MATTERS ARISING

Localised autonomic failure due to botulinum toxin injection

I read with great interest Mann's report of a patient receiving botulinum toxin injections for spasmodic torticollis who developed sialectasis and swelling of the parotid glands after each set of injections.¹ Local diffusion of the toxin and paralysis of the smooth muscle of the salivary ducts was proposed as a possible underlying mechanism.¹

The inhibitory action of botulinum toxin is not confined to the neuromuscular junction. All the autonomic cholinergic fibres including the major secretomotor fibres to salivary glands are similarly blocked. Local diffusion and "chemodenervation" of the parotid glands leading to reduction of salivary flow and the development of chronic recurrent parotitis seems to be a more likely explanation for this patient's symptoms. Dickson and Shevsky in 1923 showed that tympanic nerve-induced salivary flow was blocked by the toxin in cats.² In botulism, dry mouth is a common symptom, occurring in about 93% of patients.³ Dry mouth has also been reported in some 30% of patients after cervical injections for spasmodic torticollis.⁴ Paradoxically, excessive salivation has long been known to occur in botulism.² A similar paradoxical effect on lacrimal glands producing watering of the eyes has been reported in patients receiving periorbital injections for blepharospasm or hemifacial spasm.⁵ This paradoxical effect of the toxin on the "neuroglandular junction" remains unexplained. Increased saliva production may partly be responsible for parotid swelling after botulinum toxin injections in the patient reported.

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Mann replies:

I am grateful to Dr Bushara for his interest and comments. I too had considered other potential mechanisms for the salivary gland swelling but favoured duct paralysis for a number of reasons.

The patient clearly still secreted saliva as she was able to empty the glands "manually" with massage. Chronic infection was rejected on the basis of negative growth

from swabs and absent response to broad spectrum antibiotics.

The concept of paradoxical hypersecretion is intriguing but one would not expect a dry mouth to result. Duct paralysis best explains the combination of symptoms and signs in this patient.

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Immunoglobulin treatment in human and experimental epilepsy

The paper of van Engelen *et al*¹ mentions some positive effects of intravenous immunoglobulins (IVIg) in the treatment of refractory epilepsy. No reference about our experience in that field is mentioned, however, in the medical literature reviewed by Van Engelen *et al*.¹

In 1983, we successfully treated with IVIg a patient with severe Lennox-Gastaut syndrome who still remains seizure free.² Thereafter, in a first open study, 20 patients with Lennox-Gastaut syndrome and partial epilepsy were infused with IVIg.^{3,4} This treatment gave excellent results in two patients, who were seizure free for months but relapsed afterwards although their seizures were less severe than before the infusions. In this open study, 15 patients have partially improved including eight with a pronounced decrease of seizures. It was concluded that IVIg treatment may be very helpful not only in West and Lennox-Gastaut syndromes, but also in partial epilepsy, including Rasmussen's syndrome.⁵

At that time, however, all studies published about IVIg in refractory epilepsy were open designs—with the exception of that of Illum *et al*,⁶ which was a single blind, cross over trial—with controversial schedules and doses. Indeed the patients received from two to more than 10 infusions with doses ranging from 100 mg to 1 g/kg/perfusion and no relation was assessed between dose or schedule of IVIg and clinical responsiveness. An overview of the medical literature involving about 200 epileptic patients treated with IVIg showed a positive response to this treatment in around 50% of the patients.⁷ Taking that into account, in 1989 we initiated the first double blind study to establish a dose of IVIg for treatment of epilepsy.⁷ Sixty one patients were randomly assigned to receive either IVIg (n = 43) or a placebo (n = 18) at three different doses (100, 250, or 400 mg/kg/infusion). No dose effect was found (P = 0.31). The data for the whole study population showed an improvement in 52.5% of patients treated with IVIg (in accordance with previously reported open studies), compared with 27.8% in the placebo group; this positive trend was not significant (P = 0.09). When only the patients with partial epilepsy were assessed, a significant difference in favour of the IVIg treatment was found (P = 0.04) and this was confirmed in the subgroup of partial epilepsy with secondarily generalised seizures (n = 30) regardless of the dose (P = 0.04). Two patients became seizure free. One with Lennox-Gastaut syndrome needs no further anti-convulsant medication. The other, who had

partial epilepsy, relapsed but is still better than before the IVIg.

The mechanisms of action are unknown. We found some relation between a lower serum IgA level and a better clinical response in the first study,⁴ but could not confirm this correlation in the double blind study⁷ although we noted a trend in favour of a lower serum IgA. Infusions of IVIg in refractory epilepsy are well tolerated but the major problems related to this treatment concern its cost and the hazards of transmission of infectious diseases linked to blood derivatives. Immunoglobulins may be considered safe however, as their manufacturing procedures are known to inactivate human pathogenic viruses such as hepatitis A, B and C, and HIV I and II.

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Van Engelen *et al* reply:

We thank van Rijckevorsel and Delire for their interest in our paper on immunoglobulin treatment in human and experimental epilepsy.¹ Their point was that we did not mention their experience in that field. Our paper was an overview on some aspects of immunoglobulin effects in human and experimental epilepsies; it was not a review of the medical literature on immunoglobulin treatment in human epilepsies. We wrote a 1993 review on current immunoglobulin treatment in human epilepsies,² and there we recognised their contribution in the field by citing three papers published by van Rijckevorsel and colleagues.

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