONCLUSIONS

Diphemanil methylsulfate is a topical agent that can be used safely to control Frey's syndrome after parotidectomy. The overall relief rate was 73.3%, which was similar to the rates achieved with tympanic neurectomy. No major side effects were encountered. Our study was designed to observe the results of a single topical application of 2% diphemanil methylsulfate. We recommend nighttime application every other day, since the duration of relief varied from 2 to 4 days. Long-term prospective studies of topical appli

cation of 2% diphemanil methylsulfate cream and lotion are in progress at our institution.

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#### BIBLIOGRAPHY

1. Frey, L.: Le Syndrome du Nerf Auriculo-Temporal. *Rev Neurol (Paris)*, 2:97-104, 1923.
2. Johns, M.E. and Shikhani, A.H.: Surgery of Salivary Gland. In: *Complications in Otolaryngology Head and Neck Surgery* (Vol. 2). B.C. Decker, Inc., pp. 154-162, 1986.
3. Hays, L.L.: The Frey Syndrome: A Review and Double Blind Evaluation of the Topical Use of a New Anticholinergic Agent. *LARYNGOSCOPE*, 88:1796-1824, 1978.
4. May, J.S. and McGuirt, W.: Frey's Syndrome Treatment With Topical Glycopyrolate. *Head Neck Surg*, 11:85-89, 1989.
5. Laage-Hellman, J.E.: Gustatory Sweating and Flushing After Conservative Parotidectomy. *Acta Otolaryngol (Stockh)*, 48:85-89, 1957.
6. Singleton, G.T. and Cassisi, N.J.: Frey's Syndrome: Incidence Related to Skin Flap Thickness in Parotidectomy. *LARYNGOSCOPE*, 90:1636-1639, 1980.
7. Walter, C.: The Free Dermis Fat Transplantation as Adjunct in the Surgery of the Parotid Gland. *Laryngol Rhinol Otol (Stuttg)*, 90:419-425, 1975.
8. Sessions, R.B., Roark, D.T. and Alford, B.R.: Frey's Syndrome. A Technical Remedy. *Ann Otol Rhinol Laryngol*, 85:734-739, 1976.
9. Wallis, K.A. and Gibson T.: Gustatory Sweating Following Parotidectomy Correction by a Fascia Lata Graft. *Br J Plast Surg*, 31:68-71, 1978.
10. Laage-Hellman, J.E.: Gustatory Sweating and Flushing. Aetiological Implications of Response of Separate Sweat Glands to Various Stimuli. *Acta Otolaryngol (Stockh)*, 49:306-314, 1958.
11. Bouche, J., Freche, C. and Fontanel, J.P.: La Resection du Plexus Tympanique dans le Syndrome de Frey et les Parotidites Recidivantes. *Ann Otolaryngol Chir Cervicofac*, 88:449-454, 1971.
12. Parisier, S.C., Binder, W.J., Blitzer, A., et al.: Evaluation of Tympanic Neurectomy and Chorda Tympanectomy for Gustatory Sweating and Benign Salivary Gland Disease. *Ear Nose Throat J*, 57:51-73, 1978.
13. Smith, R.O., Hemenway, W.C., Stevens, K.M., et al.: Jacobson's Neurectomy for Frey's Syndrome. *Am J Surg*, 120:478-481, 1970.
14. Hay, C.L., Novack, A.J. and Worsham, J.C.: Frey's Syndrome: A Simple Effective Treatment. *Otolaryngol Head Neck Surg*, 90:419-425, 1982.
15. Laage-Hellman, J.E.: Treatment of Gustatory Sweating and Flushing. *Acta Otolaryngol*, 49:132-143, 306-314, 363-374, 1958.

## PanAmerican ORL Congress Set

The XXII PanAmerican Congress of Otorhinolaryngology—Head and Neck Surgery will be held at the Sheraton Hotel, Buenos Aires, Argentina, December 1-5.

The president of the congress will be Dr. Eugenio Romero-Díaz and the general secretariat will be Alejandro Terzian.

Prominent specialists from the United States and Latin American countries will attend to present

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The event will be co-sponsored by Argentine ear, nose and throat societies, the Medicine University and the National Health Secretariat.

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The Intermountain Pediatric Society, the Utah Chapter of the Academy of Pediatrics and the University of Utah School of Medicine's Department of Pediatrics are sponsoring the "12th Annual Common Problems in Pediatrics" conference, July 25-27.

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