53 - BOTULINIUM TOXIN CLINICAL PRACTICE

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INTRODUCTION

The acid Botulinum is a rich protein complex including a neurotoxin capable of promoting the botulism, a disease that involves muscle paralysis or weakness. This disease involves seven different serotypes which are classified from A to G. These toxins differ in their mechanism of action, their synthesis and intracellular action. What is known nowadays is that the type A toxin is considered the most powerful and it is also the most clinically used, but the toxins from the group B and F are used in the same way in clinical practice (FERREIRA et al., 2008).

A poisoning caused by this substance generates a cellular action, restricted to the Central Nervous System, which can be divided into three parts: (1) Link to the presynaptic nerve terminal; (2) Internalization; (3) Intraneuronal action (inhibition of neurotransmitter)

The botulinum toxin mechanism of action is restricted to the Peripheral Nervous System, but there are confirmed reports of the action of this toxin also in the central nervous system, thus a contamination in uncontrolled doses of the substance has as a consequence inhibition of neurotransmitters causing the loss of effective synapses assets (FERREIRA et al., 2008).

The Botulinum toxin (BTX) is metabolized by a Gram-positive bacillus, Clostridium botulinum, which is found in fresh and salt water, and also on the ground around the entire world. This toxin is considered nowadays as the highest incidence of death that is known, being that it has a lethal dose of 1 (one) nanogram of toxin per kilo of body weight, and despite of these high lethal rates, there is a great speculation regarding the clinical and therapeutic potential of this toxin due to its ability to treat neurological diseases at ophthalmic level and also at the cosmetic industry (BACHUR et al., 2009).

In 1817, reports were described about botulism presenting clinical evidence of this toxin, showing that this substance had the ability to interrupt transmission at peripheral and autonomic nervous system level. But at that time it was not known that the toxin was produced by a bacillus, there were just evidences of its animal origin (BACHUR et al., 2009).

Based on the C. botulinum, seven different toxins are produced from spores' germination (A, B, C1, D, E, F and G). Types A, B, E, and F are responsible for most human cases. In Brazil, reports of botulism have been caused by toxins A or B and were related to merchants and at home with canned fruit, vegetables or meat and other foods (ROWLANDS et al., 2010).

After several proposed theories about the origin of botulinum toxin, in 1895, a German microbiologist, Emile Van Ermengem, related the botulism epidemic to the isolation of a bacterium found in food served during a funeral in a Belgian village. This relation occurred after 34 people were infected being that 3 of them died. In the food served at the funeral, the microbiologist isolated spores of an anaerobic bacillus, which was named Bacillus botulinus, and with laboratory studies was possible to conclude that the bacillus showed signs of paralysis in animals (BACHUR et al., 2009).

The laboratory diagnosis of botulism is confirmed by the presence of the toxin in clinical samples and / or food remains consumed by patients. The pattern tests used for detection and identification of botulinum neurotoxin are food toxicity analyzed and bioassay neutralization test. Although other in vitro tests have been developed, none of them had a sensitivity and specificity compared with the bioassay, which is considered an efficient tool for the detection of toxin. The Food Microbiology Section from the Institute Adolfo Lutz is the only laboratory in Brazil that has made the diagnosis of botulism since 1982 (ROWLANDS et al., 2010).

Shortly after the bacillus was renamed, becoming known as Clostridium botilinum, since then many researchers began to investigate the possible therapeutic use of the substance. Almost 100 years later, in 1973, a study in monkeys used the botulinum toxin type A in the eye muscles to treat strabismus, and five years after the same treatment was applied in humans, and from this work botulinum toxin has been consolidated as a pharmaceutical product and is now known as Botox ® (BACHUR et al., 2009).

This toxin is considered a powerful substance, which was responsible for the death of many people who had contact with contaminated food, due to paralysis of all striated muscles and respiratory arrest. In contrast, among several undesirable effects, a positive one was the discovery that the same muscular blocking effect is also responsible for contributing in many clinical conditions, including the treatment of strabismus and hyperhidrosis (GILBERTONI et al., 2006).

The botulinum toxin had its study started for the correction of strabismus, and it is now also used to treat muscle spasms and dystonia from multiple sources (focals, spastic, hands, legs, etc.). (ANDRADE et al., 1997).

MECHANISMS OF ACTION

In general, the BTX acts by blocking acetylcholine, inhibiting neuromuscular transmission, and consequently results in a local paralysis. (BACHUR et al., 2009).

The mechanism of action can be explained by four sequential stages reported after the injection of BTX: (1) The internalization with toxin endocytosis; (2)Changing the pH with conformational change of the heavy chain; (3)Translocation of the light chain; (4) Proteolysis of SNARES (soluble N-ethylmaleimide fusion protein attachment receptor), - proteins by the light chain .

The SNARE complex acts mediating the fusion of synaptic vesicles with the neuronal membrane. When injected into the muscle, botulinum toxin acts at glycoprotein receptors which are specific to BTX. However, this selectivity may vary depending on the serotype of toxin used (BACHUR et al.,2009).

The TXB, one of the most potent bacterial toxins known, has known therapeutic action effective in treating some painful syndromes. However, some of its indications are still in proof process regarding its effectiveness (COLHADO et al., 2009).

The first phase , internalization, does not occur directly with the penetration in the cell membrane, but occurs so that the endocytosis remains mediated by receptor and after occurs neurotoxin cleavage. In the following stage, there is an acidification in the vesicles resulting in a structure change of the toxin, pointing the change in the heavy chain, which

consequently modifies the light chain. In the cytosol, the light chain breaks the SNARE complex, which is rich in proteins needed to carry out exocytosis, happening then the blocking of the neurotransmitter action (BACHUR et al., 2009).

The botulinum toxin, produced by Clostridium botulinum, causes blockage of cholinergic connections from the neuromotor board through inhibition of acetylcholine, damaging functionally the muscle. When injected into muscle produces weakness or temporary paralysis dose-dependent (WATTIEZ et al., 2000).

One of the bad points is that this blockage is only temporary and soon is retaken, the the clinical effect can delay from one to four months, but the functional muscle return is not fully understood, what is known is that one of the factors for the normal functioning of the muscle is the sprouting of fibers for the formation of a new muscle junction, which later will undergo retraction, and finally the original junction will be kept. This process can extend for up to 90 days, but could change depending on the serotype used. A second hypothesis for the muscle restoration is the SNARE complex regeneration (BACHUR et al., 2009).

Some reports indicate that the patient who receives repetitive injections of BTX type A, ends up losing their response to the treatment, and as an alternative, they are then treated with other serotypes of the toxin (CARDOSO, 2003).

SOME MEDICAL PATHOLOGIS TREATED WITH BTX

From 1984 to 2004 a study based on different journals (Lilacs, Medline, PubMed and Scielo) was carried out regarding therapeutic use of botulinum toxin in neurological manifestations, and the use of this toxin showed excellent results related to the improving of complications caused by central neurological lesions. The reason that leads to an intensification in the search for results in the evolution of severe neurological situations was the impact caused by this clinical situation in in people's health (GILBERTONI et al., 2006).

In general, neurological disorders affect the central nervous system, causing lesions that promote dysfunction according to the place of involvement, ranging from the inability of some members to the complete inability (GIBERTONI et al., 2006).

Botulinum toxin type A is an effective treatment for certain neurological disorders. The mechanism of action of TXB-A is by blocking the release of acetylcholine at the neuromuscular junction, and consequently generates a focal muscle paralysis (ALOÉ et al., 2003).

On this basis, in 1994 the American Academy of Neurology established rules for the treatment of neurological diseases targeting the use of botulinum toxin for this condition, emphasizing doses based on the weight and individual body mass (GIBERTONI et al., 2006).

A common symptom found in patients with neurological deficits is a significant increase in saliva production due to a failure in the coordination of the tongue muscle. The first report of reduction in saliva using botulinum toxin was in cats, in 1923, and soon after it was used in Amyotrophic Lateral Sclerosis treatment (ALS), which is characterized by atrophy and muscle degeneration, starting mainly by difficulty in swallowing saliva and difficulty in articulating the words. Approximately 50% of ALS patients present disorders in saliva control. One of the treatments to minimize the effects of this disease is the use of Botox ®, which is the alternative with the greatest positive effects on treatment (MANRIQUE, 2005).

The botulinum toxin is also the first choice in cases of focal dystonia, even with a small percentage of patients eventually show some kind of intolerance to the toxin, in general the results are relevant, and for these intolerant patients a treatment is carried out with another type of toxin serotype (CARDOSO, 2003).

Recently botulinum toxin type A (BTX-A) was used for treatment of bruxism secondary related to other movement disorders such as cervical dystonia, oromandibulofatial spams and Huntingtons disease (also called dystonia secondary or symptomatic). The clinical effect of TXB-A in the secondary bruxism is seen in approximately two to four days after injection, in order that the beneficial effects last about four months with a reduction in daytime symptoms and muscle hypertrophy. Treatment with TXB-A is relatively safe, and the occurrence of dysphagia and paralysis of the facial and masticatory muscles is unusual (ALOÉ et al, 2003).

A study carried out in 2000 reported the use of BTX-A in 18 people with gnashing of teeth related to other types of medical and dental treatment. TXB-A at doses of 25 MU to 100 MU was effective in eliminating symptoms, but there is no long term studies proving the effectiveness of TXB for the treatment of primary or secondary bruxism (ALOÉ et al., 2003).

In addition to these diseases reported, with a treatment of Botox ® was significantly effective, another situation commonly treated with this toxin is Hyperhidrosis, in which pathology is defined as sweating that exceeds the need for body thermoregulation and it is a condition that can cause displeasure to the patients. It reaches up to 1% of the population and any procedure that involves risks disproportionate to the problem should be discarded as a treatment, since it is considered a benign manifestation. Botulinum toxin began take place in the industry, and it has been safely used in wide evidence, including the control of hyperhidrosis, and it shows more and more a simple and safe alternative for controlling excessive sweating (FRANCHISCHELLI et al., 2000).

In the last decade, the introduction of botulinum toxin type A in the treatment of hyperhidrosis has been very effective. This toxin binds to nerve endings of postganglionic sympathetic fibers that innervate the sweat glands. It is then internalized via endocytosis and after released into the axonal cytoplasm. When sectioning the protein cell membrane SNAP-25, required for the release of acetylcholine, the toxin prevents the release of this neurotransmitter. The glands are therefore not receiving the stimulus for secretion. Based on this mechanism of action and the latest findings on the clinical use of botulinum toxin, this study aims to critically review the literature on the effectiveness of botulinum toxin type A in the treatment of hyperhidrosis (Dias et al., 2001).

In a study with patients treated with the toxin, two patients with armpit hyperhidrosis and two patients with handr hyperhidrosis, there was suppression of sweating in four patients for periods from 4 to 9 months. The use of the technique is new and there are not researches with large numbers of cases treated for hyperhidrosis, which allows establishing the improvement of the volumes applied and provide the lasting of the results. However, it is a safe treatment, technically simple, ambulatorial,which does not remove the patient's normal activities. Initial results allow to believe that studies should be maintained, looking for confirming the impression that the use of botulinum toxin for the treatment of hyperhidrosis is a simple solution to a condition also simple (FRANCHISCHELLI et al., 2000).

The ways of treatment of hyperhidrosis can be grouped into palliative and definitive. Antiperspirants (eg aluminum chloride 20%) have little lasting effect - an average of seven days - in addition to causing irritation and tolerance. The use of iontophoresis (introduction of chemical radicals in the tissues) only prevents sweating during treatment, and its effectiveness limited. Anticholinergic drugs, also palliative, cause effects such as changes in vision, dry mouth, sedation and nausea. The removal of the armpit gland by excision or liposuction is a definitive therapy, but may cause bleeding, infection, paresthesia, scarring and reinnervation (DIAS et al., 2001).

Cerebral palsy (CP) is the most common cause of physical disability in children, with an incidence of 1.5 to 3 cases per 1000 live births. Spasticity is a disabling clinical symptom that is prevalent in patients with PC. The mainly problem associated with spasticity are loss of strength, balance and selective motor control of muscles and also increase of muscle tonus, leading to secondary problems, such as fixed contractures and bone deformities, causing severe motor dysfunction in patients. Treatment with botulinum toxin type A (BTX-A) has been a well established option in the interdisciplinary management of spasticity since the end of 1980, providing focal reductions in muscle tonus in CP patients. However, interpretations of the literature on this subject are a challenge due to the difficulties of measuring functional changes and spasticity in children (UNLU et al., 2010).

Several studies randomized and non randomized controlled have demonstrated the efficacy of BTX-A injections in reducing muscle tonus, increasing range of motion and improve posture and gait in patients with PC. However, some studies have shown little benefit from BTX-A related to functional gains and quality of life. Although this discrepancy between the several studies may be explained by differences in method, this point requires further elucidation (UNLU et al., 2010).

The successful application of BTX has been reported in an increasing number of urologic diseases, including hypocontractility of the detrusor muscle, sensorial disturbances, interstitial cystitis and benign prostatic hyperplasia. So far, the more widespread urological application of BTX was in treatment of urinary urgency and incontinence due to detrusor overactivity. Therefore the improvement of subjective and objective results are demonstrated in numerous investigations using injection of BTX in the treatment of both populations. And despite the initial success achieved by injection of BTX in the treatment of voiding dysfunction, improvement is needed. Without doubt, the most important obstacle to the widespread urological use of BTX is the lack of standardized technique for the administration intravesical BTX (RAPP et al., 2007).

The first application of botulinum toxin type A (BoNT-A) in urology was its injection into the urinary sphincter to treat neurogenic detrusor-sphincter dyssynergia (DSD) in quadriplegic men. Since 1988, the results of BTX-A focal injections in sphincter, the bladder wall and prostate have increased the interest of urologists in this new promising therapeutic modality (PATK et al., 2008).

FINAL CONSIDERATION

Considering the facts reported since the discovery of botulinum toxin, it is possible to observe its therapeutic potential. Despite being a highly toxic substance, it is demonstrated to be safe when used within the recommended doses for clinical and esthetic indications.

The biggest obstacle to the use of BTX is undoubtedly the high cost of treatment. But another obstacle is emerging, which is the immune-resistance to BTX, which occurs most commonly in patients taking large doses of the product or do not respect the minimum time interval between applications. Despite the large number of clinical indications at the present time, there is still potential for using BTX in other scenarios, and this should occur as the understanding of molecular aspects of BTX is advancing as well as the physiological aspects of certain diseases can be related to the use of BTX as a treatment.

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BOTULINIUM TOXIN CLINICAL PRACTICE

ABSTRACT

Botulinum toxin, better known by its trade name (Botox ®) is a protein obtained from a bacterium and is used in the medical field to prevent muscle contraction. Initially it was used by the Ophthalmology and Neurology to correct involuntary muscle contractions and a few years ago it began to be used in dermatology for the correction of dynamic wrinkles, with outstanding results. Its cosmetic use has revolutionized today's dermatology aesthetics, besides the treatment forwrinkles and expression marks, it also shows excellent results in the treatment of hyperhidrosis (abnormally increased perspiration) axillary and palmar. The application of botulinum toxin should only be performedby physicians and can be done at the clinic. The substance is injected into specific points of the muscles responsible for facial movements. In order to achieve the desired effects these points are selected according to each person's characteristics as well as the dose must be determined individually. One of the most typical problems related to excessive use of botulinum toxin is the blockade of cholinergic connections in the central nervous system by inhibiting the acetylcholine which results in poor muscle function, when injected directly into muscle it produces weakness or temporary local paralysis.

KEYWORDS: Botulinum Toxin, muscle contraction, treatment.

L'UTILISATION CLINIQUE DE LA TOXINE BOTULINIQUE

RESUME

La toxine botulique est connue par son nom commercial (Botox®), et c'est une protéine obtenue d'une bactérie et utilisée dans le secteur médical pour empêcher la contraction musculaire. Initialement, elle a été utilisée à l'ophtalmologie et par la neurologie pour la correction des contractions musculaires involontaires, mais il y a quelques années elle a eté utilisée dans la dermatologie pour la correction de rides dynamiques, avec d'expressifs résultats. Son utilisation cosmétique a révolutionné la dermatologie esthétique pour le traitement des rides,des marques d'expression, et pour l'hyperhidrose des aisselles et de la main (palme)(l'augmentation de la transpiration). L'application de la toxine doit être accomplie par des docteurs et dans une clinique spécialisée. La substance est injectée aux points spécifiques des muscles responsables par la mimique faciale. Ces points sont sélectionnés d'accord des caractéristiques de chaque personne, ainsi que la dose nécessaire. Un des plus caractéristiques problèmes à l'utilisation excessive de la toxine botulique provoquant un efféct cholinergique au système nerveux Central avec réduction de l'inhibition d'effect de l'acetilcoline peripheric et du fonctionnement musculaire; aussi, l'injection directement dans le muscle produit l'affaiblissement ou la paralysie temporaire locale.

MOTS-CLÉS: toxine Botulique; contraction musculaire, traitement.

LO USO DE LA TOXINA BOTULINICA EN LA PLATICA CLINICA

RESUMEN

La toxina botulínica, mais cococida por su nombre de comércio (Botox®), es uma proteína obtida através de uma bactériay es utilizada em la área médica para impedir la contración muscular. Antigamente era utilizada por la Oftalmologia y Neurología para corrección de contraciónes musculares involuntárias y há algunos años comezó a ser utilizada em la Dermatologia para correciónes de rugas dinâmica, com optimos resultados. Su uso cosmético revolucionó la dermatologia estética de hoy, além de su tratamento de las rugas y marcas de expressión, apresenta excelentes resultados también em lo tratamento de la hiperidrose (aumento da produción de suor) axilar y palmar. La aplicación de la toxina butolínica deve ser realizada apenas por doctores y puede ser fecha em lo consultório. La substáncia es injetada em pontos específicos de los músculos responsáveis pela mímica facial. Estes pontos són selecionados de acurdo com las características de cada persona, assí como la dose necessária para se obter lo efecto deseyado deve ser determinado individualmente. Uno dos más característicos problemas relacionados a lo uso excessivo de la toxina butolínica es lo bloqueyo de las ligaciónes colinérgicas em lo Sistema Nervoso Central, por inibición da acetilcolina que resulta em um má funcionamento muscular, y cuándo injetada diretamente em lo músculo produz enfraquecimento o paralisia temporária local.

PALABRAS CLAVE: Toxina Butolínica, contración muscular y tratamiento.

USO DA TOXÍNA BOTULÍNICA NA PRÁTICA CLÍNICA

RESUMO

A toxina botulínica, mais conhecida pelo seu nome comercial (Botox®), é uma proteína obtida através de uma bactéria e é utilizada na área médica para impedir a contração muscular. Inicialmente era utilizada pela Oftalmologia e Neurologia para correção de contrações musculares involuntárias e há alguns anos começou a ser utilizada na Dermatologia para a correção de rugas dinâmicas, com ótimos resultados. Seu uso cosmético revolucionou a dermatologia estética de hoje, além do tratamento das rugas e marcas de expressão, apresenta excelentes resultados também no tratamento da hiper - hidrose (aumento da produção de suor) axilar e palmar. A aplicação da toxina botulínica deve ser realizada apenas por médicos e pode ser feita no consultório. A substância é injetada em pontos específicos dos músculos responsáveis pela mímica facial. Estes pontos são selecionados de acordo com as características de cada pessoa, assim como a dose necessária para se obter o efeito desejado deve ser determinado individualmente. Um dos mais característicos problemas relacionados ao uso excessivo da toxina botulínica é o bloqueio das ligações colinérgicas no Sistema Nervoso Central, por inibição da acetilcolina que resulta em um má funcionamento muscular, e quanto injetada diretamente no músculo produz enfraquecimento ou paralisia temporária local.

PALAVRAS-CHAVES: Toxina Botulínica, contração muscular, tratamento.