หลุมพรางที่พบบ่อยในการรักษาด้วยท็อกซินโบทูลินั่ม (common pitfalls in the therapeutic use of botulinum toxin)

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Abstract

Botulinum toxin type A (BoNT/A) has emerged as a valuable drug for various medical conditions. This perspective article explores the mechanism of action of BoNT/A and highlights key considerations for its therapeutic use. The inhibition of acetylcholine release at the neuromuscular junction is the primary mechanism underlying BoNT/A's therapeutic effects. When using BoNT/A, physicians must address essential questions regarding dosing, injection techniques, patient selection, timing and frequency of injections, co-interventions, and choice of outcome measures. Understanding the different formulations of BoNT/A is also crucial. Optimization of BoNT/A treatment also requires a comprehensive assessment and treatment plan, considering individual patient factors. Proper education and communication with patients, along with regular follow-up, are important for managing expectations and achieving optimal outcomes. By understanding the mechanism of action and carefully considering key factors, physicians can enhance the therapeutic efficacy of BoNT/A, avoid pitfalls, and improve patient function and satisfaction.

Keywords: Botulinum toxin type A (BoNT/A), dosing, injection techniques, pitfall

Introduction

Botulinum toxin type A (BoNT/A) has been extensively studied and utilized in various medical conditions. While there are specific considerations for each disorder, there are several overarching principles that apply to the therapeutic use of BoNT/A. This article aims to explore the mechanism of action of BoNT/A and highlight important questions that should be addressed when using it in different clinical settings. Rather than discussion into the detailed evidence for each condition, this perspective article focuses on practical use, common pitfalls, and controversies of significance.

Optimization of BoNT/A injections

BoNT/A reduces muscle activity by inhibiting the release of synaptic vesicles containing acetylcholine at the neuromuscular junction. This mechanism underpins BoNT/A 's therapeutic effects in a variety of disorders[1-3]. When considering the therapeutic use of BoNT/A, several essential questions arise. Firstly, the appropriate dosing and injection techniques must be determined. The dosage depends on the target muscles, muscles' size, goals of treatment including functional outcomes, and the desired effect. Secondly, the selection of patients who will benefit from BoNT/A treatment requires careful consideration. Factors such as the severity and duration of the condition, functional limitations, and potential contraindications need to be taken into account. For example, BoNT/A is not helpful if spastic patients develop severe contracture. Another critical aspect is the timing and frequency of botulinum toxin injections. Determining the appropriate intervals between treatments is crucial to maintaining the desired therapeutic effect, while minimizing the risk of developing resistance or adverse events. Factors such as the onset and duration of action of BoNT/A in specific conditions should be considered when establishing the treatment schedule. The choice of outcome measures and assessment methods is another important consideration when using BoNT/A therapeutically. These may include temporary muscle weakness, injection site reactions, or systemic effects. Objective measures, such as muscle strength assessments, gait analysis or hand functions, can provide valuable data to evaluate treatment efficacy. Patient-reported outcomes, such as quality of life assessments or pain scales, can provide additional insights into the patient's perspective.

BoNT/A has a fascinating history and has become an important drugs. It was first mentioned in the late 18th century in connection with fatal outbreaks caused by contaminated sausages, but it wasn't used therapeutically until 1977, when it was used to treat

strabismus. Since its initial FDA approval in 1989, BoNT/A has seen an increase in research and development of various formulations for various indications[1-5]. BoNT/A is produced by certain bacteria and is made up of two linked peptide chains. BoNT/A works by disrupting cholinergic synapses, which are involved in the transmission of nerve signals mediated by the neurotransmitter acetylcholine. It consists of a heavy and a light chain joined together by a disulfide bond. The process of BoNT/A action begins when it is recognized by a presynaptic receptor, which leads to its internalization into endosomes. The heavy chain of the BoNT/A helps facilitate the translocation of the toxic light chain into the cytosol of the neuron. Once inside the cytosol, the light chain interferes with the exocytosis of synaptic vesicles containing acetylcholine, preventing its release into the synaptic cleft. There are seven different serotypes of botulinum toxin (A to G), each with unique amino acid sequence variations and toxo-pharmacological properties, and a slightly different site of action within the presynaptic terminal. These serotypes have specific targets within the exocytotic mechanism of the neuron, resulting in impaired presynaptic transmission and degeneration of the distal nerve tip. The nerve terminal responds to the toxin's effects by forming axonal sprouts in an attempt to reinnervate the denervated muscle or gland. Over time, these sprouts recede, and the original terminal recovers. Its effects, however, extend beyond the neuromuscular junction and can have an impact on neurotransmission in both the peripheral and central nervous systems.There are FDA-approved BoNT/A formulations currently available: ona BoNT/A (Botox), aboBoNT (Dysport), incoBoNT (Xeomin), and rimaBoNT (Myobloc/Neurobloc). The manufacturing processes, pharmaceutical preparations, units of injection, and molecular characteristics of these formulations differ. Some formulations, such as Dysport, have a longer duration of action but may have more adverse effects outside the target site due to higher neurotoxin quantities[3].

While BoNT/A formulations are not identical or equivalent, head-to-head comparisons have been conducted. IncoBoNT/A (Xeomin) distinguishes itself by not requiring refrigeration and containing negligible amounts of albumin, which reduces the theoretical risk of antibody production against the toxin. Botox and Xeomin are also reasonably stable after reconstitution, making them suitable for sharing among patients and lowering costs. In addition to the FDA-approved formulations, other BoNT/A products are widely used in China and Korea. Hengli, Lanzhou, and Nabota are among them. Each of these formulations has unique properties and indications. Understanding the differences between BoNT/A formulations is critical to make product selection decisions. The therapeutic and non-therapeutic effects of

BoNT can be influenced by factors such as formulation-specific toxo-pharmacological properties, injection volume, toxin concentration, and dose. Efforts have also been made to reduce the amount of human serum albumin in formulations in order to potentially reduce the incidence of neutralizing host antibodies and improve efficacy[1, 4, 5].

Although the reduction in abnormal muscle contraction is the primary mechanism of action, additional effects of BoNT/A have been observed. It causes denervation of intrafusal muscle fibers innervated by gamma motor neurons, leading to relaxation of the muscle spindle and reduced afferent tone. BoNT/A may also have effects within the spinal cord and brain, affecting Renshaw cell activity and normalizing abnormal cortical sensory representation and excitability in certain conditions[1-5]. Apart from its effects at the neuromuscular junction, BoNT/A has clinical applications in the treatment of disorders characterized by excessive cholinergic autonomic activity, such as hyperhidrosis (excessive sweating) and hypersialorrhea (excessive salivation)[1-5]. Additionally, BoNT/A has been explored for the treatment of chronic pain disorders, although the mechanisms involved in pain relief are not fully understood. It may reduce neuropeptide release at the peripheral level and inhibit substance P secretion, leading to secondary central effects relevant for pain control[1-5].

A comprehensive assessment and treatment plan are vital for successful BoNT/A treatment. It is essential to thoroughly evaluate the patient's medical history, current medications, allergies, and previous experiences with BoNT/A. Proper assessment involves understanding the patient's goals and expectations as well as identifying any contraindications or potential risk factors. A detailed examination of the muscles involved, their function, and the desired outcome is crucial for determining the appropriate injection sites and dosages. Ultrasound examination before guidance for injection is essential for examination of muscles architectures and pathology[6, 7].

Optimization of BoNT/A treatment is challenging. The trick in clinical management is to use it intelligently and to know when and when not to use it. The decision to combine BoNT/A with other forms of treatment is an individual one based on many factors[8-11]. Clinical evaluation, muscle selection, dosage use, and injection technique are all important factors in successful treatment[6-11]. For safety concerns, physicians need to use the smallest amount of BoNT/A necessary to achieve therapeutic benefit, extend the time interval between treatment sessions as long as possible (with at least three months between treatments), and avoid the use of "booster" injections[12-17]. Repeated treatments every three to six months were well tolerated. Low-dose BoNT/A therapy for Thai patients and patients

in warm climate counties or during the warm season optimizes outcomes and improves function.[12-17] The pharmacological properties and dilution technique are also important issues[1-5]. Various rehabilitation programs after BoNT/A injections also enhance treatment outcomes. Improper injection technique can lead to suboptimal results or adverse effects[6-8, 12-17]. It is crucial for a thorough understanding of anatomy, muscle function, and the specific indications for BoNT/A treatment. Incorrect placement or depth of injection can result in asymmetry, unintended muscle weakness, or injection into unintended muscles. BoNT/A treatment, like any medical intervention, can have side effects. Physicians should have a thorough understanding of the potential adverse effects associated with BoNT/A injections. Common side effects may include temporary muscle weakness, bruising, pain at the injection site, or flu-like symptoms. Rarer but more serious side effects, such as difficulty swallowing or breathing, should be promptly recognized and managed[1-5]. Educating patients about potential side effects and providing them with clear instructions for when to seek medical attention is essential. Open and effective communication with patients is crucial for managing their expectations and ensuring satisfaction with the treatment outcome. The goals, limitations, and potential outcomes of BoNT/A treatment with patients should be discussed. Realistic expectations should be set regarding the degree of improvement and the duration of the effects. Patient concerns and questions should be addressed, and informed consent should be done prior to treatment. Regular follow-up appointments are important to assess the response to BoNT/A, any concerns or questions, and assessing the need for additional treatments or changes in the treatment plan. For example, comprehensive rehabilitation program after BoNT/A for spasticity aims for motor recovery and functional outcome. Adapting the treatment approach based on individual patient responses can lead to improved results and patient satisfaction.

Conclusion

BoNT/A is a valuable therapeutic drug whose primary mechanism of action is to reduce muscle activity by inhibiting acetylcholine release. Other mechanisms have been discovered, which are used to treat disorders characterized by excessive cholinergic autonomic activity. Furthermore, the mechanisms involved in pain relief may inhibit substance P secretion and reduce peripheral neuropeptide release, resulting in secondary central effects relevant to pain control. When using BoNT/A for therapeutic purposes, important considerations include appropriate dosing and injection techniques, patient selection, injection

timing and frequency, co-interventions, and outcome measure selection. By addressing these concerns, optimizing the use of BoNT/A will improve patient functional outcome, safety, and satisfaction.

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