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## **Complications and Side-Effects of Botulinum Toxin A**

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Botulinum toxin A (BTX-A) has a well-defined role in dermatology for the treatment of facial wrinkles, brow position, and palmar and axillary hyperhidrosis [1-5]. BTX-A has proved to be a safe and effective treatment. But like all other drugs, BTX-A has its indications, contra-indications and particular safety aspects that must be kept in mind. In particular, BTX is the most powerful neurotoxin known. Because of the potential hazard of BTX, physicians have a duty towards their patients to inform them about the efficacy of BTX, the side-effects and possible complications. In Switzerland, the use of BTX-A to treat hyperhidrosis has not yet been recognized by the health authorities. For this reason, BTX-A treatment is not covered by health insurance plans, and the responsibility for the treatment and any possible side-effects lies solely with the physician.

The goal of any successful medical therapy is to cure the patient of his or her illness or symptoms. There are various modalities available for the treatment of focal hyperhidrosis: topical aluminium chloride application, tap water iontophoresis, anticholinergic drugs, surgery (axillary sweat gland excision or thoracoscopic sympathectomy) and, most recently, BTX-A. Of course, the method of choice should always be the simplest that improves the patient's suffering, in this case aluminium chloride solution and/or tap water iontophoresis, which both give the patient a great deal of independence from the doctor. Only after failure of these two simple and inexpensive treatment modalities should other treatments like BTX-A or surgery be considered.

A controlled manufacturing process has been developed to produce the toxin for therapeutic purposes. The two commercial formulations (Botox® and Dysport®) are available as freeze-dried powders with good stability. However, the accurate measurement of the pharmacological activity of BTX-A batches

for clinical use is somewhat problematic. The biological activity of BTX has been measured using a variety of techniques ranging from an assessment of whole animal response to the in vitro effects on neurotransmitter release. The 'mouse unit' (MU) is defined as the median intraperitoneal dose that will kill 50% of a group of adult (18- to 20-gram) female Swiss-Webster mice over 3-4 days (i.e. 1 MU = LD<sub>50</sub>). For a 70-kg man, the LD<sub>50</sub> falls in the range of 2,500-3,000 MU [6]. But a mouse unit of Botox is clinically 4-5 times more potent than a mouse unit of Dysport. Therefore, whereas the average number of units required for the treatment of hyperhidrosis is 20-40 MU Botox per axilla or 50 MU Botox per hand, 100-200 MU Dysport are required for the axilla and 250 MU for the palm, respectively [unpubl. data].

In our department, all critical aspects of BTX-A therapy are discussed with patients before treatment. We have also prepared a leaflet which is given to all prospective patients. Before therapy is begun, the patients must sign a consent form.

### Contra-Indications

BTX-A is contra-indicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any ingredient in the formulation. Furthermore, individuals with peripheral motor neuropathic diseases (e.g. amyotrophic lateral sclerosis or motor neuropathy) or neuromuscular junctional disorders (e.g. myasthenia gravis or Lambert-Eaton syndrome) should not receive BTX-A. The toxin can cause a disturbance in neuromuscular transmission or unintentional severe muscle weakness. Finally, the use of BTX-A for hyperhidrosis is contra-indicated in pregnant or nursing women (see below).

### Precautions

Epinephrine, antihistamine and prednisolone should be kept available. Trained personnel should also be on hand who could set an infusion and maintain first aid in the case of an anaphylactic reaction.

The safe and effective use of BTX-A depends upon the proper storage of the product, selection of the correct dose and proper reconstitution and administration techniques (see below). Physicians administering BTX-A must understand the relevant anatomy of the area involved (in particular the neuromuscular anatomy) and any alterations to the patients' anatomy arising from prior surgical procedures.

### Drug Interactions

Huang et al. [6] compiled a list of drugs and medical conditions that can cause interactions with BTX. The drug types in question are aminoglycosides, aminoquinolines, cyclosporine, *d*-penicillamine, tubocurarine, pancuronium, gallamine and succinylcholine. These drugs can either increase muscle weakness (aminoglycosides or cyclosporine) or antagonize the onset of paralysis from BTX by acting at the cell membrane (by inhibiting the binding of the toxin or preventing its transport into the cell) or in the cell interior (by inhibiting the lysosomal processing of toxin).

### Pregnancy, Nursing Women

BTX-A belongs to 'pregnancy category C', meaning that there are no adequate, well-controlled studies available in pregnant women. It is not known whether this drug can pass into human milk. Therefore the use of BTX-A for hyperhidrosis in pregnant or nursing women is contra-indicated.

### Paediatric Use

There are no studies on the effect and side-effects of BTX-A in the treatment of hyperhidrosis in paediatric patients. A study has been carried out, however, on the therapeutic effect of BTX-A in a group of paediatric patients with cervical dystonia and various other focal motor problems associated with spastic muscular hyperactivity [7]. In these patients, the improved joint mobility represented a significant benefit for both daily activities and nursing care. Local paresis and local haematoma were each observed in 1/28 patients; also, 1/28 patients developed a secondary non-response. However, apart from these side-effects, no other adverse reactions to BTX-A were observed.

Gordon [8] suggests that BTX-A should sometimes be considered in focal hyperhidrosis and other autonomic disorders in older children.

### Antibody Formation

Anti-BTX-A antibodies have been detected in about 5-10% of patients chronically treated with BTX-A [9, 10]. The factors critical for preventing antibody formation have not yet been well characterized. Some studies suggest that

more frequent or higher-dose BTX-A injections may lead to a higher incidence of antibody formation [11, 12]. Karamfilov et al. [13] suggest administering a total dose of 200 MU of BTX-A (Botox) in the treatment of axillary hyperhidrosis in order to lower the rate of relapse. However, the potential for antibody formation may be minimized by injecting with the lowest effective dose at the longest feasible intervals between injections. Greene et al. [14] suggest treatment intervals of >3 months, and the avoidance of booster injections. Low-dose BTX-A (20 MU Botox per axilla) is effective for 6 months in axillary hyperhidrosis; the dose should not be increased without good reason [15]. The minimum dose and injection schedule that will induce antibody formation are as yet unknown.

Patients who develop immune resistance to BTX-A may benefit from other serotypes of BTX, such as BTX-B and -F, currently undergoing clinical trials [9]. To date, antibody formation has not been reported in patients treated for blepharospasm or dermatological indications [1].

#### **Other Side-Effects**

Localized pain, tenderness and/or bruising may be associated with the injection. A weakness in the adjacent muscles may also occur due to a spreading of the toxin (see below). Therefore, for treatment of hyperhidrosis the injections should be strictly intradermal.

Botox, and also Dysport, contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely small risk of transmission of viral diseases. A theoretical risk of transmission of Creutzfeldt-Jakob disease is also considered extremely improbable. No cases of transmission of viral diseases or Creutzfeldt-Jakob disease have ever been reported [16]. However transmission of diseases can not be excluded with absolute security.

#### **Dosage and Administration**

BTX-A is supplied in a single-use vial. Because the product and diluent contain no preservative, once opened and reconstituted (with sterile, non-preserved saline) they should be used within 4 h. Excessive shaking and air bubble formation during reconstitution may inactivate the toxin. It is recommended not to refreeze reconstituted BTX-A, but rather to discard any remaining solution. All vials, including expired ones, and equipment used with the drug should be disposed properly, as with all medical waste.

### **BTX in Neuromuscular Disorders**

The use of BTX-A to treat neurological disorders has a much longer history than its use in dermatology. Reports are available of patients receiving continuous treatment (at intervals of 3 months) for up to 8 years, with no serious side-effects (more than 1,000 treatments) [17-22]. In particular, there were no systemic side-effects. A number of mild, transient local side-effects were observed, e.g. transient weakness, but these were not correlated with the long-term use of BTX-A. These reports concluded that BTX-A is a safe and effective treatment for adults and children. Furthermore, they found no decrease in efficacy during long-term treatment with BTX-A (i.e. no antibody formation).

Three patients developed a transient generalized weakness after receiving a therapeutic dose of BTX-A for cervical dystonia (1 case) or symptomatic hemidystonia (2 cases). Clinical and electrophysiological findings were consistent with a mild botulism. All patients had received previous BTX-A injections without side-effects and 1 patient continued injections without recurrence of the generalized weakness. The treatment schedule was 600-900 MU Dysport per consultation every 3 months (equal to 120-180 MU Botox). The cause of the weakness was most likely a presynaptic inhibition of nerve signals due to systemic spread of the toxin [23].

### **BTX-A in Hyperhidrosis**

BTX-A has only recently been introduced as a therapeutic tool for hyperhidrosis. As BTX-A inhibits the release of acetylcholine at the cholinergic synapse, perspiration is arrested completely after intradermal injection.

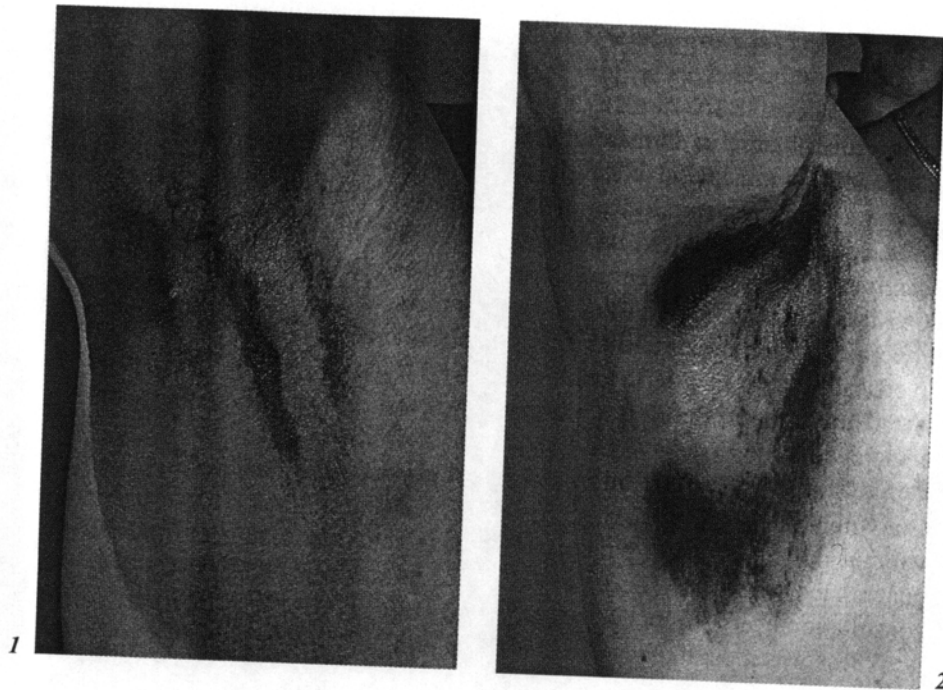
Schnider et al. [24] found that side-effects depended on the site of the injections, were rare if the dosage was optimized and were always reversible.

In the treatment of severe *palmar hyperhidrosis*, mild weakness of the thumb (lasting up to 3 weeks in one patient) can occur, but no other side-effects have been observed [25]. Naver et al. [26] noticed in two thirds of those treated for hand sweat a transient slight reduction in the power of finger grip.

No serious side-effects were noticed after treatment of *axillary hyperhidrosis* [3, 26, 27].

The average number of units required for the treatment of hyperhidrosis is 20-40 MU Botox per axilla or 50 MU Botox per hand, equal to 100-200 MU Dysport for the axilla and 250 MU for the palm, respectively.

Laskawi et al. [28] showed that intracutaneous injection of BTX-A is a highly effective, safe and minimally invasive treatment of Frey's syndrome with a long-lasting therapeutic effect.



*Fig. 1.* An iodine-starch test 2 weeks after treatment shows that the injections were too widely spaced and the diffusion of the toxin could not provide overlapping coverage of the whole area.

*Fig. 2.* An iodine-starch test 2 weeks after treatment shows a well-treated central surface with residual sweating at the perimeter, indicating that the diameter of the treated area was too small.

### **Tips and Tricks**

Before therapy the degree of sweating should be documented with a gravimetric measurement and an iodine-starch test. When treating a moderate hyperhidrosis with BTX-A, the results are obviously less dramatic than when treating an extreme hyperhidrosis, as the difference before and after treatment is more impressive in severe hyperhidrosis. Therefore patients should be chosen for BTX-A treatment with care.

In the treatment of axillary hyperhidrosis, the affected surface must be adequately covered with toxin. Figure 1 shows a case where the injections were too widely spaced and the diffusion of the toxin could not provide overlapping coverage of the whole area. This is neither a side-effect nor a complication, only a false application of toxin. Figure 2 shows a well-treated central surface with

residual sweating at the perimeter, indicating that the diameter of the treated area was too small. This misjudgement probably occurred because the patient had sweated less than normal on the day of treatment. The results of treatment were unsatisfactory for both patients. The goal of the treatment of localized hyperhidrosis is to block all sweat glands using a minimum of toxin. This is advantageous for two reasons: the toxin is expensive, and higher doses can promote the formation of anti-BTX-A antibodies.

### Conclusions

BTX-A treatment is a new, conservative alternative to surgery in the treatment of severe hyperhidrosis. Intracutaneous injections of BTX-A are safe and effective, and offer long-lasting relief of symptoms of severe localized hyperhidrosis. The recommended treatment interval is 3–6 months. For hyperhidrosis therapy, the toxin is injected intradermally rather than intramuscularly. In general there are only mild, reversible side-effects; these are usually the result of diffusion of the toxin. Weakness of muscles only occurs in the therapy of palmar hyperhidrosis or in localized hyperhidrosis of the forehead, because there the muscles are near the surface. Physicians should aim to treat with the lowest effective dose, thereby achieving a maximal dose response and minimal side-effects. A trial treatment with BTX-A should be recommended to patients with focal hyperhidrosis before sympathectomy, since the aggressive surgical techniques carry with them the risk of lifelong troublesome side-effects. For optimum therapeutic results, the treatment with BTX-A should be restricted to specialized centres.

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