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Safety of botulinum toxin short interval therapy using incobotulinumtoxin A

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Abstract The therapeutic efficacy of botulinum toxin (BT) can be completely blocked by formation of BT antibodies (BTAB), thus producing antibody-induced therapy failure (ABTF). One of the risk factors for this is the interval between two subsequent injection series. To prevent BTAB formation it is universally recommended not to use interinjection intervals of less than 12 weeks. However, BT's therapeutic efficacy may be considerably shorter than this interval, thus causing substantial reduction of quality of life. We wanted to study whether BT therapy with interinjection intervals of less than 12 weeks (short interval therapy, SIT) would be immunologically and otherwise safe. To minimise the risk of BTAB formation we used incobotulinumtoxin A which has a particularly low antigenicity. Altogether 30 patients (age 59.2 ± 13.5 years. 19 females, 11 males) with different dystonias were included in this study. They received SIT with incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals, Frankfurt/M, Germany) at interinjection intervals of 69.0 ± 8.1 days (equal 9.9 weeks or 2.2 months, min 48.9 ± 2.4 days) for 14.3 ± 2.9 injection series (equal 906 ± 169 days or 2.5 ± 0.5 years) in a dose of 259 ± 159 MU (max 670 ± 144.4 MU). None of the patients showed signs of ABTF, unusual BT effects or increased adverse effects. Information provided by this study confirms safety of SIT. With a considerable percentage of patients hitherto undertreated for prolonged periods of time with BT therapy applying 12 weeks intervals, SIT may substantially improve the quality of life for those patients. Whether SIT is also safe with other BT drugs needs to be tested.

Keywords Botulinum toxin · Therapy · Short interinjection intervals · Safety · Antibody formation

Introduction

Botulinum toxin (BT) is used to treat numerous disorders due to muscle hyperactivity and exocrine gland hyperactivity as well as chronic migraine (Truong et al. 2013). Botulinum neurotoxin, the biologically active ingredient of BT, is a 150 kD double-stranded protein (Dressler and Benecke 2007). Therefore, it bears the risk of stimulating the formation of BT antibodies (BTAB), which may interfere with BT's therapeutic efficacy. Complexing proteins contained in conventional BT drugs may be an additional antigenicity factor (Frevert and Dressler 2010). In appropriate amounts, BTAB may block BT's therapeutic effects completely (antibody-induced therapy failure, ABTF) and thus depriving many patients of their most effective treatment option. Risk factors for BTAB formation include the amount of BT applied at each injection series (single dose), the interval between two subsequent injection series (interinjection interval) and the application of booster injections, i.e. BT injections with interinjection intervals of less than 2 weeks (Dressler and Dirnberger 2000). To prevent BTAB formation it is universally recommended not to use interinjection intervals of less than 12 weeks. However, we recently demonstrated that BT's therapeutic efficacy may be considerably shorter than this interval, therefore, causing substantial reduction of quality of life (Dressler et al. 2015). We wanted to study whether BT therapy with

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interinjection intervals of less than 12 weeks (short interval therapy, SIT) would be immunologically and otherwise safe. To minimise the risk of BTAB formation we used incobotulinumtoxinA which has a particularly low antigenicity (Dressler 2012) and for which no ABTF has been reported so far.

Methods

Design

The study was based upon an open-label prospective and non-interventional design. Treatment data of all our patients receiving BT therapy are prospectively stored in our computerised BT therapy data base. At the observation point all patients fulfilling the inclusion criteria were retrieved from the data base and consecutively evaluated until the pre-set number of 30 patients was reached. All patients who were started on SIT and who stopped treatment because of efficacy problems were collected separately.

Patients

All patients were recruited from the BT clinics of Hannover Medical School Movement Disorders Section. Inclusion criteria were: (1) SIT with interinjection interval of less than 80 days. (2) Treatment with incobotulinumtoxinA throughout the observation period. (3) More than eight injection series applied within the observation period. (4) BT therapy for treatment of dystonia. Exclusion criteria beyond the general exclusion criteria for BT therapy were not applied.

BT therapy

SIT was performed exclusively with incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals, Frankfurt/M, Germany) using a dilution of 100 mouse units (MU) per 2.5 ml of 0.9 % NaCl/H_2O. Other BT type A or BT type B drugs may have been used in some patients before embarking on SIT. Target muscle selection was based upon analysis of the individual pathological muscle activity pattern. The BT dosing for each target muscle followed internationally accepted guidelines as previously published (Benecke et al. 2003). Interinjection intervals were originally set to 12 weeks as based on current recommendations. Depending on BT's duration of efficacy and based on the patient's explicit informed request they may have been reduced. Patients were eligible in this study when their interinjection interval was reduced to less than 80 days.

Parameters

Demographic data collected for each patient included name and first name, sex, date of birth (derivatives: age at inclusion) and diagnosis for which BT therapy is applied. Treatment data included the BT application dates (derivatives: interinjection intervals, number of injection series, treatment time) and the BT doses given at each injection series. Therapeutic efficacy was documented by the global clinical outcome monitored by the patient (subjective global clinical outcome) and the injector (objective global clinical outcome). Any reduction of the subjective or objective global clinical outcome in relation to the initial therapeutic efficacy was analysed neurologically, if it occurred on three subsequent injection series. If there was no other explanation, quantitative BTAB testing was performed.

Botulinum toxin antibody testing

BTAB testing was performed with the mouse hemidiaphragm assay (Toxogen, Hannover).

Statistics

All average values are given as mean ± standard deviation.

Results

General

Altogether 30 patients (19 females, 11 males) were included in this study. Their age was 59.2 ± 13.5 years. 19 patients were treated for cervical dystonia, five for blepharospasm, one for cranial dystonia, one for Meige syndrome, one for segmental dystonia, one for generalised dystonia, one for leg dystonia and one for writer's cramp. Patients received 14.3 ± 2.9 (min 9, max 20) injection series. The parameters of SIT as applied in this study are summarised in Table 1. Patients were treated with an interinjection interval of 69.0 ± 8.1 (min 48.9, max 79.6) days. Figure 1 shows a histogram of the interinjection intervals documented in this study. The overall incobotulinumtoxinA dose was 259 ± 159 (min 41, max 670, $n = 30$) MU. For cervical dystonia ($n = 19$) it was 307.0 ± 98.2 MU, for blepharospasm ($n = 5$) 84.5 ± 10.3 MU, for cranial dystonia ($n = 1$) 74.9 ± 18.0 MU, for Meige syndrome ($n = 1$) 145.3 ± 37.9 MU, for segmental dystonia ($n = 1$) 429.9 ± 179.8 MU, for generalised dystonia ($n = 1$) 670.0 ± 144.4 MU, for leg dystonia ($n = 1$)

Table 1 Treatment parameters of short interval botulinum toxin therapy (SIT) used in the present study

Interinjection interval	69.0 ± 8.1 days
	Minimum 48.9 days
	Maximum 79.6 days
Botulinum toxin single dose	259 ± 159 MU
	Minimum 41 MU
	Maximum 670 MU
Number of injection series	14.3 ± 2.9
	Minimum 9
	Maximum 20
Treatment duration	905.7 ± 169.4 days
	Minimum 543 days
	Maximum 1132 days

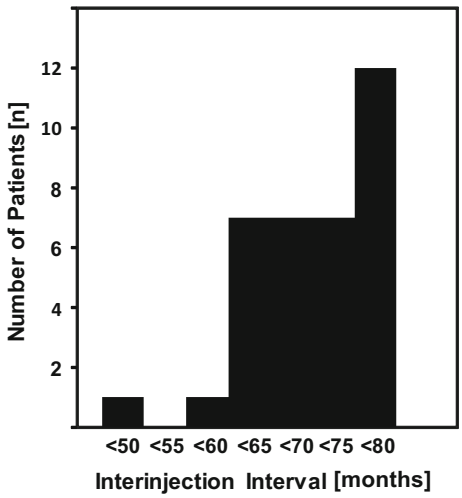

Fig. 1 Histogram of the interinjection intervals used in this study

189.1 ± 45.9 MU and for writer's cramp ($n = 1$) 41.0 ± 15.0 MU. The number of injection series was 14.3 ± 2.9 (min 9, max 20). The treatment duration was 906 ± 169 (min 543, max 1132) days or 2.5 ± 0.5 years.

Therapeutic efficacy

Throughout the observation period there was no loss of therapeutic efficacy and, thus, no indication of ABTF in any of the patients studied neither on subjective nor on objective global clinical impression. No BTAB tests had to be performed. There were no unusual BT effects or increased adverse effects. All subsequent BT injections had the effects expected from applications with regular interinjection intervals. There was also no indication of additional adverse effects not seen with BT therapy with regular interinjection intervals. There was no indication of central nervous system adverse effects.

Discussion

Interinjection intervals used in our study were 69.0 ± 8.1 days (equal 9.9 weeks or 2.2 months). The minimum interinjection interval used in an individual patient was 48.9 ± 2.4 days. Throughout the observation period of 14.3 ± 2.9 injection series (equal 906 ± 169 days or 2.5 ± 0.5 years) there was no indication of ABTF and no unusual BT effects or increased adverse effects. Effects on the central nervous system could not be detected as in all previous clinical studies. With this, our study showed for the first time that SIT with interinjection intervals of less than 80 days can be safely performed.

To minimise the risk of ABTF incobotulinumtoxinA was used in our study. IncobotulinumtoxinA is the latest major BT drug, introduced 10 years ago in Germany. It is available in most European and in all major global markets for use in various dystonia and spasticity indications. From its improved specific biological activity it was predicted to have an improved antigenicity (Dressler 2012). Removal of complexing proteins may further contribute to an improved antigenicity (Frevert and Dressler 2010), although convincing animal experiments for this are lacking. Lack of any ABTF-report in patients treated with incobotulinumtoxinA despite the drug's long and widespread global use is unique and confirms the prediction of an extremely low antigenicity.

BTAB formation usually occurs during a period of 1–2 years after initiation of BT therapy (Dressler 2004). To give the immune system enough time to react, we only included patients with an observation period of at least eight injection series. With an observation period of 14.3 ± 2.9 injection series (equal 2.5 ± 0.5 years) patients, therefore, were exposed to SIT therapy long enough to develop ABTF. Conversely, lack of ABTF was, therefore, unlikely to be caused by insufficient exposure time.

Apart from short interinjection intervals, the BT single dose is another risk factor for ABTF. We, therefore, also monitored the BT single doses used in our study. With an average dose of 259 ± 159 MU the single dose applied in our study was substantial. For example, United States summary of product characteristics recommend incobotulinumtoxinA doses of 120 MU for treatment of cervical dystonia (Merz Pharmaceuticals LLC 2015). Doses used in this study are high enough to exclude insufficient doses as a cause for lack of ABTF. They are also high enough to allow SIT for treatment of a wide range of applications even involving substantial BT doses. Maximal average BT dose given to an individual patient was 670 ± 144.4 MU. Even when these high doses were applied, SIT did not produce ABTF.

Information provided by this study confirms safety of SIT. With a considerable percentage of patients hitherto undertreated for prolonged periods of time with BT therapy applying 12 weeks intervals, SIT may substantially improve the quality of life for those patients. Whether SIT is also safe with other BT drugs needs to be tested.

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References

Benecke R, Moore P, Dressler D, Naumann M (2003) Cervical and axial dystonia. In: Moore P, Naumann M (eds) Handbook of botulinum toxin therapy, 2nd edn. Blackwell, Oxford, pp 158–194

Dressler D (2004) Clinical presentation and management of antibody-induced failure of botulinum toxin therapy. Mov Disord Suppl 8:S92–S100

Dressler D (2012) Five-year experience with incobotulinumtoxin A (Xeomin®): the first botulinum toxin drug free of complexing proteins. Eur J Neurol 19:385–389

Dressler D, Benecke R (2007) Pharmacology of therapeutic botulinum toxin preparations. Disab Rehabil 29:1761–1768

Dressler D, Dirnberger G (2000) Botulinum toxin therapy: risk factors for therapy failure. Mov Disord 15(suppl 2):51

Dressler D, Tacik P, Saberi FA (2015) Botulinum toxin therapy of cervical dystonia: duration of therapeutic effects. J Neural Transm 122:297–300

Frevert J, Dressler D (2010) Complexing proteins in botulinum toxin type A drugs: a help or a hindrance? Biologics 4:325–332

Merz Pharmaceuticals LLC (2015) http://www.xeomin.com/physicians/dosing/. Accessed 7 Sept 2016

Truong D, Dressler D, Hallett M, Zachary C (2013) Manual of botulinum toxin therapy, 2nd edn. Cambridge University Press, Cambridge