THERAPEUTIC INTERVENTION

The Little Milkmaid by Amedeo Modigliani (1884–1920). Does this represent artistic licence or cervical dystonia?

Botu
focal

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It is a truth universally acknowledged that neurology outpatients are stimulating, challenging and varied. It is a truth less universally acknowledged that patients with severe epilepsy continue to have severe epilepsy, advanced Parkinson's disease patients get worse, and patients with chronic daily headaches are untreatable. In contrast, patients who attend botulinum toxin clinics demonstrably improve with successive treatments. In addition, their complaints are unusual and fascinating – a perfect clinic for the general neurologist!

WHY DOES BOTULINUM TOXIN WORK SO WELL?

The primary action of botulinum toxin is to block acetylcholine release at the neuromuscular junction and so produce muscle weakness. However, the therapeutic effect is often greater than predicted, suggesting additional mechanisms. The drug is taken up preferentially by the most active nerve terminals and so the actively contracting muscle fibres are weakened while the strength in other fibres in the same muscle is preserved. Indeed patients commonly notice that their involuntary dystonic movements are reduced botulinum toxin and yet voluntary action is mainly preserved. Toxin also blocks muscle spindle afferent activity thereby influencing the reflex arc producing a form of selective deafferentation. (Rosales *et al*. 1996). Furthermore, transcranial magnetic studies demonstrate abnormal cerebral cortical maps

num toxin for dystonia

in focal dystonia, which revert towards normal after botulinum toxin, suggesting secondary central effects (Byrnes *et al*. 1998).

IS THE DURATION OF ACTION PREDICTABLE?

New motor nerve axon terminals start sprouting soon after the botulinum toxin injection and in most focal dystonias the effect of an individual set of injections largely subsides within 12 weeks. It is good clinical practice to postpone re-injection until the dystonic signs are recurring. Also, in the case of cervical dystonia, it is easier to re-inject when abnormal contractions can again be seen and the relevant muscles palpated.

SHOULD SINGLE OR MULTIPLE INJECTIONS BE GIVEN?

Usually there is no obvious difference between either method. Unsurprisingly, most patients prefer fewer injections. Occasionally a very hypertrophied sternocleidomastoid or splenius capitis muscle is injected in two sites.

INJECTION TECHNIQUE

It usually takes several months of repeated injection practice to become reasonably competent. Indeed, patients are quick to recognize clinicians with a clumsy or rough technique. The intramuscular injections should be slow to avoid muscle bruising, and the neurologist should search out his or her old anatomy textbook to recall the important landmarks.

SHOULD EMG BE USED?

Some sceptics suggest that the routine use of EMG in cervical dystonia means the clinician is not receiving enough referrals rather than he or she is being aided by the technology. Observation and palpation of muscles is generally accurate, rapid and effective. Nevertheless indications for EMG include:

- some cases of writer's cramp;
- all cases of spasmodic dysphonia;
- very occasional cervical dystonia cases in which there is difficulty in palpating the responsible muscles;
- jaw-opening dystonia.

WHICH BOTULINUM TOXIN?

The two botulinum toxin A preparations – Dysport and Botox – are very similar but the dose schedules in mouse units (mu) are not equivalent (Table 1). It is therefore potentially dangerous for both drugs to be used in the same clinic because almost certainly dosing mistakes will be made.

POOR RESPONDERS

Primary non-responders are those patients who have no clinical or EMG response from the outset. They are exceedingly rare. Secondary non-responders or poor responders are those who initially benefit from botulinum toxin A but then the effect declines. Although it is a common assumption that poor response is due to neutralizing antibodies, other rather mundane

Table 1 Botulinum toxin preparations

	SEROTYPE	CONTENTS OF SINGLE VIAL (MOUSE UNITS)	DOSE EQUIVALENCE (APPROXIMATE)
Dysport (Ipsen UK)	A	500	3.5
Botox (Allegan US)	A	100	1
Neurobloc (Elan US)	B	2500	
		5000	60
		10 000	

explanations are both more likely and more easily dealt with:

- The incorrect muscles have been injected, particularly in cervical dystonia where deep muscles may be difficult to palpate.
- The patient's expectations may be unrealistic. After an initial striking improvement the patient may report 'failure' of further treatment having anticipated complete recovery. If the injections are postponed for 3–6 months the worsening confirms that the immediately preceding treatment had actually been helpful.
- Patients with associated disorders, particularly alcoholism or depression, often report poor response despite clinical evidence of motor weakness.

The most useful test for a genuinely poor response – i.e. biological failure – is to inject Dysport (20 mu) or Botox (7.5 mu) into the frontal muscle above one eyebrow. A positive response should be revealed by asymmetry of the forehead on attempted frowning (Hanna & Jankovic 1998).

Laboratory tests to detect antibodies are rarely indicated. The immunoprecipitation assay and mouse protection assay both correlate with clinical lack of response. In general terms clinical resistance to botulinum toxin is best *avoided* by delaying re-injection by at least 10–12 weeks, even of booster injections at 4–6 weeks if patients are dissatisfied by the initial response. The dosage used should always be the lowest to produce a clinical response.

Botulinum toxin type B – Neurobloc (Myobloc in the USA) – is antigenically distinct from type A. It is therefore reasonable to use this agent in those cases of primary or secondary poor response if other causes have been excluded.

IS BOTULINUM TOXIN SAFE?

Botulinum toxin has turned out to be a remarkably safe product considering the large number of patients who have been treated. Excess weakness of the muscles injected as well as of adjacent muscles is the most common problem. Occasional muscle weakness, and autonomic adverse effects (dryness of the mouth), have been noted at distant sites but this is rare if the patient has received a standard dose. Allergic reactions although rare have occurred and patients should not be re-injected. Systemic anaphylaxis has not been reported.

THE BOTULINUM TOXIN CLINIC SERVICE

The peculiar feature of this outpatient service compared with other specialty clinics is that only the poor responders are discharged. Consequently, in view of the generally very positive treatment effect, the clinic inevitably grows as new patients are referred. As the distinction between 'neuroscience centre' and 'district general or community hospital' becomes more blurred, the location of the clinic depends on local expertise and availability. It is however, poor economics for an individual patient with, for example, hemifacial spasm, to be injected at the end of a general neurology clinic because a lot of toxin will be left in the vial and cannot be used later. Also, the greater the number of patients injected, the greater the experience and expertise of the injecting clinicians. Continuity of outpatient care is critical because patients are understandably upset if there is a delay or postponement of their follow-up appointment. Trained nurses are increasingly used to help in clinics and are particularly valuable in straightforward repeat injection cases. Indeed, provision of dystonia specialist nurses would greatly enhance patient care as specialist nurses have in other neurological specialties.

CERVICAL DYSTONIA

Botulinum toxin A is the treatment of first choice. Although there are familiar clinical presentations, no two cases are identical and the muscles to inject and the dosages to use are left to the clinician's discretion. The patient must be advised that the treatment is not a cure and roughly 3-monthly repeat treatment is required indefinitely. About 80% of patients benefit with a reduction in abnormal movements, and a higher percentage have a reduction in pain.

Before injecting it is worthwhile spending some time observing the head posture, watching the neck movements both with the patient

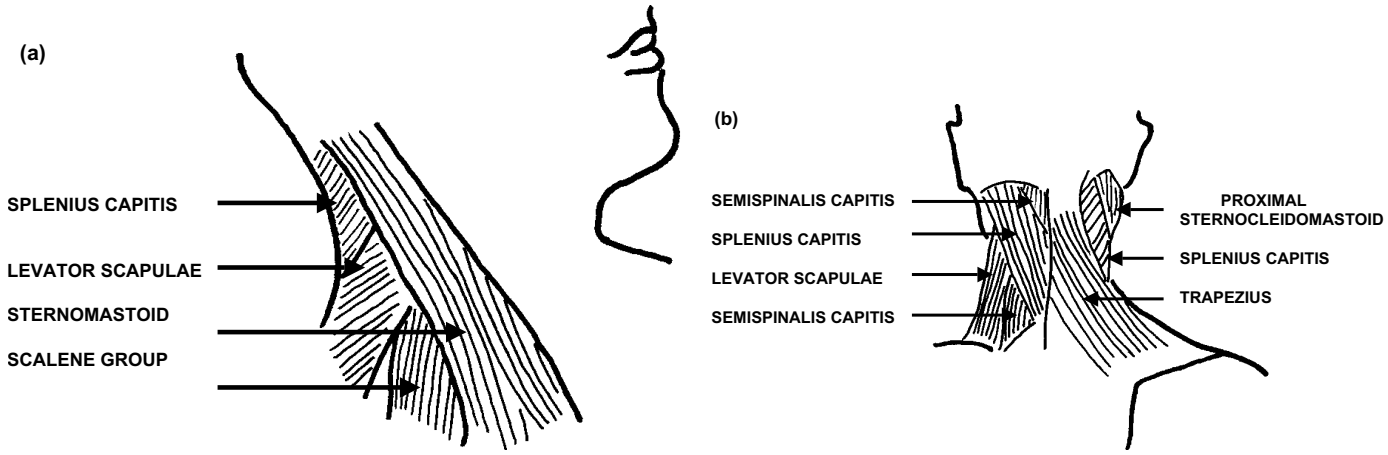

Figure 1 Important muscles viewed from the (a) lateral and (b) posterior aspects of the neck

sitting and walking, and finally palpating all the muscles on each side of the neck. Assess which muscles are hypertrophied. Gently but firmly turn the head *against* the direction of the dystonia. This will increase the activity of the dystonic muscles and allow easier identification (Fig. 1). Ask the patient which muscles are felt to be the main culprits and whether the 'pulling' is coming from one or both sides. The muscle groups injected depend on the pattern of the dystonia (Fig. 2). Generally at least two muscle groups are injected. It is often possible to place the left index finger and middle finger on each side of the dystonic muscle. Using a 25-gauge needle (0.5×16) withdraw the plunger slightly to exclude blood vessel puncture and gently inject into the bulk of the muscle. The recommended total initial dosages are Dysport 400–500 mu, Botox 100–50 mu.

Additional advice

- Dysphagia can occur if either the scalene group muscles or sternocleidomastoid muscles are injected bilaterally (a common adverse effect when treating anterocollis).
- Avoid dysphagia by injecting the upper third of the sternocleidomastoid.
- Use smaller dosages in the elderly and frail where neck weakness with the head falling forward is frequently described due to overdosage in the splenius and semispinalis capitis muscles.
- tremulous torticollis (usually 'no-no' movement) has a less satisfactory response than straightforward movement in one direction.
- Anterocollis patients generally have an unsatisfactory response.

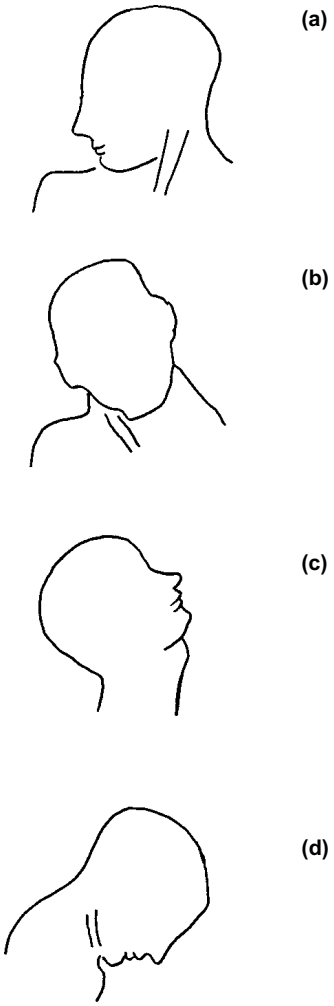

Figure 2 The patterns of cervical dystonia. (a) Torticollis with overactivity of ipsilateral sternocleidomastoid and contralateral splenius capitis and levator scapulae. (b) Laterocollis with overactivity of ipsilateral sternocleidomastoid, splenius capitis and scalene group. (c) Retrocollis with overactivity of splenius capitis and semispinalis capitis bilaterally. (d) Anterocollis with overactivity of sternocleidomastoid and scalene group bilaterally.

BLEPHAROSPASM

Botulinum toxin A is the treatment of first choice and management is shared with interested ophthalmologists. There is variation with respect to muscles injected and dosages used. A common approach is to inject into three or four separate sites in the orbital part of the orbicularis oculi on each side (Fig. 3a). A starting total dosage for both eyes is Dysport 160 units or Botox 40 units, and increased as required. Injections are subcutaneous using a 25-gauge needle (0.5 × 16). An alternative approach, usually tried if the first is unsatisfactory, is to inject the pretarsal part of the orbicularis oculi muscle, medially and laterally in the upper eyelid and 1–2 injections into the lower lid (Fig. 3b). A starting total dosage for both eyes is Dysport 80 units, or Botox 20 units. To the patients' surprise injections into the pretarsal rather than orbital parts are generally less painful and the response is more predictable.

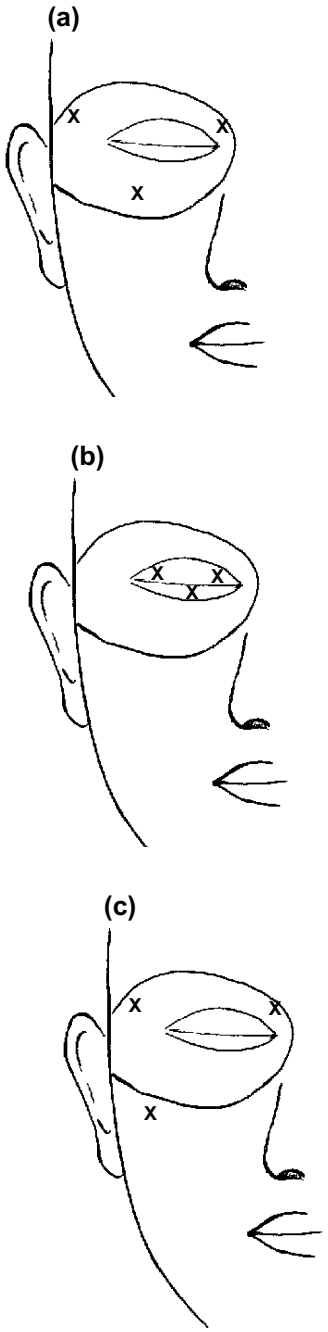

Figure 3 Injection sites around the eye for blepharospasm and hemifacial spasm

Additional advice

- The two most common adverse effects are temporary ptosis (5%) and dry eyes (5%).
- Direct the needle away from the middle of the upper eyelid to avoid spread of toxin to levator palpebrae with subsequent ptosis.

Patients with eyelid apraxia may benefit from injection into the pretarsal orbicularis oculi but the results are less predictable than with primary focal dystonia.

HEMIFACIAL SPASM

This condition is not a focal dystonia but instead reflects damage to the facial nerve itself. Botulinum toxin A is the treatment of first choice. As in blepharospasm there is fairly wide variation in the injection sites and dosages but success is the rule. A reasonable approach is to inject subcutaneously laterally into the orbital part of the orbicularis oris, with a further injection into the upper medial part of the same muscle directing the needle medially and downwards (Fig. 3c). The final injection is into the inferolateral part of orbicularis oculi where it is adjacent to the zygomatic muscles. A usual dosage is 80 mμ Dysport, or 20 mu Botox, and adjusted as required.

Additional advice

- The patient must be warned that facial asymmetry is an inevitable consequence of the natural history of this condition irrespective of botulinum toxin therapy.
- The 'lower' the injection into the face the more likely an increased droop of the side of the mouth.
- Occasional patients benefit from small dosage injections into any of the chin muscles (mentalis, depressor labii inferioris, depressor anguli oris). Platysma can be prominently affected and is easily injected.

OROMANDIBULAR DYSTONIA

In general the results of treating lower facial dystonia are disappointing. This reflects the complex muscle anatomy responsible for jaw, pharyngeal and tongue movement and the relative difficulty of injecting into the over active muscles. If there is severe associated blepharos-

pasm (Meige's syndrome) treatment of eye closure can improve the lower facial dystonia. There are some patterns worth attempting to treat in any event. Patients with jaw-closing dystonia are treated with injections into both masseter and temporalis muscles (Dysport 150 mμ, or Botox 40 mu). The masseter muscle is surprisingly powerful and the dosage can gradually be increased. A poor response suggests that the internal pterygoid muscle requires injection, a more tricky procedure requiring EMG and advice from oral surgeons. Jaw-opening dystonia is difficult to treat successfully. The injections require EMG into the external pterygoid and digastric muscles. Dysphagia is a common adverse effect.

WRITER'S CRAMP

Oral drug treatment, biofeedback and mechanical devices are strikingly ineffective for this disabling disorder. Botulinum toxin A is the most likely treatment to help but is less predictably successful than treatment for cervical dystonia and blepharospasm, presumably because the muscle activity during writing is much more complex. A further problem is that some abnormal movements may reflect the patient's response to their dystonia by assuming an abnormal posture of the wrist or fingers. which confuses the clinician.

A common dystonic pattern is that of overall wrist flexion, particularly with ulnar deviation. It is then worthwhile starting treatment with Dysport 100 mu, or Botox 30 mu, into the anterior forearm, two or three separate sites on the ulnar aspect and towards the midline. If there is a good response (about 40% of patients) then the response is likely to be maintained with further injections into similar sites. Conversely if there is significant hand-grip weakness or no clinical benefit then the prospect of success is less encouraging. EMG is valuable to help target the precise muscles but should not be a substitute for careful observation and palpation of muscles whilst the patient is writing.

Additional advice

The extensor muscles of the thumb, fingers and wrist are less powerful than their flexor counterparts and weakness readily occurs unless the botulinum toxin dose is kept low.

SPASMODIC DYSPHONIA

An interested neurologist should be part of the team, which includes an Ear, Nose and Throat surgeon who injects, and a speech therapist. Most of the patients have spasmodic dysphonia in isolation as a focal dystonia, but some have segmental dystonia with either cervical dystonia or facial dystonia. All cases, in addition to clinical assessment, require endoscopy of the vocal folds. In *adductor* dysphonia (90% of cases) there is irregular hyper-adduction of the vocal folds during speech whereas in *abductor* dysphonia (10% of cases) there is irregular abduction of the folds whilst the patient speaks.

The injection technique in adductor dysphonia is greatly helped by EMG guidance with a Teflon-coated needle through which the toxin is given. The patient lies supine with the neck partly extended. Local anaesthetic is given and the needle passed through the cricothyroid membrane and directed to either the left or right to target the appropriate thyroarytenoid muscle. The EMG pattern confirms an accurate position and Dysport 3.75 mu, or Botox 1.0 mu, given. The procedure is repeated into the other thyroarytenoid muscle. Breathy dysphonia is commonly experienced for 1–2 weeks after the injection but improvement is often striking and maintained for at least 4 months. Treatment of abductor dysphonia is less successful and more complex requiring injection of the posterior cricoarytenoid muscles.

CONCLUSIONS

- Botulinum toxin therapy should be readily available in all reasonably busy neurology departments
- There must be an infrastructure to support continuity of care for all patients
- Botulinum toxin is the treatment of first choice for cervical dystonia, blepharospasm, hemifacial spasm and spasmodic dysphonia and can be valuable in writer's cramp.
- Poor response may be due to neutralizing antibodies but is more often due to inappropriate muscle injection.

REFERENCES

Byrnes M, Thickbroom G & Wilson S *et al*. (1998) The corticomotor representation of upper limb muscles in writer's cramp and changes following botulinum toxin injection. *Brain*, **121**, 977–88.

Hanna PA, Jankovic J (1998) Mouse bioassay versus Westren blot assay for botulinum toxin antibodies. *Neurology*, **50**, 1624–9.

Rosales RL, Armimura K, Takenaga S & Osame M (1996) Extrafusal and intrafusal muscle effects in experimental botulinum toxin A injection. *Muscle Nerve*, **19**, 488–96.

FURTHER READING

Moore P, Naumann M (2003) *Handbook of Botulinum Toxin Treatment*, 2nd Edn. Blackwell Science, Oxford.