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Side-effects of intradermal injections of botulinum A toxin in the treatment of palmar hyperhidrosis: a neurophysiological study

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Focal palmar hyperhidrosis can be effectively abolished by intradermal injections with botulinum toxin. Muscle weakness of finger grip has been reported as a reversible side-effect of this new treatment. The objective of this work was to measure muscular side-effects after treatment of palmar hyperhidrosis with botulinum toxin. As botulinum toxin has been used in the treatment of pain, we studied whether the toxin might influence afferent thin-fibre function by measuring temperature perception thresholds. Thirty-seven patients treated with botulinum toxin (Botox, Allergan Pharmaceuticals, Irvine, CA, USA) showed a decrease in compound muscle action potential (CMAP) for both abductor pollicis brevis (APB) and abductor digiti minimi (ADM) compared with pre-injection values on average by 64 and 36%, respectively, at 3 weeks which returned nearly to normal at 37 weeks. Muscle power for both finger abduction and finger opposition decreased to a lesser extent. Repetitive nerve stimulation and single fibre electromyography (EMG) showed a disturbed neuromuscular transmission. Thus, despite careful technique with small doses of botulinum toxin injected intradermally, the toxin diffuses to underlying muscles. With regard to the present results, one should be careful in using higher doses of Botox than 0.8 mU/cm^2 in the palmar skin above intrinsic muscles. No influence on thin-fibre function was seen.

Introduction

Focal palmar hyperhidrosis is a common condition usually managed with antiperspiratory agents. A minority of patients with severe sweating and no effect of conservative therapy may have considerable social, psychological and occupational problems as a result of the hyperhidrosis. Until recently transthoracal endoscopic sympathectomy (TES) has been the only effective therapy in these cases (Byrne *et al.*, 1990). Since Drobik in 1995 (Drobik and Laskawi, 1995) reported an effective treatment of Frey Syndrome (post-parotidectomy gustatory sweating), several reports on treatment of excessive axillary and palmar sweating with botulinum toxin type A (BtxA) have been published (Bushara *et al.*, 1996; Naver and Aquilonius, 1997; Schnider *et al.*, 1997, 1999; Naumann *et al.*, 1998; Shelley *et al.*, 1998). These injection treatments have a long lasting effect compared with the therapy of muscle spasm disorders with BtxA (Shelley *et al.*, 1998). Many authors report no or only minor side-effects (Bushara *et al.*, 1996; Schnider *et al.*, 1997; Naumann *et al.*, 1998; Shelley *et al.*, 1998). However, in a prospective controlled study, we found that two-third of the patients had noticed a minor weakness of finger grip for a period of about 2 weeks after injection. Holmes and Mann (1998) identified subjective clinical weakness in two of eight patients receiving 25 mU BtxA (Allergan Pharmaceuticals, Vasby, Sweden) on the palmar surface of the non-dominant hand and a significant (>30%) reduction in maximum motor response to abductor pollicis brevis after injection in one patient. No effect on sensory function has been reported after intradermal injections of BtxA. Injections into pericranial muscles have been reported to reduce tension headache and migraine (Lance and Goadsby, 1993; Wheeler, 1998; Smuts *et al.*, 1999). It has been speculated whether such an effect could be mediated by an effect on afferent C-fibres. The purpose of this study was to measure muscular side-effects after treatment of palmar hyperhidrosis with botulinum toxin. We also wanted to study whether intradermal injections of the toxin might influence afferent thin-fibre function of the skin.

Methods

This study included 37 patients with primary palmar hyperhidrosis: eight male and 29 female, mean age 27 years (15–47) after their informed consent. Patients with secondary hyperhidrosis, pregnancy or muscle diseases were excluded. The patients were treated with intradermal injections of BtxA, 0.8–1 mU/cm^2 Botox

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(Allergan Pharmaceuticals), on the palmar surface of the hands and fingers. The mean dose of Botox was 161 mU (102–240) to each hand. At the first visit, one hand (patients born on an even month were injected in the right hand, odd month left hand) was treated. The other hand was treated 3 weeks (6–48 days) later. Compound muscle action potential (CMAP), was obtained after supra maximal nerve stimulation with the electrode over three hand muscles [hypothenar recordings over m. abductor digiti minimi (ADM), thenar recordings over m. abductor pollicis brevis (APB), and over m. interosseus dorsalis I (IOD)]. Muscle strength measurements (finger flexion, finger abduction, and finger opposition) and electrophysical tests were obtained before the injection and after 20 (6–48) days ($n = 37$ patients except for IOD, $n = 32$), 106 (60–163) days ($n = 8$ patients except for finger abduction, $n = 7$) and 260 (194–299) days ($n = 11$), respectively. In 24 of the 37 patients, two control observation values were obtained in one hand before the injection. Only the patients included already at the start of the study were studied at 15 and/or 37 weeks. Patients recruited late (less than 15 weeks from the end of the study) were only studied at the time for injection and after 3 weeks. The total dose Botox delivered at each session depended on the size of the hand. In some cases, injections were also given between the fingers and on their dorsal aspect. A higher dose was given on the fingerpulps than in the palm. Twelve of the 37 patients had an additional dose (mean 46 mU) at a following visit because of residual sweating. This additional dose was given just after the evaluation of the effect at 3 weeks. Three out of eight patients with follow-up at 15 weeks and six out of 11 patients with follow-up at 37 weeks had an additional dose.

One hand was treated at the first visit and the other hand at the 3-week control. Thus, for the first treated hand we obtained two observations after injection and for the other hand we had one observation.

A questionnaire was sent home to all patients 11 months (6–15) after the first injection, with questions about muscle weakness and further treatment. To those who did not answer the first questionnaire, a new one was sent home with an accompanying letter.

Temperature perception thresholds were studied in 12 out of 37 patients before and 24 weeks after injection.

Compound muscle action potentials

Studies were made with standard technique used in the laboratory (Falck and Stålberg, 1993). Stimulation was performed with surface electrodes over the median and ulnar nerves at the level of the wrist. Stimulus strength was more than 25% above that giving maximal response. Stimulus duration was set to 0.1 ms. Recording was performed with surface electrodes. For thenar studies the recording electrode was placed over the middle of the ABP and the reference electrode at the level of the distal interphalangeal joint of digit V. For hypothenar studies, the recording electrode was placed over the middle of the ADM with the reference over the distal interphalangeal joint of digit V. As a control, the recording electrode was placed over the middle of the IOD with the reference also at the joint of digit V. In two patients, recording was performed over APB using subcutaneous non-insulated needle electrodes before and after treatment. The analysis was made automatically using commercial equipment (Keypoint, Medtronic, Copenhagen, Denmark). Latency, amplitude (baseline to negative peak), area (of the negative phase), and duration from onset to first zero crossing point were measured. Before measurements, the hand temperature was measured at the back of the hand. If it was below 28°, warming by sitting on the hand for 10 min insured acceptable temperature.

Repetitive nerve stimulation

Repetitive nerve stimulation was performed for both thenar and hypothenar muscles with stimulation of the median and ulnar nerves, respectively, at the wrist. A standard protocol used in diagnosis of disturbed neuromuscular transmission was used. The fingers were immobilized by means of a tape around digits II–V. Ten supramaximal stimuli were given at 3 Hz at time 0, directly after 20 s of maximal voluntary contraction, and after 1 and 3 min thereafter. The measurements included initial amplitude, decrement in amplitude, and area between response 1 and 4. A value showing a reduction in response exceeding 5% is abnormal.

Single fibre EMG

Single fibre EMG studies of the neuromuscular transmission (Stålberg and Trontelj, 1994) were performed on the APB using standard SFEMG electrode (Oxford Instruments Medical Systems, Oxford, UK). Jitter was analysed in the EMG equipment (Keypoint) as mean consecutive difference (MCD) values. In recordings with obvious abnormalities (excessive jitter and blocking), the results were sometimes noted semiquantitatively as normal, increased jitter or blocking. For each patient, the overall result was expressed as percentage individual recordings belonging to these three classes.

Measurements of muscle power

Measurements were performed with standard technique in the laboratory. A strain gauge (Hastras

System, Umea, Sweden) was connected to an amplifier (EMG system, MS92 Medelec, Surrey, UK) with an attached PC for analysis.

The patient was sitting comfortably in a chair with the elbow forming a right angle. For testing the finger flexion, the hand gripped a handle (strain gauge). The handle was adjusted so that the tip of the thumb could just reach the tip of the middle finger at maximum force. At a given signal the patient was instructed to squeeze the handle as hard as possible. When testing finger abduction, a strap connected to the two branches of the 'tuning fork' (strain gauge) was firmly applied around the middle phalanges of digits II–V. At a given signal the patient was instructed to spread the fingers (abduct) as much as possible. For testing thumb-index opposition, the strain gauge was placed between tip of the dig I and dig II. At a given signal from the computer the patient was instructed to oppose the two digits as hard as possible.

Each test was performed with maximum force and the patient was told to press as hard and quick as possible and to keep the contraction for 15 s. The tests were performed bilaterally. A computer program specially designed for strength analysis (Swedish Electrophysiological Software, SES, Uppsala, Sweden) calculated the strength as the maximum peak value for each procedure.

Temperature perception

Thermal thresholds were measured using the Marstock Thermotest method (Fruhstorfer *et al.*, 1976). Thresholds for cold pain, warm pain, and thermo neutral zone (warm–cold discrimination threshold) were recorded from thenar and from hypothenar.

Statistical analysis

Measurements of CMAP and muscle power

Test/retest quotient was calculated. The relation between the two pre-values was used as a measure of reproducibility of the method.

The change in strength at repeated investigations was calculated in the following way. If two baseline measurements were available, the mean of the two was used. If more than one post-injection measurement was made in the same hand within a short time-interval (6–48, 60–163 and 194–299 days, after injection), the mean of these values was used. Mean values, differences, and ratios between actual values and pre-injection values were derived. Some patients had measurements on both hands within a similar interval after injection. In these cases, the mean value of the findings (means, differences and ratios) in the two hands were used. The change from baseline (actual value minus baseline value) was tested using a *t*-test with 95% confidence intervals (CI). The assumption of normality was also tested by use of the Shapiro–Wilk statistic. In cases when the distribution was found not to be normal, a trimmed mean (where the most extreme value at each end was removed) was used. *P*-values less than 0.05 were considered statistically significant. Also the ratio (result divided by the baseline value) was summarized and 95% CI were calculated for this parameter. For comparison of temperature perception, thresholds of thenar and of hypothenar before and after cholinergic denervation of the skin with botulinum toxin paired *t*-test was used. In the hands with two pre-treatment measurements and those with two post-treatment measurements, the mean of the two values was used for statistical analysis.

Results

The relationship between two pre-values (test/retest), for CMAP and muscle power measurement ranged from 0.95 to 1.1 (standard error of means 0.05–0.1).

The CMAP for APB and ADM compared with pre-injection (baseline) values decreased on average by 64 and 36%, respectively, at 3 weeks and had returned to normal at 37 weeks (see Table 1). IOD was supposed to be a control measure point but a slight decrease was observed (12%) at 3 weeks.

Table 1 Mean values of relative CMAP and muscle power measurement at different times compared with pre-injection values. Standard errors of mean are given in parenthesis

	3 Weeks ($n = 37$)**	15 Weeks ($n = 8$)***	37 Weeks ($n = 11$)
Relative CMAP			
Abductor digiti minimi (ADM)	0.64 (0.05)*	0.82 (0.08)*	1 (0.07)
Abductor pollicis brevis (APB)	0.36 (0.04)*	0.68 (0.12)*	0.97 (0.18)
Interosseus dorsalis I (IOD)	0.88 (0.04)*		
Relative muscle power			
Finger flexion	1 (0.04)	1 (0.04)	0.98 (0.04)
Finger abduction	0.92 (0.05)*	0.99 (0.15)	1.1 (0.11)
Finger opposition	0.75 (0.05)*	0.72 (0.04)*	0.83 (0.04)*

*$P < 0.05$; **IOD, $n = 33$; ***Finger abduction, $n = 7$.

	3 Weeks (n = 37) (%)*	15 Weeks (n = 8) (%)**	37 Weeks (n = 11) (%)
Relative CMAP			
Abductor digiti minimi (ADM)	9/37 (24)	0/8	0/11
Abductor pollicis brevis (APB)	31/37 (84)	3/8 (38)	2/11 (18)
Interosseus dorsalis I (IOD)	1/32 (3)		
Relative muscle power			
Finger flexion	1/37 (3)	0/8	0/11
Finger abduction	2/37 (5)	0/7	0/11
Finger opposition	5/37 (14)	0/8	0/11

Table 2 Number of individuals with a reduction of 50% or more of CMAP and muscle power measurement at different times compared with the pre-value(s)

*IOD, n = 32; **Finger opposition = 7.

Corresponding mean values of muscle power measurement for both finger abduction and finger opposition also decreased but to a lesser extent (see Table 1). Finger flexion was used as a control measure point and was not affected. The values at 15 and 37 weeks follow-up time contained both single and double dose injected patients. On group basis, there was no significant change between these two groups of patients. However, the two most affected patients (especially regarding decreased amplitude for CMAP to APB) belonged to the group who had an additional dose. The number of individuals with a reduction of 50% or more of CMAP and muscle power are listed in Table 2. CMAP in APB was the most affected parameter (Fig. 1).

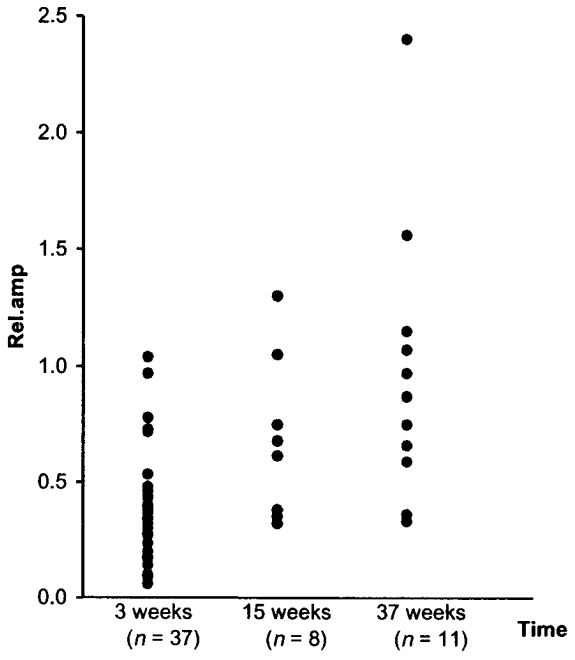

Figure 1 The CMAP for APB muscle in all patients. All measure points are related to pre-injection values.

Thirty-five out of 37 patients answered the questionnaire. Twenty-six out of 35 (74%) patients experienced muscle weakness on average during 5 weeks (range 1–24 weeks) but 32 out of 35 (91%) wanted a new treatment without a reduction in the dose of BtxA (see Table 3).

The experience of muscle weakness (n = 26) versus no weakness (n = 9) according to the questionnaire (n = 35) was not related to the reduction of the CMAP or to the muscle strength measurements. Those subjects with the experience of muscle weakness for more than 3 months (eight out of 26 patients) did not have more changes in the objective measurements than those without.

Neurophysiological tests of the neuromuscular transmission

In two patients, the CMAP was studied both with surface electrodes and with a subcutaneous non-insulated needle over the APB. This was performed in order to exclude amplitude changes after the injection of Botox because of changes in skin condition. In these two patients, recordings were performed bilaterally 7 and 14 days after the first injection of Botox in that

Table 3 Subjective data about muscle weakness. Results from a questionnaire answered by 35 of 37 patients included in the study

	Yes	No
A new treatment when relapse?	32	3*
Partial treatment of the hand to avoid muscle weakness?	3*	32
Experienced muscle weakness?	26	9
Impact of muscle weakness		
None	4	
Slight	11	
Moderate	15	
Severe	6	

*Two patients with short duration of effect and one patient unsatisfied with result.

Table 4 Decrement and SFEMG. The decrement is measured as percentage reduction in amplitude between first and fourth CMAP at repetitive stimulation (3 Hz); >5% is abnormal. SFEMG is expressed as percentage potential pairs with blocking, with increased jitter and with normal jitter. SFEMG was not performed in the normal side

Subject	APB	Rest (%)	1 min (%)	Amplitude	SFEMG (%)	Uninjected (%)	Time after injection (days)
1	Left	−8	−14	2.5	Block. 100 Jitter. 0	−3 decr	21
2	Left	−8	−16	2.0	Block. 29 Jitter. 71	−1	25
3	Right	−5	−11	2.2	Block. 25 Jitter. 44 Norm. 31	−3	25
4	Right	−14	−15	1.8			48
5	Right	−11	−17	3.4			8
6	Left	−13	−16	2.1			18
7	Right	−8	−11	1.6			28
7	Left	−6	−6	2.6			20

hand. The amplitude decreased dramatically with both types of recordings. Discrepancies are the result of methodological variations.

A moderate decrement was seen in five out of seven rested muscles and in all seven after 1 min of activation, the so-called post-exercise exhaustion. No decrement was seen in the non-injected side (see Table 4). In three subjects studied with SFEMG, distinct abnormalities were seen in all three with increased jitter and also intermittent impulse blocking in some of the recordings in all the muscles. SFEMG was not performed in the non-injected side. Normal values of decrement were seen in the non-injected side.

No change in temperature perception regarding cold pain, heat pain, or cold–warm discrimination was noticed in the thenar or hypothenar eminence after Btx A injection.

Discussion

Muscle strength was reduced considerably, most apparent after 3 weeks in median nerve innervated thenar muscles but also to a lesser extent in ulnar nerve innervated ADM and very little in IOD. At follow-up measurements at 15 weeks, power had again increased and had returned to nearly normal by 37 weeks. Repeated measurements of muscle power and of CMAPs disclosed a substantial variability, with standard deviations that did not allow analyses of whether changes in muscle power in individual patients were significant. However, on group basis amplitudes of CMAP and muscle strengths were significantly reduced.

The decrease in CMAP could theoretically be because of changed skin condition after treatment. This was tested using subcutaneous needle electrode in addition to surface electrodes. In the four tested muscles, the decrease was pronounced and of the same degree with both methods. Thus, the amplitude reduction must be because of intramuscular changes. The neurophysiological test of neuromuscular transmission show clear signs of disturbed neuromuscular transmission. At repetitive nerve stimulation abnormalities were more pronounced after activity, so-called post-exercise exhaustion. In SFEMG, which is a more sensitive test of neuromuscular transmission, abnormalities were seen in the majority of the recordings. Increased jitter is a subclinical sign of disturbed transmission and was seen in 44 and 71% of the recordings in two muscles. Impulse blocking was seen in all muscles (25–30% of the recordings in the two muscles with extensive investigation). Impulse blocking corresponds to clinical weakness and to decrement in the repetitive stimulation test.

A correlation between subjective muscle weakness and objective measurements was not found. The neurophysiological test showed abnormalities even without subjective weakness, but never the reverse. Thus, one should be aware of the occurrence of subclinical weakness when treating palmar hyperhidrosis. Considering the reduction of power of thenar and hypothenar muscles it might be of value to monitor the muscular side-effects by objective measurements in young patients and to those who need treatment more than once a year and adjust the dose of botulinum toxin accordingly. Certain precaution should be observed in patients with other conditions that may make them sensitive, such as myasthenia gravis. In our first study (Naver and Aquilonius, 1997), we used the initial dose of 0.5 mU/cm^2. Because of residual sweating patients often wanted additional doses and therefore a higher standard dose (0.8 mU/cm^2) was used in this study. With regard to the present results, one should be careful whilst using doses higher than 0.8 mU/cm^2. For those patients who need higher doses, muscle weakness may be a limiting factor and if a suboptimal result is not sufficient one might still consider TES. It is important

to carefully inform the patients of this probable side-effect before treatment and in case of post-treatment weakness, to offer a reduced dose by the time of relapse treatments. Although 76% of the patients in this study experienced muscle weakness, 91% still wanted the same dose of botulinum toxin when having a new treatment. This shows that the muscle weakness is a minor problem or that the hyperhidrosis is a more aggravating handicap than the muscle weakness.

To avoid adverse effects you can give smaller doses in the skin over the thenar and hypothenar eminence. If necessary, higher doses of Botox than 0.8 mU/cm^2 could be used distal on fingers where muscles are absent. Our observation is that the toxin injected into the dermis diffuses and affects the underlying muscles. One explanation for the pronounced decrease in the strength of finger opposition and the CMAP of the APB is that the subcutis over the thenar eminence is thin which means the toxin diffuses over a shorter distance. We cannot explain the slight changes observed in IOD.

We did not find any reduction of temperature perception or pain thresholds in treated skin. That was an expected result as no patient (more than 200 treated at our clinic) have ever complained of disturbed sensibility after treatment. However, the result is important as many observations indicate that botulinum toxin used for other indications than hyperhidrosis may have a pain reducing effect (Lance and Goadsby, 1993; Wheeler, 1998; Smuts *et al.*, 1999). It is common that patients with dystonia report a decrease in muscle pain after an injection into neck muscles. Observations on patients with tension headache and patients with migraine indicate that injections with botulinum toxin into pericranial muscles may reduce headache. Our result indicates that this effect is probably not mediated through a reduced sensibility of peripheral afferent thin-fibres.

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