Experience with botulinum toxin in the treatment of cerebral palsy

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Objectives. To assess the effect of botulinum toxin on dynamic spasticity and dystonic posturing in children with cerebral palsy.

Design. Assessment and documentation of the motor disability of children with cerebral palsy followed by injection of botulinum toxin into selected muscle groups. Reassessment of motor function after injection.

Subjects. Fifteen children with cerebral palsy: 5 with dynamic spasticity, 5 with dystonia and 5 with a mixed picture.

Results. On a standard scoring system, 13 of the children showed improved function at reassessment.

Conclusion. Intramuscular injection of botulinum toxin is effective in the treatment of selected children with spastic and dystonic forms of cerebral palsy. Improvement is not permanent, but the injection can be repeated.

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Botulinum toxin is a single-chain polypeptide that selectively inhibits acetylcholine release from peripheral nerve endings. It was first used clinically in 1980 by Scott as an alternative to surgical correction of squint.[1] The toxin has subsequently been used in the treatment of blepharospasm,[2] cervical dystonia,[3] hemifacial spasms,[4] spasmodic dysphonia,[5] multiple sclerosis[6] and, more recently, spasticity in cerebral palsy.[7-9] We are not aware of any published work on its use in dystonic forms of cerebral palsy. In this paper we report experience with botulinum toxin in the management of both dynamic spasticity and dystonic posturing in children with cerebral palsy.

Fifteen children were selected from schools for the physically disabled. Every one was in the care of a physiotherapist experienced in the treatment of cerebral palsy. Ages ranged from 5 to 17 years. There were 5 children with hemiplegia, 5 with diplegia and 5 with quadriplegia. Of the total number, 5 showed a picture of dynamic spasticity (group 1) and 5 were dyskinetic with dystonic spasms (group 2). The remaining 5 showed a mixed picture of spasticity and dystonic posturing (group 3).

During physical examination of each child the 'overactive' muscles responsible for abnormal posture and movement were identified. The examiner made sure that there were no fixed contractures. Where relevant, dye impressions were obtained of standing footprints and a video recording was made of the gait or hand function. Findings in each child were carefully documented and a realistic goal was defined for injection therapy. General anaesthesia was administered during the actual injection in all but 4 of the children. Botulinum toxin A (Botox: Allergen) was injected by one of the authors (RBG) into the appropriate muscles in each case (Table I). Calf muscles (soleus and heads of gastrocnemius) were injected in 7 cases, thigh adductor muscles in 2, and forearm, wrist and/or finger flexors in 6. In 1 case injections were also given into elbow flexor muscles. One or two injections were given into each muscle belly. The total dose administered was 4 - 6 U/kg body weight. For injection purposes the toxin was diluted with normal saline to a concentration of 100 U in 5 ml. Electromyographic monitoring was not used in this study. A second video recording was made 2 - 4 weeks after injection.

Assessment of outcome was made 6 - 8 weeks after injection. This was achieved by bringing together the doctors involved in the study and a group of physiotherapists experienced in the management of cerebral palsy. Each child was clinically examined and the videos recorded before and after injection were compared. The 18 physiotherapists and 4 doctors were then asked independently to rate achievement of the defined goal for each child on a scale of 0 - 4 (Table II). The rating recorded for each child was the figure most frequently awarded to that child by the 22 evaluators. Where feasible, patients were invited to express their subjective impressions of change.

Results

These are shown in Table I. There was close agreement among evaluators in almost every case. In group 2, 3 children showed significant improvement and 1 showed some improvement. Improvement in manual function was marred in 3 cases by persistent thumb adduction and flexion into the palm. In group 3, 1 child achieved an excellent result and some improvement was noted in the other 4. No adverse side-effects were reported by the children or their parents. Duration of improved function varied. In 1 patient the effect began to wear off after 6 weeks. In 2 others with calf muscle spasticity, heel strike on walking was still good 7 months after injection.

The range of assessments recorded for patient 6 reflect achievement of the stated aim (control of foot posture) but failure to improve gait because of increased weakness. This weakness gradually wore off and the child then experienced markedly improved gait for several months.

Patient 10 had severe dystonia with finger tremor of her right hand and arm that caused her to sit on the hand to control the movement. Following injection the finger tremor ceased and she could use the hand for support although grasp was still hampered by persistent thumb adduction and flexion in the palm. This was also a problem in patients 7 and 9.

Patient 12 in group 3 was a boy with severe dystonic spasms of the right hand and no useful function. He was

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Table I. Patient data

Patient	Diagnosis	Age (yrs)	Aim	Site	Results
Group 1 — spastic					
1	Diplegia	5	Improved gait	Calf muscles	4
2	Diplegia	7	Improved gait	Calf muscles	4
3	Diplegia	7	Improved gait	Calf muscles	3*
4	Diplegia	7	Improved gait	Calf muscles	1
5	Quadriplegia	14	Improved thigh adduction	Thigh adductors	3*
Group 2 — dystonic					
6	Hemiplegia	7	Control of foot posture	Calf muscles	4 - 1
7	Hemiplegia	12	Control of hand posture	Forearm flexors	3†
8	Hemiplegia	12	Control of hand and arm postures	Wrist and elbow flexors, finger, arm	2
9	Hemiplegia	19	Control of hand posture	Finger and wrist flexors	1†
10	Quadriplegia	17	Control of hand tremor and posture	Forearm muscles and hand	3†
Group 3 — mixed spastic/dystonic					
11	Diplegia	6	Control of foot	Calf muscles	2
12	Hemiplegia	13	Improved hand posture	Forearm muscle and hand	0 - 2
13	Quadriplegia	5	Control of foot posture	Calf muscles	4
14	Quadriplegia	16	Improved hand function	Forearm muscle	2
15	Quadriplegia	16	Improved thigh adduction	Thigh adductor muscles	2*

* A degree of fixed contracture was noted under general anaesthetic.
† Thumb in spasm in palm.

Table II. Post-injection assessment scale

Aim fully achieved	4
Aim partly achieved	3
Slight improvement	2
No change	1
Made worse	0

given a zero rating by 60% of the evaluators because he reported that his hand had become weaker and he was worse off. However, the post-injection video showed clearly that he had acquired some function in the hand. When he realised this himself at a later stage he requested a repeat injection.

Patient 13 is a very severe quadriplegic with marked dystonic posturing of his left foot and fixed contracture of his right foot (confirmed under anaesthesia). Prior to intervention he could take weight only momentarily on the balls of his feet. Following injection into the left calf the improvement was dramatic and he became able to bear weight with a flat foot (Fig. 1). Subsequently the right foot was fully corrected surgically.

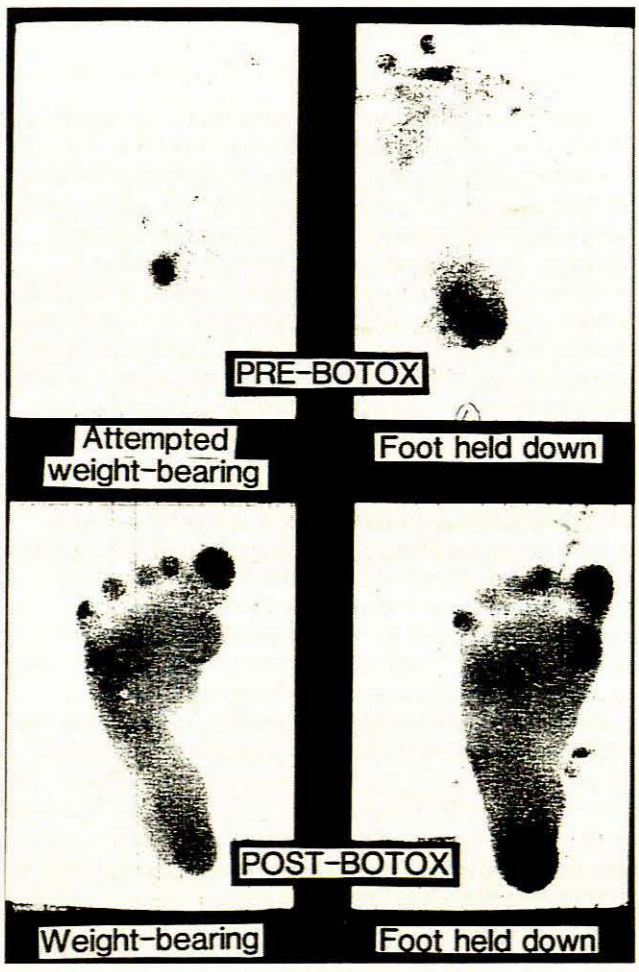

Fig. 1. Foot impressions before and after botulinum injection.

Discussion

Botulinum toxin acts selectively on peripheral cholinergic nerve endings to inhibit pre-synaptic acetylcholine release. It does this by binding to receptors on the surface of cholinergic cells, invading the cells and then breaking down a protein called synaptobrevin 2.[10] This process induces progressive inhibition of transmitter release and consequent weakness. Seven serotypes of the toxin (labelled A - G) have been identified. These are antigenically dissimilar and each

binds to a specific receptor on the cell wall. Experimental work has established that intramuscular injection of the toxin induces muscle fibre atrophy which continues for 4 - 6 weeks. There is also collateral axon sprouting at the terminal axon which re-establishes neuromuscular connections. Histological changes are completely reversed after 4 - 5 months and repeated injections do not produce permanent denervation.[11]

This study, in common with others,[7-9] has demonstrated a good response to botulinum toxin when voluntary movement is impaired by dynamic spasticity. For a satisfactory outcome in such cases there should be sufficient strength in antagonistic muscles to permit functional control after spastic muscles have been weakened by botulinum toxin. The injection is not effective in the face of fixed contractures. These become more prominent with increasing age and can usually be identified on clinical examination. When present, they constitute a contraindication to injection treatment and surgical intervention is necessary to achieve correct joint positions.

Significant improvement in dystonic forms of cerebral palsy has not hitherto been obtained, either with drug therapy or with surgery. In this study the outcome in most of the group 2 and group 3 patients was less impressive than in group 1 patients. It is possible that dosages used were not optimal, and in the hand cases treated there was not always certainty about the forearm muscles injected. More precise localisation should be possible with electromyographic assistance. Persistent thumb adduction and flexion into the palm should be avoided in future by injection into the muscles specifically responsible — the adductor pollicis[12] and flexor pollicis longus. Outcome in this group is clearly also influenced by the well-recognised spread of dystonic muscle contractions that occurs in dyskinetic subjects when voluntary actions are undertaken.

Two subjects complained of post-injection weakness. This proved to be transitory, but calls for consideration. A direct relationship can be anticipated between the dose of toxin injected and the number of nerve endings destroyed. The volume of fluid injected may also be significant, as a larger volume will diffuse more widely within the muscle envelope. In this study an impression was gained that weakness related more to the number of muscles treated than to the dose or volume injected.

The use of general anaesthesia merits some mention. It certainly made the procedure less traumatic for all subjects and avoided technical difficulties that lack of co-operation might have caused. It also made the operator's task easier in that target muscles, particularly in dystonic subjects, were well relaxed and fixed contractures could be readily identified. These advantages must be weighed against the increased cost and the marginal risk of general anaesthesia.

Consideration must also be given to the cost of injection therapy. At present the retail price of a single vial of botulinum toxin is approximately R1 000. This contains 100 units, so that more than one vial may be required for a single treatment in larger subjects. Further cost is incurred if a general anaesthetic is given. Treatment with botulinum toxin is therefore not cheap, but results achieved and the enthusiastic response of subjects and parents lead us to believe that the financial outlay is justified when case selection has been appropriate.

Conclusions

A majority of the children in this study showed definite short-term benefit following botulinum toxin injection and this form of therapy constitutes another option in the management of cerebral palsy. Injection therapy is suitable for subjects who show dynamic hypertonia or dystonia without fixed contractures or any significant weakness in antagonistic muscles. Muscles to be injected must be identified during a skilled assessment of the individual's disabling features. Relief of spasticity, albeit temporary, provides a 'window period' for intensive physiotherapy and may even prevent development of fixed contractures. Injections can be repeated when necessary as long as the spasticity remains dynamic. Patients with dystonic spasms, like those with other forms of dystonia, will require repeated injections to maintain improvement. We are continuing with studies of botulinum toxin in the management of children with cerebral palsy.

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REFERENCES

1. Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *Ophthalmology* 1980; **87:** 1044-1049.
2. Cohen DA, Savino PJ, Stern MB, Hurtig HI. Botulinum injection therapy for blepharospasm: a review and report of 75 patients. *Clin Neuropharmacol* 1986; **9:** 415-429.
3. Jankovic J, Brin MF. Therapeutic uses of botulinum toxin. *N Engl J Med* 1991; **324:** 1186-1193.
4. Savino PJ, Sergott RC, Bosley TM, Schatz NT. Hemifacial spasm treated with botulinum toxin injections. *Arch Ophthalmol* 1985; **103:** 1305-1306.
5. Miller RH, Woodson GE, Jankovic J. Botulinum toxin injection of the vocal fold for spasmodic dysphonia. *Arch Otolaryngol* 1987; **113:** 603-605.
6. Snow BJ, Tsui JKC, Bhatt MH, Varelas M, Hashimoto SA, Calne DB. Treatment of spasticity with botulinum toxin: a double blind study. *Ann Neurol* 1990; **28:** 512-515.
7. Koman LA, Mooney III JF, Smith BP, Goodman A, Mulvaney T. Management of cerebral palsy with botulinum A toxin: Preliminary investigation. *J Pediatr Orthop* 1993; **13:** 489-493.
8. Koman LA, Mooney III JF, Smith BP, Goodman A, Mulvaney T. Management of spasticity in cerebral palsy with botulinum A toxin: report on a preliminary randomized, double blind trial. *J Pediatr Orthop* 1994; **14:** 299-303.
9. Cosgrove AP, Corry IS, Graham HK. Botulinum toxin in the management of the lower limb in cerebral palsy. *Dev Med Child Neurol* 1994; **36:** 386-396.
10. Coffield JA, Considine RV, Simpson LL. The site and mechanism of action of botulinum neurotoxin. In: Jankovic J, Hallet M, eds. *Therapy with Botulinum Toxin.* New York: Marcel Dekker, 1994: 3-13.
11. Borodic GE, Ferrante RJ, Pearce LB, Alderson K. Pharmacology and histology of the therapeutic application of botulinum toxin. In: Jankovic J, Hallet M, eds. *Therapy with Botulinum Toxin.* New York: Marcel Dekker, 1994: 119-157.
12. Wall SA, Chait LA, Temlett JA, Perkins B, Hillen G, Becker P. Botulinum A chemodenervation: a new modality in cerebral palsied hands. *Br J Plast Surg* 1993; **46:** 703-706.

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