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Botulinum toxin in ophthalmology

Botulinum toxin (BTX), produced by Gram-positive rod of botuline *Clostridium botulinum*, is one of the most potent natural organic toxins. Its effects have been known since 1817 when a German doctor and poet, Justyn Kerner, described the case of fatal poisoning related to decaying sausage (7). Even small doses of the toxin introduced to the organism can cause dramatic clinical symptoms such as stomach-aches, paralysis of swallowing, breathing difficulties, aphonia, diplopia, and even death (1, 7). Botulinum toxin is captured by myoneural junctions which in effect become destroyed. Its action consists in permanent and complete destruction of myoneural junctions through blocking release of acetylcholine from the presynaptic terminals of muscarine (presynaptic ganglia) and nicotine (myoneural junction) synapses within myoneural plate. This leads to paralysis of the muscle. The effect of the toxin's action is transitory. After several weeks renewing of the destroyed myoneural endings begins, starting from the side of neural matrix – the so-called sprouting-reinnervation. So far, seven antigen-different neurotoxins have been identified produced by various strains of the botuline rod (A – G). The nervous system is sensitive only to five of them (A, B, E, F, G) (5). The molecules of each type of the neurotoxin are polypeptides with two chains – light one and heavy one, connected by a bisulphide bond. The heavy chain is responsible for selective binding of BTX by presynaptic membrane of cholinergic terminals in the peripheral nervous system. The light chain of BTX blocks the release of acetylcholine from presynaptic terminals into the synaptic cleft (7).

In 1973 ophthalmologist A l l a n S c o t t was the first to use BTX in treatment of strabismus by injecting it into extraocular muscles (13). From 1989 FDA (Food and Drug Administration) in the United States gave the permission to use BTX as a medicine in ophthalmology and neurology (1). The main indications for use of botulinum toxin are diseases with symptoms of muscular contractures or spasms. BTX finds application in treatment of segmentary facial-madibular-glossocervical dystonia, laryngeal dystonia, bruxism, torticollis, upper and lower limbs dystonia, facial nerve paralysis and diseases in which muscular spasticity occurs (1). Since 1990 it has also been used in aesthetic surgery for correction of dynamic facial lines, correction of the position of eyebrows and in treatment of hyperhydrosis (3). In ophthalmology BTX is used to treat blepharospasm, strabismus, nystagmus, dry eye syndrome and crocodile tears syndrome (1, 9).

Currently two forms of botulinum toxin are accessible: Dysport, produced by Beaufour Ipsen International Company (Great Britain) in vials of 500 international units, and Botox, produced by Allergan Incorporation Irvine Co., California, USA) in vials of 100 international units. There is also the preparation of botulinum toxin type B, Myobloc, produced by Elan Pharmaceuticals Company, used only in neck dystonia (inaccessible on the Polish market). The activity of one unit of Botox corresponds to the activity of four units of Dysport. The quantitative assessment of biological activity of BTX is carried out on mice. The toxicity of the drug is represented in international units (U), with 1 U equal to LD/50, that is the half of the dose lethal for mice when the toxin is administered intraperitoneally. The two undiluted preparations should be stored in different conditions. Botox A should be stored in temperature of approximately -5°C, whereas Dysport in the refrigerator or room temperature. BTX lyophilizate diluted in an isotonic salt solution in the amount of 2 or 2.5 ml should be used within 4 hours (FDA's guidelines). The diluted preparation

should be kept in a refrigerator in the temperature of 2–8°C. Inappropriate preservation conditions may have impact on the activity of the preparation (5).

Treatment with botulinum toxin should be thoughtfully planned, and the amount of the initial dose administered to the patient depends on age and sex. In cases of younger patients and females the initial dose is lower. The initial dose used in ophthalmology ranges from 2.5 to 25 U for Botox and from 7.5 to 75 U for Dysport (7). In following applications of the toxin, the dose is generally higher, although its amount is mainly dependent on the effects achieved after the previous injection.

Blepharospasm belongs to focal dystonies localised in eyelids. The disease consists in repeatable and involuntary closing of eyelids caused by contractions of the fibres of the orbicular muscle of eyes. The onset of the disease is usually in the fifth decade of life and patients are initially treated for conjunctivitis. First symptoms are hardly specific: burning, tackling, light intolerance, the feeling of dryness and irritation in eyes as well as frequent blinking. The onset is atypical, slow and takes the form of frequent blinking. These symptoms usually recede during sleep and are less prominent in the morning (14). Harsh light, smoke, air pollution, train or car travelling increase the symptoms of blepharospasm. Sometimes photophobia occurs. Then, ptosis and contraction of the eyelids appear. The contractions occur most often when vision is most needed. Over several years the frequency of contractions of eyelids may increase to such a degree that performing basic everyday activities becomes impossible. The patients become functionally blind. The contraction of the eyelids initially represents the disease of eye orbicular muscle alone but over time it can affect all facial mimic muscles, as well as muscles of tongue, larynx, esophagus and neck. In such cases the focal dystonia becomes the segmentary one and is called Meige's syndrome (1). Sometimes the disease begins with eyelids' ptosis without the contractory element. The patient is unable to open eyelids. This requires differentiation from myasthenia in which eyelids' closure occurs after effort and the contractory element does not occur. Pharma-cological treatment of blepharospasm usually shows poor effectiveness, it involves administration of anticholinergic medications, dopamine agonists and antagonists and neuroleptics (14). Surgical treatment is also of little efficacy and may lead to defective closure of the eyelids (14). Therefore, the treatment of choice is botulinum toxin injection to the orbicularis muscle. The drug is administered subcutaneously in the regions of both orbicularis muscles. The preparation of botulinum toxin is diluted in 0.9% solution of NaCl using 1 mm syringe calibred in such a way that 0.1-grade volume contains 20 units of Dysport or 4 units of Botox respectively. This means that one has to add 2.5 ml of 0.9% NaCl to one vial. Most commonly 2 injections are made medially and 2 laterally into the junction between the eyelid and orbital parts of the lower and upper segment of orbicularis muscles of each eye in the total amount of approximately 120 U of Dysport for each eye. It is also important that the volume of the injected medicine does not exceed 0.2 ml per injection (14).

The next indication for use of botulinum toxin is crocodile tears syndrome (9). This rare syndrome, described for the first time in 1913, manifests with unilateral hyperlacrimation which occurs while eating or drinking. It can also occur in Bell's palsy or in palsies following head traumas and in Duane's syndrome (11). The cause of this syndrome is faulty regeneration of the nerve fibres of the lacrimal gland, deriving from facial or glossopharyngeal nerves. Others believe that the nerve fibres do not regenerate but create an artificial synapse in the site of trauma which allows the impulses from one nerve to pass to the other nerve and interactions between afferent and efferent axons (12). In the management of this syndrome paraorbital injections of alcohol or cocaine have been used in order to destroy extraganglial fibres of the sphenopalatine ganglion, partial resection of the lacrimal gland, cutting facial and glossopharyngeal nerves, and in pharmacological treatment anticholinergic medications have been used (9). The treatment results were not always satisfactory. They often led to complete inhibition of lacrimation. Currently botulinum toxin finds application in the treatment of crocodile tears syndrome. The injections are made with 10 U of Botox or 50 U of Dysport into the lacrimal gland, into the region of external upper 1/3 part of the edge of orbital cavity, intracutaneously or through the conjunctiva after anaesthesia of the upper crease with a tampon. Montoy et al. think that the administration of the toxin through the conjunctiva secures penetration of the whole dose of the medication directly into the lacrimal gland (9).

In the management of strabismus, botulinum toxin is used for several indications: in the treatment of concomitant strabismus (esophoria, exophoria, hyperphoria and hypophoria); in primarily small angle of squint; in cases of maintenance of residual angle following surgery when fibrosis of the muscle caused by scarring is not considerable; in all forms of paralytic strabismus – paralysis of nerves III, IV and VI; also in strabismus occurring as the result of endocrinological diseases, for example in hyperthyroidism or diabetes (6, 7, 10). In paralytic strabismus it is important to eliminate the danger associated with overactivity of the muscle antagonistic to the palsied one, which may lead to contracture, and consequent fibrosis of the muscle with stronger activity. Injections of 2.5 U of the preparation of Dysport diluted in 0.1 ml of 0.9% NaCl are made to the chosen muscle. The injection of botulinum toxin into the overactive muscle causes its temporary palsy or weakening. Then, relaxation and lengthening of this muscle occurs which in consequence leads to strengthening of the activity (transient overactivity) of its antagonist. When the activity of botulinum toxin and the weakening of the palsied muscle have receded, the correct position of eyeballs is often found, that is the decrease of the angle of squint and development of binocular vision (6). Better results were found with the earlier onset of the treatment.

Another indication for the application of botulinum toxin is nystagmus (1). The term nystagmus is used to describe involuntary oscillatory movements of eyeballs. It can be congenital or acquired; it occurs in diseases of the middle ear, brain stem or cerebellum. In its treatment extraocular injections of 25 U of Dysport preparation are indicated. Performing the injection on one side requires temporarily covering of the other eye due to frequently occurring diplopia. Most commonly botulinum toxin finds application in the treatment of monocular nystagmus affecting a blind eye. However, the treatment results are not satisfactory.

Botulinum toxin can also be used in the treatment of dry eye syndrome (1). Into the medial section of the upper and lower eylid, from 5 to 10 U of Dysport preparation are administered in order to paralyse the lacrimal pump. Other indications for botulinum toxin include neurotrophic keratopathy, exposure keratopathy and eyelid retraction. In these cases injections of botulinum toxin in 5–10 U of Dysport into medial section of the upper eyelid are performed in order to cause its ptosis (4). Combined with intense local treatment, induced ptosis is more effective than lateral tarsorrhaphy in protection of the cornea (4, 15).

Side-effects which can appear during treatment are local and transient, seldom systemic. They occur in 10% of patients. They are not life-threatening. They retreat over several days or weeks following the injection and do not leave any permanent traces. At the injection site transient pain, sensation of burning, oedema or ecchymosis may occur. The local symptoms are due to temporary denervation of other muscles not intended for treatment to which botulinum toxin could pass through as a result of diffusion or improperly performed procedure. They do not require special treatment. Systemic complications in the form of mild intoxication occur extremely seldom (1).

Concluding, botulinum toxin being used during the last 20 years is a method of symptomatic treatment of many incurable diseases. Treatment with botulinum toxin has been recognized as safe and suitable in ambulatory settings. The relative contraindications for its use include myasthenia, myasthenic syndromes, pregnancy and breast feeding (1).

REFERENCES

1. Domżał T. M.: Toksyna botulinowa w praktyce lekarskiej. Dystonie, spastyczność, ból i inne wskazania lekarskie. Wyd. Czelej, Lublin 2002.
2. Duchen L. W., Tonge D. A.: The effect of implantation of extra nerve on axional sprouting usually induced by botulinum toxin in skeletal muscle of the mouse. J. Anat., 124, 205, 1977.
3. Fagien S.: Botox for the treatment of dynamic and hyperkinetic facial lines and furrows: adjunctive use in facial aesthetic surgery. Plast. Reconstr. Surg., 103, 710, 1999.

4. Fraco M. F. E., Fraco M. D.: An evaluation of the safety and efficacy of botulinum toxin type A (Botox) when used to produce a protective ptosis. Clin. Exp. Ophthalmol., 29, 394, 399, 2001.
5. Huang W. et al.: Farmakologia toksyny botulinowej. Dermatologica,1, 6, 2001.
6. Krzywicki S., Kruszewska-Bogusz B.: Wyniki stosowania toksyny botulinowej (BTA) w różnych postaciach zeza u dzieci. Okulistyka, 3, 37, 2002.
7. Krzywicki S.: Toksyna botulinowa (BTX) i inne sposoby chemodenerwacji w okulistyce. Okulistyka, 3, 33, 2002.
8. Lyons C. J. et al.: Botulinum toxin therapy in dysthroid strabismus. Eye, 4, 538, 1990.
9. Montoya F. J. et al.: Treatment of gustatory hyperlacrimation (crocodile tears) with injection of botulinum toxin, into the lacrimal gland. Eye, 16, 705, 2002.
10. Oliver J. M.: Botulinum toxin, a treatment of overactive corrugator supercilii in thyroid eye disease. Br. J. Ophthalmol., 82, 528, 1998.
11. Ramsay J., Taylor D.: Congenital crocodile tears: a key to the aetiology of Duane's syndrome. Br. J. Ophthalmol., 64, 518, 1980.
12. Sadjadpour K.: Postfacial palsy phenomena: faulty nerve regeneration or ephatic transmission? Brain Res., 95, 403, 1975.
13. Scott A. B. et al.: Pharmacological weakening of extraocular muscles. Invest. Ophthalmol., 12, 924, 1973.
14. Wróblewska E., Gerkowicz M.: Zastosowanie toksyny botulinowej w leczeniu samoistnego skurczu powiek. Okulistyka, 3, 30, 2002.
15. Yen M. T., Anderson R. L.: Botulinum Toxin for Ophthalmologists. Ophthalmology, 2, 14, 1, 2003.

SUMMARY

In the paper the indications for use of botulinum toxin in ophthalmology have been described. Botulinum toxin (BTX), produced by Gram-positive rod of botuline *Clostridium botulinum*, is one of the most potent natural organic toxins. In 1973 an Allan Scott, ophthalmologist, was the first to use BTX in treatment of strabismus by injecting it into extraocular muscles. The main indications for the use of botulinum toxin are diseases with symptoms of muscular contractures or spasms. BTX finds application in treatment of segmentary facial-madibular-glosso-cervical dystonia, laryngeal dystonia, bruxism, torticollis, upper and lower limbs dystonia, facial nerve paralysis and diseases in which muscular spasticity occurs. Since 1990 it has also been used in aesthetic surgery for correction of dynamic facial lines, correction of the position of eyebrows and in treatment of hyperhidrosis. In ophthalmology BTX is used to treat blepharospasm, strabismus, nystagmus, dry eye syndrome and crocodile tears syndrome.

Toksyna botulinowa w okulistyce

W pracy przedstawiono wskazania do zastosowania toksyny botulinowej w okulistyce. Toksyna botulinowa (BTX), produkowana przez Gram+ pałeczkę jadu kiełbasianego *Clostridium botulinum*, jest jedną z najsilniej działających naturalnych trucizn organicznych. W roku 1973 okulista Allan Scott jako pierwszy zastosował BTX w leczeniu zeza, wstrzykując ją do mięśni zewnętrznych gałki ocznej. Głównym wskazaniem do stosowania toksyny botulinowej są schorzenia, których objawem są przykurcze lub skurcze mięśni. BTX znajduje zastosowanie w leczeniu dystonii segmentarnej twarzowo-żuchwowo-jezykowo-szyjnej, dystonii krtaniowej, w bruksizmie, kręczu karku, w dystoniach kończyn górnych i dolnych, w porażeniu nerwu twarzowego oraz w schorzeniach przebiegających ze spastycznością mięśni. Od roku 1990 stosowana jest również w medycynie estetycznej do korekcji zmarszczek dynamicznych twarzy, do korekcji ustawienia brwi oraz w leczeniu nadmiernej potliwości. W okulistyce BTX stosowana jest do leczenia samoistnego skurczu powiek, zeza, oczopląsu, zespołu suchego oka oraz zespołu krokodylich łez.