Botulinum toxin F in the treatment of torticollis clinically resistant to botulinum toxin A

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Abstract

Two reports have shown a Japanese preparation of botulinum toxin type F (BTX-F) to be an effective alternative for patients with torticollis who develop clinical resistance to botulinum toxin type A (BTX-A). A group of patients with torticollis, comprising five secondary non-responders and one primary non-responder, were treated with a preparation of BTX-F produced in the UK (Speywood Pharmaceuticals). A low dose of BTX-F (220 mouse units (MU) in total) was given into clinically affected neck muscles, followed six weeks later by an injection of a total of 520 MU. Antibodies to BTX-A (mouse protection assay) were present in all secondary non-responders but not in the primary non-responder. No patients developed atrophy after injection of Dysport BTX-A (40 MU) into the left extensor digitorum brevis muscle whereas pronounced atrophy occurred in all patients after injection of 40 MU of BTX-F into the right extensor digitorum brevis muscle. Three patients improved subjectively after treatment with 220 MU BTX-F and five (all secondary non-responders) after the subsequent dose of 520 MU (two considerably), with reduced Tsui scores, but group scores were only significantly changed after the higher dose. The primary non-responder remained unchanged after both doses of BTX-F. One patient reported mild dysphagia with 520 MU BTX-F. Mean duration of improvement with 520 MU BTX-F was five (range 4-6) weeks. Thus BTX-F provides benefit for BTX-A non-responders with few side effects but for a shorter period than BTX-A, possibly due to relative underdosing. As with BTX-A, biological sensitivity to BTX-F does not necessarily predict a clinical response.

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Botulinum toxin (BTX) is a well established, effective treatment for torticollis,¹⁻⁷ blepharospasm,^{8,9} and laryngeal dystonia.^{10,11} New indications for BTX treatment also being evaluated include focal hand dystonias,¹²⁻¹⁷ tremor,¹⁸ and spasticity.^{19,20} Of the seven immunologically distinct types of botulinum neurotoxins, labelled A to G,²¹ the only type in

routine clinical use at present is botulinum toxin type A (BTX-A).

Although most patients with torticollis benefit from BTX, about 10% never respond to treatment (primary non-responders)²²⁻²⁴ and up to 10% of patients may become resistant to treatment after initially responding (secondary non-responders).²⁵ Technical factors such as incorrect storage or reconstitution of the toxin may be responsible for isolated secondary treatment failures. Explanations for sustained late failure of response include underdosing, injection of inappropriate muscles, a worsening or change in the pattern of dystonia, possibly with involvement of deep, inaccessible muscles, development of contractures, altered perception of response, and the development of immunity.^{23,25} Immunity is particularly suspected when injected muscles fail to become atrophic; antibodies to botulinum toxin are often present in such patients.^{25,26} Risk factors for the development of antibodies seem to be higher frequency of injections, the use of "booster" injections and higher doses of BTX per treatment,²⁵ and possibly cumulative dose and small body size.^{23,27} Antibodies have been detected after treatment with each type of BTX-A in use (Botox and Dysport).^{23-26,28-30}

Secondary non-responders who have developed immunity to BTX-A should be theoretically ideal candidates for treatment with types of BTX that are immunologically distinct from type A. It has already been established that their dystonia responds to weakening of the affected muscles with BTX but assumes that the resistance (immunity) is specific to BTX-A and that this is the only reason for failure of treatment. Two groups have reported successful treatment of patients who have developed antibodies and clinical resistance to the Botox form of BTX-A using a Japanese preparation of botulinum toxin type F (BTX-F).^{26,31,32}

We report the first results of open labelled treatment of patients with torticollis clinically resistant to Dysport BTX-A with another preparation of BTX-F.

Patients and methods

Six patients clinically resistant to BTX-A were selected from a large torticollis clinic. Five had initially obtained a definite benefit (secondary non-responders) and one had never responded to treatment (primary non-responder). All had ultimately failed to develop atrophy in injected muscles. The study had the approval of the hospital ethics committee and all patients gave informed consent. The BTX-A (Dysport) and

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BTX-F used in this study were produced and supplied by Speywood Pharmaceuticals.

INJECTION PROTOCOL

On entry into the study, the patients received one further treatment with BTX-A and were reviewed two weeks later. This was to confirm that they were still clinically resistant to BTX-A because of the sometimes long interval since the cessation of regular BTX-A injections due to treatment failure. The target muscles in the neck and the doses given to each were chosen and injected (without EMG guidance) by a physician (AJL) with considerable experience in the treatment of this condition. The doses of BTX-A (400–500 mouse units; MU) were based on this experience. Based on the LD₅₀ data for BTX-F, using the same method as that used to evaluate potency of their BTX-A product, the suppliers suggested an initial total dose of 260 MU of BTX-F, to be divided among the affected muscles. This dose was deliberately low for safety reasons as this preparation of BTX-F had not been tried on humans before. Provided that there were no adverse events with the lower dose, a subsequent total dose of 520 MU was suggested, this being comparable with the average dose of BTX-A used, again to be divided among the affected muscles. Vials of BTX-A contained 500 MU each and were diluted with 2.5 ml of sterile normal saline to a concentration of 200 MU/ml. Vials of BTX-F contained 260 MU each and were diluted with 2.5 ml of normal saline to a concentration of 100 MU/ml. The commonest muscles injected were the sternomastoid and splenius and less often the semispinalis and trapezius.

At least six weeks after the BTX-A injection, ensuring that there was no clinical effect of this injection, the patients received an injection of a total dose of 220 MU of BTX-F and were reviewed after two and six weeks. At the six week review, a second injection of a total of 520 MU BTX-F was given if there was no residual response to the first injection of BTX-F, and the patients were reviewed again two and six weeks later.

CLINICAL EVALUATION

Clinical assessment was performed at baseline and at each clinical review by one of us (AJL) using the Tsui scale.¹ Video recordings were also made at these times. These were shuffled and arranged in random order by an audiovisual technician and later reviewed by both of us, who were blind to their chronological order; only the recording made on entry into the study was identified, to serve as a baseline. The severity of the torticollis in all subsequent video recordings was compared with that made at entry and rated using a seven point scale. The baseline state was assigned a score of 0 and no change from baseline was scored as 0, and mild, moderate, or considerable improvement or deterioration were scored as + or – 1, 2, or 3 respectively. The patients were asked to report any changes after each injection of BTX-A or BTX-F using the same seven point scale.

ELECTROPHYSIOLOGICAL TESTING

Baseline electrophysiological testing was performed on the same day as the patients received the BTX-A injections to the neck. Compound muscle action potential (CMAP) was recorded from the extensor digitorum brevis muscle bilaterally in response to supramaximal stimulation of the deep peroneal nerve at the ankle. Routine EMG of this muscle was then performed with a concentric needle electrode followed by quantitative EMG (Nicolet Viking II). The peak to peak amplitude, mean voltage, root mean square voltage, and turns/s were recorded during a two second maximal voluntary contraction of the muscle from three separate sites within the muscle. To test for biological sensitivity, 40 MU of BTX-A was then injected with EMG guidance into the *left* extensor digitorum brevis muscle through a monopolar, teflon coated 25 gauge needle. Electrophysiological testing of extensor digitorum brevis muscle was repeated at two and four weeks afterwards, when the muscle was also examined for strength and bulk. The contralateral extensor digitorum brevis muscle was tested serially as a control.

Immediately after the injection of 220 MU of BTX-F to the neck, the electrophysiological tests were performed (as before), followed by an injection of 40 MU of BTX-F (the remainder of the vial of 260 MU) into the *right* extensor digitorum brevis muscle, the side opposite that which received BTX-A. Electrophysiological testing was repeated at two and four weeks as before.

SEROLOGICAL TESTING

Blood was taken on entry into the study, on the same day and just before receiving the BTX-A neck injection, to test for antibodies to BTX-A. The details of the mouse protection assay are similar to those previously reported.²⁹

STATISTICAL ANALYSIS

The Tsui scores, video ratings, and the electrophysiological data before and after the injections were compared with the Wilcoxon rank sum test. P values < 0.05 were considered significant.

Results

Table 1 gives the clinical details of the patients. There were five women and one man, ranging in age from 27 to 63 (mean 47.8) years. One patient was a primary non-responder and the remaining five were secondary non-responders. The patients were declared clinically resistant to BTX-A injections after seven to 18 treatments (mean 13, median 13.5) given over a period of 18 to 83 months (mean 43.8, median 43.5 months). The total dose of BTX-A received by the patients, before treatment was abandoned due to resistance, ranged from 4000 to 12 300 MU (mean 8383 MU, median 8850 MU).

RESPONSE TO BTX INJECTIONS

After injection of BTX-A, there was no significant change in the Tsui scores of the group at

Table 1 Clinical characteristics and antibody status of patients

Patients	Age/ sex	Clinical type†	Disease duration (y)	Treatment duration (months)	Total dose‡ (treatments)	Antibody status§
1*	47,F	Rot	4	18	4000 (7)	None
2	27,F	Rot, lat, ret	10	83	6200 (10)	Int-high
3	51,M	Rot	19	52	12300 (18)	Int-high
4	51,F	Rot	7	51	8500 (13)	Int-high
5	48,F	Rot	5	23	9200 (16)	Int-high
6	63,F	Rot, ret	18	36	10100 (14)	Int-high

*Primary non-responder; all others were secondary non-responders.

†Rot = rotation; lat = lateral flexion; ret = retrocollis.

‡Cumulative dose, in mouse units, of Dysport BTX-A received before declared resistant. Treatments = number of treatment sessions.

§Int-high = antibodies to botulinum toxin A detected in intermediate to high levels.

two weeks and all patients felt unchanged, confirming their clinical resistance. Table 2 shows the clinical response to the injections of BTX-F given to the neck. Three patients (patients 2, 3, and 5) reported improvement after the low dose of BTX-F (220 MU). For two of these (patients 3 and 5), the onset of the response was before the two week review. The third patient (patient 2) noticed a moderate response beginning just after her two week assessment; her Tsui score thus showed no change at this time. Tsui scores were reduced at two weeks in the other two patients (patients 3 and 5) who reported improvement and in another (patient 4) who was unaware of any improvement. The duration of response to this dose ranged from two to four weeks.

All patients had returned to baseline (or below) by six weeks after the low dose of BTX-F, subjectively and according to Tsui scores. None had experienced any adverse effects with the lower dose of BTX-F and therefore all received the higher dose of 520 MU at that time. After this, five patients (all secondary non-responders) reported improvement (ranging from mild to considerable) accompanied by a significant reduction in Tsui scores ($P < 0.05$) at two weeks. The primary non-responder did not change clinically after either dose of BTX-F, subjectively or objectively; her Tsui score reduced after 520 MU BTX-F by one point only.

Assessment of video recordings made two weeks after each dose of BTX-F agreed, for most patients, with the subjective reports from the patients and the Tsui scores in terms of the direction of change (improvement or deterioration) and often the degree of change (table 3). A statistically significant change in the

averaged video scores of the two reviewers for the group after 520 MU BTX-F could not, however, be demonstrated. There were too few numbers to allow separate statistical analysis of the secondary non-responders alone or of the individual reviewer's scores. Similarly for the results after 220 MU BTX-F.

The duration of response in the three patients who reported subjective improvement after the lower dose of BTX-F (220 MU) ranged from two to four weeks. The mean duration of response after 520 MU BTX-F was five (range 4–6) weeks and all responders stated that the duration of benefit was much shorter than that previously experienced with BTX-A (usually 10 to 12 weeks). Two of the three patients responding to the lower dose reported a benefit of increased magnitude and longer duration after the higher dose; the third patient reported considerable improvement after both doses but a longer duration of response with the higher dose. The onset of benefit began within two weeks, except for one patient in whom the response was delayed with the low dose of BTX-F to just beyond two weeks; with the higher dose, the onset was within two weeks.

Side effects were reported in only two patients and only after the higher dose of BTX-F. One (patient 3) experienced a dry mouth and mild dysphagia for a few days; this dose had produced a moderate subjective improvement. The other patient (patient 2) reported a dry mouth for a few days, but no dysphagia, accompanied by a pronounced benefit. All patients received injections of BTX-F into the sternomastoid and developed some degree of atrophy subsequently, although this was substantial in only two.

Table 2 Clinical response to BTX-F: Tsui scores, subjective ratings, and response duration

Patient	BTX-F 220 MU			Subjective Response	Response duration (weeks)	BTX-F 520 MU		Subjective response	Response duration (weeks)
	Tsui scores†					Tsui Scores			
	Baseline	2 weeks	6 weeks*			2 weeks	6 weeks		
1	10	11	11	—	0	10	10	—	0
2	11	11	13	+ +‡	2	7	7	+ + +	6
3	13	11	11	+	4	9	13	+ +	5
4	9	7	9	—	0	7	13	+ +	4
5	13	7	13	+ + +	3	8	11	+ + +	6
6	15	15	18	—	0	13	15	+	4

*BTX-F dose 520 MU given 6 weeks after BTX-F dose 220 MU; therefore, Tsui scores here represent baseline for BTX-F 520 MU.

Subjective clinical response: — = no change; + = mild; ++ = moderate; +++ = pronounced improvement.

†Tsui scores are calculated from severity scores (incorporating degree and duration) of the elements of head rotation, lateral tilt, and shoulder elevation, along with tremor or jerk. Scores range from 0 (normal) to 25 (very severe torticollis). For details see Tsui *et al.*¹

‡Response began after the 2 week assessment.

Table 3 Video scores of torticollis severity* at two weeks after each dose of BTX-F

Patient	BTX-F (220 MU)			BTX-F (520 MU)		
	Reviewer 1	Reviewer 2	Average	Reviewer 1	Reviewer 2	Average
1	0	-1	-0.5	1	0	0.5
2	0	0	0	2	1	1.5
3	1	1	1	0	-1	-0.5
4	2	1	1.5	2	2	2
5	2	2	2	2	1	1.5
6	1	0	0.5	1	1	1.0

* Baseline clinical state was assigned a score of 0. Thus 0 = no change, 1 = mild, 2 = moderate, 3 = pronounced change from baseline. Negative scores indicate deterioration.

SEROLOGICAL RESULTS

Table 1 gives the results of the antibody tests. The delay between the cessation of regular BTX treatment and the testing of antibodies ranged from two to 28 months (mean 12.3, median 10). Intermediate to high levels of antibodies to BTX-A were present in all five secondary non-responders but were not detected in the primary non-responder.

ELECTROPHYSIOLOGICAL RESULTS

Table 4 gives the electrophysiological data. After injection of BTX-A into the left extensor digitorum brevis muscle, there was no significant change in the CMAP amplitude of either the left or right extensor digitorum brevis muscle at two and four weeks (data for right extensor digitorum brevis muscle not shown). Similarly, there was no evidence of denervation or any motor unit changes with routine needle EMG and no significant change in the quantified EMG variables measured (not shown). No patient developed wasting or weakness of the left extensor digitorum brevis muscle. The primary non-responder (without detectable antibodies) showed a change in the left extensor digitorum brevis muscle CMAP amplitude ratio (compared with baseline) at two weeks which was similar to that of the mean of the secondary non-responders. By contrast, by two weeks after injection of BTX-F into the right extensor digitorum brevis muscle there was a dramatic reduction in CMAP amplitudes in all patients, whereby responses became nearly unrecordable. This was accompanied by near total wasting and severe weakness of that muscle. This change was so pronounced and so dramatically different from the response from injection of the left extensor digitorum brevis muscle with BTX-A that statistical analysis was hardly necessary but none the less confirmed the result to be significant.

Discussion

In this study, all secondary non-responders (previously responsive to BTX-A) had antibodies to BTX-A and all showed subjective and objective improvement with the higher dose of BTX-F. The primary non-responder, who did not have antibodies to BTX-A, also failed to respond to BTX-F. Biological resistance to BTX-A and sensitivity to BTX-F were established in all patients in the study by the responses (clinical and electrophysiological) of the extensor digitorum brevis muscle to injections of each type of BTX. The inability to show a significant change in the video scores despite close agreement with the subjective reports and the Tsui scores may reflect the difficulties inherent in this method of evaluation and possibly the lack of validation of the method. Furthermore, one of the clinical raters performing the Tsui scores also scored the videos so that, although blind to the chronological order of the recordings, this evaluation was not wholly independent.

Our results are similar to those previously reported. Greene *et al*²⁶ treated 15 antibody positive patients with torticollis with BTX-F. All patients had initially developed atrophy with BTX-A, but later failed to do so indicating secondary biological resistance. Antibodies to BTX-A were present in all patients and all ultimately failed to develop atrophy in injected neck muscles. Ten patients responded to BTX-F, including nine of the 12 secondary non-responders and one who had been a primary non-responder to BTX-A. Five patients did not respond to BTX-F, of whom two had also not responded to BTX-A; of the remaining three, two had either absent or short lived atrophy with BTX-F. Two patients developed pronounced atrophy to BTX-F but were still clinically unresponsive; one had initially responded to BTX-A.

Another group have also reported their experience with BTX-F in 10 patients, seven of whom had torticollis.^{31 32} All patients were clinically resistant to BTX-A and had antibodies detected with a bioassay; all improved after treatment with BTX-F for a period of six to 10 weeks. Side effects were reported to be similar in frequency and severity to those with BTX-A treatment.

These studies of BTX-F, including our own, have been uncontrolled and have involved few patients. Despite this, it seems that most secondary BTX-A non-responders will benefit from BTX-F. Biological sensitivity

Table 4 Electrophysiological responses to injections of BTX-A and BTX-F

Patient	Left EDB CMAP (mV)			Wasting*	Right EDB CMAP (mV)			Wasting*
	Baseline	2 weeks†	4 weeks‡		Baseline	2 weeks‡	4 weeks‡	
1	4.9	3.2	3.6	—	5.6	0.2	0.5	+++
2	7.9	5.8	5.7	—	7.3	0.1	1.4	+++
3	6.2	6.6	5.3	—	4.3	0.1	0.3	+++
4	6.1	4.4	5.0	—	6.3	0.9	0.3	+++
5	2.7	2.0	1.9	—	3.0	0.2	0.3	+++
6	4.0	4.9	4.4	—	3.3	0.1	0.3	+++

EDB = extensor digitorum brevis; MU = mouse units; CMAP = compound muscle action potential amplitude.

*Wasting: — = no wasting, +++ = severe wasting of EDB; † no significant change from baseline; ‡ significant change from baseline ($P < 0.05$, Wilcoxon rank sum test).

to BTX-F, however, as determined by the development of muscle atrophy, does not guarantee a clinical response, even if the patient was previously responsive to BTX-A. It is well known from biologically sensitive primary and secondary non-responders that factors other than immunity must be involved in a lack of clinical response. These include a change in the pattern of affected muscles, possibly involvement of deep, inaccessible muscles, insufficient doses, injection of inappropriate muscles, failure to place the toxin accurately within the muscle, or the development of contractures.^{23 24} Such factors may have contributed to the late failure of BTX-A, in addition to immunity, or may have intervened in the meantime to render the patients unresponsive to BTX-F. Although the numbers are small, primary non-responders seem less likely to respond to BTX-F (one of four patients in this study and those from Greene *et al*²⁶) suggesting that factors independent of the type of toxin used are chiefly responsible for the lack of response.

Our primary non-responder (patient 1) was resistant both biologically and clinically to BTX-A. She had been managed aggressively with escalating doses and injections of different muscles, including treatment sessions involving injections of up to four muscles at a time with a total dose of 1100 MU of BTX-A. Despite biological resistance, antibodies to BTX-A were not detectable. The frequency of antibodies detected by bioassay in cases of clinical resistance to BTX-A ranges from 11 to 60%.^{23 25 27} This may be an underestimate as not all patients with clinical resistance are tested. Furthermore, it is not always clear from these reports whether the patients are also biologically resistant (lack of atrophy). Thus factors other than this may be responsible for the clinical resistance and may partly explain the low incidence of antibodies in cases of secondary resistance. On the other hand, only three out of eight patients (38%) who were both clinically and biologically resistant had antibodies in one study.²⁵ Therefore, even when biologically resistant, antibodies may not be detectable. Such seronegative cases, including our primary non-responder, may reflect the technical difficulty and insensitivity of the mouse bioassay. Alternatively, some other non-humoral factor may underlie the resistance in antibody negative patients. Animals inoculated with botulinum toxoid may be protected from its neurotoxic effects despite the absence of antibodies with the mouse bioassay.³³

The frequency of antibodies on mouse bioassay in patients continuing to respond to BTX-A is also difficult to estimate given that such testing is usually only performed when there is a diminished clinical response. Whereas there are occasional reports of seropositivity among continuing responders,^{24 27} screens of such patients generally yield negative results.^{23 24 29} These findings should be distinguished from those of studies employing an

in vitro assay, such as enzyme linked immunosorbent assay (ELISA) or sphere linked immunodiagnostic assay (SLIDA),^{28 30} in which a high incidence of antibodies in continuing responders has been found, probably because the antibodies detected do not necessarily neutralise the biological activity of the toxin. Thus there is a better correlation between antibodies detected by a bioassay and clinical response. A more reliable indicator, however, might be a quantifiable response to the injection of BTX into a muscle, such as the extensor digitorum brevis muscle injection used in this study. This would at least determine biological sensitivity irrespective of antibody status.

A mean duration of response to BTX-F of five weeks in this study is similar to that reported by Greene *et al*²⁶ and is much shorter than our experience with BTX-A, which is around 12 weeks.⁷ The mean duration of benefit in the four patients treated with BTX-F by Ludlow *et al*³¹ was longer at 7.5 weeks (range 6–10 weeks in their later expanded report),³² although in three patients the response was shorter than that previously experienced with BTX-A. The reason for this difference in the duration of benefit using BTX-F from the same source (Japanese) is not clear but may involve the different injection techniques and the different assay estimates of toxin potency obtained by each institution. It had been suggested that the duration of response may be different in facial or laryngeal muscles,²⁶ but a study of blepharospasm seems to confirm a shorter duration of action for BTX-F, regardless of muscle size.³⁴

We have the advantage that the potencies of BTX-F and BTX-A used in this study were determined by the same method. According to the manufacturer's current information, the specific activities (units of biological activity per unit amount of toxin) of the two types of BTX are virtually identical. Thus equal amounts of each type of toxin should have the same biological activity, or at least the same lethal activity in mice. This may not mean that they have equal muscle weakening effects. Animal studies suggest that BTX-F produces less potent neuromuscular junction blockade and has a shorter duration of action than BTX-A.³⁵ The initial dose of BTX-F used in the present study was low for safety reasons whereas the higher dose of 520 MU is similar (in MU) to the doses of BTX-A used in the routine clinic. It is still possible, however, that the short duration of response we noted was due to relative underdosing. The three patients responding to the lower dose (220 MU) of BTX-F obtained benefit from the higher dose (520 MU) of BTX-F which was of longer duration, or greater magnitude, or both, suggesting that the degree and duration of response may be dose related, similar to BTX-A. Furthermore, atrophy of the sternomastoid was often not prominent and only one patient experienced side effects due to regional weakness (mild dysphagia) with the higher dose of BTX-F; dysphagia was reported after 44% of treatments with BTX-A in a review of the

results from this institution.²⁴ Therefore, even higher doses of BTX-F may have provided a greater response of longer duration. Although the dilutions of the two types of toxin used (A and F) were different, this could only be expected to affect the degree of benefit and not the duration. All of our patients developed near total atrophy of the extensor digitorum brevis muscle after injection of 40 MU of BTX-F but we have no experience of injections of this muscle with BTX-A for comparison. Although we did not follow the time course of the physiological responses of the BTX-F injections into the extensor digitorum brevis muscle, it is the duration of clinical response which is more important. Cross reactivity between the anti-BTX-A antibodies and BTX-F has also been suggested to explain the shorter duration of BTX-F.^{26,32} even though this does not occur experimentally.³⁶

If lower potency and a shorter duration of clinical action of BTX-F is confirmed, this will necessitate the use of higher doses more often, variables which have been identified as risk factors for antibody development to BTX-A.²⁵ This could limit the value of BTX-F in long term treatment and it may not prove to be a practical solution for patients with torticollis clinically resistant to BTX-A. A preliminary report³⁷ on the use of BTX-B as primary treatment in torticollis looks promising but as yet there are no data concerning its use in patients clinically resistant to BTX-A. Treatment with BTX-F might also be of value in the rare situation where treatment with BTX-A has become contraindicated because of complications which are possibly immune mediated.⁴⁰⁻⁴²

Greene *et al.*²⁶ suggested several situations in which use could be made of the shorter duration of action of BTX-F. Another may be treatment of writer's cramp and other task specific dystonias in which a stepwise approach with very fine adjustments of BTX doses and muscles injected is sometimes needed and where excessive weakness is poorly tolerated and may last for three months or more. It may be possible to optimise the treatment (muscles injected and degree of weakness) with BTX-F first and then continue with BTX-A.

In summary, BTX-F is a potentially useful alternative for those who have failed to respond to BTX-A, particularly secondary non-responders. As with BTX-A, biological sensitivity to BTX-F does not guarantee a clinical response and other causes of clinical resistance should be considered. Although there are still some questions about the dose-response relation, the duration of benefit seems to be shorter than with BTX-A. The need for higher doses more frequently could limit the clinical value of BTX-F and possibly make it more immunogenic. Further dose ranging and long term studies are needed.

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NEUROLOGICAL STAMP

Mentha piperita (peppermint)

The mints (*Mentha* species) are among the oldest of European herbs and are widely cultivated in temperate zones. Medicinal mints date from the 1st century AD. In Elizabethan times more than 40 ailments were reportedly remedied by mints. Menthol, a derivative of peppermint, has been used in upper respiratory ailments and as a soothing rub for sore muscles. Mints are also used in both home remedies and pharmaceutical preparations to relieve the stomach of intestinal gas that is often caused by certain foods. The many varieties of after dinner mints reflect its use in this role.

Mentha pulegium (European pennyroyal) taken in large doses has produced convulsions and coma.

Peppermint (*Mentha piperita*) is shown as part of a set of stamps issued by East Germany in 1960 illustrating medicinal plants (Stanley Gibbons E 490, Scott 496).

L F HAAS