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Clinical comparison of botulinum toxin in motor and autonomic disorders: Similarities and differences

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ABSTRACT

Botulinum toxin is a well established, highly effective and safe treatment option for movement disorders and autonomic diseases with excellent long term results. There is increasing evidence that the beneficial effect in both motor and autonomic indication is based on a complex mode of botulinum toxin action modulating efferent as well as afferent nerve fiber activity. In particular, this has been shown for the treatment of dystonia, spasticity and overactive bladder. A unique observation is that botulinum toxin has a markedly longer duration of action in autonomic than in motor disorders for which the reason remains unclear. Although botulinum toxin type B seems to have an initially higher affinity to autonomic nerve endings there is currently no clear evidence that type B is superior to type A in autonomic disorders. The risk of antibody formation probably does not depend on the target tissue injected and seems to be similar for movement disorders and autonomic indications. More research is needed to better understand similarities and differences of treatment outcome in motor and autonomic disorders.

1. Introduction

Botulinum toxin (BoNT) has been used to treat movement disorders for nearly three decades as a safe and effective treatment option with predictable outcome. Based on clinical observations in dystonia and spasticity patients it has become obvious that the mode of BoNT action cannot be explained exclusively by the direct blockade of acetylcholine release at the neuromuscular junction and that BoNT is capable of modulating also afferent nerve fiber activity to the central nervous system. Growing knowledge about new therapeutic areas such as autonomic disorders (i.e., focal hyperhidrosis, overactive bladder) and pain (i.e., chronic migraine) indicated that BoNT has not only a complex mode of action but also indication specific effects which are poorly understood so far. This article provides a clinical comparison of BoNT effects in motor and autonomic disorders to address similarities and differences between these two well established fields of BoNT use. Pain disorders and gastroenterological indications for BoNT will not be covered in this paper.

2. Comparison of clinical effects

2.1. Efficacy

The efficacy of BoNT in the treatment of movement disorders as well as autonomic disorders has been demonstrated in several randomized controlled trials (RCT). Although no direct comparisons are available, there are several Class 1 and 2 studies indicating that BoNT is highly effective in both motor (focal dystonias, focal spasticity, essential tremor) and autonomic indications (focal hyperhidrosis, hypersalivation, and hyperactive bladder) (Simpson, 2008; Naumann, 2008).

2.2. Duration and effect of repeat injections on duration

The definition of duration of effect after BoNT administration remains challenging and direct comparisons between autonomic and motor disorders are lacking. Duration is influenced by several parameters such as the total dose injected (Marsh et al., 2014), the chosen injection schedule (predefined fixed intervals or patient driven flexible reinjections) or the attainment of defined severity scores for reinjection. Moreover, there is also a difference between the clinical and the biological duration of BoNT application:

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clinically, the beneficial effect of BoNT lasts about three months in most cases of dystonia (Marsh et al., 2014) or spasticity patients, whereas the biological effect on muscle fiber activity can be observed for at least six months as demonstrated in animal models (Fortuna et al., 2013).

There is overwhelming evidence that the clinical effect of BoNT is markedly longer in autonomic disorders than in motor indications. A recent meta-analysis of BoNT studies in cervical dystonia showed a mean duration of 93 days (Marsh et al., 2014) similar to what has been reported in focal spasticity. In contrast, RCTs in focal hyperhidrosis (axillary sweating) have shown a relatively long duration of up to 30 months (Naumann, 2001; Heckmann, 2001). A prolonged duration is also seen after BoNT administration to the salivary glands in drooling (median duration 150 days) (Scheffer et al., 2010) or to the bladder detrusor muscle in overactive bladder (mean duration 8.5 months) (Sengoku et al., 2015). The longest duration among all BoNT indications, however, is found in gustatory sweating where intracutaneous injections of BoNT abolish pathological sweat secretion on the cheek for a period of 6–36 months (Naumann M, 1997; Laskawy, 1998; Laccourreye, 1999). The reason why autonomic disorders have this prolonged benefit compared with movement disorders is unclear and needs further scientific study.

The effect (and safety) of long term application of BoNT has been analyzed in several retrospective studies which, however, have their immanent limitations. Moreover, comparative long-term studies between motor and autonomic indications are not available. Mejia et al. (Mejia et al., 2005) and Ramirez-Castaneda J et al. (Ramirez-Castaneda, 2013) followed their focal dystonia patients for up to 15.8 and 20 years, respectively, and reported an increase of dose and duration with repeat injections (onabotulinum toxin A). In contrast, Dressler et al. (Dressler et al., 2015) found a stable duration with repeat injections of onabotulinum and incobotulinum toxin A in cervical dystonia patients. This was in accordance with a study by Kollewe et al. (2015) who reported a stable duration and treatment effect in blepharospasm patients over up to 11 years using three different type A toxins (onabotulinum, abobotulinum, and incobotulinum toxin A). Data on repeat injections in autonomic disorders are sparse and hetereogeneous showing either an increase of duration in a study on focal hyperhidrosis over a period of up to 11 years (abobotulinum toxin) (Lecouflet et al., 2014) or even a fading effect in drooling after up to seven injections (rimabotulinum toxin B) (Møller et al., 2015). Thus, in summary there is currently no clear evidence that repeat injections of BoNT would lead to a dose-independent increase of duration in motor or autonomic indications.

2.3. Safety and long-term safety

An excellent safety profile has been shown for the use of BoNT in movement disorders as well as autonomic indications based on many RCTs (Simpson, 2008; Naumann, 2008). A meta-analysis enrolled the safety data of 36 RCTs with a wide range of therapeutic uses (motor, autonomic, pain) meeting evidence-based medicine standards (Naumann and Jankovic, 2004). Mild to moderate local (and transient) side effects were more frequently observed in the BoNT treated groups, however, no study reported any severe side effects. Thus, although direct comparisons are lacking, there is no evidence for differences in safety between motor and autonomic indications.

2.4. Comparison of BoNT type A versus type B in motor and autonomic disorders

Two RCTs compared the efficacy and safety of onabotulinum toxin A with rimabotulinum toxin B in cervical dystonia (Comella, 2005; Pappert, 2008). Both studies found a significant and equally effective reduction of severity (TWSTRS) for both onabotulinum toxin A (mean dose 205 MU and 150 MU, respectively) and rimabotulinum toxin B (mean dose 8520 MU and 10,000 MU, respectively). Duration was inconsistent with no difference between the two toxins in one study (Pappert and Germanson, 2008) and a significantly longer duration of rimabotulinum toxin B in the other trial (Comella et al., 2005). In both studies, however, mild dry mouth was significantly more often reported after rimabotulinum toxin B administration raising the question if botulinum toxin type B might have a higher affinity to autonomic cholinergic nerve endings and be preferable to type A in the treatment of autonomic disorders. There are only a few studies that provide a direct comparison between botulinum toxin type A and type B in autonomic disorders. Guidubaldi et al. (Guidubaldi et al., 2011) compared the effect of abobotulinum toxin (mean 250 MU) and rimabotulinum toxin (2500 MU) in ALS and PD patients suffering from disabling drooling. Injections were given into the salivary glands under sonographic guidance. There was a significantly shorter onset of effect after type B injection, while duration and efficacy were comparable. A similar early effect of rimabotulinum toxin was observed in another small trial in patients with axillary hyperhidrosis (Frasson et al., 2011). Kranz et al. (Kranz et al., 2011) compared intradermal injections of 4–8 MU onabotulinum toxin and 150–600 MU rimabotulinum toxin in 18 volunteers and measured the effect and time course of sweat secretion over 54 weeks. Both toxins significantly reduced sweating. Type B showed a larger anhidrotic area at week 3 but also a more rapid decline compared to type A. Type A had a larger effect at week 24 and a longer duration than type B. In summary, based on preliminary data, there is no clear evidence that botulinum toxin type B is superior to type A in autonomic disorders, however, onset and loss of effect may occur earlier with BoNT type B.

3. Immunogenicity

Formation of antibodies (AB) against a specific botulinum toxin preparation may lead to secondary non-response and its frequency may theoretically differ between autonomic and motor indications as different target tissues (i.e., striated and smooth muscles, skin or glands) with potentially distinct immunological properties are exposed to BoNT. This has, however, never been studied in comparative trials. In general, the interpretation of AB data published is difficult as the results are markedly influenced by a variety of factors (Naumann, 2010; Naumann et al., 2013a,b) such as the type and sensitivity of antibody tests used, the number of injection cycles, the cumulative dose of treatment, and the definition of a “non-responder” (i.e., partial vs. full non-response). A recent comprehensive meta-analysis (Naumann et al., 2010) of the immunogenicity of onabotulinum toxin across 16 clinical trials (cervical dystonia, spasticity, glabellar lines, focal hyperhidrosis, overactive bladder) showed an overall rate of antibody-formation of 0.5% (mouse bioassay). These studies ran from a single treatment cycle to patients treated with up to 15 cycles and as long as over 4 years. 2240 patients had negative samples at baseline, and of those, 11 converted. Seven of them still responded to therapy. Irrespective of the target tissue rates of antibody formation were always lower than 1.3%. Other botulinum toxin type A preparations seem to have a similar low risk of AB formation except for rimabotulinum toxin type B with a considerably higher rate of conversion. However, it has been shown in several clinical trials that the antibody status in the latter did not correlate with the clinical response (Chinnapongse et al., 2012).

Taken together, there are no sufficient data published that