

## High-dose botulinum toxin type A therapy for axillary hyperhidrosis markedly prolongs the relapse-free interval

Uwe Wollina, MD, Theodor Karamfilov, MD, and Helga Konrad, MD *Jena, Germany*

**Background:** Axillary hyperhidrosis is a common condition that can be personally distressing and can interfere with professional and social life. Intracutaneous injections of botulinum toxin type A (BTXA) have recently been shown to induce an effective but temporary anhidrosis, usually for 4 to 6 months. High-dose BTXA was shown to have a lower relapse rate, but it remained unclear whether it could induce a prolongation of the antihidrotic effect.

**Objective:** Our aim was to evaluate the long-term effectiveness of "high-dose" botulinum toxin therapy in axillary hyperhidrosis, the response to repeated treatment, and the possible side effects.

**Methods:** In an open study in a university medical center, 47 patients with axillary hyperhidrosis unresponsive to previous therapies were treated with intracutaneous injections of botulinum A toxin. A total dose of 200 U of BTXA was used per axilla. Patients were followed up for periods up to 29 months. The main outcome measures were patients' satisfaction with the antihidrotic effect, response to repeated treatment, and safety of treatment.

**Results:** Within 6 days of the injection of BTXA, all patients reported cessation of excessive sweating. The follow-up was  $17.0 \pm 8.3$  months (range, 3-29 months). The relapse rate within 12 months of treatment was 4 of 34 patients (11.8%). The longest relapse-free interval observed was 29 months. Twenty-two patients showed a relapse-free interval of 19 months or more. The number of patients with at least 12 months of remission was significantly higher with 200 U of botulinum toxin than with lower doses reported in current literature ( $P < .05$ ). Relapsed patients (a total of 6/47) showed an unchanged excellent response to a second or third treatment. The only side effect was temporary pain and burning during the injections. No muscular weakness, insensitivity, or systemic reactions were observed.

**Conclusion:** High-dose BTXA treatment is capable of prolonging the antihidrotic effect of intracutaneous BTXA in most patients for more than 19 months. It reduces the percentage of relapses after 12 months of follow-up to less than 12%. So far, there is no clinical evidence of the induction of neutralizing antibodies. High-dose treatment seems to be as safe as low-dose treatment. (J Am Acad Dermatol 2002;46:536-40.)

Focal hyperhidrosis is a disorder of excessive sweating. Axillary hyperhidrosis, one of the most common types of focal hyperhidrosis, may cause considerable social, psychologic, and professional problems. Eccrine glands are innervated by cholinergic fibers from the sympathetic nervous sys-

tem, in which acetylcholine is the most effective sudorific neurotransmitter.<sup>1</sup>

Botulinum A toxin (BTXA) is one of 7 zinc-dependent neurotoxins produced by *Clostridium botulinum*. BTXA consists of a toxifying light chain and a binding and translocating heavy chain linked by a disulfide bond. In vitro, specific antibodies against the zinc-binding domain of the molecule restore exocytosis in cells treated with BTXA. The light chain interferes with SNAP-25, a 25-kd synaptosome-associated protein involved in acetylcholine release, resulting in truncation of this protein.<sup>2,3</sup>

The use of BTXA to inhibit axillary hyperhidrosis is well documented in several studies.<sup>5-9</sup> In previous trials BTXA has been used at a dose of 20 to 100 U of BOTOX (Allergan, Irvine, Calif, obtained from Merz Pharma) or up to 400 U of Dysport (Ipsen

From the Department of Dermatology, the Friedrich Schiller University of Jena.

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Reprint requests: Prof. Dr. med. habil. Uwe Wollina, Department of Dermatology, Hospital Dresden-Friedrichstadt, PO Box 12 09 06, D 1008 Dresden, Germany.

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**Table I.** Botulinum toxin type A therapy for focal hyperhidrosis: A review

Study	Patients/volunteers	Follow-up (mo)	No. of axillae treated per axilla	Type of BTXA and dose (U)	Relapse rate (RR)/duration of effect
Bushara et al <sup>4</sup>	Healthy volunteers	6-8	5	BOTOX 15-50	100% RR after 6 mo
Glogau <sup>7</sup>	Axillary hyperhidrosis (n = 12)	4-7	24	BOTOX 50	100% RR after 7 mo
Heckmann et al <sup>16</sup>	Axillary hyperhidrosis (n = 12)	12	12	Dysport 400	25% RR within 12 mo
Heckmann et al <sup>13</sup>	Axillary hyperhidrosis (n = 145)	4.5	290	Dysport 100 or 200	No relapse within 4.5 mo
Naumann et al <sup>8</sup> (Minor's test)	Axillary hyperhidrosis (n = 8)	Up to 5	16	BOTOX 20-52	37.5% RR after 5 mo
Odderson <sup>5</sup>	Axillary hyperhidrosis (n = 2)	About 3	4	BOTOX 50	100% RR after 11 wk
Naver, Swartling, Aquilonius <sup>9</sup>	Axillary hyperhidrosis (n = 13)	12	26	BOTOX 38-72	Effect lasted for 9 mo (median)
Goldman <sup>22</sup>	Axillary hyperhidrosis	195	?	BOTOX 30-50, Dysport 90-150	Effect lasted 5-14 mo
Karamfilov et al <sup>11</sup>	Axillary hyperhidrosis (n = 24)	Up to 15	48	BOTOX 200	16.7% RR within 15 mo
Wollina et al (present study)	Axillary hyperhidrosis (n = 47)	Up to 29	94	BOTOX 200	12.8% RR

Pharma/Ettlinger, Germany) per axilla, but the optimum dose has yet to be defined. The major disadvantage of this (low) dosage range is the reappearance of clinically relevant excessive sweating, mostly within 6 months (Table I). Repeated application may induce neutralizing antibodies; therefore the dose should be optimal. Boosting by repetition has to be minimized.<sup>10</sup>

In the present study we investigated the efficacy and safety of what we have called "high-dose" BTXA in patients with axillary hyperhidrosis. In fact, the dose might be called "medium" compared with treatment of neuromuscular disorders.<sup>10</sup> In a previous study we demonstrated that although toxicity and time to response were comparable to conventional treatment with lower doses, 200 U of BTXA markedly reduced the relapse rate after 10 months of follow-up.<sup>11</sup> It was still not known whether such treatment would prolong the anhidrotic effect. In this study we hope to answer this question by recording the follow-up of 47 patients suffering from axillary hyperhidrosis and treated with 200 U BTXA per axilla.

## PATIENTS AND METHODS

Patients with focal axillary hyperhidrosis unresponsive to other nonsurgical forms of treatment were treated with BTXA. Forty-seven patients were included: 28 women and 19 men. Their age was 18 to 60 years (mean age  $\pm$  standard deviation,  $35.4 \pm 8.9$  years). All had suffered from focal hyperhidrosis since childhood or adolescence (Table II). Patients younger than 18 years, pregnant women, and patients with symptomatic hyperhidrosis were excluded. Patients

with contraindications according to the BOTOX user leaflet were also excluded. Informed consent was obtained from all patients after full written and oral explanation.

All patients underwent a pretreatment evaluation consisting of a clinical examination, objective quantification of sweat production, and photodocumentation. Hyperhidrotic areas were evaluated by Minor's iodine-starch test.<sup>12</sup> In this test, 2 g of iodine and 4 g of potassium iodide in alcohol to 100 mL is painted over the skin area. After it has dried, a fine starch powder is applied. Sweat causes the color to turn dark blue. In all cases the iodine-starch test made it very easy to identify the location of excessive sweating in the axillary skin.

For each axilla, 200 U of BTXA (BOTOX) were diluted with 4.0 mL of 0.9% sterile physiologic saline without preservative. The toxin was injected in amounts of 0.1 to 0.2 mL (2.5-5.0 U) intradermally using a 30-gauge needle. Analgesic therapy was not necessary. We started with single-site treatment. Three to 5 days later the second axilla was treated the same way.

The follow-up of patients was 3 to 29 months ( $17.0 \pm 8.3$  months). The iodine-starch test was used to assess the clinical antisudorific activity 6 days after treatment. A relapse was defined as a noticeable increase in sweating as experienced and reported by the patient. Telephone interviews were performed with all patients at the end of the follow-up period.

The two-sided chi-square test was used for comparing our data with reported data from the literature. A *P* value of less than .05 was considered statistically significant.

**Table II.** Epidemiologic data and outcome

Patient No.	Age (y)	Follow-up (mo)	Duration of effect (mo)	Repeated treatments
1	36	28	8	Once
2	60	24	24+	
3	46	24	24+	
4	46	23	23+	
5	36	25	25+	
6	30	25	25+	
7	46	25	25+	
8	28	25	19	Once
9	49	25	25+	
10	18	17	7	Twice
11	29	25	25+	
12	25	23	23+	
13	27	23	23+	
14	49	23	23+	
15	34	28	28+	
16	19	25	25+	
17	35	24	24+	
18	53	25	25+	
19	22	29	29+	
20	19	19	16	Once
21	30	18	18+	
22	54	20	20+	
23	34	28	28+	
24	23	19	19+	
25	20	19	19+	
26	24	20	10	Once
27	36	19	19+	
28	41	17	17+	
29	27	16	16+	
30	34	14	14+	
31	38	14	14+	
32	21	16	16+	
33	24	13	13+	
34	42	12	7	Once
35	21	11	11+	
36	22	10	10+	
37	22	8	8+	
38	29	8	8+	
39	33	6	6+	
40	29	4	4+	
41	24	4	4+	
42	22	3	3+	
43	22	3	3+	
44	21	3	3+	
45	24	3	3+	
46	37	3	3+	
47	36	1	1+	

## RESULTS

### Acute toxicity and side effects

Intracutaneous injections of BTXA were well tolerated. Mild pain was experienced during the injection. Burning sensations sometimes lasted up to 1 hour ( $n = 8$ ). We never observed hematomas or

allergic or other systemic side effects. Muscular power and sensation in the axillary region remained unchanged as assessed clinically. Electromyography was not performed, so subclinical impairments cannot be ruled out. None of the patients experienced a compensatory hyperhidrosis on other body sites.

### Relapse rate within 12 months

During a follow-up of 12 months, 4 patients experienced a clinically relevant relapse of axillary hyperhidrosis after 7 ( $n = 2$ ), 8 ( $n = 1$ ), and 10 ( $n = 1$ ) months (relapse rate 11.8%). The relapse rate of the whole group of patients was 12.8% ( $n = 47$ ), with 2 additional relapses after 16 and 19 months, respectively.

### Duration of antihidrotic efficacy and patient satisfaction

An interview at the end of the follow-up showed that all the patients were completely satisfied with the response to BTXA treatment and did not experience undesirable side effects in the long term. The mean duration after treatment was  $28.0 \pm 18.4$  months. The maximum period observed was 29 months without a relapse. Among the 34 patients with a follow-up of at least 12 months, there were 29 with a clinically relapse-free interval of at least 19 months. Within the group of patients with a shorter follow-up (patients 37 through 47 in Table II), none had a relapse, but comments on long-term efficacy are not yet possible.

### Response to repeated treatment

Six patients underwent repeated treatment (Table I). Three patients had 3 treatments each. A failure of repeated BTXA injections or a decreased response was not observed in any of them. To date there has been no clinical evidence of the induction of neutralizing antibodies to BTXA.

### High-dose versus low-dose BTXA therapy

In the literature we found 4 BTXA studies on axillary hyperhidrosis including 29 patients (43 axillae) with a detailed description of outcome and relapses.<sup>6,8,13</sup> They have been compared with 47 patients (ie, 94 axillae) in the present study. A significantly larger number of patients and BTXA-treated axillae showing a remission of 12 months or more was observed with high-dose therapy than with low-dose therapy ( $P < .05$  for patients and  $P < .001$  for axillae treated) (Table III).

## DISCUSSION

Axillary hyperhidrosis is still a management dilemma.<sup>14</sup> Sympathectomy has become more convenient

through minimally invasive surgery but has its own risks, including Horner's syndrome, pneumothorax, pneumonia, and compensatory hyperhidrosis. The response rate of sympathectomy in upper limb hyperhidrosis is about 90%, with complete satisfaction of patients in about 70% of cases. Compensatory hyperhidrosis has been reported to occur in 50% to 80% of patients.<sup>15</sup> Other treatment modalities available are axillary liposuction and surgical excision. The latter should no longer be used because it is disfiguring and secondary lymphedema may occur. On the other hand, tap water iontophoresis and topical antiperspirants are used in milder cases only.

The use of BTXA was introduced recently. Previous studies have shown that a minimum dose of 50 U of BTXA is necessary to induce anhidrosis of the axilla in healthy volunteers.<sup>3</sup> In axillary hyperhidrosis 36 to 50 U of BOTOX<sup>5,7</sup> or 400 U of Dysport<sup>6</sup> were effective in the short term, but clinical remission usually lasted less than 12 months (Table I). In a multicenter trial using Dysport intradermal injections, there was no substantial difference in reduction of sweat production between 100 U and 200 U per axilla.<sup>13</sup>

Our results show that intracutaneous BTXA, 200 U per axilla, is an effective and safe treatment for axillary hyperhidrosis without severe side effects. No systemic side effects have been observed. The safety profile for acute side effects is comparable to "low"-dose BTXA.<sup>11</sup> The dosage used is far below the LD<sub>50</sub> of 3000 U for BOTOX.<sup>2</sup> One major advantage is the smaller number of relapses.<sup>11</sup>

Only 4 relapses occurred within 12 months (11.8%). Heckmann et al<sup>16</sup> observed relapses in 25% of patients with axillary hyperhidrosis within 7 months. Odderson<sup>17</sup> reports an anhidrotic response lasting between 2 and 8 months for axillary sweating. The higher dosage used in the present study reduced the number of relapses within the first year after injection by more than 50%. Even more important is the observation that long-term remissions of up to 29 months can be induced. The number of both patients and treated axillae with a remission of 12 months or more in the high-dose group of patients was significantly greater statistically than in low-dose patients in 4 published studies (Table III;  $P < .05$  and  $P < .001$ , respectively).

The mechanisms responsible for the prolonged relapse-free interval in high-dose BTXA therapy are not yet clear. BTXA shows a mechanism of pore formation in target cells that is different from that of other toxins.<sup>18</sup> Cultured spinal cord cells exposed to 0.4 pM BTXA converted approximately half of the SNAP-25 into a truncated form lacking the C-terminal residues. The proteolytic activity persisted for more

**Table III.** Comparison of low-dose and high-dose BTXA treatment of axillary hyperhidrosis

BTXA	Low-dose	High-dose	Σ
Remission <12 mo	20 (34)	4 (8)	24 (42)
Remission > 12 mo	9 (9)	43 (86)	52 (95)
Total	29 (43)	47 (94)	76 (137)

The numbers refer to patients; the numbers in brackets refer to axillae treated. Data on low-dose BTXA therapy were obtained from the studies of Heckmann et al,<sup>6</sup> Glogau,<sup>7</sup> Naumann et al,<sup>8</sup> and Odderson.<sup>17</sup> Data on high-dose BTXA were obtained from the present study.

than 11 weeks.<sup>19</sup> Whether higher doses of BTXA lead to a diminished or more persistent reduction of functional active SNAP-25 has yet to be shown. The clinical data presented herein show a longer efficacy of BTXA at higher doses (200 U of BOTOX) than with traditional dose regimens (about 50 U of BOTOX).

Because neutralizing antibodies have been described in patients treated with subdermal and intramuscular injections of BTXA, which may account for a secondary nonresponse,<sup>10,20</sup> the exact intradermal injection technique is a crucial point.<sup>21</sup> Subcutaneous injections have proved less effective in focal hyperhidrosis and may result in a higher rate of temporary muscular weakness.<sup>21,22</sup> There are, in fact, no published data on the development and frequency of BTXA antibodies in patients treated for focal hyperhidrosis.<sup>13</sup> As far as we observed, the patients with a relapse did respond to a second treatment as well as to the initial treatment.

The available data seem to argue for a markedly prolonged efficacy of "high-dose" BTXA. Fewer relapses and a significantly longer relapse-free interval may justify the use of a higher dosage even in terms of cost-benefit calculations.

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