Botulinum toxin in upper limb spasticity: study of reciprocal inhibition between forearm muscles

To establish whether botulinum A toxin (BTX-A) acts on modifying reciprocal inhibition between forearm muscles in spasticity, 20 patients with post-stroke upper limb spasticity lasting for more than 1 year were studied. Clinical examination, physiotherapeutic evaluation, standardized video-tape assessment and electrophysiological testing (flexor carpi radialis muscle M and H responses with study of reciprocal inhibition) were performed at baseline and 2 weeks, 1, 2, 3, 4 months after BTX-A treatment. BTX-A induced a significant decrease of tone and an improvement of motility and functional status, with a significant decrease of the M wave and the H reflex. The reduction in both inhibitory phases of reciprocal inhibition did not change after BTX-A treatment differently from that reported in upper limb dystonia. These findings indicate that the efficacy of BTX-A in upper limb spasticity is mainly due to peripheral effects.

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Introduction

Spasticity is characterized by a velocity-dependent augmentation in tonic stretch reflexes and is due to cerebral or spinal injuries which interrupt the descending pathways that control the reflex and therefore induce an increased excitability of its central processing.[1] While spasticity may help a patient to stand and walk, it often produces discomfort because it can induce muscle spasms and pain, interfere with walking and moving and impede nursing.[1] Oral medications are unsatisfactory in the majority of cases unless high dosages are used, causing possible unpleasant side effects. Surgery may be risky and the results obtained may not be permanent.[2] Intrathecal infusion of baclofen is doubtless effective but is not indicated in focal spasticity, is a quite complicated procedure and requires monitoring of the patient.[3] Apart from physical therapy, no safe and achievable treatment for spasticity is presently available.

Intramuscular injections of botulinum A toxin (BTX-A) have been proposed as a treatment for spasticity of various aetiologies, and clinical studies have suggested that BTX-A may be a useful antispastic agent.[4–7] However, the clinical role of BTX-A in the treatment of spasticity has not yet been settled nor has the proper timing, dosage, sites and technique of administration, possible side effects, duration of the benefit, significance in the rehabilitation plans and quality of life for the patient. In addition, the mechanism of action of the toxin in spasticity is uncertain. Not only having a presynaptic blocking effect on neuromuscular junctions of extrafusal fibers, the toxin might also affect the intrafusal fiber endplates, thus reducing the discharge from muscle spindles. Animal experiments showed that BTX can enter the CNS, being carried by retrograde intraaxonal transport to the motor neuron cell body and possibly transynaptically,[8–10] and can inhibit the release of neurotransmitters in the CNS.[11] In humans the toxin might be transported back to the spinal cord, inducing an effect on the regulation of the stretch reflexes by the CNS.[12,13] Priori *et al.*[14] reported that BTX-A increases the abnormally decreased second phase of reciprocal inhibition in dystonic patients, suggesting that a concurrent indirect effect on spinal cord circuitry may take place.

A reduction of both inhibitory phases of reciprocal inhibition between forearm muscles is reported in spastic hemiplegia.[15,16] To ascertain whether BTX-A modifies reciprocal inhibition between forearm muscles in spasticity we studied reciprocal inhibition in patients with post-stroke spasticity treated with the toxin.

Materials and Methods

Patients: We studied 20 patients, 12 men and 8 women, aged 60 ± 7 years (mean ± s.d.) with upper

limb post-stroke spasticity. Fifteen patients had had ischaemic stroke in the middle cerebral artery territory and four patients had had primary intracerebral haemorrhage. In all subjects the duration of the disease was > 1 year (6 ± 4 years) and residual motility was present. No patient complained of notable pain in the affected upper limb. Patients who had received any other medication affecting spasticity in the 4 months preceding the study or having fixed contractures were excluded. Throughout the whole study the patients continued their conventional physiotherapy.

The study was approved by the Ethics Committee of our Institute and all the patients gave their informed consent.

Treatment: A maximum dosage of 100 units BTX-A (Botox Allergan), diluted 2.5 units/0.1 ml, was injected into the flexor forearm muscles. The muscles were chosen on the basis of clinical involvement. The flexor carpi radialis (FCR) muscle was always injected with 30 units (15 units in two sites). If involved, other flexor forearm muscles were injected according to the following scheme: 30 units (15 units in two sites) in flexor carpi ulnaris, 20 units (in one site) in brachioradialis, flexor digitorum profundus, flexor digitorum sublimis and flexor pollicis longus. If spasticity involved biceps brachii, this muscle was also injected with 50 units divided over three sites. Injections were made under electromyography (EMG) guidance without having sought the motor point.

Clinical examination: Muscle tone was quantified using the modified Ashworth scale.[17] Deep reflexes of upper limb were scored using the following scale: 0 = absent; 1 = reduced; 2 = normal; 3 = increased; 4 = markedly increased with diffusion. Muscle strength was evaluated using the Medical Research Council (MRC) scale.[18] Tone, deep reflexes and muscle strength were always rated by the same researcher who did not administer BTX-A injections. Motility and functional abilities were assessed by using a standardized plan. All performances were video-taped. Tapes recorded at the various time-points of the study were arranged randomly and reviewed blindly by three different medical observers who scored the manoeuvres (Table 1). The maximum possible score was 18 (Table 1). Disability was measured using the Barthel Index.[19]

Electrophysiological study: Reciprocal inhibition in forearm muscles was studied using the method of Artieda *et al.*[16] Patients were lying down supine with the forearm muscles relaxed. During all the recordings the temperature of the laboratory was kept at a

Table 1. Standardized evaluation of motility and functional abilities of paretic upper limb from video-tape

Manoeuvre (command)	Score
Flexor synergy (touch your ear) (paretic side)	0 absent 1 only proximal 2 proximal and distal 3 complete
Extensor synergy (touch your knee) (normal side)	0 absent 1 only proximal 2 proximal and distal 3 complete
Pronation–supination (turn the palm of your hand up and down) (first with the shoulder at 0° and the elbow at 90° and then with the shoulder at 30° and the elbow at 0°)	0 absent 1 only minimal 2 partial 3 complete
Flexion–extension of the wrist (turn your hand right and left) (the hand was maintained with the ulnar side on the top of a table with the elbow at 90°)	0 absent 1 only minimal 2 partial 3 complete

Functional abilities
  Take the glass
  Take the spoon and draw it near your mouth
  Turn over the pages of the book
	0 unable to do
	1 able to do

constant 22–24°C. Compound motor action potentials (M) and H reflexes were recorded from Ag/AgCl surface electrodes (diameter 1 cm) placed 3 cm apart over the bellies of FCR and extensor carpi radialis muscles. The same kind of electrodes were used for nerve stimulation. Filters were set at 3 Hz–10 kHz. The median nerve was stimulated at the cubital fossa and the radial nerve at the spiral groove. The electrical stimulus was 1 ms in duration. Stimulus strength on median nerve (test stimulus) was adjusted to elicit an H reflex amplitude equal to 50% of the maximum H response (H_{max}). The intensity of the electrical stimulation of radial nerve (conditioning stimulus) was below motor threshold which was verified with high gain on extensor muscles. The delays between conditioning and test stimuli were –1, 0, 1 ms for investigating the first disynaptic phase of reciprocal inhibition and 10, 20, 30 ms for studying the second phase of inhibition. A negative interval means that the stimulus on median nerve was before the conditioning stimulus. The shocks were given randomly at intervals > 5 s. For each delay the amplitude of 16 conditioned H waves were averaged and compared with the averaging of 16 unconditioned reflexes. The amplitude of conditioned response was expressed as a percentage of the unconditioned H-reflex amplitude.

Data obtained from all patients for each inter-stimulus interval and also the point of maximal inhibition within the two normal inhibitory phases were

statistically compared at different time points of observation. The amplitude of the maximum H response and of the maximum M response were also recorded and H_{max}/M_{max} ratio was calculated. Recordings were performed by a Mystro Medelec MS25 device.

Timing of evaluation: All clinical, physiotherapeutic and electrophysiological assessments and video-tapes were obtained in baseline conditions and repeated 2 weeks, 1, 2, 3 and 4 months after BTX-A injections.

Statistical analysis: Statistical analysis included Student's *t*-test, Wilcoxon signed rank test, ANOVA, simple and multiple regression.

Results

Clinical findings: BTX-A induced no significant systemic or local side effects. Muscle strength was not decreased since the MRC score of injected muscles did not reveal any statistically significant variation after treatment. Tone of the injected muscles showed a statistically significant decrease in the modified Ashworth scale. The reduction of muscle tone was present as early as 2 weeks after treatment and returned to baseline over 3 months (Table 2). In rating of the video-tapes, the inter-observer agreement was substantial (κ = 0.72; *p* < 0.001).[20]

Motility and functional abilities of the paretic limb slightly improved. The improvement reached a statistically significant level 2 weeks after BTX-A injection and continued during the entire period of investigation (Table 2). Deep reflexes and Barthel Index showed no significant changes after BTX-A treatment. All the patients wished to continue treatment.

Electrophysiological findings: The patients showed a clear reduction of both inhibitory phases of reciprocal inhibition between forearm muscles (Fig. 1). BTX-A induced no statistically significant change in the first inhibitory phase of reciprocal inhibition
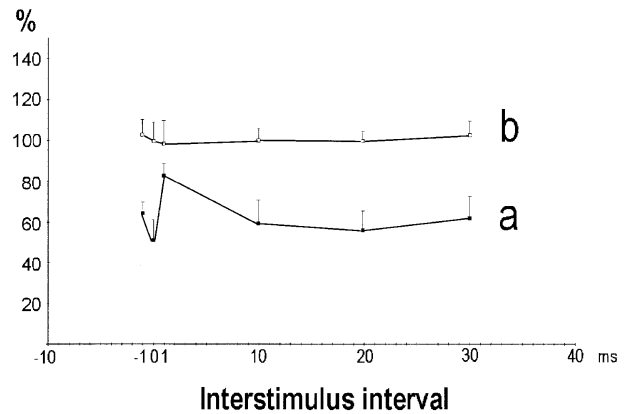

FIG. 1. Reciprocal inhibition between forearm muscles in normal subjects (**a**) and in patients with post-stroke upper limb spasticity (**b**). Bars indicate 1 s.e. Amplitudes of conditioned H responses (H TS + CS) are expressed as percentage of unconditioned control H response (H TS). A reduction of reciprocal inhibition both of the first and the second phase is evident. *p* < 0.05 was considered significant (unpaired *t*-test).

at the different time-points of investigation after treatment (Figs 2, 3). The second inhibitory phase of inhibition also showed no significant change after BTX-A injection (Figs 2, 4). For the statistical analysis reported in Figs 3 and 4, the point of maximal inhibition within each of the two normal inhibitory phases was considered. The amplitude of the compound motor action potential recorded over the FCR muscle by supramaximal stimulation of the median nerve was decreased after BTX-A therapy and the reduction reached a statistically significant level 2 weeks and 1 month following injection (Table 3). The amplitude of H_{max} also lessened after toxin injection. The comparison with baseline values revealed a statistically significant difference which was present 2 weeks following treatment and continued (Table 3). The H_{max}/M_{max} ratio was not affected by botulinum toxin (Table 3).

Discussion

Botulinum toxin induced a statistically significant reduction of muscle tone as measured following the Ashworth scale in upper limb muscles affected with

Table 2. Changes of tone of forearm muscles and in motility and functional abilities of paretic upper limb after therapy with BTX-A. Motility and functional abilities are measured by adding the scores of single items shown in Table 1

Parameter		Baseline	2 weeks	1 month	2 months	3 months	4 months
Tone (Ashworth)	(median;	7	5	5.5	6	7	7
treated muscles	(min–max))	(5–15)	(4–11)	(4–12)	(5–13)	(5–14)	(5–14)
Wilcoxon (*p*)			< 0.01	< 0.01	< 0.02	N.S.	N.S.
Motility and	(median;	4	5	6	6	6	6
functional ability	(min–max))	(1–11)	(2–11)	(2–13)	(2–14)	(2–16)	(1–14)
Wilcoxon (*p*)			< 0.02	< 0.01	< 0.02	< 0.02	< 0.05

baseline   BTX-A
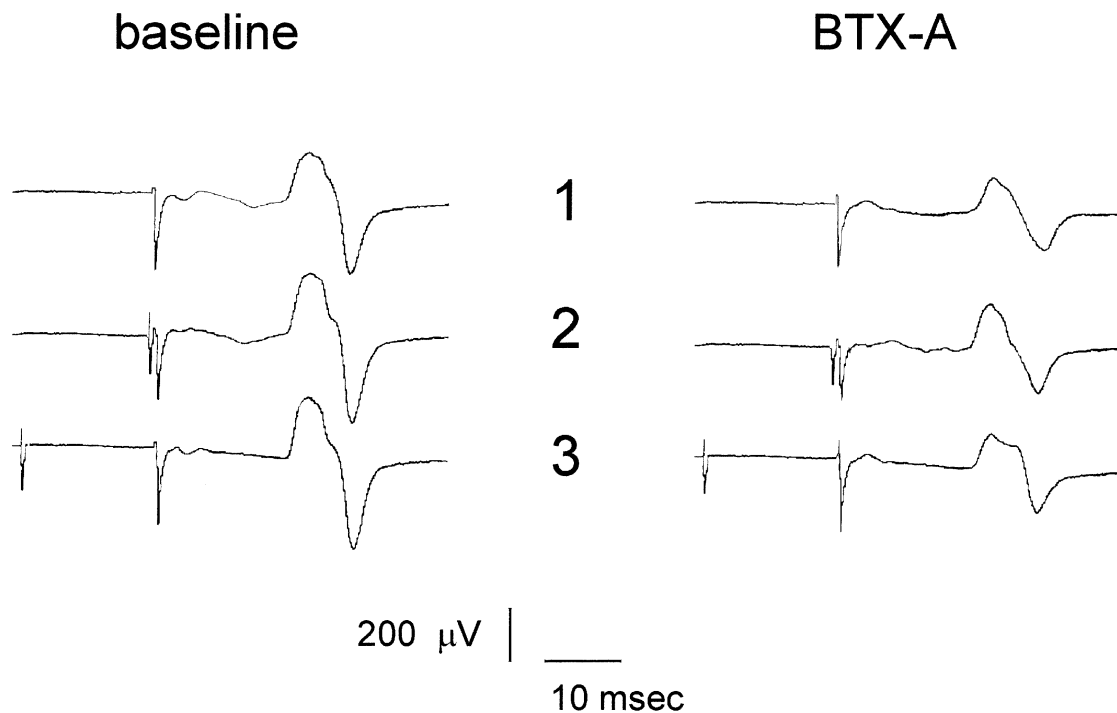

200 μV

10 msec

FIG. 2. Reciprocal inhibition of forearm muscles in a patient with upper limb post-stroke spasticity in baseline conditions and 1 month after BTX-A treatment. 1 = unconditioned H responses; 2 = first phase of reciprocal inhibition – conditioned H responses. The shock over the radial nerve was delivered 1 ms before that over the median nerve; 3 = second phase of reciprocal inhibition – conditioned H responses. The shock over the radial nerve was delivered 20 ms before that over the median nerve. Note the lack of reciprocal inhibition both in baseline and after BTX-A injection. The amplitude of H responses decreased after treatment.
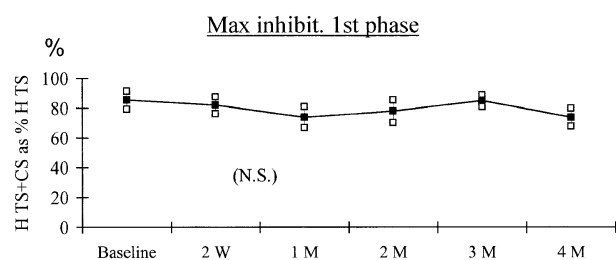

FIG. 3. Effect of BTX-A treatment on the first phase of reciprocal inhibition between forearm muscles in patients with upper limb spasticity. The point of maximal inhibition within each of the three intervals (–1, 0, 1 ms) between conditioning and test stimulus was taken for statistical analysis. The amplitude of conditioned H response (H TS + CS) is expressed as percentage of the unconditioned H reflex (H TS). No statistically significant variation occurred. $p < 0.05$ was considered significant (paired t-test). N.S. = not significant; W = weeks; M = months.
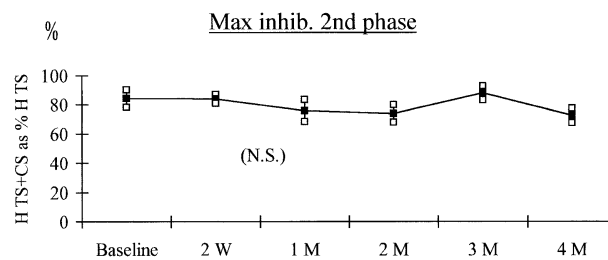
FIG. 4. Effect of BTX-A treatment on the second phase of reciprocal inhibition between forearm muscles in patients with upper limb spasticity. The point of maximal inhibition within each of the three intervals (10, 20, 30 ms) between conditioning and test stimulus was taken for statistical analysis. The amplitude of conditioned H response (H TS + CS) is expressed as percentage of the unconditioned H reflex (H TS). No statistically significant variation occurred. $p < 0.05$ was considered significant (paired t-test). N.S. = not significant; W = weeks; M = months.

spasticity after a stroke. We conclude that patients with upper limb spasticity improve after BTX-A treatment and that the effect has a latency of about 2 weeks and a duration of about 2 months, in agreement with the data reported by other authors.[4–7]

BTX-A is not an inexpensive treatment and thus the impact of therapy on the quality of life of the patients must be carefully evaluated. A reduction on the Ashworth scale may not be the equivalent of an improvement of function, which is the goal of treat-

ment. Our data confirmed the impression that the Barthel Index is insensitive to changes in disability induced by BTX-A treatment of spasticity, and therefore is not useful as an outcome measure. A simple home video, if standardized, can provide a helpful evaluation and be reliable. In our experience inter-observer agreement was adequate, and the plan that we used for assessing motor performances was adapted to reveal changes induced by BTX-A therapy.

Table 3. Changes in compound motor action potential maximal amplitude (M_{max}), H response maximal amplitude (H_{max}) and H_{max}/M_{max} ratio in flexor carpi radialis muscle after injection with BTX-A

Parameter	Baseline	2 weeks	1 month	2 months	3 months	4 months
M_{max}						
(mV; mean ± s..e)	9.6 ± 2.7	5.1 ± 1.6	5.3 ± 1.5	6.9 ± 1.8	7.2 ± 1.1	8 ± 2.1
(*p* *t*-test)		< 0.05	< 0.05	N.S.	N.S.	N.S.
H_{max}						
(mV; mean ± s.e.)	4.3 ± 0.9	2 ± 0.7	1.9 ± 0.6	2.6 ± 0.9	2 ± 0.3	2.3 ± 0.8
p (*t*-test)		< 0.01	< 0.005	< 0.01	< 0.01	< 0.01
H_{max}/M_{max}						
(mean ± s.e.)	0.5 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.7 ± 0.2	0.5 ± 0.2
p (*t*-test)		N.S.	N.S.	N.S.	N.S.	N.S.

The beneficial effect that we were able to show on motility and motor performances was slight, but statistically significant, and lasted longer than the reduction of tone. On clinical grounds we believe that in selected patients with after-stroke upper limb spasticity and residual motility BTX-A therapy is worth trying, because it can help in the management of patients, if combined with physiotherapy.

There is evidence that BTX-A injected in a muscle can reach the CNS,[9] and possible effects on CNS were postulated to explain why a reduction of spasm frequency occurred after BTX therapy in blepharospasm.[21] Both extrafusal and intrafusal muscle fibers are cholinergically innervated and experimental studies showed that both are affected by botulinum toxin.[22] Therefore the clinical effect of BTX-A in spasticity could be related to modified spindle afferent discharge.

Since Priori *et al.*[14] reported that BTX-A causes a trend toward normalization of the second phase of reciprocal inhibition which is altered in patients with upper limb dystonia, and since changes of reciprocal inhibition between forearm muscles is described in spastic hemiplegia,[15,16] the primary intent of our study was to verify whether BTX-A could induce modifications of reciprocal inhibition.

Our findings in upper limb post-stroke spasticity are dissimilar from those of Priori *et al.*[14] in dystonia because we failed to reveal any statistically significant variation in either the first or the second phase of reciprocal inhibition after BTX-A injections. The reason for this discrepancy is not clear. There are no significant differences in the methodology apart from the position of the patients; the subjects studied by Priori *et al.*[14] were seated while ours were lying. On the other hand the pathophysiologies of dystonia and spasticity are distinct and it is possible, therefore, that abnormalities of spinal interneuronal pathways may be influenced to a different extent by BTX-A therapy.

Under the same experimental conditions as used in our study almost all dystonic patients manifest a reduction in presynaptic reciprocal inhibition,[14,15] probably due to the strong influence of basal ganglia to the reticulospinal route, while early disynaptic inhibition is normal.[15] In addition, the disynaptic and presynaptic inhibition deficit may vary in patients with post-stroke hemiplegia, since stroke can differently alter central projections to the Ia inhibitory interneurons and to presynaptic inhibitory interneurons.[15,16] It is possible that the changes reported by Priori *et al.*[14] in writers' cramp in the presynaptic phase of the reciprocal inhibition after BTX-A reached a statistically significant ($p < 0.05$) level because the behaviour of reciprocal inhibition in dystonic patients is more homogeneous than in hemiparetic patients. Even if they are put together there is a clear reduction of both phases of inhibition.

Conclusion

Our data further sustains the assumption that BTX-A has no direct action on the spinal cord since the H_{max}/M_{max} ratio was unchanged, supporting the hypothesis that BTX-A does not change the excitability of motor neurons.[23] Moreover, the lack of variations in reciprocal inhibition makes the hypothesis of a direct effect on interneurons unlikely. The reduction of M wave and H wave amplitude induced by the toxin are probably due to BTX-A peripheral effect on neuromuscular transmission. Such peripheral action also on intrafusal muscle fibers has been viewed as responsible for the changes in reciprocal inhibition seen in dystonia.[14] Indeed paralysing the intrafusal muscle fibers would decrease activity in group I and group II muscle afferents. Antagonistic group I afferents would be therefore less inhibited thereby releasing their greater inhibitory action on the muscular afferents from the injected muscle.[14] It is conceivable that, unlike dystonia, the intrinsic mechanical changes that occur within spastic muscles may play a role in inducing a poor efficacy of BTX-A in the modification of reciprocal inhibition in this syndrome.

We believe therefore that just as BTX-A does not modify the enhanced excitability of brain stem interneurons in blepharospasm,[21,24,25] it also fails to reduce the enhanced excitability of spinal interneurons occurring in spasticity and therefore the clinical effects must be explained considering only the 'peripheral' actions of the toxin.

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