UDK 615.918:616.857
Review
Received: 14. 01. 2009.
Accepted: 16. 09. 2009.

ANTINOCICEPTIVE EFFECTS OF BOTULINUM TOXIN TYPE-A IN PAIN AND HEADACHES TREATMENT

Maja Relja

Department of neurology, Medical school University of Zagreb, Zagreb, Croatia

Summary

Since its development for clinical use in 1980s botulinum toxin, the most potent biological toxin known to man has become a useful drug in various field of medicine. It was initially used to treat neurological disorders characterized by excessive muscle contractions. Since many patients report alleviation of pain before the muscle relaxing effect of botulinum toxin type-A has started, a direct analgesic action of Botulinum toxin has been discussed. There have been a number of recent investigations concerning the efficacy of botulinum toxin type-A applications for treatment of headache and chronic pain. Most of the known effect of botulinum toxin has been attributed to its ability to inhibit the release of acetylcholine from cholinergic nerve terminal. However, this effect alone does not explain the apparent antinociceptive effect of botulinum toxin. Other peripheral and central neurogenic effect should be considered. Current data suggest that Botulinum toxin is safe and effective in headache and pain treatment if used in specialist centres by experienced doctors.

Key words: botulinum toxin; dystonia; pain; tension type headache; migraine.

INTRODUCTION

Botulinum toxin type-A (BTX-A), the most potent of poisons, is one of seven distinct serotypes (A to G) of neurotoxin produced by the anaerobic bacterium *Clostridium Botulinum*. When injected into muscles, BTX-A binds to the presynaptic nerve terminal, becomes internalized, and blocks the release of the neurotransmitter acetylcholine (ACh) by cleaving the synaptosomal-associated protein (SNAP-25) [1]. This action causes chemical denervation at neuromuscular junction, thereby inhibiting muscle contractions and producing muscle relaxation or weakness [2]. It has been used since the mid 1980s to treat patients

Corresponding author: Maja Relja
e-mail: mrelja@mef. hr

suffering from uncontrolled muscle activity and/or increased muscle tone. First, local injections of BTX-A were successfully used in the management of dystonia – an extrapyramidal condition involving uncontrolled muscle over-activity. Second, BTX-A was used in the treatment of limb spasticity and more particularly in juvenile cerebral palsy. The weakening effect is not seen for approximately 10 days and the effects are temporary because the presynaptic terminal sprouts new accessory terminals and the main terminal recovers its ability to release ACh. But the number of therapeutic uses of botulinum toxin has grown considerably over the past decade. Nowadays BTX-A is also used to treat disorders of the smooth muscle systems, such as anal fissure, or disorders like hyperhidrosis and other secretory disorders. All this clinical application of BTX-A can be clearly associated with temporary chemodenervation of peripheral somatic or vegetative cholinergic nerves.

CLINICAL EXPERIENCE OF BTX-A ANTINOCICEPTIVE ACTION

There has been increasing clinical evidence that BTX-A might also have analgesic properties. It has been generally recognized the marked analgesic effect of BTX-A when used in the treatment of pain associated with dystonia and spasticity.[1] The clinical observation confirmed that the pain relief experienced may be considerably more marked than the degree of motor benefit obtained and may lasted beyond the period of muscle relaxation. Several studies suggest that a direct antinociceptive affect distinct from reduction in muscle spasm may be involved. We performed the first study investigating the effect of tree different doses of BTX-A on pain in cervical dystonia. The major benefit of BTX-A treatment of pain reduction compared to dystonia improvement was the duration of action and the lower effective doses. In addition, pain relief occurs before muscle relaxation can be observed. Our results suggest that a direct antinociceptive affect distinct from reduction in muscle over activity and spasm may be involved [3]. Moreover, BTX-A also seems to have analgesic properties in primary pain syndromes such as chronic tension type headache, migraine, neuropatic pain, certain types of myofascial pain and low back pain without obvious correlation to muscular hyper contractility. Therefore, clinical observations suggest an antinociceptive action independent of its neuromuscular junction-blocking effect.

HEADACHE

Headache is one of the most common neurological symptoms in clinical practice. The primary headache disorders consist of tension-type headache, migraine, and cluster headache. Tension-type headache (TTH) and migraine are

extremely common cause of chronic pain in clinical practice. The lifetime prevalence of headache approaches 99% in women and 93% in men [4].

The current therapeutic approaches to tension-type headache and migraine consist of acute and/or prophylactic therapy that offer relief for many patients but are often unsatisfactory for many others. Therefore, headache patients still represent a group of patients with unmet treatment needs.

TENSION TYPE HEADACHE

Tension-type headache is the most common primary headache type that is not associated with a serious underlying disease. Duration of attacks can vary from a few hours to several days and the intensity of pain is usually less severe than in the migraine, with no accompanying symptoms. TTH is classically described as aching, tenderness and band-like pain surrounding the head. The episodical variant prevailing in more than one third of the population, while chronic TTH, when attacks occur more frequently than 15 days per month, is found in about 3%. TTH is classically described as aching, tenderness and band-like pain surrounding the head. Current therapies are still unsatisfactory because pathophysiology is not well understood. Muscular causes accounting for the TTH are still the most commonly debated. Since the involvement of pricranial muscles over-activity may contribute to TTH, we were the first who investigated the effectiveness of BTX-A therapy in chronic TTH [5-7]. In addition to short-term studies we performed the first prospective long-term study of 15 months duration where BTX-A injections were found to be an effective and safe prophylactic treatment for TTH patients for whom standard therapy has failed [8].

Chronic TTH should not be treated for long time by analgesics because of the risk of overuse. According to our investigations and published results, BTX-A treatment should be considered when the patients have verified chronic TTH, and after the preventive drug treatment has failed [7].

MIGRAINE

Migraine is characterised by unilateral, pulsating pain, aggravation by routine physical activity, and association with nausea, photophobia and phonophobia. With a lifetime prevalence of approximately 13% to 18% in women and 8% to 14%i in men, migraine is the second most frequently occuring form of headache after TTH [4]. Contrary to TTH, the effect of migraine on quality of life is significant. All migraine patients experienced functional impairment and more than half required bedrest with significant loss of working days.

Although the eraliest modern theory on the pathophysiology of migraine was the 'vascular' theory current opinion show that sensory stimuly can lead to a permanent sensory overflow of the central nervous system with the result in hyperactivity of the sensory brain stem nuclei. BTX-A can interfere at various point, but it is clear that antinociceptive effects of BTX-A in migraine could not be explained by 'clasic' anticholinergic denervation.

The first evidence for the efficacy of BTX-A in migraine was reported as surprising side effect in patients primary treated for hypefunctional facial lines by otorinolaringoligist Wiliam Binder [1]. Until recently the efficacy of BTX-A in preventing migraine attacks remains controversial. Contrary to the first multicener double-blind, placebo-controled study with 954 patients screened and 495 randomized, second big multicenter study with 705 patients randomized confirms that BTX-A is effective for the prophylaxis of patients with chronic migraine [19,10]. Investigating the clasic migraine symptoms that would differentiate responders from non-responders to prophylactic BTX-A tretament in episodic migraine we have shown for the first time that patients with cutaneous allodynia are highly associated with significnat prevention of migraine attacks using BTX-A treatment [11]. Comparative study with standard migraine therapy is still needed.

NEUROPATIC PAIN

Neuropathic pain is associated with injury to the peripheral and/or central nervous system. Conditions such as post herpetic neuralgia, spinal cord injury and diabetic neuropathy are examples of neuropathic pain [12]. Contrary to headaches and pain associated with increased muscle tone there were only a limited number of case reports suggesting that BTX-might be useful in pain which is not associated with a muscle spasm. Our experimental data showed effectiveness of BTX-A in experimental neuropathic pain in classical model of surgical neuropathy as well as in diabetic neuropathy [13]. Knowing these results we performed the first clinical study in diabetic neuropathy patients. In a prospective double-blind study we showed for the first time the efficacy and safety of BTX-A for the treatment of painful diabetic neuropathy [14]. More results today indicate clear benefit of BTX-A therapy for the treatment of neuropathic pain disorders. There is need for more studies in nociceptive and neuropathic disorders to better define BTX-A role as analgesics.

CONCLUSION

BTX-A is known to alleviate pain when it is used to treat certain diseases associated with muscle over activity. But the mechanism for pain relief is not completely understood. Clinical observations suggest an antinociceptive action of BTX-A independent of its neuromuscular junction-blocking effects. Thus mechanism of action, its duration, doses and application points are still awaiting carefully designed preclinical and clinical experiments. Thus, the current use of BTX-A headache and chronic pain disorders is only justified after all standard therapeutic procedures have been exhausted and only following evaluation in specialist centres. Its use requires extensive experience and practice in its application with precise functional-anatomical knowledge.

Acknowledgments

We acknowledge the support of the Croatian Ministry of Science, Education and Sport and Deutscher Akademischer Ausrausch Dienst (DAAD).

References

[1] *Brin MF, Hallet M, Jankovic J* (Eds): Scientific and Therapeutic Aspects of Botulinum Toxin. Lippincott Williams & Wilkins, Philadelphia 2002

[2] *Meunier FA, Schiavo G, Molgo J.* Botulinum Neurotoxins: from paralysis to recovery of functional neuromuscular transmission. *J Physiol (Paris)* 2002;96:105-113

[3] *Relja M, Klepac N.* Different doses of botulinum toxin A and pain responsiveness in cervical dystonia. *Neurology,* 2002;58:A474

[4] *Rasmussen BK, Jensen R, Schroll M,* et al. Epidemiology of headache in a general population: a prevalence study. *J Clin Epidemiol* 1991;44:1147-57

[5] *Relja M.* Treatment of tension-type headache bylocal injections of botulinum toxin.*Eur J Neurol* 1997; 4(2):S71-S72

[6] *Relja M, Telarović S.* Botulinum toxin in tension-type headache. *Eur J Neurol* 2004;251(1):12-14

[7] *Jost WH, Heinen F, Marziniak M, Relja M, Schulte-Mattler W, Schmidt U, Volmer-Hasse J.* Botulinum toxin in tension-type headache. *Eur J Neurol* 2004;251(1):33-35

[8] *Relja M, Klepac N.* Botulinum toxin type-A as prophylactic treatment of chronic TTH: Long-term follow-up study. *Neurology* 2001;56(Suppl 3):A349-50

[9] *Relja M, Poole AC, Schoenen J, Pascual J, Lei X, Thompson C* for the BoNTA Headache Study Group. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of btulinum toxin type A

(BoNTA) for prophylaxis of episodic migraine headahes. *Cephalgia* 2007;27:492-503

[10] *Dodic DW, Smith TR, Becker WJ, Gendolla A, Relja M, Martin V, Reyes C, Lei X, Turkel CC.* Botulinum neurotoxin type-A for the treatment of chronic migraine: PREMPT 2 trial double-blind phase. *IHC 2009* (in press)

[11] *Relja M, Miletić V.* Cutaneous Allodinia in migraine patients as predictive factor for effectiveness of Botulinum toxin treatment. *Neurology*. 2007; 68: A195-196

[12] *Argoff CE.* A focused review on the use of botulinum toxin for neuropathic pain. *The Clin J of Pain*. 2002;18:S177-181

[13] *Bach-Rojecky L, Relja M, Lacković Z.* Botulinum toxin type-A in experimental neuropathic pain. *J Neural Transm* 2005;112:215-219

[14] *Relja M, Miletić V.* Botulinum toxin type-A in the treatment of painful diabetic nuropathy: A prospactive study. *Neurology* 2006;66:A70

Sažetak

Antinociceptivni učinak botulinum toksina tip-A u terapiji boli i glavobolje

Nakon razvoja botulinum toksina za kliničku primjenu 80-tih godina, ovaj za čovjeka najpotentniji biološki otrov našao je primjenu u raznim granama medicine. Prva upotreba botulinum toksina bila je u neurološkim poremećajima karakteriziranim mišićnim spazmom i nekontroliranim kontrakcijama poput distonije. Zapaženi učinak na smanjenje boli prije pojave mišićne relaksacije ukazao je na direktni analgetski učinak botulinum toksina na patogenezu boli. Javljaju se zatim brojna klinička zapažanja o učinkovitosti botulinum toksina u liječenju glavobolje i kroničnе boli. Većina poznatih učinaka botulinum toksina na relaksaciju mišića pripisuje se učinku na otpuštanje acetilkolina na neuromuskularnoj sinapsi. Kako se ovim djelovanjem ne može objasniti njegov antinociceptivni učinak brojni periferni i centralni mehanizmi djelovanja botulinum toksina se istražuju. Sadašnji rezultati kliničke primjene ukazuju da je botulinum toksin siguran i djelotvoran lijek u liječenju glavobolje i nekih oblika kronične boli otpornih na standardne oblike liječenja, ukoliko se primjenjuje u specijaliziranom centru od strane iskusnih liječnika.

Ključne riječi: botulinum toksin; distonija; bol; tenzijska glavobolja; migrena.