

REVIEWS

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Botulinum Toxin in Conventional and Aesthetic Medicine

Zastosowanie toksyny botulinowej w medycynie konwencjonalnej i estetycznej

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Abstract

Botulinum toxin, also known as “sausage poison”, is a potent neurotoxin produced by the anaerobic bacterium *Clostridium botulinum*. By inhibiting acetylcholine neurotransmitter release in neural cells, it causes muscle paralysis. Botulinum toxin type A is considered an extremely dangerous biological weapon due to its properties. Applied in low doses as one toxin, it serves as an effective medication in the treatment of dermatological and neurological diseases. The biochemical and biophysical properties of botulinum toxin as well as its mechanism of action are described in the first part of this paper. The authors discuss the medical uses of botulinum toxin in ophthalmology, abnormal secretion, esophageal achalasia, and above all neurological diseases that involve increased muscle activity (including dystonia, tremor, spasticity) and its effectiveness in these disorders. The paper shows that besides its aesthetic medical application (usually the elimination of facial wrinkles), botulinum toxin is more commonly used to treat the above disorders which, in many cases, were previously deemed incurable (*Adv Clin Exp Med* 2010, 19, 2, 271–278).

Key words: botulinum toxin, ophthalmology, neurology, aesthetic medicine.

Streszczenie

Toksyna botulinowa – popularnie zwana jadem kielbasianym – jest niezwykle groźną neurotoksyną, wytwarzaną przez beztlenowe bakterie *Clostridium botulinum*. Blokując uwalnianie neurotransmitera: acetylocholino w komórkach nerwowych, powoduje porażenie skurczu mięśni. Toksyna botulinowa typu A ze względu na swoje działanie jest uważana za niezwykle niebezpieczną broń biologiczną. Równocześnie w małych dawkach, jako jedyna toksyna, znajduje zastosowanie jako skuteczny lek przeciwko różnym schorzeniom dermatologicznym i neurologicznym. W pierwszej części pracy zostały opisane właściwości biochemiczne i biofizyczne toksyny botulinowej oraz mechanizm jej działania w organizmie. Następnie omówiono zastosowanie toksyny botulinowej w wielu dziedzinach medycyny: okulistyce, nieprawidłowym wydzielaniu, achlazji przełyku, a przede wszystkim chorobach neurologicznych przebiegających z nadmiernym napięciem mięśni (m.in. dystoniach, drżeniu, spastyczności) oraz skuteczność działania toksyny w tych schorzeniach. Z przedstawionych informacji wynika, iż preparaty zawierające toksynę botulinową są stosowane nie tylko w medycynie estetycznej (zwykle do usuwania zmarszczek mimicznych), ale także coraz częściej w wyżej wymienionych schorzeniach, które w wielu przypadkach uważano dawniej za nieuleczalne (*Adv Clin Exp Med* 2010, 19, 2, 271–278).

Słowa kluczowe: toksyna botulinowa, okulistyka, neurologia, medycyna estetyczna.

Recent years have brought increased interest in botulinum toxin. Its most common use is as an aesthetic and cosmetic medicine. It is not widely known that botulinum toxin plays an important role in conventional medicine, but it can also

cause harm to the organism. Botulinum intoxication is called botulinism. In Poland, several dozens of people become intoxicated with this poison. Botulinum toxin has been used in various branches of medicine for 25 years. It is applied in rare,

difficult to treat cases. It also serves as a drug of choice. There is great potential for the use of the toxin in medicine.

Properties of Botulinum Toxin

Botulinum toxin (botulin or sausage poison) is produced by the anaerobic bacterium *Clostridium botulinum* [1–11]. *C. botulinum* is ubiquitous, widely present in forests, cultivated soil, and marine sediments. It is also found in the intestinal tract of mammals and fish and the bronchi and viscera of crabs and crustaceans. Its spores are found in dust and animal fur. *C. botulinum* is motile, ciliated, and noncapsular. It forms spores with a mean size of $0.5\text{--}2 \times 6\text{--}9 \mu\text{m}$. The spores are formed at the polar regions, which is why the bacterium is rod or spindle shaped. Botulinum toxin is produced under anaerobic conditions in the course of *C. botulinum* spore development [12, 13]. The toxin is released when autolysis occurs in the bacterium. Botulinum toxin is a colorless, odorless, and tasteless exotoxin. The toxin may be inactivated by high temperature and an alkaline environment. Eight serotypes of botulinum toxin have been described: A, B, C1, C2, D, E, F, and G. They are produced by various strains. Differences between the serotypes are due to different amino acid structures, antigenic properties, biosynthesis, pharmacological properties, and sites of binding to presynaptic nerve endings [1, 5, 12]. Botulinum toxin type A molecule is a polypeptide with a mass of 150 kDa. It has 1296 amino acids [14]. It is composed of a heavy chain (H) and a light chain (L). The heavy chain has a mass of 100 kDa and 848 amino acids and the light chain a mass of 50 kDa and 448 amino acids. Both chains are joined by disulfide bridges and noncovalent bonds. To display neurotoxic properties, the toxin must contain both chains [4, 6, 10, 14].

Botulinum toxin activity is measured in mouse units (MUs). One mouse unit is equal to one Botox unit. A mouse unit is the smallest dose of botulinum toxin and is equivalent to an amount that will kill 50% of a group of 18- to 22-g Swiss Webster mice when injected intraperitoneally in 3–4 days (DL50) [1, 5, 6, 11, 14, 15].

Two preparations containing botulinum toxin type A are manufactured on a mass scale: Botox (Alergan, Inc, Irvine, CA, USA) and Dysport (Ipsen, Ltd., Maiden, England). Only one preparation containing botulinum toxin type B is produced and sold under the trade name of Myobloc (Solstice Neurosciences, Inc, San Francisco, CA, USA) [1, 9, 14]. Both Botox and Dysport are reg-

istered in Poland [4, 6]. The doses of drug in the preparations are not equal. One Botox unit is clinically equivalent to 2–2.5 Dysport units or 50–125 Myobloc units [1, 4, 6, 14, 15].

There are three stages of botulinum toxin activity in the nerve-muscle synapse: binding, internalization, and the neuromuscular blocking effect (Fig. 1). In the first stage, the botulinum toxin type A molecule (BTX-A) binds to a receptor located on the nerve ending's presynaptic membrane. The receptor is a membrane-specific peptide, synaptotagmin. The binding takes place using the 50-kD C-terminal heavy chain of the toxin molecule [1, 3, 5, 6, 8, 9, 11, 12, 14, 15]. In the second stage, the toxin is internalized via endocytosis. An endosome is created in which the disulphide bond between the heavy and light chains breaks down. Then the 50-kD N-terminal fragment of the heavy chain creates an ion channel through which the light chain is released into the neuronal cytoplasm [1, 8, 9–11, 14–16]. In the final stage, the light chain, via its N-terminal fragment, joins the SNARE peptide complex. The light chain contains a specific zinc-endopeptidase with proteolytic properties that causes enzymatic fragmentation of peptides in the complex. Acetylcholine exocytosis into the synaptic matrix and further transmission of a nerve impulse become impossible. The SNARE complex is formed by three membrane-bound proteins: VAMP/synaptobrevin, SNAP-25, and syntaxin. Depending on the botulinum toxin serotype, a different SNARE complex peptide is fragmented. Ca. 10 days after botulinum toxin injection, the reinnervation process starts. New synapses are formed in neuromuscular endings and the process causes a temporary botulinum toxin therapeutic effect [1, 3, 5, 7–11, 12, 15, 16].

Therapy effectiveness is influenced by some drugs used concurrently with botulinum toxin procedures. Some aminoglycoside antibiotics, such as canamycin and streptomycin, have an intensifying effect, while aminocholines, such as chlorochine and hydroxychlorochine, have a weakening effect [14, 15].

Peptides forming a botulinum toxin molecule may trigger the organism's immunological response. Antibodies inactivating the toxin are then produced and the treatment is consequently ineffective. The minimum dose to trigger an immunological response in humans is unknown. Patients resistant to toxin serotype A may be treated with other serotypes, for example B. Immunogenicity depends on the single injection dose, the cumulative dose, and the frequency of use. Factors intensifying immunogenicity include large size, aggregation, denaturation, and a large amount of peptide molecules. To minimize the risk of immunization,

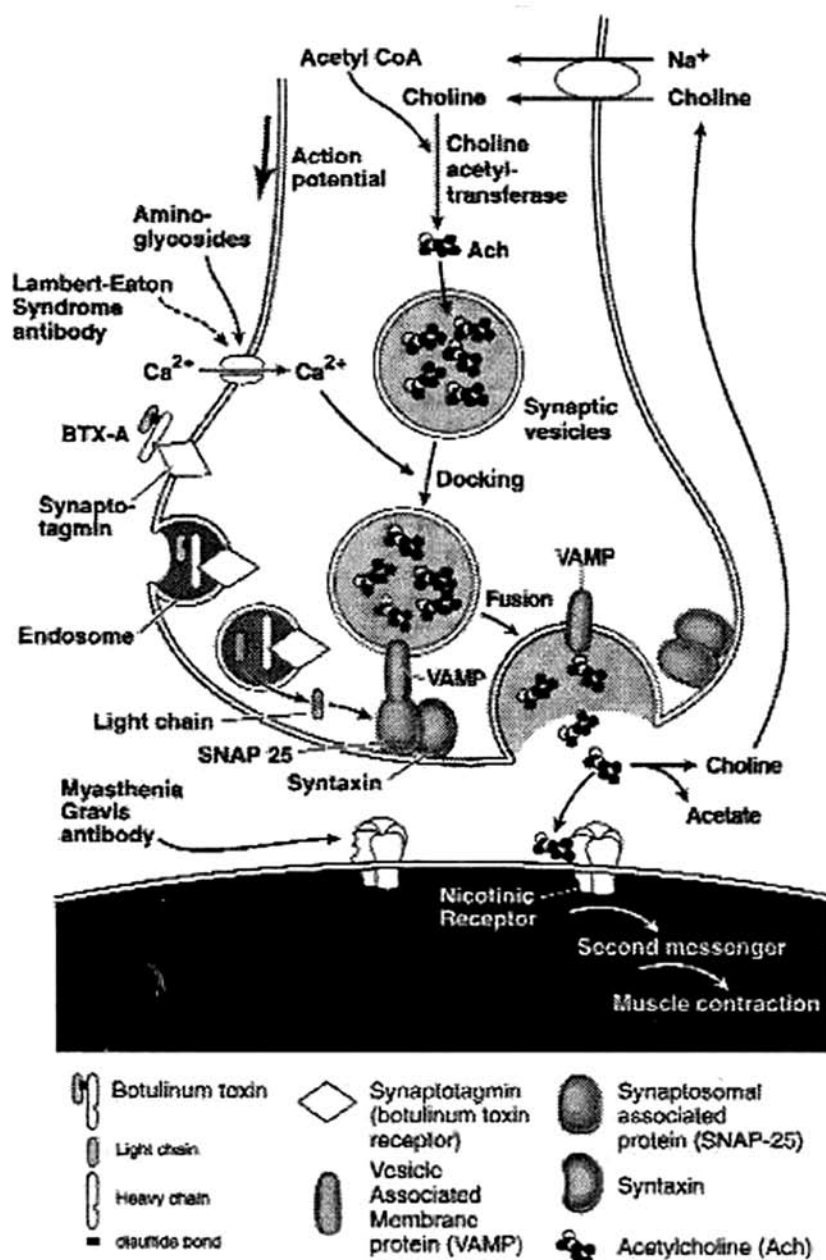


Fig. 1. Botulinum toxin's mechanism of action [15]

Ryc. 1. Mechanizm działania toksyny botulinowej [15]

one should use the smallest possible doses of the drug, keep 8- to 12-week intervals between procedures, avoid control injections, and use highly purified preparations [1, 5, 9, 15].

Botulinum Toxin in Conventional Medicine

Botulinum Toxin in Ophthalmology

Blepharospasm

Blepharospasm is a focal dystonia. Its probable cause is abnormal functioning of the brain's basal ganglia. Patients suffer from involuntary cyclic

blinking and spasms of the orbicular muscle of the eye. A relationship between spasm frequency and daytime has been found. The frequency is lower at night and dawn. Some external factors, such as bright light, smoke, and polluted air, may intensify symptoms. Blepharospasm may lead to permanent disorders in the organ of sight, which may result in blindness. The pharmacological therapy of blepharospasm is ineffective, as is surgical treatment. The drugs of choice are botulinum toxin preparations. They are injected into 3–4 sites of the orbicular muscle of the eye, mainly into 2 medial and 2 external points. A double dose should be applied into the external points as the muscle is larger there. The initial doses of the drug should be 120 MU Dysport or 25 MU Botox applied into one side of the muscle. Clinical improvement is found

in ca. 70% of patients. First effects are visible after 3 days, and maximal improvement is observed after 14 days of the procedure. The positive therapeutic result is maintained for 12 weeks [4, 14, 20].

Strabismus

Strabismus is caused by misalignment of the eyeballs. It is classified as heterophoric, paralytic, and concomitant. Strabismus treatment should be initiated as early as possible to reduce the chances of irreversible lesions in the organ of sight that may pose an obstacle to treatment. The effects of strabismus can be partly corrected using proper eyeglasses or physical therapy. Alan Scott was the first to use a botulinum toxin preparation in the treatment of esotropia in 1981. From then on, botulinum toxin was used in medicine. The procedure is carried out under local anesthesia. Anesthetic agent is applied in drops into the conjunctival sac. In the first procedure, a 2.5-MU single dose is applied. Clinical improvement is found in 50–80% of patients. A positive therapeutic effect is maintained for 2–6 weeks [4, 6, 20, 21].

Dry Eye Syndrome

Dry eye syndrome is caused by decreased tear production or abnormal tear composition. Lack of tears dries the cornea and makes it more sensitive to damage. The eyes become red and scratchy. A sticky discharge from the eyes may also appear. To relieve the pain, artificial tears containing polyvinyl alcohol are applied. Laser surgical operations are also performed to close the lacrimal canaliculi. Very good results in dry eye syndrome treatment are achieved when using a botulinum toxin preparation. It causes paralysis of the eye's orbicular muscle which, consequently, cannot push the tears out of the eye onto the cheek. The tears remain inside the conjunctival sac, where they can wet the cornea and ocular conjunctiva [4, 20, 21].

Crocodile Tears Syndrome

The crocodile tears syndrome is caused by abnormal regeneration of the lacrimal gland's nerve fibers, which may follow a head trauma. It manifests as increased flow of tears, especially when drinking or eating. Anticholinergic drugs and transection of a facial nerve have been found ineffective. The application of botulinum toxin preparations brings good results. Before the procedure, Schirmer's test must be done to identify the most active area of the lacrimal gland. Botulinum toxin preparations are injected into the lacrimal gland in doses of 10 MU Botox or 50 MU Dysport [20, 22].

Botulinum Toxin in Abnormal Secretion

Hyperhidrosis

Hyperhidrosis is caused by abnormal activity of endocrine sweat glands. It may lead to other disorders, such as skin mycosis and Gram-negative bacterial infection of the feet. Antiperspirants, anticholinergic drugs, and excision of the axillary sweat glands are used to treat patients with hyperhidrosis, but these methods are not fully effective and may produce side effects. Botulinum toxin has been used in the treatment of axillary, palmar, and plantar sweating since 1997. Before treatment, Minor's test should be done to show the most active regions of sweating. In excessive palmar sweating, the proper dose is 25 MU Botox or 100 MU Dysport. This procedure features very high effectiveness. Initial effects are visible after 4–6 days and maximal after 14 days. The improvement is maintained for 6–7 months on average [2, 4, 11, 14, 23, 24].

Hypersalivation

Hypersalivation is caused by excessive saliva secretion by salivary glands. Acute oral and pharyngeal infections, alimentary intoxication, oral, pharyngeal and esophageal malignant tumors, and gastrointestinal reflux are etiological agents of hypersalivation. The disorder is unpleasant and embarrassing for the patient. The pharmacological treatment does not produce expected results and surgical treatment, for example denervation of parotid salivary glands, is associated with a high risk of undesired side effects. Botulinum toxin preparation is subcutaneously injected in the vicinity of the parotid gland, above the mandibular angle between the bone and the sternocleidomastoid muscle attachment. The doses applied are 75–100 MU Dysport or 15–20 MU Botox for each gland. Sixty percent of the dose is injected into the gland parenchyma and the remaining 40% into the masseter muscle. Good therapeutic results are maintained for several months [4, 25].

Lucy Frey Syndrome

Lucy Frey syndrome is caused by trauma of the auriculotemporal nerve or the great auricular nerve. The main symptoms include hyperhidration, redness, hypersalivation, hyperesthesia, and pain in facial regions when eating and drinking. They are intensified when consuming sour, spicy, and hot food. The treatment involving surgical

procedures or anticholinergic drugs is ineffective and associated with numerous side effects. Botulinum toxin is a drug of choice in treating Lucy Frey syndrome. Depending on the dominant symptoms (sweating or hypersalivation), the toxin is injected into the salivary gland or the facial skin. The facial skin injections are performed at several points in doses of 1.25 MU Botox per point. In the case of salivary gland injection, the doses applied are 10–20 MU Dysport or 2–4 MU Botox. First therapeutic results are achieved in as soon as a few minutes following the procedure and are maintained for over a year [4, 6, 22, 26, 27].

Botulinum Toxin in Neurology

Laryngeal Dystonia

The direct causes of laryngeal dystonia are brain stem injury and functional disorders of the basal ganglia, red nucleus, and ganglion of Soemmering. The most common type of this disorder is adductor spasmodic dystonia. Lesions mostly occur in the thyroarytenoid muscles, which are overactive and, consequently, are subject to excessive spasms that cause the larynx to close. As the patient needs to make an effort to speak, his speech has reduced volume, with sound breaks. Conventional phoniatric, pharmacological, and surgical treatment brings only minor effects, while botulinum toxin applied in adductor spasmodic dystonia treatment is very effective. The preparation is injected bilaterally, each dose being 2–3 MU Botox or 10 MU Dysport. Patients notice a significant beneficial effect as early as a few days after toxin administration. The therapeutic result is maintained for ca. six months. The abductor type of spasmodic dystonia occurs less frequently than adductor spasmodic dystonia. It involves spasms of the cricoarytenoid muscles. Vocal cords remain excessively open and the patient loses his voice. The treatment of this type of dystonia is more difficult and the results are not as good as in case of the adductor type. Doses applied and the procedure are the same in both types of dystonia [4–6, 28].

Bruxism

Bruxism is a focal dystonia. It is defined as excessive grinding of the teeth, mostly during sleep. Due to intensive grinding, the teeth are worn down, speaking, swallowing, and chewing problems appear, the patient feels pain in the mandibular joint, and trismus may occur. The botulinum toxin preparation is applied into the overactive temporal, masseter, and pterygoid muscles at dose of 80 MU Botox or 50–100 MU Dysport.

Botulinum toxin works very well to weaken the mandibular joints [4, 6].

Cervical Dystonia

Cervical dystonia, also known as spasmodic torticollis, is the most common form of focal dystonia. A characteristic symptom of the disorder is abnormal position of the head and neck, which results from frequent sustained involuntary contractions of the neck muscles. The direction of head movement depends on which muscle is overactive. The abnormal head position is accompanied by pain in neck muscles, swallowing and breathing disorders, nystagmus, head tremor, and paresthesia. The pharmacological treatment has positive results only at the initial stage. Surgical treatment is ineffective. Very positive therapeutic results are achieved when botulinum toxin is injected into the overactive muscles. Larger muscles may be injected at two sites, while smaller ones at only one. The preparation doses are 25–75 MU Botox or 100–300 MU Dysport for the splenius capitis, sternocleidomastoid muscle, and platysma, 15–30 MU Botox or 50–150 MU Dysport for the scalenus muscle, and 25–50 MU Botox or 100–300 MU Dysport for the cucullaris muscle. Patients notice improvement as early as 2–3 days after the procedure. The positive effect is maintained for 3–6 months [4–6, 14].

Writer's Cramp

Excessive cramp involves mainly extensor and flexor muscles of the fingers and wrists. It occurs as a result of excessive fine motor activity in, for example, musicians (violinists, pianists), secretaries, hair dressers, and athletes (golfers). The symptoms occur only when an individual is performing the particular activity. Pharmacological treatment and psychotherapy are ineffective. Botulinum toxin injections are the therapy of choice for writer's cramp. As extensor muscles are weaker than flexor muscles, the former are injected with doses smaller by 1/3 than the latter. In the first procedure, 50–100 MU Dysport or 20–40 MU Botox is applied. Good therapeutic results are maintained for 2 months [4, 6].

Foot Dystonia

Symptoms of this type of dystonia are foot muscle cramps that result in an equinovarus position of the foot or contraction of the toes. The patient is unable to place his foot correctly and his gait is impaired. Pharmacological treatment brings no results. Botulinum toxin injections are effective.

tive. They are applied into overactive calf muscles at doses of 80–160 MU Botox or 200–400 MU Dysport or into the short flexor muscle of the toes at doses of 40–60 MU Botox or 100–200 MU Dysport [4, 6].

Tourette's Syndrome

The most characteristic symptom of the disease is a tic. The patients show involuntary, paroxysmal, brief muscle spasms of the head, neck, or extremities, produce strange movements, for example wave their hands or put their tongue out, and also utter sounds, both undetermined, such as throat clearing, and words, often obscene. All these symptoms occur beyond the awareness and control of the patient. The most common treatment of Tourette's syndrome is pharmacological. When the symptoms are limited to one location, the patient can be qualified for botulinum toxin treatment. It brings good therapeutic results. The dose and drug administration depend on the group of muscles into which the toxin is going to be applied [4].

Hemifacial spasm

Hemifacial spasm is caused by a facial nerve defect. It is characterized by frequent involuntary spasms of the eyelid muscle. The spasm may then gradually spread to involve the orbital and mouth corner muscles. Long-lasting pharmacotherapy is ineffective. Surgical treatment improves the patient's condition, but it is associated with a risk of side effects so high that patients do not want to be subjected to it. Botulinum toxin treatment has excellent results. When the symptoms occur only in the eyelid, drug administration is identical to the management of blepharospasm, but only one side of the orbicular muscle is injected. In more severe cases, the preparation is applied into one site beneath the orbicular muscle of mouth, from where it is diffused into the muscle and into the zygomatic muscles that raise the corners of the mouth. The doses applied are 10 MU Dysport or 2–3 MU Botox. Complete recovery is achieved by 90% of patients for 3–5 months [4, 6, 14].

Tremor

Symptoms of tremor are rhythmic oscillatory movements involving one or more body parts. Tremor is associated with conditions which affect the cerebellum or inferior olivary nucleus or red nucleus. Pharmacological treatment is ineffective. Surgery is performed in serious and advanced cases only. Botulinum toxin has been

widely used in treating tremor since 1991. When an upper extremity is affected, botulinum toxin is injected into the extensor and flexor muscles of the forearm. The dose for an extensor muscle is 30–100 MU Botox or 100–200 MU Dysport and for a flexor muscle 30–100 MU Botox or 100–300 MU Dysport. Although the results are not fully satisfactory, the treatment offers relief for the patient and improves his quality of life [4].

Spasticity

Spasticity symptoms include an increase in muscle tone on stretching. It involves mostly anti-gravity muscles. Spasticity is caused by a central motor neuron defect. Spasticity treatment should be multistage and comprehensive. In the initial stage, drugs and physiotherapy are engaged. In later stages, surgery or botulinum toxin injections offer positive results. Botulinum toxin may help neutralize any adduction in the humeral joint, knee joint, or lower extremity joint and excessive contraction in the elbow joint, campus, fingers, and sole of the foot. It improves gait in equinovarus foot deformity and walking on tiptoes, enabling the patients to walk correctly. The doses applied vary depending on the muscle type, size, and activity. Positive therapeutic results are maintained for 8 months or longer [4–6, 16, 28–30, 31].

Other Medical Uses

An excessive lower esophageal sphincter spasm induces dysphagia in achalasia. This condition is caused by degenerative changes in the postganglionic vagus nerve. Pharmacological treatment brings only minor effects and surgery is associated with pain and a high risk of side effects. Botulinum toxin has been used in the treatment of achalasia since the 1990s and has brought good results. The preparation is injected into the sphincter of the esophagus with a sclerotherapy needle under endoscopic guidance. During a single procedure the patient receives 100 MU Botox into one or more sites. Relaxation of the sphincter is maintained for 6 months [4, 6, 32].

Botulinum toxin injections are also used in the treatment of other disorders. They are of smaller importance and efficacy. Sample applications include, but are not limited to, nystagmus, anal fissure, persistent constipation, anismus, vaginismus, and neurogenic bladder [2–5, 6, 14, 25, 31, 33].

Contraindications

A complete list of absolute contraindications has not yet been proposed. There are relative con-

traindications which must be observed to ensure the patient's safety. They include pregnancy, lactation, age under 12, oversensitivity to any component of the drug, specific drug use (e.g. aminoglycoside antibiotics), infection or inflammation at the site of application, myasthenic syndrome, myasthenia, Lambert-Eaton syndrome, Charcot-Marie-Tooth disease, sclerotic lateral atrophy, and peripheral neuropathy [3, 4, 6, 14, 15, 25, 31].

Side Effects

Most side effects are usually local and temporary. They do not suggest discontinuation of therapy. The most common include nausea, vomiting, fatigue, weakness, xerostomia, flu-like symptoms, fever, vertigo, headache, pain and burning sensation, itching at the injection site, hematoma, bruise, dermatomyositis, rash, allergic response, local inflammation, adjacent muscles weakness, ptosis, loss of motor coordination, diarrhea, intestinal gas incontinence, fecal incontinence, dysphagia, dysphonia, eversion of the eyelid, blepharoptosis, diplopia, and blurred vision [3–5, 7, 10, 14–16, 25, 30, 31].

Botulinum Toxin in Aesthetic Medicine

Botulinum toxin has been used in cosmetology and aesthetic medicine for the treatment of mimic facial wrinkles since the 1980s. It is more effective than other methods as it removes the cause of wrinkle formation. Botulinum toxin paralyzes and relaxes mimic facial muscles. Significant improvement is achieved in over 90% of patients. The best results are achieved in smoothing wrinkles in the upper third of the face (forehead, glabella, eye region). Procedures performed in the face's lower regions are not recommended as there are several fine and entangled muscles there. Therefore

it is more difficult to find the chosen muscle and the risk of side effects is higher. First effects can be noticed after 1–4 days. The maximal effect is achieved after 2–3 weeks and lasts for 3–6 months [1, 4, 11, 15, 34–36].

Wrinkles most frequently appear on the forehead and the glabella. They include horizontal wrinkles over superciliary arches, vertical wrinkles between eyebrows, horizontal forehead wrinkles, and latitudinal nose root area wrinkles. They are caused by hyperactivity of the frontal muscle, corrugator supercilii muscle, and procerus muscle. The frontal muscle is injected with 10–15 MU Botox into 4–5 sites, the corrugator supercilii muscle is injected with 5–10 MU Botox into 5 sites, and the procerus muscle is injected with 3 MU Botox. The treatment gives a frozen forehead effect and a normal position and shape of the eyebrows [4, 11, 15, 34–36]. Crow's feet are lines that extend from the lateral canthus. They appear as the first symptom of ageing. They are caused by hyperactivity of the eye's orbicular muscle, the risorius muscle, and the zygomaticus muscle. 8–12 MU Botox is injected into 2–4 sites of the orbicular muscle [4, 11, 15, 34–36].

Botulinum toxin preparations are also used in other branches of cosmetology and aesthetic medicine. Injections into wound edges prevent the formation of unsightly scars and improve the appearance of existing scars. Botulinum toxin may also be used for removing unwanted hair and chemical liposuction [2, 11, 14].

The authors concluded that botulinum toxin is used in various branches of medicine, most widely in neurology, ophthalmology, gastrology, and urology. It is applied to treat rare and difficult cases, often as a drug of choice. It is safe and may be used to cure both adult and pediatric patients. In the near future, some surgical operations and pharmacotherapy may be replaced by botulinum toxin treatment. Interest in botulinum toxin is constantly growing and research on its other uses is underway.

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