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# Clinical Use of Non-A Botulinum Toxins: Botulinum Toxin Type B

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**Botulinum neurotoxin type B (BT, BT-B) has been used as NeuroBloc®/MyoBloc™ since 1999 for treatment of cervical dystonia, hyperhidrosis, spastic conditions, cerebral palsy, hemifacial spasm, bladder dysfunction, spasmodic dysphonia, sialorrhoea, anal fissures, piriformis syndrome, various pain conditions and cosmetic applications. Generally, its therapeutic effects are comparable to BT type A (BT-A). The adverse effect profiles of BT-B and BT-A, however, differ considerably. BT-B has been found to produce more regional as well as systemic anticholinergic adverse effects, such as dryness of mouth, accommodation difficulties, conjunctival irritation, reduced sweating, dysphagia, heartburn, constipation, bladder voiding difficulties and dryness of nasal mucosa. In BT-B the relationship between autonomic and motor effects known from BT-A is substantially shifted towards autonomic effects. BT-B, therefore, should be used carefully in patients with autonomic disorders and in patients with concomitant anticholinergic therapy.**

**If NeuroBloc®/MyoBloc™ is used to treat cervical dystonia patients with antibody-induced failure of BT-A therapy, 86% of those will develop complete secondary therapy failure after five applications. If NeuroBloc®/MyoBloc™ used to treat cervical dystonia patients without prior exposure to BT, 44% of those will develop complete secondary therapy failure after nine applications. NeuroBloc®/MyoBloc™, therefore, is associated with substantial antigenicity problems originating from a particular low specific biological potency.**

**Systemic anticholinergic adverse effects and high antigenicity limits the clinical use of NeuroBloc®/MyoBloc™ considerably.**

*Keywords:* Botulinum toxin type B; Botulinum toxin type A; Therapy; Anticholinergic adverse effects; Systemic spread; Antigenicity; Antibodies

## INTRODUCTION

Botulinum toxin type B (BT, BT-B) has been used for therapeutic purposes since 1999 in the US as MyoBloc™, and since 2000 in Europe as NeuroBloc® (Elan Plc., Dublin, Ireland). The first clinical experience was published in 1999 (Brashear *et al.*, 1999; Brin *et al.*, 1999). As shown in table I BT-B has been used since then for treatment of various conditions, including cervical dystonia (Brashear *et al.*, 1999), hyperhidrosis (Dressler *et al.*, 2002), spasticity syndromes (Oechsner, 2002; Brashear *et al.*, 2003), cerebral palsy (Schwerin *et al.*, 2004), hemifacial spasm (Tousi *et al.*, 2004), bladder dysfunction (Dykstra *et al.*, 2003), spasmodic dysphonia (Sataloff *et al.*, 2002), sialorrhoea (Racette *et al.*, 2003), anal fissures (Jost, 2001), piriformis syndrome (Lang, 2004), various pain conditions (Fadeyi and Adams, 2002) and cosmetic applications (Kim *et al.*, 2003).

To compare therapeutic effects of different BT preparations conversion ratios between their biological potencies have to be applied. For use at the neuromuscular junction a conversion ratio between BOTOX® and MyoBloc™ of 1 : 40 has been suggested (Dressler *et al.*, 2002) and this ratio was selected in the double-blind, randomized study designed to compare the two serotypes (Comella *et al.*, 2005). For use at autonomic synapses the conversion ratio might be 1:20 (Dressler *et al.*, 2002). Using this conversion ratio BT-B produces therapeutic effects generally comparable to BT type A (BT-A). This refers to BT-B's maximal therapeutic effect and to BT-B's duration of effect. Occasionally reported differences of the duration of effect may be caused by the use of different end points and by the particular methodology to determine the duration of effect.

Substantial differences have been reported concerning the adverse effect profiles of BT-B and BT-A. This will be discussed in the first section of this contribution. After BT-B's development and introduction was

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stimulated by the hope to offer a therapeutic alternative for patients with antibody-induced BT-A therapy failure (ABTF-A). Antigenicity aspects will be addressed in the second section of this contribution.

**Adverse Effect Profile**

BT-B was introduced 1999 by a company-sponsored study on 109 patients with cervical dystonia (Brashear *et al.*, 1999). All patients received BT therapy for the first time. The study consisted of three arms. In the first arm 36 patients received MyoBloc™ 5000 MU; in the second, 37 patients received MyoBloc™ 10000 MU and in the third arm, 36 patients were treated with placebo. After BT-B became commercially available, the first experience indicated a special adverse effect profile (Dressler and Benecke, 2002) stimulating the first independent adverse effect study on BT-B (Dressler *et al.*, 2003). In this study 24 patients with cervical dystonia were included. Nine of them were treated with BT therapy for the first time. Fifteen had experienced ABTF-A. None of the patients received anticholinergics and in none of them autonomic dysfunction was detected prior to treatment. BT therapy was performed with NeuroBloc® 11834.7 ± 2039.3MU.

Table I Therapeutic use of botulininum toxin type B.

| |
|---|
| cervical dystonia |
| hyperhidrosis |
| cerebral palsy |
| hemifacial spasm |
| bladder voiding difficulties |
| spasmodic dysphonia |
| sialorrhoea |
| anal fissures |
| piriformis syndrome |
| pain syndromes |
| cosmetic applications |

Table II shows the BT-B adverse effect profiles as described in both studies. Dryness of mouth was reported in 21/24 (88%) patients in study 2, whereas it was documented in up to 24% of the patients in study 1 only. In study 2, 10/21 patients reported their dryness of mouth as severe, 7/21 as moderate, and 4/21 as mild. The duration of their dryness of mouth was 4.5 ± 1.9 weeks. In addition, 7/24 (29%) patients in study 2 com-

Table II Adverse effect profiles of botulinum toxin type B (NeuroBloc®/MyoBloc™) in patients with cervical dystonia as described in two recent studies.

| Adverse Effects | Dressler & Benecke, 2003 | Brashear *et al.*, 1999 | | |
|---|---|---|---|---|
| | % | MB5k | MB10k | PLC |
| | | % | % | % |
| dryness of mouth | 88 | 14 | 24 | 2 |
| accommodation difficulties | 29 | 0 | 0 | 0 |
| conjunctival irritation | 21 | 0 | 0 | 0 |
| reduced sweating | 17 | 0 | 0 | 0 |
| dysphagia | 13 | 11 | 22 | 3 |
| heartburn | 13 | 3 | 11 | 8 |
| constipation | 13 | 0 | 0 | 0 |
| bladder voiding difficulties | 8 | 0 | 0 | 0 |
| soor | 4 | 0 | 0 | 0 |
| dryness of nasal mucosa | 4 | 0 | 0 | 0 |
| head instability | 4 | 0 | 0 | 0 |
| neck pain | 0 | 31 | 27 | 25 |
| pain | 0 | 6 | 24 | 14 |
| headache | 0 | 25 | 14 | 8 |
| deterioration of cervical dystonia | 0 | 8 | 14 | 6 |
| accidents | 0 | 8 | 11 | 3 |
| injection site pain | 0 | 6 | 11 | 8 |
| infections | 0 | 25 | 8 | 28 |
| flu-like syndromes | 0 | 8 | 8 | 3 |
| taste alterations | 0 | 15 | 8 | 0 |

MB5k: MyoBloc™, 5000MU
MB10k: MyoBloc™, 10000MU
PLC: placebo

plained of accommodation difficulties, 5/24 (21%) of conjunctival irritation, 4/24 (17%) of increased sweating, 3/24 (13%) of constipation, 2/24 (8%) of bladder voiding difficulties and 1/24 (4%) each of soreness and dryness of nasal mucosa, and head instability. None of those adverse effects were documented in study 1. Dysphagia was found in 3/24 (13%) patients in study 2 and in up to 22% of the patients in study 1. Heartburn was reported in 3/24 (13%) patients in study 2 and in up to 11% of the patients in study 1. In study 1 deterioration of cervical dystonia was seen in up to 14% of the patients, accidents in up to 11%, injection site pain in up to 11%, infections in up to 25%, flue-like symptoms in up to 8% and taste alterations in up to 15%. None of these unspecified adverse effects were seen in the patients in study 2.

Classifying these adverse effects with respect to their underlying aetiology, dryness of mouth, accommodation difficulties, dryness of nasal mucosa, reduced sweating, dysphagia, heartburn, constipation, bladder voiding difficulties, conjunctival irritation represent autonomic dysfunctions. Additionally, study 2 also reports similar systemic autonomic adverse effects in patients treated for hyperhidrosis with BT-B doses starting from 4000 MU.

BT-B produces substantial autonomic adverse effects caused by regional as well as systemic spread. These observations were confirmed in subsequent studies (Baumann and Halem, 2003; Brashear *et al.*, 2003; Baumann *et al.*, 2005). In one study anticholinergic adverse effects of BT-B were described in children with cerebral palsy (Schwerin *et al.*, 2004). Frequent dryness of mouth was classified by the authors as a therapeutically useful side effect. If saliva reduction is required therapeutically, direct BT injections into the parotid and submandibular glands can easily be performed (Dressler, 2003).

In comparing BT-B with BT-A it becomes apparent that the relationship between motor and autonomic effects is different in BT-B and in BT-A. Whereas BT-B produces substantial autonomic effects and usual motor effects, BT-A produces usual motor effects and minor autonomic effects. This situation is shown in figure 1. The reason for these differential effects on autonomic and motor synapses remains unclear. Acceptor structures for BT-B and BT-A may differ and their density on motor and autonomic synapses may be different, but there is yet no evidence to support this hypothesis.

With respect to its clinical use higher doses of BT-B may be problematic. In patients with autonomic dysfunctions and in patients with contraindications for anticholinergics BT-B should only be used cautiously. Whether the strong anticholinergic effects of BT-B can be used therapeutically remains unclear at the moment. Since BT-B does not exert principally stronger autonomic effects than BT-A, BT-B might only be used when BT-A therapy is restricted by strong motor side effects. So far, this situation has not been identified clinically.

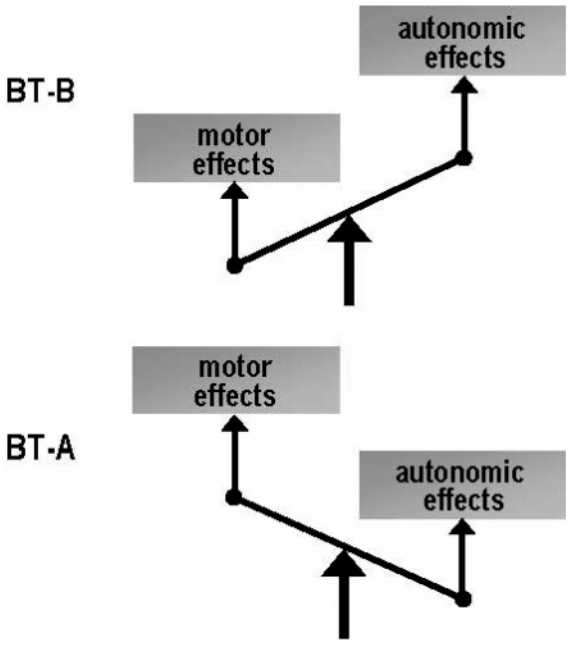


FIGURE 1 Relationship between autonomic and motor effects in botulinum toxin type A (BT-A) and in botulinum toxin type B (BT-B). BoNT-A produces relatively stronger motor and relatively weaker autonomic effects. In BoNT-B this relationship is reversed.

**Antigenicity**

In 1999 a company-sponsored study presented 39 patients with cervical dystonia and ABTF-A received MyoBloc™ 10000 MU and were compared to 38 patients of a placebo-treated control group (Brin *et al.*, 1999). The observation period was restricted to one injections series. In a second study 10 patients with cervical dystonia and ABTF-A received NeuroBloc® 12370 ± 1804 MU and were followed up for 4.9 ± 3.0 injection series (Dressler and Bigalke, 2005). Both studies showed a solid therapeutic effect on the first BT-B application. In study 1 the Toronto Western Spasmodic Torticollis Rating Scale score (TWSTRS score) (Consky *et al.*, 1990) dropped from 22.6 ± 3.9 to 18.9 ± 4.7, whereas in study 2 the TWSTRS score fell from 20.1 ± 3.0 to 11.9 ± 3.4 indicating a slightly better therapeutic outcome. Subsequently, up to five follow-up injection series were applied in study 1 (Dressler and Bigalke, 2005). Follow-up injection series 1 and

2 reproduced the initial therapeutic outcome, whereas in follow-up injection series 3, four of 10 patients showed complete secondary therapy failure. In a follow-up injection series seven out of nine patients and in follow-up injection series 5 six out of seven patients (86%) presented with complete secondary therapy failure. With this outcome BT-B turned out to be only temporarily effective in patients with ABTF-A.

In another study (Dressler and Bigalke, 2005) BT-B antigenicity was studied in patients without prior exposure to BT (*de novo* patients). For this, nine patients with cervical dystonia were treated with NeuroBloc® 11435 ± 2977 MU at 4.9 ± 3.0 injection series. After the first BT-B application the TWSTRS score fell from 17.7 ± 9.4 to 5.3 ± 4.8. At follow-up injection series 1, all patients continued to respond. At follow-up injections series 2, two patients showed complete secondary therapy failure and at follow-up injections series 8 and 9, one additional patient each showed complete secondary therapeutic failure. In all patients with therapy failure the mouse diaphragm assay revealed BT-B antibody titres in excess of 10 mU/ml. Altogether, four out of nine patients (44%) developed complete secondary therapy failure. Out of the five patients with continued therapeutic response one received nine injection series, two received six, one received four and another one received three. With this, NeuroBloc®/MyoBloc™ also shows a high antigenicity in *de novo* patients.

Suspicion of a high antigenicity of NeuroBloc® /MyoBloc™ arose already, when Elan Pharmaceuticals submitted the results of their studies #201, #302, #351 and #352 to the Department of Health & Human Services, Public Health Service, Food and Drug Administration, Center for Biologics Evaluation and Research, Division of Clinical Trial Design and Analysis as part of their registration documents (Health & Human Services, Public Health Service, Food and Drug Administration, Center for Biologics Evaluation and Research, Division of Clinical Trial Design and Analysis, 2000). In these studies on 468 patients with cervical dystonia treated with MyoBloc™ in doses of 5000 to 15000 MU BT-B antibodies could be detected by the mouse lethality assay in 9.6% of the patients after 12 months, in 18.2% after 18 months, and in 22.6% after 610 days. The Food and Drug Administration comments that 'these results indicate that there is substantial formation of antibodies in response to treatment with BT-B, and that many patients will convert to having neutralizing antibodies within 2 years of beginning treatment' (Health & Human Services, Public Health Service, Food and Drug Administration, Center for Biologics Evaluation and Research, Division of Clinical Trial Design and Analysis, 2000). When these patients develop BT-B antibody-induced therapy failure, they are more likely to also develop antibody-induced therapy failure to BT-A (Dressler and Bigalke, 2005), thus being excluded from further BT therapy (Dressler, 2004).

Whereas the specific biological activity in NeuroBloc® /MyoBloc™ is 5.0 MU/ng BNT, it is 60 MU/ng BNT in BOTOX®, 100MU/ng BNT in Dysport® and 167 MU/ng BNT in Xeomin® (Benecke *et al.*, 2005; Dressler and Hallett, 2006). When NeuroBloc®/MyoBloc™ is used in *de novo* patients with cervical dystonia it also shows a high antigenicity which cannot be explained by a special immunological situation of those patients, but only by its high protein load. NeuroBloc®/MyoBloc™'s high antigenicity limits its clinical use considerably.

## CONCLUSION

BT-B as NeuroBloc®/MyoBloc™ produces substantial systemic anticholinergic adverse effects. Apart from this, NeuroBloc®/MyoBloc™ features considerable antigenicity. Its clinical usefulness - apart from few special indications such as ABTF-A, - is limited considerably.

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