

## INVESTIGATIVE REPORT

# Effect of Botulinum Toxin Concentration on Reduction in Sweating: A Randomized, Double-blind Study

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**Dose–response studies of botulinum toxin for reduction of sweating are sparse in the literature. The aim of this study was to determine the most appropriate concentrations of Botox<sup>®</sup>, Dysport<sup>®</sup>, Xeomin<sup>®</sup> and NeuroBloc<sup>®</sup>, respectively, in order to achieve the greatest reduction in sweating, thus reducing the costs and increasing the safety of treatment. Four concentrations of each product were investigated. Intradermal injections of all products and concentrations were applied to the backs of 20 consenting subjects, in a randomized, double-blind manner. Areas of anhidrotic and hypohidrotic skin were measured with an iodine-starch test after 4, 8 and 12 weeks, respectively. Optimal concentrations were found to be 25 U/ml for Botox and Xeomin, approximately 100 U/ml for Dysport, and 50 U/ml for NeuroBloc. When comparing the mean anhidrotic area per unit for 100 U/ml of each product, the calculated dose conversion ratios were 1:1.6:1.2:1.3 (Botox:Dysport:Xeomin:NeuroBloc). If, instead, the optimal concentration for each product was compared, the dose conversion ratios were 1:4.8:1.3:2.2. Thus, it is crucial to consider botulinum toxin concentration in a treatment regimen. *Key words:* Botox; Dysport; Xeomin; NeuroBloc; botulinum toxin; hyperhidrosis.**

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The effect of botulinum toxin (BTX) in muscular diseases and on  $\alpha$ -motor neurones has been studied widely. However, there has been little research into the mechanism of action of BTX on autonomic neurones, and in diseases such as hyperhidrosis.

BTX prevents the release of acetylcholine and other co-transmitters in peripheral cholinergic nerve endings. In patients with hyperhidrosis, nerve signalling is increased, and BTX consequently blocks the impulses at the autonomic sudomotor neurone synapses in the skin (1). The effect duration of BTX is longer on a group basis for hyperhidrotic patients compared with patients with muscular disorders, but the intra-individual variation is substantial.

BTX is commercially available in 4 different brands: Botox<sup>®</sup> (Allergan Inc., Irvine, CA, USA); Dysport<sup>®</sup> (Ipsen Ltd, Slough, UK); and Xeomin<sup>®</sup> (Merz Pharma GmbH & Co. KGaA, Frankfurt/Main, Germany), all of which contain BTX type A; and NeuroBloc<sup>®</sup> (Eisai Ltd, Hatfield, UK), which is a BTX type B product.

BTX type A and B are structurally similar, but diverge in their acceptor binding, enzymatic activity, antigenicity and species sensitivities (2). Furthermore, the 4 products are formulated differently and their dosing units (U) are unique.

Studies of muscular disorders have reported that Botox is 3–6 times more potent than Dysport, and NeuroBloc has been used in doses 50–100 times higher than Botox (3–10). Xeomin has been used in the same doses as Botox, with similar treatment response (11).

Dose–response studies of sweating are sparse in the literature. The effect of Botox, Dysport and NeuroBloc in different concentrations was compared in a study performed on 9 healthy volunteers (12). In this study the difference in effect between the 3 products at a concentration of 100 U/ml was as small as 1:1.2:1.1 (Botox:Dysport:NeuroBloc). This clearly suggests that the level of dilution was significant to achieve optimal effect of each BTX product, and that BTX B has a greater effect on autonomic sudomotor neurones than on  $\alpha$ -motor neurones. Kranz et al. (13) also concluded that the dilution level is of importance for the sweat-reducing effect in a study comparing Botox and Dysport. The dose conversion ratio in that study was found to be 1:1.3 (Botox:Dysport) for anhidrosis.

The aim of the present study was to find the most appropriate concentrations of Botox, Dysport, Xeomin and NeuroBloc, respectively, to achieve the greatest level of sweat reduction.

## MATERIALS AND METHODS

This exploratory study was based on the results of previous research at the departments involved (12). The study was approved by the local ethics committee and the Swedish Medical Products Agency, and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice (EudraCT number: 2009-013684-19).

The randomized, double-blind study included 20 consenting subjects, of whom 13 were female. The mean age of the sub-

jects was 36 years (range 19–66 years). None of the subjects had received BTX previously. Ongoing skin disease or local pharmaceutical therapies involving the upper part of the back were criteria for exclusion.

#### Randomization and injection procedure

At the first study visit all subjects received injections of Botox, Dysport, Xeomin and NeuroBloc diluted with physiological, unpreserved saline to the following concentrations: Botox and Xeomin: 100, 50, 25 and 10 U/ml; Dysport: 500, 200, 100 and 50 U/ml; and NeuroBloc: 500, 250, 100 and 50 U/ml. Each subject was given a total of 16 injections, each of 0.1 ml volume, as follows.

A research nurse, working at the department of neurology, diluted the BTX products and prepared 16 identical syringes containing the same volume, for each subject. Each syringe was labelled with an injection point, P1–P16 (Fig. 1), and a subject number. The concentration and product used at the different injection points varied between the subjects in accordance with 4 different randomization sequences, thus making the study double-blind.

The injections were administered on the subjects' backs in 4 vertical rows; P1–P4, P5–P8, P9–P12 and P13–P16 (Fig. 1). All 4 concentrations of each product were injected within the same vertical row; however, the products were allocated to different vertical rows in accordance with the randomization sequence. Furthermore, injections with higher doses of BTX, for which large anhidrotic areas were expected, were placed far away from each other, in order to obtain a distinct border for all injection points. The first vertical row was placed 14 cm in the left lateral direction from the spinal column, the second vertical row 7 cm in the left lateral direction from the spinal column, the third vertical row 7 cm in the right-hand direction from the spinal column and the 4<sup>th</sup> vertical row 14 cm in the right-hand direction from the spinal column. The top injection in each vertical row was given at the level 5 cm below the seventh cervical vertebra and the injections beneath were given at 6–7 cm intervals.

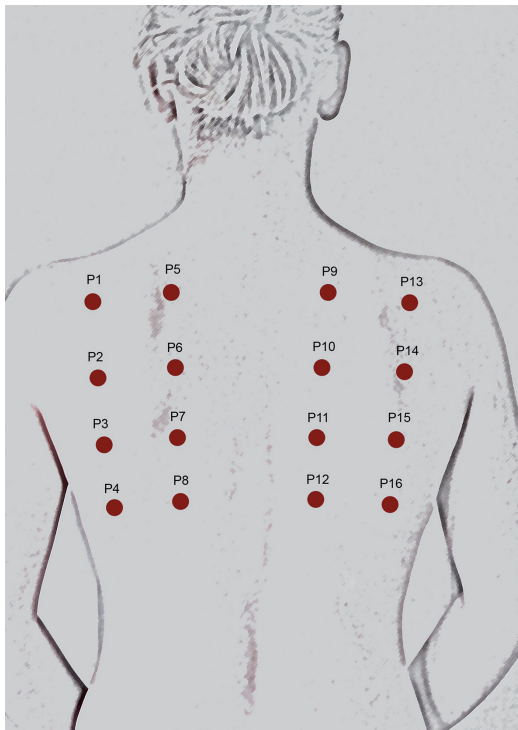


Fig. 1. Positions where the 16 injections were given. P1 represents injection-point 1, P2 represents injection-point 2, and so on.

#### Iodine-starch test and measurement of area

The areas of anhidrotic and hypohidrotic skin were identified with an iodine-starch test 4, 8 and 12 weeks after the injections (12, 14). Iodine alcohol solution was applied to each participant's back. Subjects then entered and remained in a sauna until a small amount of sweat was visible on the skin. A sheet of white paper (45 g/m<sup>2</sup>) was thereafter pressed against the back and stained black in contact with wet skin. Anhidrotic areas appeared as white circles on the paper and hypohidrotic areas, where only a small amount of sweat was present, could be seen as dots at the borders between the white circles and the black area.

All imprints were scanned and thereafter used in the computer program Adobe Photoshop CS4, where anhidrotic and hypohidrotic areas were measured for each injection point. The data referred to as hypohidrotic area in the Results section, are, in fact, the anhidrotic area and the hypohidrotic area in total, as measured in the computer program.

Since all injections in the study had a volume of 0.1 ml, the dose differed between the concentrations used. The anhidrotic and the hypohidrotic mean areas per unit, respectively, were therefore calculated for each concentration in order to compare the effect of the different concentrations.

#### Objective and end-points

The primary objective of the trial was to study the anhidrotic effect at 4 weeks after intradermal injections of Botox, Dysport, Xeomin and NeuroBloc diluted to 4 different concentrations each.

The primary end-point of the study was the anhidrotic area per unit (cm<sup>2</sup>/U) for each treatment (i.e. the 16 different product-concentration combinations) at 4 weeks post-treatment.

Secondary objectives were to investigate the anhidrotic area per unit at 8 and 12 weeks after intradermal injections of the different products and concentrations and the hypohidrotic area per unit at week 4, 8 and 12. A further objective was to study the longitudinal changes in effect.

#### Statistical analyses

The sample size estimation in this exploratory study was not based on statistical criteria, but on similar studies (12, 13).

The optimal concentration of the 4 products was evaluated using descriptive statistics and graphs. Optimal concentration was defined as the concentration generating the largest mean anhidrotic area per unit for each product. In addition, treatment comparisons were made by differences of least squares means from a mixed model analysis of variance (ANOVA) with treatment and position on the back (lateral/medial) as fixed effects, and subject as a random effect.

Due to the exploratory nature of this study, no adjustments for multiple comparisons were undertaken. Confidence intervals and *p*-values were used for exploratory purposes. All statistical analyses were performed with SAS<sup>®</sup> version 9.3.

## RESULTS

Eighteen of the 20 included subjects completed the study. Two participants were not able to attend the follow-up visit at week 12; however, the data from weeks 4 and 8 were included in the analyses. The subjects were divided evenly between the randomization sequences, resulting in 5 subjects in each sequence. Due to indistinct sections of some imprints, it was not possible to measure 217 of 928 injection points. The

results are therefore based on 711 injection points. The exclusion was made before un-blinding.

Descriptive statistics of the anhidrotic area per unit at weeks 4, 8 and 12 are given in Table S1 (available from: <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1606>). The mean anhidrotic area per unit 4 weeks after injection of the 4 different products and concentrations is shown in Fig. 2 and Fig S1 (available from: <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1606>). The optimal concentration for both Botox and Xeomin was 25 U/ml. The largest mean anhidrotic area per unit for Dysport appeared where the concentration 100 U/ml had been injected; however, the difference between Dysport 100 U/ml and Dysport 50 U/ml was not statistically significant, nor was the difference between Dysport 100 U/ml and 200 U/ml. The optimal concentration appears to be approximately 100 U/ml. The optimal concentration for NeuroBloc was 50 U/ml.

When comparing the mean anhidrotic area per unit obtained after injection of the same concentration and dose of each product, the calculated dose conversion ratios were 1:1.6:1.2:1.3 (Botox:Dysport:Xeomin:NeuroBloc) for concentration 100 U/ml (10 U). For concentration 50 U/ml (5 U) the corresponding dose conversion ratios were 1:3.3:1.2:1.1.

If, instead, the optimal concentration for each product was compared, i.e. Botox 25 U/ml, Dysport 100 U/ml, Xeomin 25 U/ml and NeuroBloc 50 U/ml, the dose conversion ratios were 1:4.8:1.3:2.2. Statistical analyses of anhidrotic area per unit at week 4 are shown in Tables I and SII (available from: <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1606>).

A secondary objective was to investigate the hypohidrotic area per unit of the 4 different products and concentrations. The results, 4 weeks after injection, are shown in Fig. S2 (available from: <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1606>). The relationship between the different concentrations within each product showed approximately the same pattern

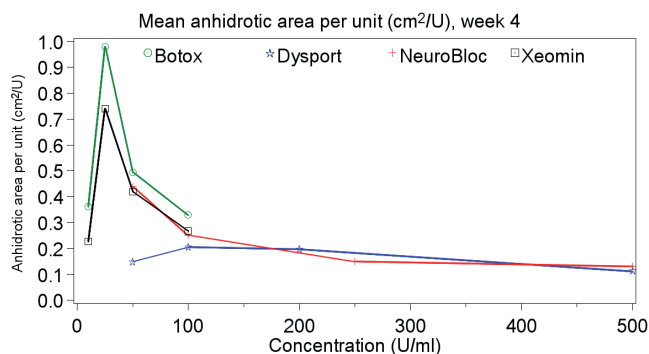


Fig. 2. Mean anhidrotic area per unit 4 weeks after injection of Botox®, Dysport®, Xeomin® and NeuroBloc® in 4 different concentrations. Clear peaks can be seen for Botox and Xeomin, demonstrating that the optimal concentration for both products is 25 U/ml. The optimal concentration for Dysport is approximately 100 U/ml, and for NeuroBloc 50 U/ml.

as for anhidrotic area per unit 4 weeks after injection. Compared with the graph exhibiting the anhidrotic area per unit, it can be seen that Dysport 50 U/ml is closer to the concentrations 100 U/ml and 200 U/ml. A further objective was to study the longitudinal changes in effect. At week 8 it was clearly seen that the optimal concentration was still 25 U/ml for Botox and Xeomin and 50 U/ml for NeuroBloc (Fig. S3; available from: <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1606>). The mean anhidrotic area per unit for Dysport 50 U/ml, 100 U/ml and 200 U/ml was approximately the same.

The graph at week 12 is similar to the graph at week 4 and 8, showing that the optimal concentration was 25 U/ml for Botox and Xeomin and 100 U/ml for Dysport (Fig. 3). However, the mean anhidrotic area per unit obtained after injection of NeuroBloc was, at this time-point, nearly the same for all 4 concentrations.

The results for the mean hypohidrotic area per unit at weeks 8 and 12 were in agreement with the results of the mean anhidrotic area per unit for the corresponding weeks, with the exception that Botox at the concentrations 10 U/ml and 25 U/ml was approximately the same (data not shown).

Six subjects reported adverse events related, or possibly related, to the study interventions. One participant reported local burning sensations when receiving BTX injections. Five subjects experienced dryness of the skin on the back for a couple of days after the iodine-starch test, which may have been due to the alcohol-containing iodine solution.

## DISCUSSION

This double-blind, randomized study on healthy volunteers shows that 25 U/ml is the optimal concentration of Botox and Xeomin to reduce sweating. For Dysport the optimal concentration was approximately 100 U/ml. No clear peak effect was seen for Dysport in this study, with

Table I. Statistical analysis of anhidrotic area per unit (cm²/U), week 4, mixed model analysis of variance (ANOVA). Differences between the optimal concentration and the other 3 concentrations studied are shown for each product

Products (U/ml)	LS mean	95% CI	p-value
Botox® 10 – Botox 25	-0.601	-0.946, -0.256	0.0015
Botox 50 – Botox 25	-0.477	-0.776, -0.177	0.0038
Botox 100 – Botox 25	-0.640	-0.935, -0.346	0.0003
Xeomin® 10 – Xeomin 25	-0.514	-0.856, -0.173	0.0048
Xeomin 50 – Xeomin 25	-0.331	-0.643, -0.019	0.0387
Xeomin 100 – Xeomin 25	-0.485	-0.787, -0.183	0.0039
Dysport® 50 – Dysport 100	-0.047	-0.125, 0.030	0.2200
Dysport 200 – Dysport 100	-0.001	-0.066, 0.064	0.9711
Dysport 500 – Dysport 100	-0.093	-0.166, -0.021	0.0135
NeuroBloc® 100 – NeuroBloc 50	-0.182	-0.317, -0.047	0.0105
NeuroBloc 250 – NeuroBloc 50	-0.279	-0.403, -0.156	0.0002
NeuroBloc 500 – NeuroBloc 50	-0.306	-0.430, -0.182	<0.0001

LS mean: least squares mean; CI: confidence interval.



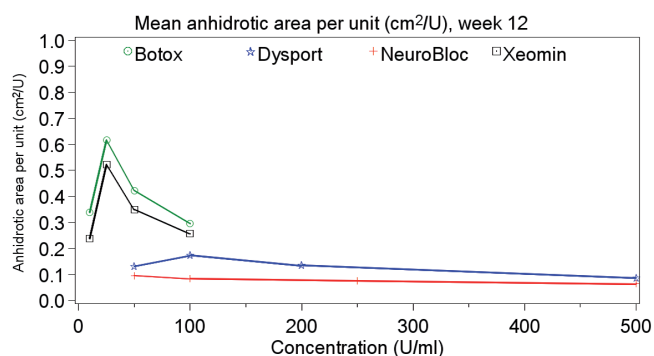


Fig. 3. Mean anhidrotic area per unit 12 weeks after injection of Botox®, Dysport®, Xeomin® and NeuroBloc® in 4 different concentrations. Clear peaks can be seen for Botox and Xeomin, demonstrating that the optimal concentration for both products is 25 U/ml. One, presumably erroneous, outlying observation for Xeomin 10 U/ml has been omitted. The deletion of this observation altered the mean anhidrotic area per unit for Xeomin 10 U/ml from 0.49 to 0.24 cm<sup>2</sup>/U. The optimal concentration for Dysport is 100 U/ml. The mean anhidrotic area per unit, emerging where NeuroBloc has been injected, is nearly constant for all 4 concentrations.

small differences in potency for concentrations of 50 U/ml, 100 U/ml and 200 U/ml. However, Dysport 100 U/ml was more effective than Dysport 500 U/ml. A larger cohort study would increase the chances to capture the most appropriate concentration to use for Dysport, which appears to be approximately 100 U/ml. For NeuroBloc, the optimal concentration was 50 U/ml; however, considering the shape in the graph, the optimal concentration may be even lower. Future studies with NeuroBloc should include the concentrations 10 U/ml, 25 U/ml, 50 U/ml and 100 U/ml, in the search for a peak effect and an optimal concentration for the B-toxin. NeuroBloc and the type A toxins had a similar anhidrotic effect, but the effect of NeuroBloc seemed to diminish more prominently at measurement week 12. This is in accordance with previous clinical studies (15, 16). Moreover, the study confirms previous observations of NeuroBloc as an autonomic and sudomotor neurone-specific agent with comparatively poor effect on muscles (12, 15, 17). When comparing the dose conversion ratios between type A and B toxins for anhidrotic effect (ratio 1:1–2) and relaxing effect on muscles (ratio 1:50–100), an opportunity to treat hyperhidrosis in special groups becomes apparent. Dilution enables treatment of general hyperhidrosis on large areas, such as the trunk, without exceeding the maximum dose. Furthermore, the smaller doses cause fewer side-effects on the underlying muscle tissue when treating sensitive parts of the body, such as the central area of the face. The benefits of using low concentrations of BTX can likewise be seen for the other products, although not to the same extent as for NeuroBloc.

This study, as well as others, shows that the level of dilution of the products is important for optimal effect (12, 13, 18, 19). However, although Botox and Dysport are approved for treatment of axillary hyperhidrosis, most dose–response studies are still performed on muscles and  $\alpha$ -motor neurones, which differ from autonomic sudomotor neurones.

Allergan (Botox) and Ipsen (Dysport) have used predetermined doses for axillary hyperhidrosis, which is sufficient for good results on a group basis. However, when treating a chronic disease such as hyperhidrosis, it is convenient to use an individual and minimal dose with an optimal effect, partly to reduce the risk of side effects and immunization, partly to reduce the costs.

As far as we know, the medical companies have no assay for studying the effect of toxins on autonomic sudomotor neurones. The method used in this study is very simple and easy to perform with reproducible results (12). Kranz et al. have compared the sweat reducing effect of Botox and Dysport with corresponding results (13). They have used a similar method but chose abdominal skin, which provides homogenous sweating conditions. We performed the measuring on the back in favor of the even surface and less hairy skin. Pitfalls with this method are described in SAppendix (available from: <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1606>).

For a clinician it is necessary to have a dose- and concentration regimen for each product, especially if switching between them. Dose conversion ratios between Botox and Dysport have, in the literature, been reported to vary considerably among different studies performed on muscles. The dose conversion ratio has been found to be 1:3–6 (Botox:Dysport) when the concentrations have been dissimilar (4–7). On the other hand, when both Botox and Dysport were diluted to the concentration 100 U/ml and the solution contained the same amount of albumin there was no difference in effect, investigated on muscles in healthy volunteers and *in vitro* (19).

The present study, performed on sweating and autonomic sudomotor neurones, gives further evidence that it is crucial to consider the concentration of BTX when comparing different products. On diluting all products to a concentration of 100 U/ml, the clinical effect was relatively similar, which was also seen in our previous study (12). In contrast, when comparing the mean anhidrotic area per unit obtained after injection of 50 U/ml, the calculated dose conversion ratio was 1:3.3 for Botox:Dysport, and if the optimal concentrations in the study were compared, i.e. Botox 25 U/ml and Dysport 100 U/ml, the ratio was 1:4.8. The same pattern can be seen for NeuroBloc. Undiluted solution with the concentration 5,000 U/ml has been used when treating muscular disorders with NeuroBloc in doses 50–100 times higher than Botox. However, when both products were diluted to a concentration of 100 U/ml in the present study, the dose conversion ratio was 1:1.3 (Botox:NeuroBloc) and even lower, 1:1.1, for a concentration of 50 U/ml. Although this study was performed on sweating, it is possible that the concentrations are of similar importance when treating muscular disorders. It would be of special interest to study NeuroBloc at concentrations lower than 5,000 U/ml, which is the recommended concentration for cervical dystonia, since it has been suggested that this

product is associated with a higher degree of antibody formation (20). If lower concentrations and doses can be used for this indication the risk for immunization may decrease. The optimal doses must, nevertheless, be further investigated in dose–response studies where optimal concentrations are used.

There appears to be a limit, specific for each product, where further dilution does not increase the effect. This might be explained by the diverging formulation, in particular the amount of albumin, which is an import additive, since it decreases aggregation of the BTX molecules and adsorption of BTX in the vial and syringe. Furthermore, different methods are used when establishing the potency of a batch with the mouse unit assay. Ipsen and Eisai use a stabilizing gelatine-phosphate buffer when testing Dysport and NeuroBloc in their assays. This is due to the very low concentrations used in the LD<sub>50</sub>-test, consequently inactivating some of the present toxin when saline is used as a diluent (21, 22). When saline is used as a diluent, which is the case in the Botox assay, the determination of the potency in the product may result in an underestimation of the units per given amount. This will subsequently lead to an effect that is comparatively higher in clinical practice. However, since NeuroBloc is a liquid formulation it contains supplementary additives to keep the toxin stable in solution, and therefore is not fully comparable with the other 3 products, which are formulated as powders.

In conclusion, it is crucial to consider the concentration of BTX in a treatment regimen, especially when switching between different products. The optimal concentration for reducing sweating varies between products; in the present study it was 25 U/ml for Botox and Xeomin, approximately 100 U/ml for Dysport, and 50 U/ml for NeuroBloc.

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