ELSEVIER

Journal of the Neurological Sciences 235 (2005) 1 – 9

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Review

Expanding use of botulinum toxin

Roongroj Bhidayasiri [a,b,c], Daniel D. Truong [c,*]

[a]Department of Neurology, UCLA Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA
[b]Movement Disorders Group, Division of Neurology, Chulalongkorn University Hospital, Bangkok, Thailand
[c]The Parkinson's and Movement Disorder Institute, 9940 Talbert Ave, Fountain Valley, CA 92708, USA

Received 26 July 2004; received in revised form 14 April 2005; accepted 18 April 2005
Available online 28 June 2005

Abstract

Botulinum toxin type A (BTX-A) is best known to neurologists as a treatment for neuromuscular conditions such as dystonias and spasticity and has recently been publicized for the management of facial wrinkles. The property that makes botulinum toxin type A useful for these various conditions is the inhibition of acetylcholine release at the neuromuscular junction. Although botulinum toxin types A and B (BTX-A and BTX-B) continue to find new uses in neuromuscular conditions involving the somatic nervous system, it has also been recognized that the effects of these medications are not confined to cholinergic neurons at the neuromuscular junction. Acceptors for BTX-A and BTX-B are also found on autonomic nerve terminals, where they inhibit acetylcholine release at glands and smooth muscle. This observation led to trials of botulinum neurotoxins in various conditions involving autonomic innervation. The article reviews the emerging use of botulinum neurotoxins in these and selected other conditions, including sialorrhea, primary focal hyperhidrosis, pathological pain and primary headache disorders that may be of interest to neurologists and related specialists.

Keywords: Botulinum toxin; Sialorrhea; Drooling; Hyperhidrosis; Pathological pain; Headache

Contents

1. Introduction

Botulinum toxin type A (BTX-A) is best known to neurologists as a treatment for neuromuscular conditions such as dystonias and spasticity and has recently been publicized for the management of facial wrinkles. The property that makes botulinum toxin type A useful for these various conditions is the inhibition of acetylcholine release at the neuromuscular junction [1]. The efficacy of BTX-A without systemic side effects has led to the rapid development of its application in various conditions in addition to

* Corresponding author. Tel.: +1 714 378 5062; fax: +1 714 378 5061.
E-mail address: dtruong@pmdi.org (D.D. Truong).

0022-510X/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.jns.2005.04.017

dystonia and spasticity, including hypersecretory disorders, tics, tremor, stuttering, different pain syndromes, detrusor sphincter dyssynergia or overactivity and gastrointestinal smooth muscle/sphincter spasms [2–5]. Following local injection into muscles, the toxin enters the nerve terminal via endocytosis, interacts with intracellular proteins (SNARE proteins) and inhibits the vesicular release of the acetylcholine (Ach) neurotransmitter at the neuromuscular junction [1,6]. Inhibition of Ach produces chemical denervation and paralysis of the striated muscles. Paralysis usually peaks 2 weeks after the injection. Because of the molecular turnover within the neuromuscular junction and neuronal sprouting, neuronal activity begins to return at 3 months, with restoration of complete function at approximately 6 months [7].

Table 1
Current evidence of botulinum toxin in various disorders with the least reasonable trial of evidence shown to be at least moderately effective by BTX-A

(1) Focal dystonias
Blepharospasm[a]
Cervical dystonia[a]
Spasmodic dysphonia
Meige syndrome
Writer's cramp
Foot dystonia
Oromandibular dystonia
Axial dystonia
Occupational cramps
(2) Tremor
Dystonia head tremor
Essential head tremor
Essential hand tremor
Palatal tremor
(3) Hemifacial spasm[a]
(4) Focal spasticity in adults
Lower limb
Upper limb
(5) Focal spasticity in children
Upper limb
Lower limb
(6) Ophthalmic conditions
Strabismus[a]
Ptosis
(7) Autonomic disorders
Focal hyperhidrosis
Gustatory sweating
Hyperlacrimation
Sialorrhea
(8) Urological disorders
Detrusor sphincter dyssynergia
Hyperreflexive bladder
Vaginismus
(9) Gastrointestinal disorders
Anal fissure
Achalasia
Upper esophageal sphincter
Anismus
(10) Pain
Tension-type headache
Migraine
Low back pain
Chronic daily headache
Myofascial pain
(11) Wrinkles (Glabellar wrinkles[a])

[a] Indicates conditions that have been approved by the United States Food and Drug Administration; modified from Moore [105].

BTX-A is 1 of 7 botulinum neurotoxin serotypes known alphabetically as types A to G [8]. Although these toxins have different intracellular targets, their biological activity at the neuromuscular junction is similar. Of these serotypes, only A and B are currently available as commercial preparations [9]. Types C and F have also been used in humans, but only on an experimental basis [10,11]. The first commercial preparation of botulinum neurotoxin to be used clinically was based on the A serotype (Botox®), and this product continues to be used in many countries throughout the world. Another preparation based on the A serotype (Dysport®) was later introduced in several countries and may become available in the United States within several years. In the year 2000, a product based on the B serotype (Myobloc®/Neurobloc®) became commercially available. Although all of these formulations inhibit acetylcholine release, they do so at different doses [7,9,12]. Thus, all of these products are used clinically at different unit doses that may vary up to several orders of magnitude [9].

Although botulinum toxin types A and B (BTX-A and BTX-B) continue to find new uses in neuromuscular conditions involving the somatic nervous system, it has also been recognized that the effects of these medications are not confined to cholinergic neurons at the neuromuscular junction [13,14]. Acceptors for BTX-A and BTX-B are also found on autonomic nerve terminals, where they inhibit acetylcholine release at glands and smooth muscle [15]. This observation led to trials of botulinum neurotoxins in various conditions involving autonomic innervation [16–18]. The rest of this article considers the emerging use of botulinum neurotoxins in these and selected other conditions that may be of interest to neurologists and related specialists (Table 1).

2. Sialorrhea

Excessive drooling, which occurs in many different neurological conditions, may pose significant risks of choking with aspirations and pneumonia and may affect patients' social activities and self-image. Up to 20% of patients with bulbar amyotrophic lateral sclerosis (ALS) and 78% of patients with Parkinson's disease (PD) manifest this problem [19]. It is usually caused by swallowing dysfunction, although primary sialorrhea rarely occurs. The mechanism of action by which botulinum toxins reduce saliva production may relate to the inhibition of cholinergic autonomic parasympathetic and postganglionic sympathetic acetylcholine release, which innervates the salivary glands. Over the past few years, BTX-A has been studied for the treatment of sialorrhea associated with parkinsonism, cerebral palsy, head and neck carcinoma, neurodegenerative