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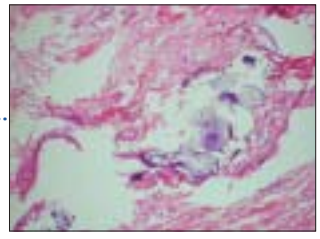

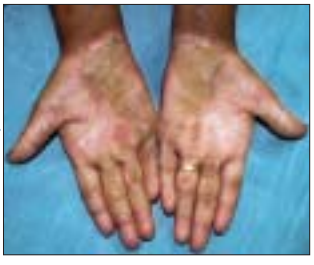

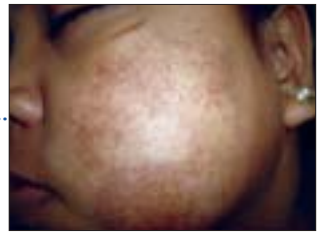

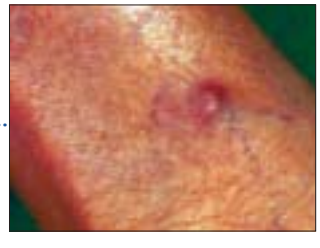

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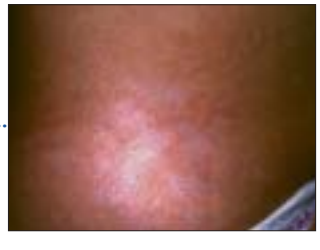

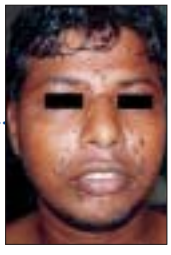

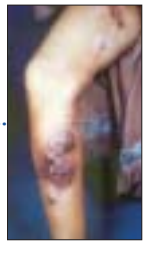

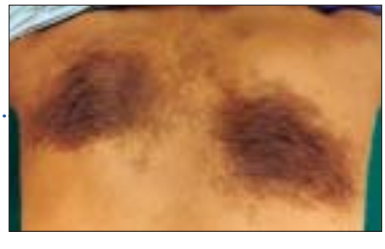

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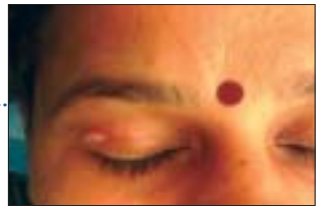

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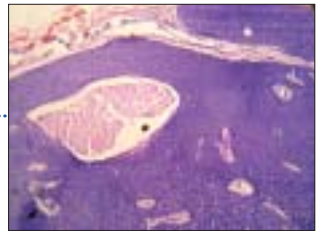

Botulinum toxin

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INTRODUCTION

Cosmetic dermatology is fast emerging as the preferred subspeciality of budding dermatologists. Its recent and sudden rise in popularity has much to do with the efficacy of botulinum toxin that has become a part of lay person's vocabulary.

HISTORY

The word "*Botulus*" in Latin means "sausage".[1] Botulism is a bilaterally symmetric descending neuroparalytic illness which derives its name from the ingestion of spoiled sausage in Napoleonic times.[1] Food-borne botulism and its clinical symptoms were first described by the German physician, Justinus Kerner during the period between 1817-1822.

In 1946, Schantz isolated botulinum toxin type A in its crystalline form[2] and in 1970, it was first used for strabismus and blepharospasm due to its property to paralyze muscles. In 1989, botulinum toxin got the Food and Drugs Administration's (FDA) approval and is now used worldwide for therapeutic and cosmetic purposes, the quantity of the toxin used varying according to the size of the muscle and the desired action.

Botulinum toxin (Botox®) is a neurotoxin produced by fermentation of the Hall Strain of *Clostridium Botulinum* type A, a Gram-negative, anaerobic bacterium.[1] The growth medium contains casein hydrolysate, glucose and yeast extract. Dialysis purifies the toxin complex (neurotoxin and several accessory proteins) from the culture solution. Serologically, there are eight distinct types designated as A, B, C1, C2, D, E, F and G.

PHARMACOKINETICS

Patients usually notice a clinical effect 1-5 days following injection and the peak effect is observed by 1-2 weeks. A 10-unit injection into the frontalis muscle produces a circular area of paresis with a radius of approximately 1.5 cm making the spacing of injection sites very important. Clinical effects are expected to last 2-6 months when the amount of Botox® used only serve to soften the movements of the muscles.

When the recommended dosage is used, Botulinum toxin Type A is not expected to be present in the peripheral blood at measurable levels following intramuscular (IM) or intradermal injection. The recommended quantities of neurotoxin administered at each session do not usually result in systemic effects or muscle weakness in patients unless they have neuromuscular dysfunction. However, subclinical systemic effects have been shown by single-fiber electromyography after appropriate IM doses of botulinum toxin to produce clinically observable local muscle weakness.[3]

Effects of botulinum toxin can get potentiated with the administration of aminoglycosides or other agents interfering with neuromuscular transmission, *i.e.*, curare-like compounds. Different botulinum toxin serotypes, *e.g.*, Myobloc/Neurobloc® (2500/5000 unit vials) or Dysport® (500 units per vial) are not interchangeable as their simple dose ratios are inappropriate. They should not be administered at the same time or in the same person as

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excessive neuromuscular weakness may result from their administration.[3] It is advised not to freeze Botox® once reconstituted as ice crystals may form which damage the toxin and reduce the potency.

MECHANISM OF ACTION

Neurotransmission at the neuromuscular junction occurs once acetylcholine is released from the presynaptic nerve terminals. The botulinum toxin (BT) blocks acetylcholine release and causes chemical denervation.[4] Initially, binding of the toxin to specific receptors on the surface of the presynaptic nerve cell surface occurs in approximately 30 minutes. Then, due to endocytosis, the plasma membrane of the nerve cell invaginates around the toxin-receptor complex, forming a toxin-containing vesicle inside the nerve terminal. The disulfide bond is then cleaved within the toxin-containing vesicle and the 50-kDa light chain of the toxin molecule is released across the endosomal membrane of the endocytic vesicle into the cytoplasm of the nerve terminal. Finally, the 50-kDa light chain (of serotypes A and E) cleaves a cytoplasmic protein (SNAP-25) required for the docking of acetylcholine vesicles on the inner side of the nerve terminal plasma membrane. This blocks acetylcholine release into the neuromuscular junction resulting in paralysis of that muscle. The clinical effects of botulinum toxin injections last for 2-6 months after which, the inactivated terminals slowly recover function in an average period of four months. Then, the new nerve terminal sprouts and their end plates regress. Recovery of inactivated terminals appears to be the basis of the loss of clinical effects several months after the injection.

INDICATIONS AND USES

For cosmetic purposes, BT is commonly used on the upper half of the face to target horizontal forehead lines, glabellar frown lines and lateral canthal lines (Crow's Feet). It is also used for temporal brow lift, bunny lines (Levator labia superioris) and nasal flare.[3]

An adjunctive use of BT is to provide presurgical chemodenervation of the brow depressor muscles giving better results with surgical repositioning of the brow. Other uses of BT[3,5] include achalasia, blepharospasm, cervical dystonia, detrusor hyperreflexia, essential tremor, hemifacial spasm, hyperhidrosis, migraine and headache, myofascial pain syndrome, occupational dystonia, pain due to muscle spasm, rectal fissure, sialorrhea, spasmodic dysphonia, strabismus, spasticity and thoracic outlet syndrome.

Advanced uses of BT include mental crease, popply chin, platysmal bands, horizontal neck lines, hypertrophic mandibular angles and facial asymmetry.

CONTRAINDICATIONS

These include prior allergic reaction, injection into areas of infection or inflammation, pregnancy (Category C drug: safety for use during pregnancy has not been established) or lactation. Women who inadvertently were injected during pregnancy, this far have had uneventful deliveries and to date, no teratogenicity has been attributed to botulinum toxin. Relative contraindications include disorders of the neuromuscular junction, myasthenia gravis, Eaton Lambert syndrome,[6] and disorders with muscle weakness like multiple sclerosis, amyotrophic lateral sclerosis.

DOSAGES AND ADMINISTRATION

Depending upon the size of the muscle and action required, the amount of BT used varies in cosmetic use or other purposes. The small muscles of the face require 3-10 units depending on the bulk of the muscle. Usually < 100 units are used for cosmetic indications and 300-600 units for other indications. The human lethal dose for Botox® type A purified neurotoxin complex is estimated to be approximately 3000 units.[4]

The vial is to be stored in a freezer $\leq -5^{o}C$. Once reconstituted, it is to be refrigerated at 2-8^{o}C. After reconstitution, Botox® can be used for a month if kept refrigerated. The diluent, a sterile saline solution, is injected gently into the vial to avoid agitation or foaming as the toxin can get easily denatured. One hundred units are commonly diluted in 2-4 ml of diluent. Theoretically, more concentrated solutions reduce reliability in delivering a specific unit dose and more dilute solutions lead to greater diffusion of the toxin. Preferably, a 30-gauge needle is used for injection purposes.

ADVERSE EFFECTS

1) Lid ptosis which usually resolves in 1-6 weeks may occur if BT is injected too medially, within a centimeter from the lateral orbital rim margin.[6] When this occurs, apraclonidine 0.5% eyedrops (Albalon®) administered every three hours will temporarily resolve symptoms and phenylephrine 2.5% eye drops can be used if apraclonidine is not available.
2) Brow ptosis may occur if the injection is close to or

within a centimeter of the eyebrow. Consideration of infrabrow injection at the arch to raise the brow has been suggested.

3) A local temporary swelling like upper eyelid edema sometimes occurs in Asian patients.[6]
4) Bruising: This can be avoided by advising patients to avoid aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), *gingko biloba* and vitamin E starting ten days prior to BT treatment.
5) Headaches
6) Diplopia - rare
7) Excessive brow elevation or "quizzical" brows,[5] which can be corrected with 2-4 units of Botox® injected into the frontalis, two centimeters above the lateral brow.

Chemodenervation with botulinum toxin has become an integral part of the facial plastic armamentarium.[5,6] Traditional treatment for deformities on face by surgical intervention is slowly being replaced by BT wherever possible. With a complete understanding of facial anatomy and muscular interactions, and pharmacokinetics of botulinum toxin, the dermatologist or plastic surgeon can produce magnificent results with botulinum toxin.

REFERENCES

1. Erbguth FJ, Naumann M. Historical aspects of botulinum toxin: Justinus Kerner (1786-1862) and the "sausage poison". Neurology 1999;53:1850-3.
2. Schantz EJ, Johnson EA. Preparation and characterization of botulinum toxin type A for human treatment. In: Jankovik J, Hallet M, editors. Therapy with Botulinum Toxin. Vol 109. New York: Marcel Dekker; 1994. p. 10-24.
3. Benedetto AV. The cosmetic uses of Botulinum toxin type A. Int J Dermatol 1999;38:641-55.
4. Garcia A, Fulton JE Jr. Cosmetic denervation of the muscles of facial expression with botulinum toxin: A dose-response study. Dermatol Surg 1996;22:39-43.
5. Niamtu J 3rd. Aesthetic uses of botulinum toxin A. J Oral Maxillofac Surg 1999;57:1228-33.
6. Balikian RV, Zimbler MS. Primary and adjunctive uses of botulinum toxin type A in the periorbital region. Facial Plast Surg Clin North Am 2005;13:583-90.