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Topical review

Botulinum toxin A in the treatment of headache syndromes and pericranial pain syndromes

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1. New areas of application for botulinum toxin A

For 20 years, botulinum toxin A has been used for treating a variety of disorders characterized by pathologically increased muscle contraction. Current research efforts focus on new areas of application for botulinum toxin A in specific pain therapy, particularly in primary headache syndromes and in myofascial pain syndromes of the neck, shoulder girdle and back. This opens up new options for patients with hitherto therapy-resistant chronic pain syndromes. From a scientific view, it offers new perspectives for basic research and clinical analyses of these syndromes. There is also a need to rethink and analyze the modes of action of botulinum toxin A. The use of botulinum toxin A in pain therapy, however, calls for a detailed knowledge of functional anatomy and for expertise in practical applications.

2. Modes of action of botulinum toxin A in pain therapy

2.1. Normalization of muscular hyperactivity

Marked analgesic effects of botulinum toxin A have long been known from the treatment of painful craniocervical dystonia (CCD). The neurotoxin causes an irreversible presynaptic blockade of the release of acetylcholine at the motor end plates, and thereby brings about a normalization of the permanent contraction of the musculature. Depending on the dose, this may occur after a period of hours or days. The neuromuscular end plates react with a collateral sprouting of axons that restores the initial situation within a period of 3–6 months (Aoki, 1998). The therapeutic influence on the pain is particularly successful (Greene et al., 1990; Jankovic and Schwartz, 1990; Göbel and Deuschl, 1999) and is achieved in virtually all patients treated. The actual motor disturbance, however, is less easy to influence effectively; improvements are achieved in about 90% of treated cases of blepharospasm and spasmodic dystonia, and about 80% of treated cases of spasmodic torticollis. The pain alleviation frequently sets in considerably earlier, before the muscular relaxation can be observed. Moreover, the pain reduction may be considerably more marked than the muscular improvement (Brin et al., 1987). At first glance, the common denominator of pain syndromes in which botulinum toxin A is used successfully would appear to be the disturbance of normal muscle activity. The normalization of this activity is an obvious reason for the pain reduction. Clinical observations, however, argue in favour of a more complex mechanism. For example, pain alleviation may also be observed in areas of muscle where no reduction in muscular tension takes place (Brin et al., 1987). The pain alleviation, e.g. in the treatment of spasmodic torticollis, may set in only a few days after the injection, long before any relaxation of the excessive muscle contraction. Also, the pain alleviation may sometimes last beyond the period of muscle relaxation. In cases of multifocal or segmental dystonia, the administration of botulinum toxin often has a favourable effect on the untreated muscle groups. Neuromuscular denervation due to a blockade of acetylcholine transmission is therefore not a sufficient explanation of the analgesic effects of therapy.

2.2. Normalisation of excessive muscle spindle activity

The muscle-relaxing properties of botulinum toxin A are used for therapeutic purposes in a number of other muscular disorders of the striated muscles, e.g. spasticity and myofascial pain syndrome. In myofascial pain syndromes, the progressive and persistent muscular relaxation due to botulinum toxin A may permit decompression of afferent nociceptive neurons of the muscle and the muscular blood vessels. There may also be an influence on the excessive

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muscle spindle activity (Filippi et al., 1993; Rosales et al., 1996). Studies by Filippi et al. (1993) have already shown that botulinum toxin A can also act directly on sensory muscle properties. A blockade of gamma fibres can be detected within 80 min after administration. A reduction in muscle spindle activity causes by reflex a reduction in the activity of the alpha motor neurons without any need for chemical denervation. Studies by Rosales et al. (1996) have also shown that botulinum toxin A acts on both extrafusal and intrafusal muscle fibres, and that the change in muscle spindle activity is an important action mechanism. The change in motor reflex activity is not confined entirely to peripheral mechanisms. Indeed, it is also possible to modulate and reorganize central afferent and efferent control mechanisms of muscle activity (Giladi, 1997). This even makes effects possible in areas outside the injection zone.

2.3. Retrograde neuronal uptake into the CNS

Further studies suggest a retrograde uptake of botulinum toxin A in the peripheral and central nervous system. Only 48 h after peripheral injection, radioactively-labelled botulinum toxin A was found in the dorsal root and the spinal cord (Wiegand et al., 1976; Wiegand and Wellhoner, 1977). This also corresponds roughly to the point when the analgesic effect can be clinically observed. Other studies show that botulinum toxin A administered spinally has a direct inhibitory effect on motor neurons (Benecke et al., 1975; Hagenah et al., 1977). Recent studies by Aoki (1998) with radioactively-labelled botulinum toxin A show that there is a retrograde neuronal uptake of botulinum toxin A into the CNS. At the same time, it diffuses into wide areas around the muscular injection site. These studies suggest that it is not the entire protein that undergoes retrograde transport in the CNS, but rather metabolites. It is conceivable that these have an effect on sensory nociceptive systems that go far beyond the peripheral chemodenervation by botulinum toxin A, and have hitherto remained unnoticed (Guyer, 1999). It is possible that such effects relate, in general, to exocytosis of neurotransmitters and neuropeptides, which are important in the triggering and maintenance of pain.

2.4. Inhibition of the release of substance P and effect on other neurotransmitters

Botulinum toxin A inhibits not only the release of acetylcholine, but also the release of substance P from trigeminal nerve ends (Ishikawa et al., 2000). Substance P is a powerful neurotransmitter in the activation of a neurogenic inflammation (Purkiss et al., 1997), which is regarded as a mechanism of migraine headaches. Calcium-dependent substance P inhibition in the spinal cord neurons of the rat can also be used for testing various toxin subtypes (Yokosawa et al., 1994; Welch et al., 2000). Humm et al. (2000) studied the effect of chemodenervation with botulinum toxin A injected into the gastrocnemius muscle on the expression of enkephalin, neurotension, galanin, substance P, vasoactive intestinal polypeptide (VIP) and neuropeptide Y in the spinal cord of the rat. The expression of enkephalin in the spinal cord was bilaterally elevated, and even remote areas of the relevant dorsal root were included. Activation reached a maximum at 7–14 days after injection and lasted for 3 months. Botulinum toxin A can also activate the expression of substance P in the raphe nuclei (Van den Bergh et al., 1996). This core area is particularly associated with the pathophysiology of migraine as a so-called 'migraine generator' (Weiller et al., 1995). These studies all show that botulinum toxin A can exert powerful effects on headache mechanisms of the central nervous system.

2.5. Rationale for the treatment of primary headaches

An area of particular interest in the treatment of headache is the possible modes of action. Several modes of action are evident in tension-type headache. The reduction of muscular stress due to direct muscle relaxation leads to a reduced sensory input into the nervous system. The elimination of the oromandibular dysfunction as an aggravating factor in the chronic headache syndrome helps to ease the burden on the sensory and motor systems. Direct treatment of tender points and trigger points (Travell and Simons, 1993) leads to decompression of afferent nociceptive neurons of the muscle. The compression of muscular blood vessels is eliminated, the elevated concentration of excitatory metabolites is reduced. A normalization of the excessive muscle spindle activity can reduce the permanent tonicity of the pericranial musculature in the tension-type headache.

More than half of patients with frequent migraine attacks also suffer from tension-type headaches. The rationale for prophylactic treatment of frequent migraine attacks therefore consists in first improving or eliminating the tension-type headache with botulinum toxin A. This reduces or eliminates an important stress factor as a trigger for further migraine attacks. At the same time, it makes it possible to reduce the intake of acute medication for the treatment of the tension-type headache. This reduction in acute medication helps to reduce a high medication intake rate, and hence, to avoid medication-induced headache. In the transitional period prior to the emergence of a medication-induced headache, there is usually an increased migraine attack frequency, which can be reduced by treatment with botulinum toxin A. Another important factor, however, is the direct elimination of muscular triggers for migraine attacks. These may exist in the form of local painful muscle areas and act as permanent and powerful triggers of migraine attacks. It is understandable that eliminating them directly avoids migraine attacks. The consequence is that the CNS is protected from excessive sensory overflow. Just as excessive noise and light may trigger migraine attacks, permanent pain stimulation from the pericranial muscles may also act as a migraine trigger. Elimination of this trigger avoids the triggering of further migraine attacks.

A new study by Cui and Aoki (2000) has also demon-

strated direct antinociceptive effects of botulinum toxin A on inflammation-induced pain in an animal experiment. This showed a dose-dependent reduction in the nociceptive response in cases of formalin-induced arthritis in rats' paws 12 days after injection. The administration of 3.5 or 7 U/kg per paw resulted in a reduction of 29 or 46%, respectively compared with placebo. It is interesting to note that no muscular effect was observed at the chosen doses. The basis for migraine pain is a neurogenic inflammation of the dural and meningeal arteries. In view of the investigations by Cui and Aoki (2000), it is conceivable that as a result of retrograde uptake of botulinum toxin A into the central nervous system, these inflammatory changes are blocked by direct effects on the trigeminovascular system and that botulinum toxin A thus has a direct impact on the pathophysiology of migraine.

In cluster headaches, venous phlebitis in the region of the cavernous sinus is regarded as the mechanism of the pain. For example, a study by Göbel et al. (2000) showed a marked plasma extravasation of 99m-Tc-labelled human serum albumin in the region of the cavernous sinus and the superior petrosal sinus in patients during an active cluster period. Recent pilot studies using botulinum toxin A for the treatment of therapy-resistant cluster headache show evidence of clinical efficacy. Here too, the prevention of inflammatory changes by retrograde neuronal uptake and inhibition of excitatory neurotransmitters is a possible rationale for therapeutic use.

3. Clinical studies on treatment of chronic pain with botulinum toxin A

The influence on pain during treatment with botulinum toxin A was first publicized in clinical case reports. The treatment was for myofascial pain syndromes (Acquadro and Borodic, 1994; Cheshire et al., 1994), disorders in the region of the mandibular joint (Moore and Wood, 1994), facial pain (Girdler, 1994) and tension-type headache (Zwart et al., 1994). The numbers of cases were small and the findings contradictory. In view of the increasing evidence of efficacy, placebo-controlled, double-blind and randomized studies with larger numbers of cases have also been conducted in recent years.

In the year 2000, no less than five studies have been published which investigated the efficacy of botulinum toxin A in the treatment of migraine. It is interesting to note that all the studies show evidence of good and consistent efficacy of botulinum toxin A. Special mention must be made of the controlled studies by Brin et al. (2000) and Silberstein et al. (2000). Both studies were conducted in a double-blind and placebo-controlled fashion using a standardized injection design. These studies observed a significant reduction in the intensity of the migraine attacks, and Silberstein et al. also found a reduction in the frequency of the attacks. The required doses of botulinum toxin A were relatively low, particularly in the case of the study by Silberstein et al. with 25 MU Botox®. The non-significant clinical efficacy of 75 MU in the study by Silberstein et al. is probably explained by a randomization error due to the standardized choice of injection sites. Mauskop and Basdeo (2000), using 25–100 MU Botox® in an open study with individual injection choice, documented a reduction in the frequency of migraine attacks or a reduction in pain intensity in 23 out of 27 patients. Using a similar open study design, Smuts and Barnard (2000) and Binder et al. (2000) found positive results.

For the cluster headache, there are only individual case reports, and thus, it is not yet possible to make any pronouncement about the efficacy of botulinum toxin A. An important improvement is nevertheless found here too in some cases that were hitherto therapy-resistant. In all documented case reports so far, botulinum toxin A was used in an open design with individual injection choice. Ginies et al. (1996) were the first to present positive results. In three out of five patients they managed to end the current cluster period. In the case report of Freund and Schwartz (2000a), the cluster period ended in two out of two patients, whereas Smuts and Barnard (2000) found positive results in two out of four patients. Larger studies are currently in progress to permit a better assessment of the therapeutic effect.

The largest number of clinical studies is available for the tension-type headache. The results, however, are contradictory. After the first negative report of Zwart et al. (1994), who, in an open study with individual injection choice, did not find an improvement in any of six patients treated with 30–40 MU Botox®, all later case reports and open studies presented positive results. Krack et al. (1995) first described a patient with tension-type headache who became pain-free after injection of 160 MU Dysport®. Relja (1997) treated ten patients with 15–35 MU Botox® using individual injection sites. She found a significant reduction in headache duration, pain intensity and pain sensitivity. In a further 24 patients treated using the same design, Relja (2000) found a lasting effect in long-term use over 15 months. An important point to note is the fact that the repeat injections had a step-like therapeutic effect: the consecutive therapeutic effect of each injection built on the effect previously achieved. In an open study, but using a standardized injection design (200 MU Dysport®), Schulte-Mattler et al. (1999) significantly reduced the product of pain duration and pain intensity in a group of eight patients. Smuts and Barnard (2000) showed positive results in 30 out of 50 patients treated with 100 MU Botox® in an open and individual fashion.

However, when double-blind and placebo-controlled studies were performed, it was not possible to detect any significant efficacy of botulinum toxin A. Göbel et al. (1999) treated ten patients each with either 80 MU Botox® or placebo, Rollnik et al. (2000) treated 11 patients with 200 MU Dysport® and ten patients with placebo. In both cases,

no reduction was found either in pain intensity, pain-free days or in the use of analgesics.

These studies chose a standardized design with defined injection sites. For standardization reasons, there was no individual selection of trigger points. Furthermore, as a rule, only patients with a long therapy-resistant case history were included in the studies.

Thus, an important finding of the experience to date with botulinum toxin A in therapy of tension-type headache is that the injection should be performed at the site of the pain or the trigger points, and not on a standardized basis. Just as the injection is made specifically into the affected muscle in the treatment of dystonia cases, this must also be done in the treatment of pain. It would not be surprising if botulinum toxin A failed to have a therapeutic effect on spasmodic torticollis under a bilateral standardized injection regime, and the same applies to the treatment of tension-type headaches. It is essential that this crucial point be observed in future controlled studies and in open use. If one considers the range of doses of botulinum toxin A used, which in the positive studies ranged from 15 to 100 MU Botox® or from 160 to 200 MU Dysport®, the total dose injected would appear to be of secondary importance.

It would also appear to be important that a particularly good efficacy seems to result in cases where both migraine and tension-type headaches exist (Klapper et al., 2000; Wheeler, 1998). Most studies dealt with either one syndrome or the other. Klapper et al. treated patients with chronic daily headache in a double-blind, placebo-controlled trial using 25.5–72.5 MU Botox®. In a subgroup with two injection regions ($n = 19$, active drug), they found a reduction in headache duration and in the frequency of moderate and severe headaches. Wheeler achieved the same results in a group of four patients treated open with 20–120 MU Botox®.

In the case of the cervicogenic headache, all open studies or case reports published so far demonstrated the efficacy of botulinum toxin A. The first case report was presented by Hobson and Gladish (1997). In one patient, 50 MU Botox® lead to a 50% reduction in headache frequency. Freund and Schwartz (1999) found a reduction in pain intensity and an increase in neck mobility in a group of eight patients treated. Smuts and Barnard (2000) treated one patient successfully.

In a double-blind, placebo-controlled study, Freund and Schwartz (2000b) managed to underpin the positive results of these open studies. After injection of 100 MU Botox® in 14 patients, there was both a reduction in the pain intensity and an increase in neck mobility compared with the placebo group with 12 patients.

Botulinum toxin A has been in successful use for several years now for the treatment of temporomandibular dysfunctions or masseteric hypertrophy. Despite several case reports and open studies, however, there are no positive, controlled studies yet. In 1994, Moore and Wood first described a positive result after injection of 100 MU Botox® in one patient (Moore and Wood, 1994). Rijsdijk et al. (1998) achieved freedom from pain in one out of two patients treated with 40–60 MU Botox®. The biggest number of patients was treated by Freund et al. (1999). The 15 patients treated individually with 150 MU Botox® showed a significant reduction in pain intensity, an improvement in opening of the jaw, a reduction in pain sensitivity, however, no change in biting power.

4. Special features

Botulinum toxin A represents a completely new option for patients with chronic pain syndromes, especially migraine and tension-type headaches. The use of this active substance does not result in any side-effects on the CNS. Owing to the undesirable side-effects of the medication used, headache patients in particular frequently suffer considerably from fatigue, giddiness, reduced concentration, increased appetite and weight, hair loss and changes in libido. These side-effects are unknown with botulinum toxin A. No cases of damage to organs have been reported to date; nor have allergic complications been observed to date. Thus, the tolerability and safety of this therapeutic measure are very high. Its long-term action lasting several months obviates the need to remember to take medication several times a day. The efficacy of follow-up injections does not start from the starting point of the first injection, but builds on the therapeutic results of the preceding treatment in a step-like effect. If muscular stress, self-sustaining trigger points and tender points are the cause of or an aggravating factor in the headache syndrome, a single treatment is sufficient to break the vicious circle of chronification of the pain syndrome. No further treatments are then required. Numerous clinical studies are currently investigating in detail the new applications of botulinum toxin A in the field of specific pain therapy. The data and findings already available open up new approaches to the treatment and analysis of the pathomechanisms of these widespread chronic pain syndromes.

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