SHORT REPORT

Injections of botulinum toxin A into the salivary glands improve sialorrhoea in amyotrophic lateral sclerosis

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Abstract

Sialorrhoea is a socially disabling problem in bulbar amyotrophic lateral sclerosis (ALS). Botulinum toxin A (BoNT/A) was injected into the salivary glands in five patients with bulbar ALS and sialorrhoea. The effect of BoNT/A was measured by the number of paper handkerchiefs used each day and by salivary gland scintigraphy. BoNT/A ameliorated sialorrhoea and quality of life without major adverse effects. BoNT/A may be a relatively safe and effective treatment for sialorrhoea in selected patients.

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Sialorrhoea is a disabling symptom in patients with bulbar amyotrophic lateral sclerosis (ALS) affecting up to 20% of patients with ALS.¹ The use of oral anticholinergic drugs is often limited by lack of efficacy or by unacceptable adverse effects with higher doses.

Botulinum toxin A (BoNT/A), which blocks the release of acetylcholine in motor and autonomic nerve terminals,² was recently introduced for the treatment of autonomic disorders including hyperhidrosis and gustatory sweating.^{3,4} In animals, immunohistochemical studies have shown a significant reduction of acetylcholinesterase in the salivary glands and a reduction of saliva production after local treatment with BoNT/A.⁵⁻⁷ Inhibition of secretion of the salivary glands by local application of BoNT/A could therefore be considered as a therapeutic approach for sialorrhoea in patients with bulbar ALS.⁸ Here, we report preliminary results in five patients who were treated prospectively according to an open label protocol.

Patients and methods

We treated five patients (two women, three men; mean age 63.8 (SD 1.7) years, with mean duration of bulbar ALS 23.4 (SD 18.8) months) with disabling sialorrhoea. Approval by the institutional review board was obtained, and all patients gave their written informed consent. Six to 20 mouse units (MU) BoNT/A

type A (Botox®, Allergan, Irvine, CA, USA; 100 MU/2 ml 0.9% saline) were injected into each parotid gland (cranial, middle, and caudal part, one injection each) using a 27G3/4 needle. If the clinical response was insufficient, as judged by the patient, the same dose was reinjected into each parotid gland 2 weeks later. The submandibular glands were only injected (5 MU each) if parotid gland injections alone were not effective.

As a simple method of quantifying drooling, all patients assessed the response to BoNT/A by counting the number of one brand of paper handkerchiefs used (Tempo Taschentücher®, Germany) each day. The number used each day was stable during a 3 day observation period before BoNT/A injection (Pearson correlation analysis $r=0.99$; $p<0.01$). In addition, improvement of quality of life (QoL) was evaluated by a structured interview (modified DLQI⁹) which was performed before and 4 weeks after the last treatment (0 points=no impairment to 30 points=maximum impairment). Improvement of QoL was rated semiquantitatively (no improvement; slight improvement (by 1 to 33%); moderate improvement (by 34 to 66%); marked improvement (by 67 to 100%)).

Before the first and 2 weeks after the last BoNT/A treatment, salivary secretion in patients was quantified by salivary gland scintigraphy as previously described.¹⁰ To compare these data with a control group, salivary gland scintigraphy was also performed on 32 healthy subjects (mean age 41 (SD 13.7) years; 21 women). Seventy Megabecquerels of technetium-99m pertechnetate were injected intravenously, and 25 frames were acquired (one frame/minute). For quantitative analysis, scans were evaluated by a physician who was masked to treatment. Uptake of technetium-99m pertechnetate in percentage of the activity in the parotid glands was calculated, and integrals over the first 15 minutes were determined.

To evaluate possible adverse effects, bulbar function (tongue movement; eye, lip and mouth closure; swallowing) was monitored weekly.

The decrease of paper handkerchiefs used each day and the differences of the uptake

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Figure 1 (A) Need for paper handkerchiefs each day (baseline and 1 month after BoNT/A injection; mean (SD)). The number of used paper handkerchiefs each day seems markedly, but, due to small numbers, not significantly reduced 1 month after BoNT/A injection ($p=0.068$, Wilcoxon test). (B) Radiotracer uptake in the parotid glands (integral over the first 5 minutes; mean (SD)) in healthy controls ($n=32$ probands, 64 glands) and patients with ALS before BoNT/A injection and 2 weeks after the last BoNT/A injection ($n=5$ patients, 10 glands). Each parotid gland is used for calculation separately. Note that there is a baseline reduction of radiotracer uptake in the parotid glands in patients with ALS compared with healthy controls ($p<0.001$).

curves of parotid gland scintigraphy in patients with ALS were assessed for significance using the Wilcoxon test. Salivary gland scintigraphy of patients with ALS before treatment versus healthy controls was compared using Student's t test. Each parotid gland was considered separately, because each gland constituted a separate injection, and injection into one gland would not be expected to influence secretion rate of the contralateral gland.

Results

Three patients received BoNT/A injections into the parotid glands only, two patients required subsequent injections into the parotid glands and an additional injection of 5 MU into each submandibular gland. The mean total dosage injected into the parotid glands was 46 (SD 16.9) MU Botox® (range 30–72

MU). A reduction of sialorrhoea was first noticed 3 to 5 days after injection. A pronounced reduction measured by the number of paper handkerchiefs used each day was found 4 weeks after the last injection (before injection 11 (SD 6.0), range 3–20; 4 weeks after the last injection 2.6 (SD 0.5), range 2–3; $p=0.068$; fig 1 A). Three patients showed a marked improvement of QoL after treatment, one patient showed moderate improvement, and one patient did not benefit from treatment. In the follow up interval of up to 3 months no worsening of sialorrhoea or bulbar function was seen except for one patient who experienced a slight increase of sialorrhoea 10 weeks after injection.

Scintigraphy of the parotid glands showed a significantly lower mean value of the integral over the first 5 minutes in patients with ALS (0.92 (SD 0.28)) compared with healthy controls (1.88 (SD 0.4); $p<0.001$; fig 1 B)).

Two weeks after the last injection a marked reduction of radiotracer uptake (integral over the first 5 minutes) in both parotid glands ($n=10$; before BoNT/A 0.92 (SD 0.28); after BoNT/A 0.7 (SD 0.26); $p=0.059$) was demonstrated, figures 1 B, and 2.

One patient with a very rapidly progressive course of the disease did not show a clinical benefit after repeated parotid and submandibular gland injections (total 72 MU into the parotid glands, 10 MU into the submandibular glands) despite a markedly reduced radiotracer uptake.

Discussion

Our preliminary study shows that the injection of BoNT/A into the parotid or submandibular glands is beneficial in patients with sialorrhoea secondary to bulbar ALS. In four of the five

Figure 2 Representative example of scintigraphy of the salivary glands using technetium-99m pertechnetate as tracer: Parotid glands (arrows), submandibular glands (asterisks), nose (arrowheads). Secretion of the radiotracer into the oral cavity is also visible. (A) Before BoNT/A injection, (B) Marked reduction of radiotracer uptake in the parotid glands 2 weeks after the last BoNT/A injection.

patients treated, a marked reduction of sialorrhoea was shown. This finding is in line with the reduced radiotracer uptake in both parotid glands after BoNT/A injections, as documented by salivary gland scintigraphy. The effect is likely to be based on BoNT/A induced blockade of acetylcholine release at the cholinergic neurosecretory junction of the salivary glands. Although clinical data are lacking, experiments in animals have shown that BoNT/A application into the salivary glands results in a reduction of acetylcholinesterase activity and saliva production.⁵⁻⁷

As an additional finding, there was marked baseline reduction of radiotracer uptake in the parotid glands in patients with ALS compared with healthy controls, indicating a disordered function as part of the neurodegenerative process.

We did not find any major adverse effects of BoNT/A even after repeated doses. In particular, no drying of the mouth and no deterioration of dysphagia due to a diffusion of the toxin into the pharyngeal muscles were seen. The risk for these potential adverse effects may be diminished but certainly cannot be excluded by cautiously escalating the dose and number of treated glands. However, this pilot study did not investigate the individual upper dose tolerated by patients with ALS, which may be low. Other potential adverse effects which were not

seen in our study may include infections of the salivary glands or salivary ducts, haematomas, salivary duct calculi, and local injuries of the carotid artery or of branches of the facial nerve.

The results of our pilot study are encouraging. A full clinical trial would be needed to formally evaluate risks and benefits of BoNT/A for palliative treatment in bulbar ALS.

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