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Applications, impacts and consequences of botulinum toxin usage in medicine.

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Abstract:

Introduction

Botulinum toxin is a neurotoxin produced by the gram-positive bacteria *Clostridium botulinum*. Botulinum toxin has found great interest in the field of aesthetic medicine, but it has many other applications in other areas of medicine.

Aim of the study

The aim of this comprehensive review is to provide an overview of the usage of botulinum toxin in medicine, with a focus on specific areas of medicine. Attention will be paid to the safety of the use of this substance, taking into account its molecular structure and mechanism of action.

Materials and methods

An analysis of the scientific articles available in the Pubmed, Google Scholar and web of science databases was performed. Recent publications which most appropriately encompassed

the issues under discussion have been selected for the purpose of this study. The process of search was carried out with the following keywords: neurotoxin, botulinum toxins, botulism, muscle paralysis.

Summary

Despite numerous studies, there is ample room for further research into the safety of using botulinum toxin in patients as well as new therapies with this substance. Botulinum toxin is a neurotoxin that is widely used in medicine, but has many side effects.

Key words: neurotoxin; botulinum toxin; botulism; Clostridium botulinum; botulinum toxin treatment

Introduction

Botulinum toxin is one of the most potent neurotoxins discovered to date and is derived from the strictly anaerobic gram-positive bacillus *Clostridium botulinum.* Due to its diverse properties, it has garnered significant interest in medicine, particularly in neurology and aesthetic medicine. The neurotoxins inhibit the release of acetylcholine from the axon terminals of neurons, resulting in muscle paralysis.3 The inhibitory effect on the neurotransmitter is long-lasting but reversible, which is why botulinum toxin can be used in the treatment of various conditions–spasmodic torticollis, dysphonia, cerebral palsy, strabismus, abnormalities of the anorectal sphincter and myofascial pain.2 Botulinum toxin injections are also one of the most popular non-invasive procedures used in aesthetic medicine. Depending on the injection site, wrinkles can be reduced, or the appearance of almost any part of the face can be enhanced. However, it is a highly dangerous substance and can be used as a biological weapon. Ingestion of botulinum toxin by eating contaminated food causes a disease called botulism.1 Symptoms associated with botulism include loss or blurring of vision, difficulties with speech and swallowing. Almost always, asphyxia and death follow 18-36 hours after the toxin has been ingested. There is a mortality rate of between ten and sixty-five percent if left untreated.4 Even though it is well-known among the masses as a name for a cosmetic procedure, botulinum toxin are used for many medical indications clinically off-label in the fields of ophthalmology, neurology, and dermatology.1

In this review we will focus on analyzing various effects and consequences of the use of botulinum toxin on a human body with particular emphasis on its impact on its side effects . We will explore the use of botulinum toxin in medicine and how safe these treatments are.

History

In 1817, Justinus Kerner provided a very detailed description of botulinum toxin. His description was based on the analysis of patients suffering from botulism—Kerner conducted autopsies of the deceased and experiments involving the injection of extracts from infected human tissues into animals.456 Unfortunately, he was unable to isolate the botulinum toxin. However, Kerner accurately described its mechanism—disruption of signal transmission in the nervous system and he asserted that despite its toxicity, this substance could be used as a medicine.5

In 1895, after an outbreak of botulism in Belgium, microbiologist Emile Van Ermengem analyzed the food responsible for the infection, as well as the patients, and successfully isolated the bacterium manage for the production of botulinum toxin, naming it *Bacillus botulinum*.5 This name was changed to *Clostridium botulinum* a few years later.5

Microbiologist Georgina Burke classified the strains of *Clostridium botulinum*, distinguishing their serological characteristics as type A and type B.5

Types of botulinum toxin

Botulinum toxin is used in medicine to treat many conditions and diseases. Botulinum toxin type A is used for clinical applications of botulinum toxin, and with the development of botulinum toxin applications, interest in other serotypes of botulinum toxin (B-G) has grown. 9 Each of the botulinum toxin serotypes produces an antigen-specific neurotoxin. They are designated as A, B, C-α, D, E, F, G (there is also an eighth serotype, C-β, but it is not a neurotoxin).6 Depending on the type of botulinum neurotoxin, it blocks various proteins of the protein receptor complex at cholinergic nerve endings at neuromuscular synapses. Botulinum toxin type A shows the longest duration of action.8 Botulinum toxin type F has been proven to have a shorter duration of action than type A toxin, while type B toxin must be given in large doses to be effective. Botulinum toxin type C has similar effects to type A. 7 Differences between botulinum toxin serotypes result in different efficacy, duration of action and safety during its clinical application.9

Mechanism

Acetylcholine is a neurotransmitter found in the peripheral and central nervous systems. Cholinergic nerve endings are responsible for the production of acetylcholine. Choline uptake and synthesis with acetyl-coenzyme A via the enzyme choline acetyltransferase is required to produce this neurotransmitter. Acetylcholine is a major neurotransmitter of the autonomic nervous system and nerves innervating skeletal muscles. 10 After axon depolarization, acetylcholine is released into the synaptic cleft. This occurs due to a specific chain of transport proteins and the SNARE (synaptobrevin, SNAP-25, syntaxin) protein receptor complex.3 There are many toxins that interfere with the action of acetylcholine at the neuromuscular junction 20, and botulinum toxin is one of them. After botulinum toxin is injected into the target tissue, the heavy chain of the neurotoxin by attaching to glycoprotein structures located on cholinergic nerve endings, and the light chain binds to the SNARE protein complex. The SNARE protein complex is cleaved, and thus the attachment of the acetylcholine vesicle to the inner surface of the cell membrane. As a result, vesicle fusion is blocked and thus the release of acetylcholine is blocked. The effects of botulinum toxin administration are dependent on the target tissue. If the toxin is injected into the muscle there is paresis of the muscle. When botulinum toxin is injected into an exocrine gland (for example the sweat gland), its secretion is blocked.13

Description of the state of knowledge

Role in medicine

Botulinum toxin has found many applications in various fields of medicine. Due to its mode of action, it has been used to reduce muscle contractility, strength and tension, which leads to improved clinical results.14 It is a non-invasive therapy that has found applications in neurology, ophthalmology, urology, rehabilitation medicine, aesthetic medicine and many others.15

Aesthetic medicine

Botulinum toxin has found its application in improving people's appearance, not only eliminating complexes but also eliminating the effects of, for example, nerve palsy. This is a minimally invasive procedure that can improve people's self-esteem and well-being.

Facial nerve palsy can result in facial asymmetry. After injecting the neurotoxin in the right dose and into the right muscles, the patient experiences relief from asymmetry and their facial expression is correct.16

One of the most popular botulinum toxin treatments is to inject it into the muscles to reduce facial wrinkles. Botulinum toxin inhibits excessive muscle contractions and as a result, wrinkles are softened.17,30

Neurology

Palate tremor is a disease that leads to rhythmic lifting of the soft palate, which can result in speech disorders, but also swallowing disorders. The administration of botulinum toxin to the soft palate causes the disappearance of persistent symptoms and results in a return to patient comfort.18

Botulinum toxin is effective in treating dystonia, which is the occurrence of involuntary movements and incorrect body posture. Injecting botulinum toxin into muscles that are overactive inhibits involuntary contractions and relaxations of these muscles.23 Some of the more common side effects of this therapy are dysphagia and muscle weakness. 24

Chronic migraine is a disease that makes life difficult. Botulinum toxin treatment effectively reduces the frequency of severe headaches while causing few side effects of therapy. It is a safe and effective method that improves the quality of life of patients.25,26,27,30 It has been found that botulinum toxin treatment, i.e. injection into the frontal and temporal muscles, produces a much longer effect than traditional pharmacological therapy. 29 Unfortunately, it is unknown whether botulinum toxin treatment of patients with episodic migraine is effective because there is insufficient evidence.28

A study was conducted on the effect of botulinum toxin on allergic rhinitis. Botulinum toxin was injected into the nasal turbinate and a significant reduction in symptoms was noted (24.1%-41.5%) compared to the placebo group. Botulinum toxin treatment has been found to be a non-traumatic, effective method of relieving nasal mucosa sensitization.29

In lichen simplex, there is a persistent pruritus that is its characteristic feature. A positive response and no relapses after 4 months have been demonstrated in patients who received intradermal botulinum toxin injections. Dermatological conditions involving pruritus have been shown to be relieved by botulinum toxin therapy. 29

Glands

Botulinum toxin is also used to treat excessive salivation. Patients who suffer from this condition are at risk of choking, which is very dangerous. Injecting botulinum toxin into the salivary glands effectively reduces salivation.18 A reduction in salivary flow rate has been observed during botulinum toxin therapy and no side effects of this therapy have been noted. 19 Botulinum toxin has also been found to alleviate salivation occurring in amyotrophic lateral sclerosis. Botulinum toxin is a relatively safe and effective treatment for salivation significantly improving patients' quality of life. 20 Positive results have also been noted in children with cerebral palsy who have excessive drooling. Trial have shown that most of the subjects achieved good results.21

Botulinum toxin therapy is also recognised as a treatment for focal hyperhidrosis, which usually affects areas of the body such as the palms of the hands, soles of the feet and skin under the arms. The activity of the eccrine sweat gland is dependent on the release of acetylcholine, so botulinum toxin has an inhibitory effect on sweat secretion as it blocks the release of acetylcholine and thus inhibits the transmission of nerve impulses. Administration of botulinum toxin to the target organ, which in this case is the sweat gland, reduces its activity. 22,29

Ophthalmology

Botulinum toxin was first used in ophthalmology by Alan Scott. The aim of this procedure was to find an alternative to strabismus surgery for those patients who should avoid general anesthesia. Injecting botulinum toxin into the appropriate muscle has a positive effect in the treatment of strabismus, especially in children. Unfortunately, the frequency of complications after this procedure depends on the dose of the administered preparation - the higher the dose, the greater the likelihood of adverse effects.30, 31

The indication for botulinum toxin treatment is the treatment of patients suffering from hemispasm or blepharospasm. These diseases interfere with patients' daily lives - the eyelids of the eyes contract, leading to complete eye closure or their facial muscles contract tonically. Injecting botulinum toxin into the appropriate, hyperactive muscles eliminates the symptoms of these diseases.18,30

Urology

Botulinum toxin can also be used to treat displacement and urinary sphincter dyssynergia. It is also effective in reducing urinary urge and incontinence and in treating bladder dysfunction. Injection of botulinum toxin into the urethral sphincter muscles resulted in improved urinary output. Administration of this preparation into the bladder or into the urethral detrusor muscles results in inhibition of urinary urge and incontinence. Research into the efficacy of this therapy is still ongoing, as treatment outcomes are uncertain and there are many adverse events, and botulinum toxin may prove to be an effective alternative to pharmacotherapy in the treatment of urinary dysfunction. 32,33,34

Bruxism

Bruxism is an involuntary work of the masticatory muscles. Injecting the preparation into the masticatory muscles weakens their activity, which reduces the frequency of bruxism incidents. It is considered that botulinum toxin treatment effectively and beneficially affects the reduction of bruxism episodes and reduces the level of pain caused by this disease. 35-39

Safety

Botulinum toxin treatment carries the possibility of side effects. Eyelid drooping, eyebrow drooping and facial asymmetry have been observed. These events resolve spontaneously after a certain period of time. Botulinum toxin is considered an effective and safe substance when used as indicated and at the correct dose. It has a short-term and long-term safety profile. Safety in its use in children under 2 years of age has also been confirmed. 11, 20, 40, 41, 42

Discussion

Botulinum toxin has many applications in medicine, in many specialities. Unfortunately, not all applications have been sufficiently studied in terms of duration of action and occurrence of side effects. More studies need to be carried out to determine the risk of side effects as well as the exact duration of action of the administered preparation. The safety of this substance depends on the correct way of administering it to a specific tissue as well as the correct dose. It is important to remember that botulinum toxin is a neurotoxin that can be life-threatening. Undoubtedly, this preparation can be a great alternative to pharmacotherapy in the treatment of many diseases. It can certainly be said that research to date has produced satisfactory results in the treatment of many neurological diseases. Botulinum toxin is also a very popular preparation in aesthetic medicine. Its use in urology, on the other hand, requires further studies and a closer look at side effects. It is also possible that botulinum toxin has applications in areas such as cardiology or will be effective in the treatment of respiratory diseases. Botulinum toxin is a substance that once caused people to die, but is now used in medicine and helps to treat or alleviate the symptoms of many diseases.

Conclusion

Botulinum toxin is a safe substance that is used to treat or alleviate many diseases. However, it is important to remember that every substance has a therapeutic range and, when exceeded, becomes dangerous. As Paracelsus said: '*Omnia venenum sunt: nec sine veneno quicquam existit. Dosis sola facit, ut venenum non fit.* 'meaning 'everything is poison and nothing is poison, for it is only the dose that makes the poison 'which is why, once a safe and effective therapeutic dose was determined, botulinum toxin became widely used in medicine.

Author's contribution

Conceptualization, Aleksandra Kudła, Rozalia Czapiewska and Barbara Wajdowicz; methodology, Aleksandra Wróbel; software, Gabriela Broniec; check, Julia Kozłowska; Aleksandra Dziewulska and Klaudia Kowalska; formal analysis, Laura Pacek and Weronika

Kiełt; investigation, Barbara Wajdowicz and Aleksandra Wróbel; resources, Weronika Kiełt; data curation, ; writing - rough preparation, Aleksandra Kudła; writing - review and editing, Julia Kozłowska, Aleksandra Dziewulska; visualization, Aleksandra Kudła; supervision, Rozalia Czapiewska; project administration, Laura Pacek; receiving funding, Gabriela Broniec.

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