DOI 10.1007/s00702-004-0234-8
J Neural Transm (2005) 112: 905–913

Journal of Neural Transmission
Printed in Austria

Efficacy and tolerability of a botulinum toxin type A free of complexing proteins (NT 201) compared with commercially available botulinum toxin type A (BOTOX®) in healthy volunteers

W. H. Jost[1], **A. Kohl**[1], **S. Brinkmann**[2], and **G. Comes**[2]

[1] Department of Neurology, Deutsche Klinik für Diagnostik, Wiesbaden, and
[2] Merz Pharmaceuticals GmbH, Frankfurt/Main, Germany

Received May 26, 2004; accepted September 11, 2004
Published online November 3, 2004;

Summary. *Purpose*: This randomized controlled trial was performed to compare the novel botulinum toxin type A free of complexing proteins (NT 201) with the marketed preparation BOTOX® regarding efficacy and tolerability. *Methods*: Fourteen healthy volunteers received a single intramuscular injection into the *extensor digitorum brevis* (EDB) muscle of either 4 units NT 201, or 4 units of BOTOX® randomised by foot. Compound muscle action potential (CMAP) measurements were recorded for up to 90 days after injection. *Results*: Both drugs produced a maximum decline between Day 7 and Day 14. At Day 90, administration of both drugs resulted in approximately a 40% CMAP decline as compared to baseline. Duration of paralytic effect was comparable in both groups, at all response thresholds tested. Both drugs were well tolerated. *Conclusion*: The effects of small amounts of NT 201 and BOTOX® injected into the EDB muscle are comparable in terms of efficacy, time to onset of action, duration of action, and tolerability.

Keywords: Botulinum toxin type A, EDB test, NT 201.

Abbreviations

AE Adverse Event, *CMAP* Compound Muscle Action Potential, *EDB* Extensor Digitorum Brevis Muscle, *EMG* Electromyography, *GCP* Good Clinical Practice, *ICH* International Conference on Harmonization, LD_{50} Calculated median lethal intraperitoneal dose, *NT 201* Botulinum Neurotoxin Type A free of complexing protein, *SAS* Statistical Analysis System, *SD* Standard Deviation, *SPSS* Statistical Package for Social Science.

Introduction

Botulinum neurotoxin type A has been in clinical use since the 70s (Scott, 1981; Erbguth and Naumann, 1999) and is widely used in the treatment of dystonic and non-dystonic movement disorders, including hyperactive muscles of the arm, leg or gastrointestinal tract (e.g. achalasia), spasticity, cerebral palsy and pain (e.g. lower back pain and migraine), as well as hyperhidrosis and glabellar lines. However, despite the good efficacy and tolerability in the beginning of botulinum toxin type A treatment, a significant number of patients develop secondary resistance to ongoing treatment. This is demonstrated in 4.3 to 10.5% of subjects following previous prolonged treatment (Kessler and Benecke, 1997; Greene et al., 1988b).

The resistance is believed to be mainly due to the production of secondary antibody to extraneous clostridial proteins present in the toxin preparation (Jankovic et al., 2003). Even if the purity of commercially available products such as Dysport® (Ipsen, UK) and BOTOX® (Allergan, USA) has improved markedly in recent years (total protein content per 100 LD_{50} units of BOTOX® has been reduced tenfold) preparations still contain fairly high amounts of proteins (for BOTOX® 4.8 ng) per LD_{50} unit of therapeutically active toxin (Aoki, 2001).

The objective of the present study was to compare the effect of a new, highly purified preparation of botulinum neurotoxin, NT 201 (Merz Pharmaceuticals GmbH, Frankfurt, Germany), with the original BOTOX® preparation, in healthy male volunteers. NT 201 is free of complexing protein and contains only 600 pg of active clostridial protein (manufacturer's information). Therefore it is expected to have markedly reduced immunogenicity (Chen et al., 1997; Jankovic et al., 2003).

Methods

Study population

Subjects included in this study were healthy, male volunteers, 27–46 years (32.1 ± 4.7), with EDB muscle compound muscle action potential (CMAP) ≥ 5.0 mV (average of the 2 largest CMAP values from the 3 measurements made at baseline). Subjects were not allowed any medication affecting neuromuscular transmission for a minimum of 2 weeks prior to the study. Main exclusion criteria were concurrent or previous BOTOX® (botulinum neurotoxin type A) treatment for any other indication, or childhood botulism, participation in another study of an investigational drug within the preceding 90 days, polyneuropathy or diabetes, history or presence of alcoholism or other drug abuse and hypersensitivity to botulinum neurotoxin, human serum albumin, sucrose, or lactose. Fourteen subjects out of 15 screened were included in the trial.

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (18th World Medical Congress in Helsinki 1964 and amendments adopted in Hong Kong 1989 and Somerset West in 1996). In addition, the study was conducted in accordance with the German Drug Law (Arzneimittelgesetz September 1998), the Principles for the Proper Conduction of Clinical Trials of Pharmaceuticals (Bundesanzeiger, December 30, 1987), and the International Conference on Harmonization (ICH) Harmonized Tripartite "Guidelines for Good Clinical Practice (GCP) 17. January 1997". The study was approved by the local ethic committee and all participants gave their written informed consent.

Study design

This was an open-label, intra-individual controlled, single-centre study. After screening and baseline measurements at Visits 1, 2 and 3, (Days -8 to -1, -1 and 0, respectively) 14 subjects received an injection of the study medication into the EDB muscles of the right and left foot in a

randomised order at Visit 3. In group 1 (n = 7), subjects were given one injection of 4 U of NT 201 into the right EDB and 4 U of BOTOX® into the left EDB (0.2 ml reconstituted solution with normal saline 0.9% NaCl). In group 2 (n = 7), subjects were given one injection of 4 U of BOTOX® into the right EDB and 4 U of NT 201 into the left EDB. This was done to ensure that both groups were comparable at baseline, and allow subsequent comparison of CMAP values between groups at all timepoints.

To measure the CMAP a Nicolet Viking IV™ electromyography machine (Nicolet Company™, Madison, WI, USA) was used. All responses were measured following supramaximal electrical stimulation of the peroneal nerve at the ankle. Electrical stimulation was performed with a single impulse of 0.2 ms. Recording electrodes positions and environmental conditions were kept constant at each visit. Skin temperature was between 32° and 34° Celsius. All measurements were performed by the same examiner and were recorded from the EDB muscle with a minimum stimulation distance of 8 cm. Each subject had 3 nerve conduction measurements before intramuscular injection of the study medication in the EDB muscle. All CMAP M-wave values were calculated as the mean of the two largest values of the 3 measurements made. To ensure that no subclinical neuropathy was present, the sural sensory nerve action potential amplitude and the distal latency were recorded at Visit 1. In addition the CMAP M-wave amplitude (peak-to-peak-amplitude), the distal latency, and conduction velocity of the peroneal nerve was measured.

Subjects were monitored for a minimum of 7 days and a maximum of 90 days. Monitoring and CMAP measurements were done at Days −2, −1, 0, 1, 2, 3, 4, 7, 9, 11, 14, 30, 60 and 90. At all study visits (Day 1 to Day 90), surface EMGs were evaluated in both EDB muscles, concomitant medication noted and any adverse events (AEs) monitored. In addition, subjects underwent a physical and neurological examination, and clinical laboratory tests at Visit 1 and Visit 14 (Day −2 and Day 90 ± 5).

Primary outcome variable

Efficacy was assessed by determination of the surface electromyograph (EMG) of the *extensor digitorum brevis* (EDB) muscle in one foot, a common neurological model for treatment effects of botulinum A toxin (Hamjian and Walker, 1994; Sloop et al., 1997; Kessler and Benecke, 1997). The EDB test is expected to be sufficiently sensitive to detect meaningful differences between treatments in terms of onset and duration of effect (Sloop et al., 1996; Gordon et al., 2002).

The primary outcome variable was the CMAP amplitude of surface EMG at the same location in EDB muscles during maximum electrical activation, up to 90 days after injection of NT 201 or BOTOX®. The maximal effect of the injections was expressed as a percentage decrease in CMAP amplitude.

The efficacy measurement was used to evaluate time to onset of paralytic effect (defined as the first day of reduction of CMAP value to ≤70% of the individual mean baseline value) with injection of NT 201 compared with BOTOX®. To model the kinetic effects of individual CMAP values over time, duration of constant paralytic effect in NT 201 compared with BOTOX® was evaluated using the same variable.

Clinical laboratory tests

Laboratory tests were performed at Visits 1 (baseline) and 14 (end of study). Blood samples were analysed by a central laboratory using standard methods. Haematology (haemoglobin, erythrocytes, leukocytes, thrombocytes and QUICK) and liver function (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, alkaline phosphatase, creatine kinase and bilirubin) were assessed; urea, glucose, creatinine, albumin, sodium and potassium were also measured.

Statistical evaluations

The working hypothesis was that NT 201 and BOTOX® would show equivalent effects in terms of time to onset and duration of paralysis. The equivalence criterion ''irrelevant inferiority'' for time to onset of paralytic effect was 1 day, and for the paralytic activity during the 90 days observational period it was −15%. The sample size estimation (a minimum of 12 EDB muscles for each treatment) was based on data from a pilot trial with 10 healthy volunteers (Wohlfarth et al., 2004).

The overall effect of NT 201 compared with BOTOX® was evaluated by examining the ratio of CMAP values (NT 201: BOTOX®) over the course of the study and by analysis of variance (ANOVA) on repeated measurements.

Statistical tests for equivalence were performed in an exploratory manner, and p-values and confidence intervals were interpreted as having descriptive significance. All calculations were carried out using SPSS (Statistical Package for Social Science Version 8) and SAS (Statistical Analysis System Version 8.1). Due to the variability in CMAP amplitude between individuals, statistical analyses of variance used the baseline CMAP as covariate.

Results

Baseline data

The mean age of the study population was 32.1 ± 4.7 years. All 14 subjects in the analysis were male white Caucasians. Mean height was 184.2 ± 6.5 cm and mean weight 82.8 ± 12.3 kg (61–107 kg). Mean baseline CMAP values were 12.1 mV for NT 201 and 11.4 mV for BOTOX®.

Onset of action

Time to onset of action was similar for both medications. Over 50% of the subjects responded to both treatments 1 day after injection. A CMAP reduction of 30% was seen on Day 1 in 9 subjects for NT 201 and in 7 subjects for BOTOX®. Time to onset was slightly shorter with NT 201 than with BOTOX® although these differences were not statistically significant (median difference in time to 30% CMAP reduction between NT 201 and BOTOX® 0 days; 96.5% confidence intervals $= -1, 0$ days). By Day 7, all subjects had shown a 30% CMAP reduction after NT 201 injection. Response to BOTOX® was similar, with 5 subjects showing a 30% reduction in CMAP on Day 2, and 1 subject on Day 7 and 9 each.

CMAP reduction and responder rates

On Day 1, the EDB muscles injected with NT 201 showed a 30% CMAP decline compared to baseline whereas the CMAP decline of the EDB muscles

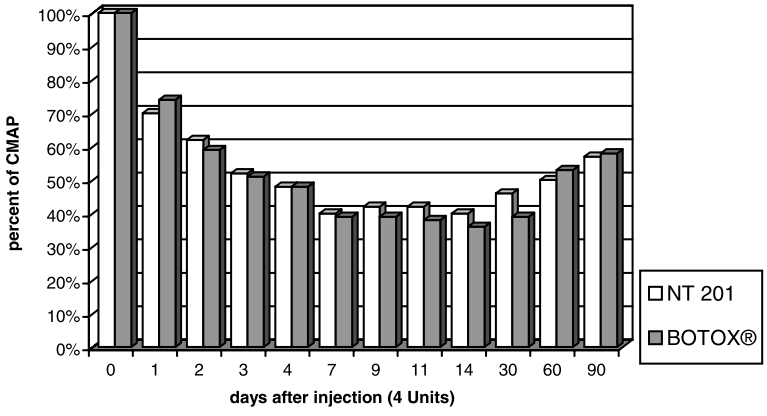

Fig. 1. Percent of CMAP (median values) after injection of NT 201 (open bars) and BOTOX® (black bars)

Table 1. Percent compound muscular action amplitude values (%CMAP) at each visit

Subj. no.	Age	BoNT	Foot	Base-line	Day 1	Day 2	Day 3	Day 4	Day 7	Day 9	Day 11	Day 14	Day 30	Day 60	Day 90
1	32	NT 201	right	100.0	66.4	48.7	46.1	46.1	49.8	43.6	42.6	45.0	30.5	45.7	53.0
		BOTOX®	left	100.0	77.6	52.8	46.2	42.8	37.4	31.0	35.7	35.4	39.1	44.8	48.9
2	46	NT 201	left	100.0	98.3	66.8	73.6	72.3	67.1	58.2	60.1	53.1	68.8	75.4	80.0
		BOTOX®	right	100.0	85.0	78.1	87.8	73.1	61.4	61.4	72.9	54.1	55.4	56.3	75.1
3	28	NT 201	left	100.0	91.6	62.1	63.9	73.9	41.5	41.1	51.5	68.1	42.5	47.4	54.5
		BOTOX®	right	100.0	83.0	53.6	53.6	46.9	36.0	31.6	34.8	39.7	36.2	35.6	41.2
4	37	NT 201	right	100.0	63.4	53.9	40.4	41.7	34.4	25.7	26.5	25.5	41.2	41.7	40.9
		BOTOX®	left	100.0	68.8	48.5	25.4	39.9	27.9	26.2	30.3	26.5	35.2	37.8	50.8
5	34	NT 201	right	100.0	69.4	58.1	43.3	40.3	30.2	27.1	27.7	19.9	36.3	42.4	49.9
		BOTOX®	left	100.0	68.0	35.4	35.2	35.1	35.4	29.2	28.9	27.4	36.7	48.4	60.1
6	29	NT 201	left	100.0	47.2	27.6	42.0	22.2	32.7	31.2	25.8	32.3	21.0	28.8	35.1
		BOTOX®	right	100.0	60.5	30.0	25.8	30.6	27.8	26.0	22.3	26.6	29.9	25.6	38.3
7	30	NT 201	left	100.0	95.6	94.8	56.3	54.4	45.4	52.9	62.9	49.6	62.2	64.1	75.2
		BOTOX®	right	100.0	67.7	59.2	37.8	42.4	31.3	38.9	31.5	25.3	33.6	51.8	39.6
8	27	NT 201	right	100.0	60.9	56.4	35.0	31.6	23.3	24.6	25.9	19.1	20.1	29.1	29.8
		BOTOX®	left	100.0	90.3	49.3	34.8	24.5	29.3	21.2	26.8	20.2	36.5	71.1	74.4
9	31	NT 201	right	100.0	57.6	41.0	45.7	30.8	18.3	26.9	21.3	21.6	80.0	35.6	43.8
		BOTOX®	left	100.0	95.5	118.8	120.9	99.0	75.7	66.1	51.7	48.3	20.3	94.1	84.1
10	32	NT 201	left	100.0	55.1	74.6	30.0	42.9	26.4	34.2	38.4	28.5	55.2	54.5	80.7
		BOTOX®	right	100.0	57.2	61.8	34.4	52.3	27.7	31.6	32.0	29.6	40.5	47.4	42.7
11	33	NT 201	left	100.0	74.7	79.6	80.2	50.7	52.7	70.8	59.5	56.0	53.2	68.3	54.3
		BOTOX®	right	100.0	67.7	66.3	65.6	38.1	44.5	55.2	51.7	43.8	49.0	62.8	47.0
12	30	NT 201	right	100.0	82.1	100.2	95.8	80.4	66.7	70.3	69.8	63.8	45.5	53.8	56.0
		BOTOX®	left	100.0	89.2	62.0	53.0	51.7	37.8	42.4	41.0	46.4	49.5	48.9	84.1
13	30	NT 201	right	100.0	58.4	54.3	30.5	29.3	23.1	25.9	27.4	22.6	17.8	19.7	26.9
		BOTOX®	left	100.0	54.5	41.4	31.2	32.6	13.7	16.3	15.4	22.5	12.5	27.7	29.5
14	29	NT 201	left	100.0	58.0	54.5	47.1	50.2	43.5	50.9	52.8	53.3	70.9	92.4	111.9
		BOTOX®	right	100.0	77.2	67.2	66.7	64.0	61.8	63.5	59.6	60.5	67.7	87.8	91.6

injected with BOTOX® was 22%. Both drugs produced a maximum decline between Day 7 and Day 14 (at around 60%, Fig. 1). At Day 90, administration of both drugs resulted in approximately 40% of CMAP decline as compared to baseline. The reduction of CMAP values were similar for both drugs over the course of the study. An individual subject data listing is provided in Table 1.

The maximal response occurred between Days 7 and 14. A 40% reduction in CMAP was observed in a maximum of 86% of subjects on Days 7, 9 and 14, and the proportion of subjects with a 50% CMAP reduction peaked at 79% on Day 7. The maximum proportion of subjects (50%) showing a 60% reduction in CMAP in response to NT 201 was observed on Days 7, 9, 11 and 70% was seen in 43% of subjects on Days 11 and 14.

For BOTOX®, response rates were very similar. All subjects had a CMAP reduction of 30% in response to BOTOX® on Days 9, 14 and 30 of the study. A 40% CMAP reduction was observed in a maximum of 93% of the subjects on Days 11, 14 and 30. In 86% of the subjects a 50% CMAP reduction was seen. The highest proportion of subjects showing 60% CMAP reduction was 71% on Day 7. A response of 70% reduction in CMAP to BOTOX® was observed in a maximum of 50% of subjects, and occurred on Day 14 of the study.

Between-treatment comparison

CMAP ratios of NT 201 to BOTOX® are summarised in Fig. 2. The means of the CMAP ratios were >1 for all time-points of the study with the exception of Days 2 and 3, where it was -0.59 ± 1.24 and -0.76 ± 1.15 (mean $\pm$ SD), respectively. Overall, the data imply that NT 201 is at least as effective as BOTOX® in paralysing the EDB muscle over the study period. The trend towards higher efficacy of NT 201 was not statistically significant ($p = 0.41$ for between-treatment comparison).

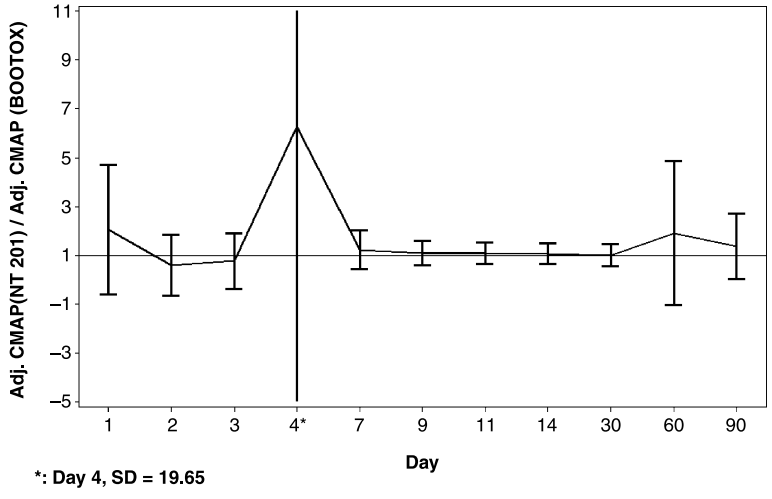

Fig. 2. Ratio of adjusted CMAP values (NT 201/BOTOX®). Mean $\pm$ SD

Tolerability

The injected dosage was very low and as expected no AEs, serious AEs or deaths, and no abnormal clinically relevant laboratory values were reported for treated subjects during the study. These observations were interpreted as indications that NT 201 and BOTOX® are equally well tolerated.

No subject prematurely terminated the trial.

Discussion

This study evaluates the paralytic activity and tolerability of NT 201 after intramuscular injection in comparison with the commercially available formulation BOTOX® in healthy human volunteers. Based on the EDB test and comparing time to onset of action, responder rate, CMAP ratios of NT 201 to BOTOX® and tolerability, no statistically significant differences between the preparations were found.

At the moment the EDB test is the best in-vivo tool to assess the clinical effect of botulinum toxin type A preparations in humans. As a surrogate paradigm, the EDB test has shown great value in a number of studies, both in assessing efficacy and in identifying cases of clinical resistance to treatment (Kessler and Benecke, 1997; Sloop et al., 1996, 2001; Eleopra et al., 1998). With this method, both toxins can be injected in parallel at easily accessible sites and no clinical disturbances result from EDB weakness. Only low doses are necessary, reducing the risk of systemic effects. In the current study, the EDB test appeared to perform reliably and in a reproducible fashion.

To ensure that both groups had comparable CMAP values at baseline, a parallel study design was used, where half of the population received NT 201 injected into the right foot and BOTOX® into the left foot, with the order reversed for the other half. Slightly more pronounced effects were observed in the right EDB muscle than the left in both groups. An analysis of CMAP values by right or left EDB muscle did not show significant differences in effect in different muscles and this general agreement of the data between groups support the robustness of the overall results.

As NT 201 and BOTOX® consist of botulinum A toxin as active agent, the mode of action is identical. However, the two agents show large differences in purity, which may affect their efficacy and tolerability. BOTOX®, which has long been commercially available, contains an appreciable amount of haemagglutinins and clostridial proteins in addition to the active neurotoxin. The presence of such extraneous proteins is believed to be responsible for the development of clinical resistance to botulinum A toxin, due to inhibitory antibody formation. This is in accordance with the recent study results obtained with the current BOTOX® preparation (Jankovic et al., 2003). Antibody formation is a frequent phenomenon in the clinical use of botulinum A toxin in the treatment of dystonic and non-dystonic movement disorders, where secondary resistance to treatment has been reported in up to 10.5% of patients (Greene et al., 1988a; Kessler and Benecke, 1997).

In contrast, NT 201 is a novel, highly purified product containing botulinum A toxin free of complexing proteins, stabilised with serum albumine and sucrose.

This is expected to lead to lower rates of secondary resistance and to have additional benefits, markedly improved handling safety and reduced oral toxicity. In this study, the two preparations performed equally well on all parameters assessed. These results were confirmed in two large studies in patients with cervical dystonia and blepharospasm (Benecke, 2004; Roggenkämper, 2004). Neither in this experimental study nor in the two clinical studies any differences in the safety and tolerability profile of NT 201 and BOTOX were found.

A possible advantage of higher purity may be a shorter time to onset, as the action of a high-purity preparation may be less susceptible to interference by extraneous proteins or immunogenic reactions. Although differences between responses in the current study were not significant, analysis of time to onset of action suggested that most subjects responded to NT 201 injection similar or even earlier than to BOTOX®.

The lower immunogenicity of NT 201 compared with BOTOX® has been shown in rabbits, where BOTOX® but not NT 201 elicits antibody production (Data unpublished). It was not the object of this study to evaluate differences in inhibitory antibody formation and currently available assays in humans are insufficiently sensitive to allow for a differentiation between immune response to different botulinum toxin type As (Chen et al., 1997; Binz et al., 1990; Dressler and Dirnberger, 2001). Hence, the possible differences between the two preparations in terms of immunogenicity will be tested long-term clinical studies.

In conclusion, this study indicates that NT 201 is at least as effective as BOTOX® in paralysing EDB muscles in a population of healthy volunteers. The higher purity of NT 201 compared with other currently available botulinum neurotoxin type A agents suggests that NT 201 theoretically elicits less clinical resistance than BOTOX®. Further studies would be needed to address the question whether these differences translate into clinical short-term and long-term advantages with NT 201 over currently available botulinum toxin type A.

Acknowledgements

The study was sponsored by Merz Pharmaceuticals GmbH, Frankfurt, Germany. S. Brinkmann and G. Comes are employees of Merz Pharmaceuticals, GmbH Frankfurt and are involved in the development of NT 201. Parts of the results have been presented as an abstract in *Abstracts of the Sixth International Congress of Parkinson's Disease and Movement Disorders*, Barcelona, Spain, June 11–15, 2000 (Vol 15, Suppl 3).

References

Aoki KR (2001) A comparison of the safety margins of botulinum neurotoxin serotypes A B and F in mice. Toxicon 39: 1815–1820

Benecke R (2004) Efficacy and safety of a new botulinum toxin type A free of complexing proteins in treatment of cervical dystonia. Mov Disord 19 [Suppl 9]: S110–S111

Binz T, Kurazono H, Wille M, Frevert J, Wernars K, Niemann H (1990) The complete sequence of botulinum neurotoxin type A and comparison with other clostridial neurotoxins. J Biol Chem 265: 9153–9158

Chen F, Kuziemko GM, Amersdorfer P, Wong C, Marks JD, Stevens RC (1997) Antibody mapping to domains of botulinum neurotoxin serotype A in the complexed and uncomplexed forms. Infect Immun 65: 1626–1630

Dressler D, Dirnberger G (2001) Botulinum toxin antibody testing: comparison between the immunoprecipitation assay and the mouse diaphragm assay. Eur Neurol 45: 257–260
Eleopra R, Tugnoli V, Rossetto O, De Grandis D, Montecucco C (1998) Different time courses of recovery after poisoning with botulinum neurotoxin serotypes A and E in humans. Neurosci Lett 256: 135–138
Erbguth FJ, Naumann M (1999) Historical aspects of botulinum toxin Justinus Kerner (1786–1862) and the 'sausage poison'. Neurology 53: 1850–1853
Gordon PH, Gooch CL, Greene PE (2002) Extensor digitorum brevis test and resistance to botulinum toxin type A. Muscle Nerve 26: 828–831
Greene P, Shale H, Fahn S (1988a) Analysis of open-label trials in torsion dystonia using high dosages of anticholinergics and other drugs. Mov Disord 3: 46–60
Greene P, Shale H, Fahn S (1988b) Experience with high dosages of anticholinergic and other drugs in the treatment of torsion dystonia. In: Fahn S, Marsden CD, Calne DB (eds) Dystonia 2. Raven Press, New York, pp 547–556 (Adv Neurol 50)
Hamjian JA, Walker FO (1994) Serial neurophysiological studies of intramuscular botulinum-A toxin in humans. Muscle Nerve 17: 1385–1392
Jankovic J, Vuong KD, Ahsan J (2003) Comparison of efficacy and immunogenicity of original versus current botulinum toxin in cervical dystonia. Neurology 60: 1186–1188
Kessler KR, Benecke R (1997) The EBD test – a clinical test for the detection of antibodies to botulinum toxin type A. Mov Disord 12: 95–99
Roggenkämper P (2004) Efficacy and safety of a new botulinum toxin type A free of complexing proteins in treamtent of blepharospasm. Mov Disord 19 [Suppl 9]: S84–S85
Scott AB (1981) Botulinum toxin injection of eye muscles to correct strabismus. Trans Am Ophthalmol Soc 79: 734–770
Sloop RR, Cole BA, Escutin RO (1997) Human response to botulinum toxin injection: type B compared with type A. Neurology 49: 189–194
Sloop RR, Cole D, Patel MC (2001) Muscle paralysis produced by botulinum toxin type A injection in treated torticollis patients compared with toxin naive individuals. Mov Disord 16: 100–105
Sloop RR, Escutin RO, Matus JA, Cole BA, Peterson GW (1996) Dose-response curve of human extensor digitorum brevis muscle function to intramuscularly injected botulinum toxin type A. Neurology 46: 1382–1386
Wohlfarth K, Kampe K, Bigalke H (2004) Pharmacokinetic properties of different formulations of botulinum neurotoxin type A. Mov Disord 19: S65–S67

Authors' address: Prof. Dr. med. W. H. Jost, Department of Neurology and Clinical Neurophysiology, Deutsche Klinik für Diagnostik, Aukammallee 33, 65191 Wiesbaden, Germany, e-mail: neuro@dkd-wiesbaden.de