Treatment of Sinusitis Related Chronic Facial Pain and Headache with Botulinum Toxin

This application claims benefit to U. S. Provisional Application Serial No. 60/453,037 that was filed on March 3, 2003.

TECHNICAL FIELD OF THE INVENTION

This invention relates to methods for treating headache and facial pain associated with acute recurrent or chronic sinusitis with botulinum toxin.

BACKGROUND OF INVENTION

Botulinum neurotoxin, a toxin isolated from a strain of *Clostridium botulinum*, a deadly toxin at higher concentrations and quantities, has been used as a valuable therapeutic for the treatment of many neuromuscular diseases (*e.g.*, dystonia, hemifacial spasm, bruxism, spasticity, cerebral palsy, torticollis), as well as sensory disorders and cutaneous disorders (myofacial pain, migraine, tension headaches, neuropathy, hyperhydrosis). Although botulinum toxin has been used for the treatment of migraine and tension headaches, botulinum toxin has not been recognized as an effective therapy for headache and facial pain associated with acute recurrent or chronic sinusitis.

Sinus-related headaches are distinctly different from migraine headache, myofascial headaches, and headaches associated with bruxism, temporal mandibular joint syndrome (TMJ) and temporal mandibular muscle dysfunction (TMD), trigeminal neuralgia, tooth related facial pain, pain associated with elevated intraocular pressure, or internal ocular inflammation. Sinus headaches are associated with pressure, or irritating processes within the sinus cavities, sometimes associated with inflammation and impaired flow of mucous secretion. At some point in the diagnostic workup, excessive signs of inflammation within the sinus or nasal cavity, or edema within the sinus or nasal cavity is demonstrated on exam or via radiographic methods. The present inventors have discovered that botulinum toxin relieves the headache and facial pain associated with sinusitis.

CONFIRMATION COPY

SUMMARY OF THE INVENTION

The present invention provides methods of treating headache and facial pain associated with acute recurrent or chronic sinusitis in a subject in need thereof, comprising the step of administering a therapeutically effective amount of a composition comprising botulinum toxin to the nasal mucosa or to the subcutaneous structures overlying the sinuses, wherein the administration of the composition reduces the headache and facial pain associated with acute recurrent or chronic sinusitis. In a preferred embodiment, the sinuses are one or more of the sinuses selected from the group consisting of: ethmoid; maxillary; mastoid; frontal; and sphenoid. Preferably, the subcutaneous structures overlying the sinuses lie within one or more of the areas selected from the group consisting of: forehead; malar; temporal; post auricular; and lip.

Botulinum toxin may be administered to the nasal mucosa or to the subcutaneous structures overlying the sinuses by any number of methods. Preferably, the composition comprising botulinum toxin is administered by injection at one or more injection sites. More preferably, the composition comprising botulinum toxin is administered to the cutaneous projections of the trigeminal nerve innervating the sinus.

In one embodiment of the present invention, a subject is treated by administration of a composition comprising botulinum toxin, wherein the subject, prior to the onset of facial pain or headache, exhibits symptoms or history of sinus rhinorrhea (nasal hypersecretion) and purulent nasal discharge.

The methods of the present invention may be practiced with various botulinum toxin immunotypes. In one embodiment, the botulinum toxin is any one or more botulinum toxin immunotypes selected from the group consisting of: A; B; C; D; E; F; and G. Furthermore, the methods of the present invention may utilize compositions of botulinum toxin wherein the composition is administered at a dose between 0.5 and 50,000 mouse LD_{50} units of botulinum toxin. In a preferred embodiment, between 15 and 200 mouse LD_{50} units spread over multiple injections within a dermatome corresponding to the sinus sensory innervation.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the projection of the trigeminal nerve both to the sinuses and the cutaneous and soft tissue structures of the face.

Figure 2 shows the major divisions and branches of the trigeminal nerve.

DETAILED DESCRIPTION OF INVENTION

A. Definitions.

As used herein, "Botulinum toxin" means a protein toxin and its complexes isolated from strains of *Clostridium botulinum*, including various immunotypes such as A, B, C1, C2, C3, D ,E, F and G.

As used herein, "a therapeutically effective amount" is an amount sufficient to produce a therapeutic response. An effective amount may be determined with dose escalation studies in open-labeled clinical trials or bin studies with blinded trials.

As used herein, "subject" means a mammal.

B. Sinusitis.

Sinusitis is defined as any inflammatory pathology involving the ethmoid, maxillary, frontal, or sphenoid sinuses. It is generally accepted that the cause of pain occurring with acute sinusitis involves infiltration of sinus mucosa with inflammatory cells, as well as increased pressure within the sinuses. What is generally not appreciated, and is herein disclosed, is that sinusitis can cause sensitization of the trigeminal nerve in cutaneous and subcutaneous tissues overlaying the sinus structures. When sensitization of sensory nerves occurs from repeated bouts of sinusitis, the patient can experience a chronic facial pain syndrome or headache. The mechanism by which sensory nerves become up-regulated or sensitized still is not clear. Nerve sensitization is provoked by alterations in the afferent first-order-sensory nervous system, such that thresholds are lowered to the perception of pain (hyperalgesia) and central second-order or higher-neuronal alterations can occur, resulting in an exaggerated response and interpretation of sensory stimuli (central sensitization). This process has been experimentally associated with increased expression and/or responsiveness of NMDA receptors on membranes of nociceptors and possible alterations in transcription and translation of proteins within the nerve cell. The trigeminal ganglia represent a very large collection of afferent sensory neurons, which send projects not only into cutaneous regions of the head, but also internally into osseous sinus structures, and mucous membranes of the nasal and sinus cavities (see **Figure 2**). The arborization pattern of afferent sensory nerve distribution is extensive, but reactivity within any region of the afferent sensory nerve

distribution has the capability of altering the genetic and cellular-protein expression of the sensory nerve cell body within the ganglion. The process of changing cell physiology has been variously coined neuroplasticity or sensitization. Alterations can be in the form of increased expression of nerve cell receptors, such as AMPA and NMDA receptors, modulation of effectors of inflammation, alteration of cellular responses from blood-vessel neural regulation via nitric oxide, substance P, histamine, CRGP, prostaglandins, other known cellular autocoids, and not yet defined autocoids and neuropeptides. The mechanism for sensitization of human nerve cells is still not well understood, and invoking inflammatory mediators, neurogenic inflammatory autocoids, and transcriptional and phenotypic changes of nociceptors and sensory neurons as the only mechanisms for nerve sensitization is not necessary to elicit responses from therapeutic botulinum toxin for this indication. Sensitization in the periphery is thought to occur following a sufficient or prolonged exposure to inflammatory substances, causing altered physiology, possible conformational changes of certain biochemical receptors, responsiveness, and lowered thresholds for nociceptor and sensory nerve depolarization.

Sinus pain usually begins in the mid facial region over the maxillary sinus and can radiate to temporal regions, ocular regions, vertex, and over the forehead. At times, referred pain can project into the posterior cervical region or peri-auricular areas. Generalized headaches can occur. The trigeminal nucleus is somatotropically well organized, and from the brain stem area, directly extends and connects anatomically to the upper-cervical areas of the dorsal horn of the spinal cord. In addition, there are interneuronal connections between the trigeminal nucleus and other cranial nerve nuclei, the autonomic nervous system, the reticular activating system, and other descending and ascending pathways. This interconnecting system has been described as the trigeminal sensory complex. Since there are many more peripheral upper cervical and trigeminal sensory nerves synapsing on fewer central nerves, this has been described as convergence and projection. This can explain the referral patterns of head and neck pains, and the therapies employed in one area of the head and neck to affect an outcome on a another area of the head and neck with shared and referred sensory pathways.

Distinct differences in headache diagnosis have been formulated at international conventions and remain the basis for both general and research practice. For migraine headaches, the presence of episodic headaches lasting 4-48 hrs, associated with light

sensitivity (photophobia), sound sensitivity (phonophobia), nausea or vomiting, pain of a throbbing or pulsating quality, and more often unilateral than bilateral location of headache. Cluster headaches can be associated with some basal transient nasal congestion but occur over a distinct time period (cluster period) and are not associated with any persistent sinus abnormalities on MRI or computerized tomography. Myofascial and tension headaches often have a cap-like squeezing pain across and around the top of the head, often associated with a cervical musculoskeletal pain location, frequently associated with trigger points, and sometimes associated with decreased jaw motility and bruxism if the masseter and temporalis muscles are involved. Ocular-related headaches are associated with increased intra-ocular pressure or signs of intra-ocular inflammation on slit lamp microscopic exam or measured refractive error. Dental-related headaches are associated with findings on dental examination and radiographs. Trigeminal neuralgia is usually limited to one or two dermatomes and is sharp and stabbing in quality, with a rapid "on-off" episodic pattern sometimes associated with stimulation of trigger points.

Chronic-sinusitis-related headache and facial pain can linger for many months to years after an acute or subacute bout of sinus disease or bout of repeated acute sinus headaches. Often, the patient complains of continued pain when radiologic imaging studies, such as computerized tomography and magnetic resonance imaging fail to show any persisting signs of inflammation such as mucosal thickening or fluid accumulation. Often out of desperation, the surgeon performs decompressive surgery via endoscopes or direct approaches (Culdwell luc, external ethmoidectomy) with poor results with respect to the chronic pain. The above observation explains a very common clinical phenomenon associated with chronic facial pain and headache caused by sinusitis. The reason for the persisting pain despite the absence of active sinus findings is peripheral sensory nerve upregulation or sensitization. Direct treatment of sinus-related headache by botulinum toxin injected into the subcutaneous region to down-regulate sensory nerves is therapeutic.

The convention in treating sinus-related headaches involves decongestants to augment mucous clearance and drainage from sinus cavities, antibiotics to treat bacterial infection, anti-inflammatory medication (e.g. corticosteroids), and surgical decompression. Conventional analgesics such as aspirin and acetaminophen may be used. The present inventors have made the unexpected discovery that administration of botulinum toxin over the surface dermatomes containing the sensory branches corresponding to the neurons

projecting into the sinus cavity effectively treats facial and headache pain associated with sinusitis.

C. Formal Classification and Nosology of Sinus Related Head and Neck Pain.

A convention held in 1985 by the International Headache Society (I.H.S.) put forth an exhaustive classification of distinct headache syndromes. Experts in the headache therapeutic field formulated this classification, and such experts explicitly agreed on the importance of headache distinction both for practice and research. The reasons for distinctions are to promote better communication among practitioners and to provide more exacting therapy for specific headache syndromes. For instance, procedures used to treat trigeminal neuralgia, such as glycerol injections, gamma knife application, and microvascular decompression at the level of the brainstem are not effective for the treatment of recurrent sinus headache. Tryptin-related pharmaceuticals (e.g. Imitrex-TM, Zomig-TM)) would be ineffective for the treatment of sinus headache and laser iridectomy for the treatment of narrow angle glaucoma would be ineffective for the treatment of migraine. Cluster headache needs to be distinguished from migraine. Hence, one skilled in the art of treatment of pain would require specific and professionally acceptable diagnosis in order to recommend reasonable therapy or to conduct clinical trials with potentially effective new therapies. The convention held in 1985 and subsequently published in Cephalgia (1988 Vol 8 (supplement 7), 1-96) has served as a benchmark for diagnosis and classification of human headaches (nosology) for the past 15 years.

In order for the physician to function and recommend therapeutic interaction with patients suffering from pain, classification with diagnostic criteria of an affliction must be determined. Classification of disease must be operationally specified with quantitative parameters and not just descriptive. The International Headache Society (I.H.S.) formed a committee in 1995 which lead to the first adopted international headache classification, which in turn permitted uniform operational criteria for diagnosis. The I.H.S. is internationally accepted and has been incorporated into the World Health Organization (W.H.O.) classification of disease. This classification has been translated into multiple languages and competes with no other classification system (see Jes Olesen Classification of Headache in Chapter 2, The Headaches, 2nd Edition, Lippincott, Williams and Wilkins ed Olesen, Hansen, Walsh, Philadelphia, 1999). An outline of the operational classification system is presented in Table 1.

In the classification system, headaches in category 1-4 are primary headache disorders with no associated anatomic pathologic process. Groups 5-11 are headaches and cervical pain associated with some other demonstrable disease process (trauma, vascular disease, increased intracranial pressure, withdrawal from substances, systemic infection, metabolic disorder, eye, ear, nose, and throat disease, or dental disease. Group 12 relates to cranial neuralgias.

The classification is quantitative, which allows for specific diagnosis. An excellent example of operation of the classification can be noted with the diagnosis of common migraine:

I.H.S. Classification 1.1 (Migraine without aura—common migraine)

Diagnostic criteria for migraine without aura:

A. At least 5 attacks fulfilling B-D.

B. Headache attacks lasting 4-72 hours.

C. Headache has at least two of the following characteristics:

1. Unilateral location.

2. Pulsating quality.

3. Moderate to severe intensity (inhibits or prohibits daily activities).

4. Aggravation by walking stairs or similar routine physical activity.

D. During headache, at least one of the following:

1. Nausea and /or vomiting.

2. Photobobia and/or phonophobia.

E. At least one of the following:

1. History and/or physical and/or neurological examinations do not suggest any one of the disorders listed in groups 5-11.

2. History and/or physical and/or neurological examinations do suggests any one of the disorders listed in groups 5-11, but it is ruled out by appropriate investigations.

3. Such a disorder (groups 5-11) is present, but migraine attacks do not occur for the first time in close temporal relationship to the disorder.

The I.H.S. classification of common migraine presented above is the method most reliably used for the diagnosis of migraine headaches and has been used in large multi-centered multinational double blinded drug trials used in the investigation of triptan based drugs for treatment of migraine (The Subcutaneous Sumatriptan International Study Group. Treatment of Migraine Attacks with Sumatriptan. N Engl J Med 1991:325: 316-321). In these studies, the I.H.S. was operatively used to distinguish migraine headaches from all other types of head and neck pain syndromes.

Sinusitis related headaches and pain is distinctly different than primary headaches, such as migraine and tension headaches, because of the demonstrable evidence of sinus disease. Because of the presence of associative pathology within the sinuses, sinus related head pains are examples of secondary headache syndromes, and receive unique classification under the I.H.S. and World Health Organization diagnostic systems. Under the I.H.S., diagnostic system, sinus headache is categorized as 11.5.1 (Acute sinus headache). The diagnostic operational criteria under this system is as follows:

A. Purulent or mucous discharge in the nasal passage, either by suction or spontaneous.

B. Pathologic findings in one or more of the following tests:

1. Radiologic exam.

2. CT/MRI.

3. Transillumination.

C. Simultaneous onset of headache and sinusitis.

D. Headache location:

1. In acute frontal sinusitis, headache directly over the sinus, or to the vertex, or behind the eye.

2. In acute maxillary sinusitis, headache is located over the antral area and may radiate to the upper teeth and forehead.

3. In ethmoidal sinusitis, the headache is located between and behind the eyes and radiates to the temporal area.

4. In acute sphenoiditis, headache is located in the occipital area, the vertex, the frontal region, or behind the eye.

E. Headache disappears after the treatment of acute sinusitis.

Chronic sinusitis under the I.H.S. criteria is considered to be multiple relapses of acute sinusitis. Additionally, the World Health Organization code and diagnosis for sinus related head and neck pain is G44.845 (Headache associated with disease of the respiratory system) JO1 (Acute sinusitis headache) and J32 (Chronic sinusitis).

Table 1: Outline of International Headache Society Classification of Headache Syndromes

1. **Migraine**
   - 1.1 Migraine without aura
   - 1.2 Migraine with aura
     - 1.2.1 Migraine with typical aura
     - 1.2.2 Migraine with prolonged aura
     - 1.2.3 Familial hemiplegic migraine
     - 1.2.4 Basilar migraine
     - 1.2.5 Migraine aura without headache
     - 1.2.6 Migraine with acute onset aura
   - 1.3 Ophthalmoplegic migraine
   - 1.4 Retinal migraine
   - 1.5 Childhood periodic syndromes that may be precursors to or associated with migraine
     - 1.5.1 Benign paroxysmal vertigo of childhood
     - 1.5.2 Alternating hemiplegia of childhood
   - 1.6 Complications of migraine
     - 1.6.1 Status migrainosus
     - 1.6.2 Migrainous infarction
   - 1.7 Migrainous disorder not fulfilling above criteria

2. **Tension-type headache**
   - 2.1 Episodic tension-type headache
     - 2.1.1 Episodic tension-type headache associated with disorder of pericranial muscles
     - 2.1.2 Episodic tension-type headache unassociated with disorder of pericranial muscles
   - 2.2 Chronic tension-type headache
     - 2.2.1 Chronic tension-type headache associated with disorder of pericranial muscles
     - 2.2.2 Chronic tension-type headache unassociated with disorder of pericranial muscles
   - 2.3 Headache of the tension-type not fulfilling above criteria

3. **Cluster headache and chronic paroxysmal hemicrania**
   - 3.1 Cluster headache
     - 3.1.1 Cluster headache periodicity undetermined
     - 3.1.2 Episodic cluster headache
     - 3.1.3 Chronic cluster headache
       - 3.1.3.1 Unremitting from onset
       - 3.1.3.2 Evolved from episodic
   - 3.2 Chronic paroxysmal hemicrania
   - 3.3 Cluster headache-like disorder not fulfilling above criteria

4. **Miscellaneous headaches unassociated with structural lesion**
   - 4.1 Idiopathic stabbing headache
   - 4.2 External compression headache
   - 4.3 Cold stimulus headache
     - 4.3.1 External application of a cold stimulus
     - 4.3.2 Ingestion of a cold stimulus
   - 4.4 Benign cough headache
   - 4.5 Benign exertional headache
   - 4.6 Headaches associated with sexual activity
     - 4.6.1 Dull type
     - 4.6.2 Explosive type
     - 4.6.3 Postural type

5. **Headache associated with head trauma**
   - 5.1 Acute posttraumatic headache
     - 5.1.1 With significant head trauma and/or confirmatory signs
     - 5.1.2 With minor head trauma and no confirmatory signs
   - 5.2 Chronic posttraumatic headache
     - 5.2.1 With significant head trauma and/or confirmatory signs
     - 5.2.2 With minor head trauma and no confirmatory signs

6. **Headache associated with vascular disorders**
   - 6.1 Acute ischemic cerebrovascular disease
     - 6.1.1 Transient ischemic attack (TIA)
     - 6.1.2 Thromboembolic stroke
   - 6.2 Intracranial hematoma
     - 6.2.1 Intracerebral hematoma
     - 6.2.2 Subdural hematoma
     - 6.2.3 Epidural hematoma
   - 6.3 Subarachnoid hemorrhage
   - 6.4 Unruptured vascular malformation
     - 6.4.1 Arteriovenous malformation
     - 6.4.2 Saccular aneurysm
   - 6.5 Arteritis
     - 6.5.1 Giant cell arteritis
     - 6.5.2 Other systemic arteritides
     - 6.5.3 Primary intracranial arteritis
   - 6.6 Carotid or vertebral artery pain
     - 6.6.1 Carotid or vertebral dissection
     - 6.6.2 Carotidynia (idiopathic)
     - 6.6.3 Post endarterectomy headache
   - 6.7 Venous thrombosis
   - 6.8 Arterial hypertension
     - 6.8.1 Acute pressor response to exogenous agent
     - 6.8.2 Pheochromocytoma
     - 6.8.3 Malignant (accelerated) hypertension
     - 6.8.4 Preeclampsia and eclampsia
   - 6.9 Headache associated with other vascular disorder

7. **Headache associated with nonvascular intracranial disorder**
   - 7.1 High cerebrospinal fluid pressure
     - 7.1.1 Benign intracranial hypertension
     - 7.1.2 High-pressure hydrocephalus
   - 7.2 Low cerebrospinal fluid pressure
     - 7.2.1 Postlumbar puncture headache
     - 7.2.2 Cerebrospinal fluid fistula headache
   - 7.3 Intracranial infection
   - 7.4 Intracranial sarcoidosis and other non-infectious inflammatory diseases
   - 7.5 Headache related to intrathecal injections
     - 7.5.1 Direct effect
     - 7.5.2 Due to chemical meningitis
   - 7.6 Intracranial neoplasm
   - 7.7 Headache associated with other intracranial disorder

8. **Headache associated with substances or their withdrawal**
   - 8.1 Headache induced by acute substance use or exposure
     - 8.1.1 Nitric oxide induced headache
     - 8.1.2 Monosodium glutamate induced headache
     - 8.1.3 Carbon monoxide induced headache
     - 8.1.4 Alcohol-induced headache
     - 8.1.5 Other substances
   - 8.2 Headache induced by chronic substance use or exposure
     - 8.2.1 Ergotamine induced headache
     - 8.2.2 Analgesics abuse headache
     - 8.2.3 Other substances

8.3 Headache from substance withdrawal (acute use)
8.3.1 Alcohol withdrawal headache (hangover)
8.3.2 Other substances
8.4 Headache from substance withdrawal (chronic use)
8.4.1 Ergotamine withdrawal headache
8.4.2 Caffeine withdrawal headache
8.4.3 Narcotics abstinence headache
8.4.4 Other substances
8.5 Headache associated with substances but with uncertain mechanism
8.5.1 Birth control pills or estrogens
8.5.2 Other substances

9. Headache associated with noncephalic infection
9.1 Viral infection
9.1.1 Focal noncephalic
9.1.2 Systemic
9.2 Bacterial infection
9.2.1 Focal noncephalic
9.2.2 Systemic (septicemia)
9.3 Headache related to other infection

10. Headache associated with metabolic disorder
10.1 Hypoxia
10.1.1 High-altitude headache
10.1.2 Hypoxic headache (low-pressure environment, pulmonary disease causing hypoxia)
10.1.3 Sleep apnea headache
10.2 Hypercapnia
10.3 Mixed hypoxia and hypercapnia
10.4 Hypoglycemia
10.5 Dialysis
10.6 Headache related to other metabolic abnormality

11. Headache or facial pain associated with disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures
11.1 Cranial bone
11.2 Neck
11.2.1 Cervical spine
11.2.2 Retropharyngeal tendinitis
11.3 Eyes
11.3.1 Acute glaucoma
11.3.2 Refractive errors
11.3.3 Heterophoria or heterotropia
11.4 Ears
11.5 Nose and sinuses
11.5.1 Acute sinus headache
11.5.2 Other diseases of nose or sinuses
11.6 Teeth, jaws and related structures
11.7 Temporomandibular joint disease (functional disorders are coded to group 2)

12. Cranial neuralgias, nerve trunk pain, and deafferentation pain
12.1 Persistent (in contrast to tic-like) pain of cranial nerve origin
12.1.1 Compression or distortion of cranial nerves and second or third cervical roots
12.1.2 Demyelination of cranial nerves
12.1.2.1 Optic neuritis (retrobulbar neuritis)
12.1.3 Infarction of cranial nerves
12.1.3.1 Diabetic neuritis
12.1.4 Inflammation of cranial nerves
12.1.4.1 Herpes zoster
12.1.4.2 Chronic postherpetic neuralgia
12.1.5 Tolosa-Hunt syndrome
12.1.6 Neck-tongue syndrome
12.1.7 Other causes of persistent pain of cranial nerve origin
12.2 Trigeminal neuralgia
12.2.1 Idiopathic trigeminal neuralgia
12.2.2 Symptomatic trigeminal neuralgia
12.2.2.1 Compression of trigeminal root or ganglion
12.2.2.2 Central lesions
12.3 Glossopharyngeal neuralgia
12.3.1 Idiopathic glossopharyngeal neuralgia
12.3.2 Symptomatic glossopharyngeal neuralgia
12.4 Nervus intermedius neuralgia
12.5 Superior laryngeal neuralgia
12.6 Occipital neuralgia
12.7 Central causes of head and facial pain other than tic douloureux
12.7.1 Anaesthesia dolorosa
12.7.2 Thalamic pain
12.8 Facial pain not fulfilling criteria in groups 11 and 12

13. Headache not classifiable

TABLE 3 Conversion table between the codes of the IHS Classification and ICD-10 [ICD-NA

D. Botulinum Toxin

Treatment of headache and facial pain associated with recurrent or chronic sinusitis according to the methods of the present invention may be practiced by administering botulinum toxin at a biologic activity dose ranging from 0.25-50,000 mouse LD_{50} units. Although one of ordinary skill evaluates dosing of the botulinum toxin based on several factors, including patient-specific factors, the proper dosing, depending on the composition and botulinum toxin immunotype, may be determined by using a regional denervation bioassay. Preferably, a composition comprising botulinum toxin is administered at multiple sites along any dermatome, corresponding and sharing sensory innervations with a paranasal sinus (see **Figures 1 and 2**) **Figure 1** shows the trigeminal dermatomes. Note that V1 corresponds to projected sensory areas of the frontal and ethmoid sinuses. V2 corresponds to the maxillary, sphenoid, and mastoid sinuses. V3 corresponds to the maxillary sinus. **Figure 2** shows the projection of the trigeminal nerve both to the sinuses and the cutaneous and soft tissue structures of the face. Note that the opthalmic division of the trigeminal nerve projects into the frontal and ethmoid sinuses. The

maxillary division and small portions of the mandibular division project into the maxillary sinuses. Sphenoid and mastoid sinuses also receive sensory innervation in part from the trigeminal nerve.

Administration of a composition comprising botulinum toxin by injection, according to the methods of the present invention, is accomplished without directly injecting the zygomatic minor and major muscles to avoid distortion of the lower face from the muscular effects of botulinum toxin.

The methods of the present invention may be practiced with any one or more botulinum toxin immunotypes. The present invention also contemplates the use of compositions comprising botulinum toxin and sequestration agents such as albumin which are disclosed in U.S. Patent Application Serial No.: 10/740,755, filed on December 22, 2003, which is incorporated herein by reference, in its entirety.

EXAMPLES

The following Example serves to further illustrate the present invention and is not to be construed as limiting its scope in any way.

Example 1

RR is a 43-year-old man who suffered from repeated bouts of sinusitis. Radiologic studies revealed sinusitis. Treatment with decongestant and corticosteroid-type anti-inflammatory medications did not produce a sustained beneficial effect. Decompressive surgery via Culdwell-Luc approach for decompression and sinus drainage failed to produce symptomatic relief. The headaches progressed to be incapacitating. The patient had no prior history of migraine or tension (muscle contraction) headaches. Pain was experienced within the mid-face radiating and involving the temporal regions. Botulinum toxin, injected over multiple points with a 30-gauge needle, produced substantial improvement and reduction in pain, allowing the patient to return to his daily activities.

Example 2

JC is a 36-year-old woman with a history of chronic headache and face pain associated with sinus surgery. Treatment with oral analgesics and decongestants failed to produce any beneficial effects. She underwent decompressive sinus surgery months before

the evaluation without pain relief. Conventional oral pain medications were ineffective. Multiple botulinum injections to the malar region and forehead at multiple sites produced over an 80% reduction in pain that was sustained for least three months. There was no past history of migraine, muscle contraction headaches, or trigeminal neuralgia. There was a history of recurrent allergies.

Example 3

JI is a 40-year-old with headache associated with recurrent sinusitis. MRI confirmed evidence of sinus mucosal edema and nasal exam showed excessive mucus and purulent secretions. The patient had no prior history of migraine or tension (muscle contraction) headaches. Conventional pain medications (decongestants, antibiotics, and anti-inflammatory nasal sprays) were not effective in relieving pain. Multiple injections of botulinum toxin were administered to soft tissues covering the maxillary, frontal and ethmoidal sinuses, resulting in at least a 50% reduction in pain.

Example 4

WR is a 38-year-old court clerk, referred for severe bifrontal headaches associated with maxillary sinusitis demonstrated on radiographic evaluations. External sinus surgery was performed without relief of the headaches. Most of the pain was localized to the left maxillary sinus region, which was tender to palpation. No past history of muscle contraction headache or migraine were identified.

Multiple injections of botulinum toxin over the sinus region, and away from the surgical incisions sites, relieved 80% of the pain. She has remained responsive for at least three years, using repeated injections of type A botulinum toxin.

Example 5

Fifteen patients with severe sinus-related headaches were evaluated in this open label trial. Each patient underwent either magnetic resonance imaging or computerized tomography of the sinus cavities that showed fluid levels, mucosal thickening, or mucous accumulation. All but one patient underwent generalized anesthesia and decompression via endoscopic osteotomies, or externally via Culdwell-Luc or frontal sinus approach. Many (>30%) underwent multiple surgical procedures to drain and decompress the sinus cavities.

The duration of disease ranged from 2-9 years with an average of 3.9 years. Age of the patients ranged from 29-90 years. 8 patients were female and 7 male. Total dose per botulinum toxin injection cycles ranged from 25 to 90 international units, with an average of 49 IU. Injections were made over the soft tissues of the involved sinuses in multiple locations as well as the corresponding dermatome (see **Figures 1 and 2**). In this group, only botulinum immunotype A was used. Follow-up visits were generally made at 3 and 12 weeks. Booster injections were given if no initial response on first injection cycle was achieved. Response to injections was determined on week 12.

Of 15 patients treated, 12 patients benefited from the therapy (80%). A beneficial response was considered to be a positive response to the question: " Have you experienced at least a 50% reduction in the severity or frequency of the pain." Complications were related mainly to weakness created by the botulinum toxin injections, which caused drooping of the mouth or asymmetric smile. No side effects were permanent. Duration of benefit was approximately 12 weeks for most patients, consistent with the known duration of benefit for botulinum toxin for other uses.

We claim:

1. A method of treating headache and facial pain associated with acute recurrent or chronic sinusitis in a subject in need thereof, comprising the step of administering a therapeutically effective amount of a composition comprising botulinum toxin to the nasal mucosa or to the subcutaneous structures overlying the sinuses, wherein the administration of the composition reduces the headache and facial pain associated with acute recurrent or chronic sinusitis.

2. The method of claim 1, wherein the sinuses are one or more of the sinuses selected from the group consisting of: ethmoid; maxillary; mastoid; frontal; and sphenoid.

3. The method of claim 1, wherein the subcutaneous structures overlying the sinuses lie within one or more of the areas selected from the group consisting of: forehead; malar; temporal; post auricular; and lip.

4. The method of claim 2, wherein the subcutaneous structures overlying the sinuses lie within one or more of the areas selected from the group consisting of: forehead; malar; temporal; post auricular; and lip.

5. The method of claim 1, wherein the botulinum toxin is any form of immunotypes A, B, C, D, E, F, or G.

6. The method of claim 2, wherein the botulinum toxin is any form of immunotypes A, B, C, D, E, F, or G.

7. The method of claim 3, wherein the botulinum toxin is any form of immunotypes A, B, C, D, E, F, or G.

8. The method of claim 4, wherein the botulinum toxin is any form of immunotypes A, B, C, D, E, F, or G.

9. The method of claim 1, wherein the composition is administered by injection.

10. The method of claim 2, wherein the composition is administered by injection.

11. The method of claim 3, wherein the composition is administered by injection.

12. The method of claim 4, wherein the composition is administered by injection.

13. The method of claim 9, wherein there are at least two injection sites.

14. The method of claim 10, wherein there are at least two injection sites.

15. The method of claim 11, wherein there are at least two injection sites.

16. The method of claim 12, wherein there are at least two injection sites.

17. The method of claim 1, wherein the composition is administered to the projections of the trigeminal nerve innervating the sinus.

18. The method of claim 2, wherein the composition is administered to the projections of the trigeminal nerve innervating the sinus.

19. The method of claim 3, wherein the composition is administered to the projections of the trigeminal nerve innervating the sinus.

20. The method of claim 4, wherein the composition is administered to the projections of the trigeminal nerve innervating the sinus.

21. The method of claim 9, wherein the composition is administered to the projections of the trigeminal nerve innervating the sinus.

22. The method of claim 10, wherein the composition is administered to the projections of the trigeminal nerve innervating the sinus.

23. The method of claim 11, wherein the composition is administered to the projections of the trigeminal nerve innervating the sinus.

24. The method of claim 12, wherein the composition is administered to the projections of the trigeminal nerve innervating the sinus.

25. The method of claim 13, wherein the composition is administered to the projections of the trigeminal nerve innervating the sinus.

26. The method of claim 14, wherein the composition is administered to the projections of the trigeminal nerve innervating the sinus.

27. The method of claim 15, wherein the composition is administered to the projections of the trigeminal nerve innervating the sinus.

28. The method of claim 16, wherein the composition is administered to the projections of the trigeminal nerve innervating the sinus.

29. The method of claim 1, wherein the composition is administered to the nasal mucosa.

30. The method of claim 1, wherein the composition is administered at a dose between 0.5 and 50,000 mouse LD_{50} units of botulinum toxin.

31. The method of claim 1, wherein, prior to onset of headache or facial pain, the subject exhibits symptoms or history of sinus hypersecretion and purulent nasal discharge.

32. Use of botulinum toxin for the preparation of a medicament for the treatment of headache and facial pain associated with acute recurrent or chronic sinusitis.

33. The use of claim 32, wherein the botulinum toxin is any form of immunotypes A, B, C, D, E, F, or G.

34. The use of claim 32, wherein the botulinum toxin is in the form of a composition comprising a sequestration agent in an amount between 550 and 550,000 μg sequestration agent per 100 LD_{50} units botulinum toxin.

35. The use of claim 34, wherein the sequestration agent is albumin.