Double-blind comparison study of two doses of botulinum toxin A injected into calf muscles in children with hemiplegic cerebral palsy

Frances Polak*, The Movement Laboratory, Derbyshire Royal Infirmary;
Richard Morton, The Ronnie Mac Keith Centre, Derby Children's Hospital;
Christopher Ward, University of Nottingham Division of Rehabilitation and Ageing, Derby City General Hospital, Derby;
W Angus Wallace, University of Nottingham, Queen's Medical Centre, Nottingham, UK.
Leonard Doderlein, Consultant Orthopaedic Surgeon;
Andrea Siebel, The Gait Laboratory, Heidelberg University Hospital, Heidelberg, Germany.

**Correspondence to* Frances Polak, The East Midlands Physiotherapy Clinic, Wyverne House, 107 Ashby Road, Loughborough LE11 3AB, UK.
E-mail: f.polak@empc.co.uk

Despite several trials showing reductions in tone and improvements in gait, the relation between botulinum toxin A (BTX-A) dose and response has rarely been investigated. A double-blind randomized comparison of two doses of BTX-A in children with spastic hemiplegic cerebral palsy (n=48, mean age 7 years 6 months, range 3 to 15 years) was undertaken. The two doses selected were representative of the lower and the higher doses used in clinical practice (24 units/kg body weight and 8 units/kg body weight). Using gait analysis we evaluated hip, knee, and ankle joint kinetics and sagittal kinematics throughout the gait cycle. Gastrocnemius muscle length was calculated at each visit using the method described by Eames and used as our primary outcome measure. Our secondary outcome variable was maximum ankle angle measured during stance and swing phases. In summary, we found that there were indications that 24 units/kg body weight was more effective and lasted longer than 8 units/kg. Analysis in terms of absolute dose suggested that the dose–response correlation was non-linear, and that the optimal range lay between 200 and 500 units BTX-A (Dysport).

Botulinum toxin A (BTX-A) has been used for several years in children with cerebral palsy (CP) with the aim of reducing spasticity, thereby improving function, facilitating physiotherapy, and possibly reducing muscle contractures and the need for surgery (Calderon-Gonzalez et al. 1994, Cosgrove et al. 1994, Koman et al. 1994, Chutorian et al. 1995)

Despite several trials showing reductions in tone and improvements in gait, the relation between BTX-A dose and response has rarely been investigated. One reason for the shortage of dose–response data is that the pharmacokinetics of BTX-A are poorly understood. Following intramuscular injection, the toxin is avidly bound by regional receptors (Moore 1995). If most of the active drug remains within the injected muscle, absolute dose might be a better predictor of response than a dose standardized in terms of body weight.

Lack of evidence on the optimal paediatric dose means that clinicians hesitate to inject large doses into children (Gormley et al. 1997), both on grounds of cost and because of concerns about the development of an immune response with higher and frequent dosages (Tsui et al. 1988). We, therefore, undertook a double-blind randomized comparison of two doses of BTX-A in children with spastic hemiplegic CP. The two doses selected were representative of the lower and the higher doses used in clinical practice (Cosgrove et al. 1994).

Method

PARTICIPANTS

We included children aged 15 years or less, with hemiplegic CP (spasticity largely confined to one side). Participants were recruited over 9 months from hospitals in Derby, Nottingham, Mansfield in the UK, and Heidelberg, Germany. They were ambulant, with gait impairment due primarily to reversible spastic ankle plantar flexion. Exclusion criteria were: BTX-A treatment within the previous year; ankle–foot orthoses supplied within the previous 3 months; and previous surgery to the ankle or calf. We obtained written parental consent, supported by an information sheet, as well as oral consent from the child. Injections and gait analysis were carried out in Derby, Nottingham, and Heidelberg. The protocol was approved by appropriate local research ethics committees.

PROCEDURE

Randomization and study design

Using a parallel group design, children were randomized to receive one of two doses of BTX-A (Dysport, Ipsen): 8 units/kg body weight, and 24 units/kg up to a maximum of 1200 units. The patient and family, as well as those involved in clinical and objective assessments, were blind to treatment status. The physicians who injected the children were not involved in assessment but could not be blind to treatment as volume of injectate varied with dose.

Clinical assessments and gait analysis took place immediately before the first injection and 4, 12, and 24 weeks later (Fig. 1). Questionnaires were completed at each visit.

Physiotherapy treatment programmes were continued unchanged throughout the study. No changes were made in orthoses, except to accommodate growth.

Botulinum toxin injection

The child was sedated with medazolam 0.5 to 0.7mg/kg given orally (UK) rectally (Heidelberg) 20 minutes before the injection, when lignocaine/prilocaine cream was applied to

the calf. BTX-A was dissolved in saline to a concentration of 100 units/mL. Injections were designed to target both gastrocnemius and soleus muscles. The appropriate dose of BTX-A was injected in six equal fractions, using the technique of Cosgrove and Graham (1995) on either side of a reference line originating midway between the medial and lateral malleoli and terminating midway between the medial and lateral femoral epicondyles. Four fractions were given 0.5 to 1cm into the muscle, two at 2cm either side of a point at the lower boundary of the first (proximal) fifth of the reference line and two fractions at points 2cm more distally. At the distal sites a further two fractions were given 1 to 1.5cm into the muscle.

Gait analysis and clinical assessment

We performed the assessments using a Kistler force plate (Kistler Instruments, Switzerland) at each centre, and a six-camera Elite Motion Analysis system (BTS, Milan, Italy; used in Derby), a CODA-3 mpx 30 kinematic scanner (Charnwood Dynamics, Loughborough, UK; used in Nottingham), and a six-camera Vicon system (Oxford Metrics, Oxford, UK; used in Heidelberg). The data from the three systems were judged compatible following interlaboratory reliability studies (Polak and Attfield 1996).

We evaluated hip, knee, and ankle joint kinetics and sagittal kinematics throughout the gait cycle. A minimum of three trials were completed in which the force plate was struck, allowing the mean for each kinematic and kinetic parameter to be calculated. Gastrocnemius muscle length was calculated at each visit using the method described by Eames and coworkers (1999). The model, based on anthropometric data obtained from healthy children, defines the length of the gastrocnemius muscle from origin to insertion, including the musclo-tendonous unit. Muscle lengths were standardized as a percentage of a theoretical length for the individual child in the anatomical position. This process allows direct comparison between children of differing ages and heights, who are growing during the treatment period. Mean gastrocnemius length was calculated for each data point during the three gait cycles. The primary outcome variable was mean maximum gastrocnemius length (maxGL), expressed as a percentage of the theoretical length.

The dynamic component of gastrocnemius muscle shortening was defined as the difference between maximum passive length and maxGL, divided by the passive length (Eames et al. 1999). Fixed contracture was measured as the difference between maximal passive dorsiflexion on the affected side and maximal passive dorsiflexion on the unaffected side.

We used goniometry to measure passive joint angles required for gastrocnemius length calculation, as well as contracture and range of movement at the hips, knees, and ankles. Ankle angles were measured with the subtalar joint locked in inversion and the knee at 90° and at 180°.

At each visit parents completed an adverse events checklist, which included specific symptoms previously reported and related to the pharmacology of BTX-A, and an equal number of filler questions.

Analysis of results

Our primary criterion for successful treatment was an increase in the maximum length attained by gastrocnemius during the gait cycle (maxGL). This was interpreted as a positive treatment response, provided it was not associated with decreased ankle power at toe-off. Our secondary outcome variable was maximum ankle angle measured during stance and swing phases. All statistical tests were two-tailed; significance was accepted at the 5% level.

Due to doubts about the appropriate basis for comparing doses of BTX-A (see above), secondary analysis compared responses in terms of absolute dose, which varied according to body weight.

Results

Table I shows the characteristics of participants. Full data are available on 48 children aged 3 to 15 years (mean age 7 years 6 months). All were assessed at 4 weeks but one withdrew before visit 3 at 12 weeks post injection (see *Adverse effects* section below).

Power did not decrease at toe-off in any child, and increased maxGL was therefore interpreted as a positive treatment response. Compared with baseline, maxGL increased significantly at 4 weeks in both the high-dose (24 units/kg) and the low-dose (8 units/kg) groups. For all the children injected, the mean increase in maxGL at 4 weeks was 0.96 % ($n=48$; $p<0.001$; t-test).

COMPARISON OF TREATMENT GROUPS AT 4 WEEKS POST INJECTION

Compared with baseline, the mean increase at 4 weeks in the low-dose group ($n=23$) was 0.79% ($p<0.01$), and for the high-dose group ($n=25$) was 1.1% ($p<0.01$). However, there

Table I: Characteristics of patients

	High-dose group n=25	*Low-dose group n=23*
Female	10	9
Male	15	14
Mean age at visit 1 (y)	7.5	7.8
Age range at visit 1 (y)	3 to 13	3 to 15

Week:	0	4	12	24
BTX-A injection (8 or 24 units/kg)	■			
Gait analysis	■	■	■	■
Anthropometry and joint angles for gastrocnemius length calculation	■	■	■	■
Passive joint angles	■	■	■	■

Figure 1: *Schedule of injections and assessments*

was no significant difference between the two groups in mean increase of maxGL ($p=0.29$; unpaired t-test).

At 4 weeks in the high-dose group, ankle angle in stance showed significantly greater maximal dorsiflexion in stance ($p<0.001$) and swing ($p<0.05$) than at baseline, but these differences were not seen in the low-dose group ($p>0.05$).

DURATION OF TREATMENT RESPONSE

At 12 weeks following injection, maxGL remained significantly above baseline in the high-dose group ($p<0.05$) but not in the low-dose group. At 24 weeks maxGL did not differ significantly from baseline in either group.

At 12 weeks, there was still significantly greater dorsiflexion in stance in the high-dose group ($p<0.01$) when compared with baseline, but with no difference in dorsiflexion in swing. Neither of these variables was improved at 12 weeks compared with baseline in the low-dose group. At 24 weeks neither group significantly differed from baseline.

ANALYSIS IN TERMS OF ABSOLUTE DOSE

We plotted maxGL change against absolute dose at 4 weeks and at 12 weeks post injection. The plot shown in Figure 2 suggests a peak response in the middle dose range. To test this, we divided children into four quartiles according to absolute dose (quartile 1: 100 to 180 units BTX-A; quartile 2: 181 to 350 units BTX-A; quartile 3: 351 to 500 units BTX-A; quartile 4: >500 units BTX-A). Mean change in maxGL was significantly greater in the second and third quartiles than in the first and fourth quartiles ($p<0.001$, t-test).

ASSESSMENT OF RESPONSE IN TERMS OF SPASTICITY AND CONTRACTURES

For the sample as a whole, the mean dynamic component before injection was 1.78%. There was no correlation between the extent of pretreatment dynamic component (an index of severity of spasticity) and change in maxGL (an index of treatment response). Similarly, we found no correlation between treatment response and the pretreatment extent of passive ankle dorsiflexion, expressed as a percentage of the extent of dorsiflexion measured in the non-hemiplegic ankle.

ADVERSE EFFECTS

The child who received the highest dose (1200 units) was withdrawn from the trial because he fell at school 3 days after injection, and reported mild generalized weakness lasting 4 weeks. Table II shows the reported adverse events and the number of filler questions reported in the adverse event questionnaire.

Discussion

The purpose of this study was to compare the pharmacological effectiveness of two doses of BTX-A. Our outcome criteria were therefore measures of impairment rather than of disability. Measurement of changes in spasticity over time in response to BTX-A is not easy, because of the magnitude and variability of responses in heterogeneous patient groups. We used gait analysis to assess changes in maximum muscle length as the primary outcome, as developed by Eames and coworkers (1999). Our secondary measure was an increase in ankle dorsiflexion in stance and swing; this is less reliable as it depends on variations in simultaneous knee flexion altering the position of origin of gastrocnemius. Nevertheless, this measure has been used satisfactorily by others in BTX-A trials, either by objective gait analysis (Sutherland et al. 1999, Wahl et al. 2000) or by observation (Koman et al. 2000).

Table II: Symptoms reported in adverse events questionnaire 4 weeks following injection

Treatment group	*Filler symptoms*	*Specific symptoms*
High dose	4	6
Low dose	2	6

Three specific symptoms were listed on adverse effects form: pain at injection site, increased difficulty in swallowing, and weakness of the limbs on the 'good side'. All reported specific symptoms were pain at injection site except one child in high-dose group reported generalized weakness in lower limbs. No one reported increased difficulty with swallowing. Filler questions included headache, off food, nausea, dizziness, difficulty sleeping, sore throat.

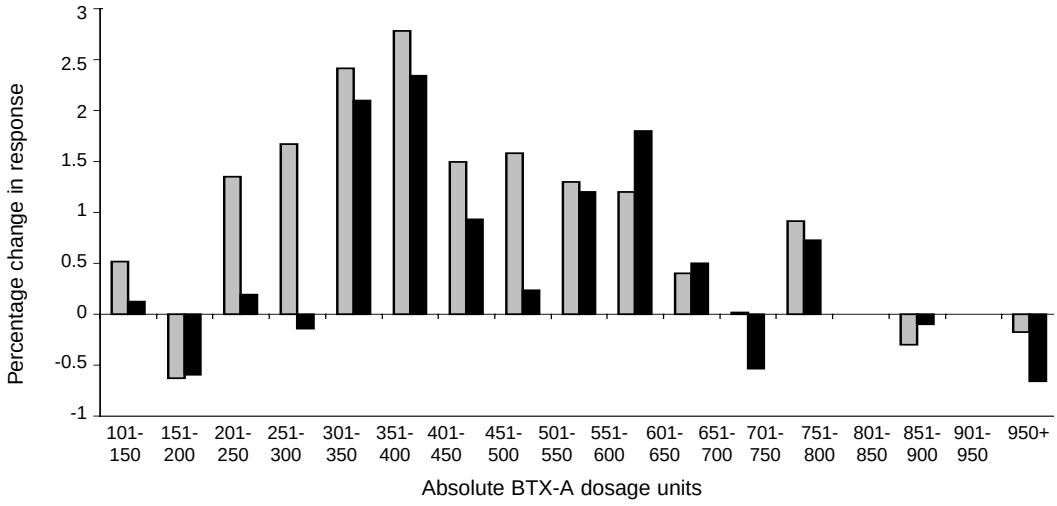

Figure 2: *Plot of absolute dose and response. Cohort groups dosage versus percentage response* ▒ *visit 1 versus 2; and* ■ *visit 1 versus 3.*

We found that BTX-A injections in the spastic gastrocnemius muscles of children with hemiplegia result in significant muscle elongation at 4 weeks in low or high dosage. A mean change in maxGL of 0.96% compares with 1.1% reported by Eames and colleagues (1999), 4 weeks following injection of BTX-A of children with hemiplegia and diplegia. The two doses we compared, 8 and 24 units/kg body weight, were within the range reported to be employed in clinical practice (Calderon-Gonzalez 1994, Cosgrove et al. 1994). Four weeks following injection, there was no significant difference between the two doses in their effect on maximum length of gastrocnemius during the gait cycle (maxGL). However, the higher dose (24 units per/kg) was superior at 4 weeks in its effect on dorsiflexion in swing and stance (high-dose group ankle dorsiflexion in stance $p<0.01$ and ankle dorsiflexion in swing $p<0.05$ compared with baseline). Moreover, significant improvement in maxGL and in dorsiflexion in stance was maintained at 12 weeks in the high-dose group but not in the low-dose group. There was no difference in reporting of adverse events.

Fixed contractures are an important confounding factor in any study of the efficacy of treatment for spasticity. Wissel and coworkers (1999), in finding a better response in children under 7 years of age, suggested that they might have had less contractures. Eames and colleagues (1999) found that the magnitude of response to BTX-A was proportional to a measure of dynamic spasticity. Using the same measure, and also an index of muscle contracture, we found no significant difference between the two treatment groups in terms of the extent of dynamic spasticity or irreversible muscle shortening.

One interpretation of our findings is that 24 units/kg body weight is slightly more effective than 8 units/kg body weight, as there was a significant effect on ankle angle at 4 weeks in the high- but not the low-dose group. There was longer duration of action on both maxGL and ankle angle in the high-dose group with little increase in unwanted effects. However, we found no significant difference in our primary outcome variable (maxGL) between the high-dose and low-dose groups.

There are few published data on the correlation between dose of BTX-A and clinical effects. The situation is further complicated because of uncertainties about the relative potency of two available preparations: Dysport and Botox. No consistent picture has emerged from dose-ranging studies in either children or adults. Wissel and colleagues (1999), comparing high and low doses of Botox to various lower-limb muscles in children with CP, found a better response to the high dose in terms of tone reduction, gait velocity, and stride length. Baker (European Dysport Dose Ranging Study 2000) compared three doses of BTX-A (Dysport) divided between both gastrocnemii in 126 children with diplegia, and found that a total dose of 20 units/kg gave better response at 4 weeks than 10 units or 30 units/kg. There have been two recent dose-ranging studies of Dysport in adults. Bakheit and colleagues (2000) compared three doses in upper-limb spasticity following stroke, and found that the middle dose (1000 units) was superior to the lowest dose (500 units) and as effective as the highest dose (1500 unit). In a comparison of three doses for the treatment of hip adductor spasticity, Hyman and colleagues (2000) found a trend towards greater efficacy with increasing dose, but no statistically significant dose–response correlation was noted.

Previous studies have analyzed dose–response relations in terms of body-weight adjusted doses of BTX-A. Analysis in terms of absolute dose is consistent with the pharmacology of BTX-A. The neurotoxin is known to be rapidly and avidly bound by muscle receptors in the vicinity of injection (Moore 1995), and effective dose may therefore be determined largely by the number of end plates in the target muscle. The number of end plates is constant from birth (Marian 1995), and does not vary with body weight.

We found a peak response in the absolute dose range of 200 to 500 units. A non-linear correlation between dose and response, perhaps due to saturation of motor end plates in the target muscle, could explain the failure to show that the higher dose was significantly more effective than an intermediate dose either in our study or in others (Marian 1995, Bakheit et al. 2000, Hyman et al. 2000). In our study, a fall-off in effectiveness with higher doses could have arisen in two ways. Regional spread of toxin could have caused weakening of tibialis anterior, thereby antagonizing the effect on gastrocnemius length. Regional spread could have been more likely as we chose to use a relatively low concentration (100 units BTX-A/mL), in order to promote distribution of the agent within the injected muscle. An alternative explanation arises from the fact that we targeted soleus as well as gastrocnemius. This was justified by the assumption that soleus makes a major contribution to spastic equinus in children with hemiplegia (Siebal et al. 2000) but it has been suggested that soleus weakness could have allowed excessive ankle dorsiflexion in stance with knee flexion, thus relieving the stretch on gastrocnemius (A Baker, personal communication).

Only one patient, receiving 1200 units, experienced a serious adverse effect. He felt generally weak although his muscle power was not objectively reduced on kinetic assessment at 4 weeks. A multicentre group reporting on dose regimes for Dysport, in which we participated, have recently recommended a maximum dose of BTX-A in children of 30 units/kg body weight, up to a maximum of 1000 units (Bakheit et al. 2001).

In summary, we found that BTX-A treatment was effective in children with hemiplegic CP. There were indications that 24 units/kg body weight was more effective and lasted longer than 8 units/kg. Analysis in terms of absolute dose suggested that the dose–response relation was non-linear, and that the optimal range lay between 200 and 500 units BTX-A (Dysport). This approach to analysis is compatible with what is known about the properties of BTX-A and requires further investigation.

Accepted for publication 6th February 2002.

Acknowledgements

We would like to acknowledge the significant contribution the following made to this work: Mr Steve Attfield, Derbyshire Royal Infirmary, Derby; Dr Lesley Henderson, Queen's Medical Centre, Nottingham; Mr James Hunter, Queen's Medical Centre, Nottingham; Dr D Mexatiosis, Heidelberg University Hospital, Heidelberg; Mr Alan Moulton, King's Mill Centre for Health Care Services, Mansfield, Nottinghamshire; Miss Lisa Phillips, Queen's Medical Centre, Nottingham; Mr Jonathon Starck, Derbyshire Royal Infirmary, Derby; Dr Chris Dott, Ipsen Pharmaceuticals.This research was funded by: NHS R and D Directorate (Trent), Ipsen Pharmaceuticals and Heidelberg Gait laboratory.

References

Baker R, European Dysport Dose Ranging CP Study Group. (2000) Botulinum toxin A (Dysport) for the treatment of dynamic equinus spasticity associated with CP: results of a double-blind, placebo-controlled dose-ranging study *Gait and Posture* **12:** 64–5.

Bakheit AMO, Thilmann AF, Ward AB, Poewe W, Wissel J, Muller J, Benecke R, Collin C, Muller F, Ward CD, Neumann C. (2000) A randomized, double-blind, placebo-controlled, dose-ranging study to compare the efficacy and safety of three doses of botulinum toxin Type A (Dysport) with placebo in upper limb spasticity after stroke. *Stroke* **31:** 2402–6.

Bakheit AMO, Severa S, Cosgrove A, Morton R, Rousso SH, Doderlein L, Lin JP. (2001) The safety profile and efficacy of botulinum toxin type A [Dysport] in children with muscle spasticity. *Developmental Medicine & Child Neurology* **43:** 234–8.

Calderon-Gonzalez R, Calderon-Sepulveda R, Rincon-Reyes M, Garcia-Ramirez J, Mino-Arango E. (1994) Botulinum Toxin A in management of cerebral palsy. *Paediatric Neurology* **10:** 284–8.

Chutorian A, Root L, the BTA Study Group. (1995) A multi-center, randomized, double-blind, placebo-controlled trial of botulinum toxin type A (BTA) in the treatment of lower limb spasticity in pediatric cerebral palsy. *Movement Disorders* **10:** 364. (Abstract).

Cosgrove A P, Corry IS, Graham HK. (1994) Botulinum Toxin in the management of the lower limb in cerebral palsy. *Developmental Medicine & Child Neurology* **36:** 386–96.

Cosgrove AP, Graham HK. (1995) Cerebral palsy. In: Moore AP, editor. *Handbook of Botulinum Toxin Treatment*. Oxford: Blackwell. p 222–47.

Eames NW, Baker R, Hill N, Graham K, Taylor T, Cosgrove A. (1999) The effect of botulinum toxin A on gastrocnemius length: magnitude and duration of response. *Developmental Medicine & Child Neurology* **41:** 226–32.

Gormley ME, Herring GM, Gaebler-Spira DJ. (1997) The use of botulinum toxin in children: a retrospective study of adverse reactions and treatment of idiopathic toe-walking. *European Journal of Neurology* **4** (Suppl. 2)**:** 27–30.

Hyman N, Barnes M, Bhakta B, Cozens A, Bakheit M, Kreczy-Kleedorfer B, Poewe W, Wissel J, Bain P, Glickman S, Sayer A, Richardson A, Dott C. (2000) Botulinum toxin treatment of hip adductor spasticity in multiple sclerosis: a prospective, randomised, double blind, placebo controlled, dose ranging study. *Journal Neurosurgery Psychiatry* **68:** 707–12.

Koman LA, Mooney III J F, Smith BP, Goodman A, Mulvaney T. (1994) Management of spasticity in cerebral palsy with Botulinum A Toxin: report of a preliminary, randomised, double blind trial. *Journal of Pediatric Orthopedics* **14:** 299–303.

Koman LA, Mooney JF, Smith BP, Walker F, Leon JM, (BOTOX Study Group). (2000) Botulinum toxin type A neuromuscular blockade in the treatment of lower extremity spasticity in cerebral palsy: a randomized, double-blind, placebo-controlled trial. *Journal of Pediatric Orthopedics* **20**: 108–15.

Marian MH. (1995) Indications for botulinum toxin injections in children with cerebral palsy. *Botulinum toxin in spasticity; a European forum, Evian, France, 26–28th October, 1995*.

Moore AP. (1995) *Handbook of Botulinum Toxin Treatment.* Oxford: Blackwell.

Polak FJ, Attfield SF. (1996) Compatibility of two 3D kinematic motion analysis systems during simultaneous real time gait acquisition. *Gait and Posture* **4:** 201. (Abstract).

Siebel A, Zeifang F, Metaxiotis D, Pappas A, Doederlein L. (2000) Botulinum toxin A treatment in CP equinus feet – is there a difference between hemiplegic and diplegic children? *Gait and Posture* **7:** 167–8.

Sutherland PH, Kaufman KR, Wyatt MP, Chambers HG, Mubarak SJ. (1999) Double-blind study of botulinum A toxin injections into the gastrocnemius muscle in patients with cerebral palsy. *Gait & Posture* **10:** 1–9.

Tsui JK, Wong NLM, Wong E, Calne DB. (1988) Production of circulating antibodies to Botulinum A Toxin in patients receiving repeated injections for dystonia. Programme and Abstracts. *American Neurological Association* **24:** 219.

Wahl H, Siebel A, Mexatiosis D, Doederlein L. (2000) The use of botulinum toxin in children with spastic equinus: evaluation of side-effects using instrumented gait analysis *Gait and Posture* **12:** 53–4.

Wissel J, Heinen F, Schenkel A, Doll B, Ebersbach G, Muller J, Poewe W. (1999) Botulinum toxin A in the management of spastic gait disorders in children and young adults with cerebral palsy: randomized, double-blind study of "high-dose" versus "low-dose" treatment. *Neuropaediatrics* **30:** 120–4.