Authors:

Areerat Suputtitada, MD

Affiliations:

From the Department of Rehabilitation Medicine, Faculty of Medicine, Chulalongkorn University Hospital, Bangkok, Thailand.

Disclosures:

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Correspondence:

All correspondence and requests for reprints should be addressed to Areerat Suputtitada, MD, Department of Rehabilitation Medicine, Jarern-Somsri Building, Floor 1, Faculty of Medicine, Chulalongkorn University Hospital, Rama IV Road, Putumwan, Bangkok 10330, Thailand.

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Local Botulinum Toxin Type A Injections in the Treatment of Spastic Toes

ABSTRACT

Suputtitada A: Local botulinum toxin type A injections in the treatment of spastic toes. *Am J Phys Med Rehabil* 2002;81:770–775.

Objective: To investigate the efficacy and safety of botulinum toxin type A treatment of spastic toes using varying doses based on the degree of spasticity (Modified Ashworth Scale).

Design: Single-center, open-label, prospective study. Hemiplegic patients with either hitchhiker's great toes (persistent extension of the great toes) or toe flexor spasms with pain during walking were treated with local intramuscular injections of botulinum toxin type A. Initial botulinum toxin type A dose per muscle was 25 units for patients with a baseline Ashworth score of 2, 50 units for a score of 3, and 75 units for a score of 4. Additional botulinum toxin type A injections were allowed if there was an insufficient clinical response to initial treatment. The muscles injected included flexor digitorum, extensor hallucis longus, and/or flexor hallucis longus. All injections were made using electromyographic guidance. Outcome measures were the Modified Ashworth Scale, a visual pain scale, a visual percentage of function scale, and adverse effects.

Results: Twenty patients were enrolled. The dose of botulinum toxin type A used ranged from 25 to 35 units per muscle for an Ashworth score of 2, from 50 to 70 units per muscle for a score of 3, and from 75 to 95 units per muscle for a score of 4. There were improvements in all outcome measures. In most patients, the benefits lasted 5–6 mo, with a few patients exhibiting benefits for ≥2 yr. There were no adverse effects.

Conclusions: Botulinum toxin type A treatment using doses based on spasticity severity seems to be safe and effective in the treatment of spastic toes, and further study is warranted.

Key Words: Botulinum Toxin Type A, Spastic Toes, Modified Ashworth Scale

Persistent extension of the great toe is common in patients with chronic spasticity as a result of stroke or traumatic brain injury. Such patients typically complain of pain at the tip of the great toe and under the first metatarsal head during the stance phase of gait, and they may be unable to wear a shoe. Flexor spasms in the other toes may lead to pain under the tips while walking.

Oral antispastic drugs and physical therapy may not provide sufficiently beneficial results; in addition, oral medications may induce undesirable systemic effects.[1] Injection of alcohol or phenol into the overactive muscles or their supplying nerve may also be beneficial; however, these agents damage sensory and motor nerves and are associated with local tissue necrosis, chronic painful dysesthesia, local muscle transformations, vascular reactions, and severe pain during injection.[2]

Botulinum toxin type A (BTX-A) injections reduce muscle activity by selectively blocking the release of acetylcholine from motor nerve endings[3] and are widely used to treat a variety of conditions characterized by undesirable muscle hyperactivity. BTX-A is not associated with sensory nerve damage or permanent neurolysis and is therefore appropriate for use in situations in which sensation still exists and at least some functional recovery is anticipated.[2]

Although there are several reports of the successful use of BTX-A injections in the treatment of spasticity,[4,5] no study has evaluated BTX-A for the treatment of spastic toes with dosing adjusted for spasticity severity. For reasons of safety and cost, it is best to use the lowest dose that produces the desired clinical effect. Therefore, the objective of this study was to investigate the efficacy and safety of BTX-A treatment of spastic toes using varying doses based on the degree of baseline muscle tone.

Objectives: On completion of this article, the reader should be able to (1) describe how spasticity severity influences the dose of botulinum toxin type A required for a successful clinical response, (2) list appropriate target muscles and starting doses for several different presentations of spastic toes, and (3) describe the degree and time course of improvements (in pain during walking and functional ability) that should be expected after treatment of spastic toes with botulinum toxin.

Level: Advanced.

Accreditation: The Association of Academic Physiatrists is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

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Disclosure: Disclosure statements have been obtained regarding the authors' relationships with financial supporters of this activity. There is no apparent conflict of interests related to the context of participation of the authors of this article.

MATERIALS AND METHODS

Study Design and Subjects. This was a single-center, open-label, prospective study. Hemiplegic patients with spastic toes who visited the Spastic and Dystonia Clinic at King Chulalongkorn Memorial Hospital were enrolled between February 1996 and January 2000. Patients of either sex were included if they had persistent extension of the great toe (in the manner of a positive Babinski response, also called "hitchhiker's great toe"), flexor spasm of the other toes, or flexor spasm of all toes (including the great toe); complained of pain during walking (stance phase) and an inability to wear shoes; and had a spasticity score on the modified Ashworth scale of ≥ 2 for extensor hallucis longus, flexor digitorum longus, and flexor hallucis longus. Eligible patients were also neurologically stable, were capable of independent walking without assistance, had no notable cognitive deficits, and had returned to work or normal activities. All patients had received at least 6 mo of rehabilitation therapy before enrollment in this study.

Patients were excluded from the study if they had fixed contracture of the toes, previous phenol block or surgery for spasticity in the limb to be studied, profound atrophy of the muscles to be injected, known sensitivity to any components of the study medication, active infection at the injection sites, systemic infection, or were currently being treated with aminoglycoside antibiotics or other agents that may interfere with neuromuscular transmission. Patients were followed for 2 yr posttreatment.

This study complied with the Declaration of Helsinki recommendations regarding biomedical research involving human patients. The study design, purpose, and potential risks of participation were discussed with each patient before enrollment.

Study Medication and Treatment. A 100-unit vial of BTX-A (BOTOX®, Allergan, Irvine, CA) was reconstituted with 2 ml of 0.9% sterile unpreserved saline. Patients with a baseline Ashworth score of 2, 3, or 4 received 25 units, 50 units, or 75 units of BTX-A per muscle, respectively. These doses were based on the low, middle, and high end of the consensus spasticity dosing recommendations[6] and my personal clinical experience. For each muscle, the entire dose was injected into a single site. Patients who presented with hitchhiker's great toe were given injections into the extensor hallucis longus muscle. Patients with small toe flexor spasms were

TABLE 1
Patient characteristics and treatment

Patient No.	Age, yr	Sex	Diagnosis	Months Since Neurological Event	BTX-A Dose (units)				Duration of Response to BTX-A[a]
					EHL	FHL	FD	Total	
1	54	M	Stroke	8		50+10	50+10	120	5 mo
2	55	M	Stroke	14		50		50	6 mo
3	50	M	Stroke	13		50+10		60	5 mo
4	28	M	TBI	12	75+10+10		75+10	180	≥2 yr
5	62	M	Stroke	18			50	50	6 mo
6	50	M	TBI	9	50		50	100	6 mo
7	32	M	TBI	12	75+10+10		75	170	6 mo
8	55	M	Stroke	10			25	25	6 mo
9	58	F	Stroke	11		75	75	150	≥2 yr
10	60	F	Stroke	7		50+10	50+10	120	≥2 yr
11	56	F	Stroke	8		50	50	100	5 mo
12	58	F	TBI	9	50+10+10			70	4 mo
13	44	F	TBI	8	75		75	150	6 mo
14	50	F	Stroke	10		25+10+10	25	70	6 mo
15	54	F	Stroke	11			50	50	6 mo
16	55	F	TBI	6			50	50	≥2 yr
17	47	F	Stroke	7			50	50	6 mo
18	48	F	Stroke	7			25	25	6 mo
19	50	F	Stroke	8	75		75	150	6 mo
20	52	F	Stroke	8		75+10+10	75	170	≥2 yr

BTX-A, botulinum toxin type A; EHL, extensor hallucis longus; FHL, flexor hallucis longus; FD, flexor digitorum; +, an additional dose given because of inadequate response with previous dose; TBI, traumatic brain injury.

[a]Duration is defined as the time to return to baseline Ashworth Score.

given injections into the flexor digitorum longus muscle. Patients with great toe flexor spasm were given an injection into the flexor hallucis longus muscle.

A 27-gauge Teflon-coated combination electromyographic electrode/injection needle (BOTOX Injection Needle, Allergan) was used both to locate the optimum injection site within each muscle and to inject the toxin. The choice of injection site was also guided by anatomic knowledge of the location of the motor endplate for each muscle. The injections followed the application of EMLA cream (Astra, Westborough, MA), a lidocaine-based local anesthetic. After injection, all patients received rehabilitation therapy that consisted of stretching exercises in warm water every day.

Patients were evaluated 2 wk after injection, and a decision was then made whether to administer an additional 10 units of BTX-A based on the degree of tone reduction and functional response. If an additional injection was given, the patient was reexamined 2 wk later.

Outcome Measures. Active and passive muscle tone were rated using the Modified Ashworth Scale (0 = no increase in muscle tone to 4 = affected part rigid in flexion or extension). Patients rated pain during the stance phase of gait using a visual analog scale (0 = no pain to 100 = maximum pain) in answer to the question "How severe is the pain in your toes during walking?" Functional ability was rated by the patient as a percentage of normal function by using a visual scale ranging from 0% (no function) to 100% (normal function).

The same physician evaluated all patients at baseline, 2 wk, and 4 wk posttreatment and every month thereafter until their Ashworth scores returned to baseline. For most patients, an evaluation was also performed by a third-year resident in the clinic. The results obtained by the two observers were the same, although no formal interobserver reliability testing was performed. Descriptive statistics were used to report patient demographics and efficacy results; tests of significance were not performed due to small sample sizes. Adverse events were evaluated based on spontaneous patient reports.

RESULTS

Patient Population and Dosage. Twenty patients (mean age, 50 ± 4 yr; range, 28–62 yr) were enrolled in the study. In 14 patients, spasticity was secondary to stroke, and in six patients, it was secondary to traumatic brain injury. The duration of brain lesions ranged from 6 to 18 mo

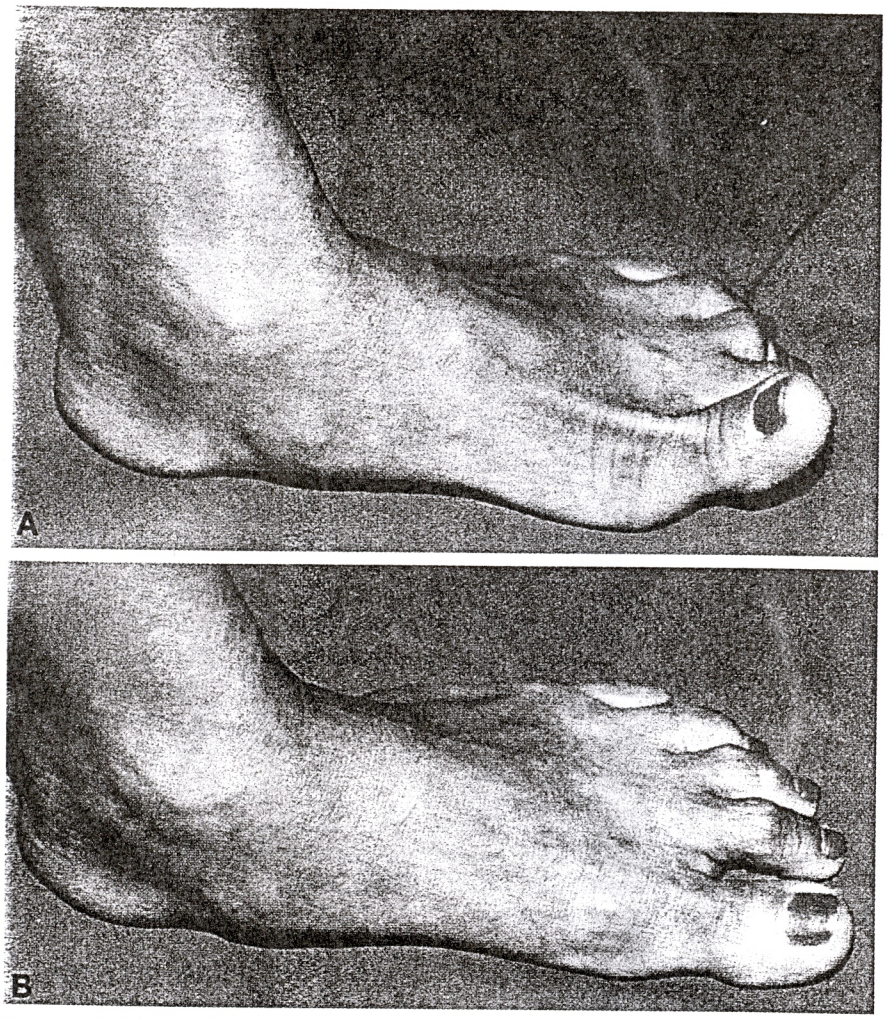

Figure 1: Patient photographs before (*A*) and after (*B*) treatment with botulinum toxin type A. The patient was treated with 75 units of botulinum toxin type A injected into the extensor hallucis longus and 25 units injected into the flexor digitorum.

at the time of study enrollment (Table 1). Of the 20 patients enrolled, three had a baseline Ashworth score of 2, 11 had a score of 3, and six had a score of 4.

The total dose of BTX-A required for a successful response ranged from 50 to 95 units for extensor hallucis longus, 45 to 95 units for flexor hallucis longus, and 25 to 85 units for flexor digitorum (Table 1). Doses varied according to baseline spasticity severity. For patients with a baseline Ashworth score of 2, the dose ranged from 25 to 35 units per muscle (average: 45 units for flexor hallucis longus and 25 units for flexor digitorum). For patients with a baseline Ashworth score of 3, the dose ranged from 50 to 70 units per muscle (average: 60 units for extensor hallucis longus, 56 units for flexor hallucis longus, and 53 units for flexor digitorum). For patients with a baseline Ashworth score of 4, the dose ranged from 75 to 95 units per muscle (average: 85 units for extensor hallucis longus, 85 units for flexor hallucis longus, and 77 units for flexor digitorum). Eight of the 20 patients required additional injections to achieve the desired clinical benefit: one of three patients (33%) with a baseline Ashworth score of 2, 4 of 11 patients (36%) with a score of 3, and three of six patients (50%) with a score of 4.

Efficacy and Safety Findings. An example of a patient with spastic toes before and after BTX-A treatment is shown in Figure 1. Mean Ashworth scores dropped within 2 wk of treatment, approached 0 at week 8, and gradually increased throughout the 6-mo study period (Fig. 2). For the majority of patients (16 of 20, 80%), Ashworth scores did not return to baseline until at least 6 mo posttreatment (Table 1). Five of these patients exhibited beneficial effects for >2 yr after treatment. One patient returned to baseline spasticity levels at month 4, and three patients returned to baseline at month 5.

Mean visual analog pain scores also decreased during the first 4 wk after treatment (Fig. 3). Mean pain scores were 0 at week 8 and remained below 10 through week 16. At the end

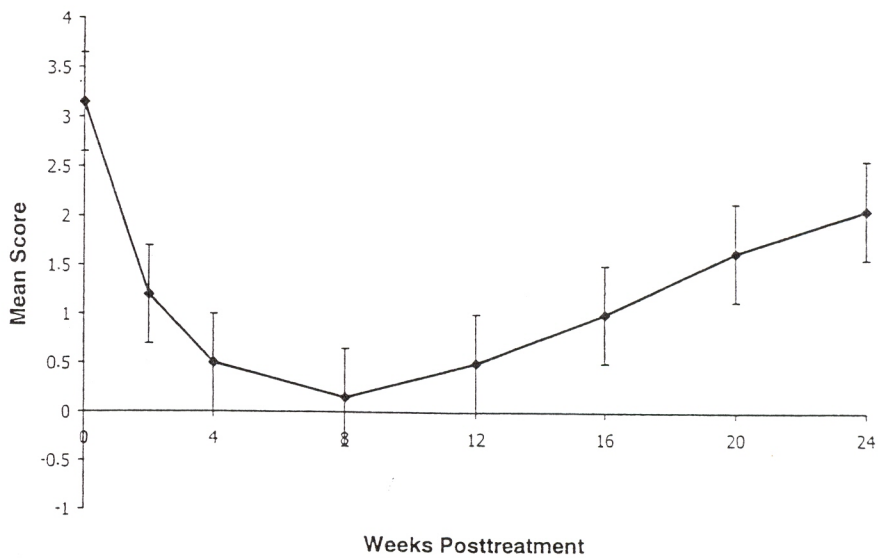

Figure 2: Effect of botulinum toxin type A on mean Modified Ashworth scores. Note the rapid and prolonged decrease in muscle tone.

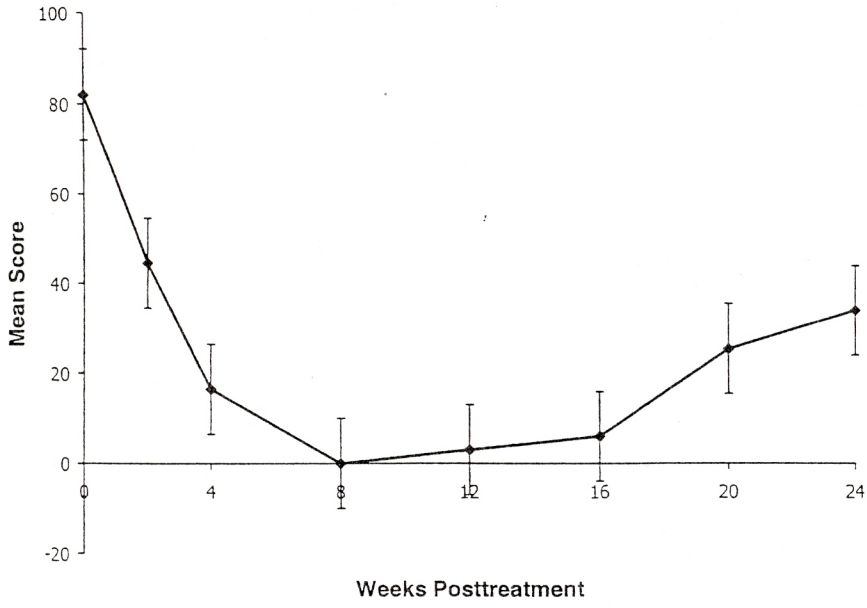

Figure 3: Effect of botulinum toxin type A on pain during walking. Pain was rated by the patient using a visual analog pain scale ranging from 0 to 100.

of the 6-mo study period, the mean pain score was still less than half of that at baseline. Mean functional ability increased during the first 4 wk posttreatment, reached 100% at week 8, and remained above 60% throughout the study period (Fig. 4). No adverse events were reported.

DISCUSSION

Results of this preliminary study suggest that treatment of spastic toes with BTX-A using doses adjusted for baseline Ashworth scores is a promising therapy. The treatment was safe and provided long-lasting improvements in spasticity, pain during walking, and functional ability for most patients. However, almost half of patients required additional injections to achieve the desired clinical benefit. Consequently, the doses required for efficacy were somewhat higher than the 25, 50, and 75 units BTX-A per muscle called for in the protocol for patients with baseline Ashworth scores of 2, 3, and 4, respectively. This suggests that the dosing paradigm employed in this study may need to be adjusted to use slightly higher initial doses. Because of the high cost of BTX-A and general safety concerns, it is always desirable to use the lowest dose that gives the desired clinical benefit. Thus, a larger, double-blind, randomized clinical trial is needed to further explore dosing issues.

In the present study, small additional injections were allowed 2 wk after the initial treatment if the initial dose did not provide the desired clinical benefit. Such additional injections are not recommended (because frequent injections can promote antibody formation) and are not part of my normal clinical practice. They were allowed as part of this study because the key objective of the study was to evaluate the lowest effective BTX-A dose for the treatment of this condition, and it was anticipated that the initial dose might be too low for some patients. In addition, the small doses used here were unlikely to put the patients at significant risk of antibody formation.

The majority of patients experienced reductions in spasticity, pain, and functional disability within a few weeks of treatment. No patients returned to baseline spasticity scores before 4 mo posttreatment, and most experienced benefits for 5–6 mo or longer. The duration of effect reported in this study is at the high end of the 2–6 mo range commonly reported for BTX-A therapy.[4,7,8] Five of these patients still exhibited beneficial effects >2 yr after treatment. This may be the result of both the effects of the rehabilitation therapy after injection and the improvement that can be experienced by brain injury patients and stroke patients over a long period of time.

The success of BTX-A treatment

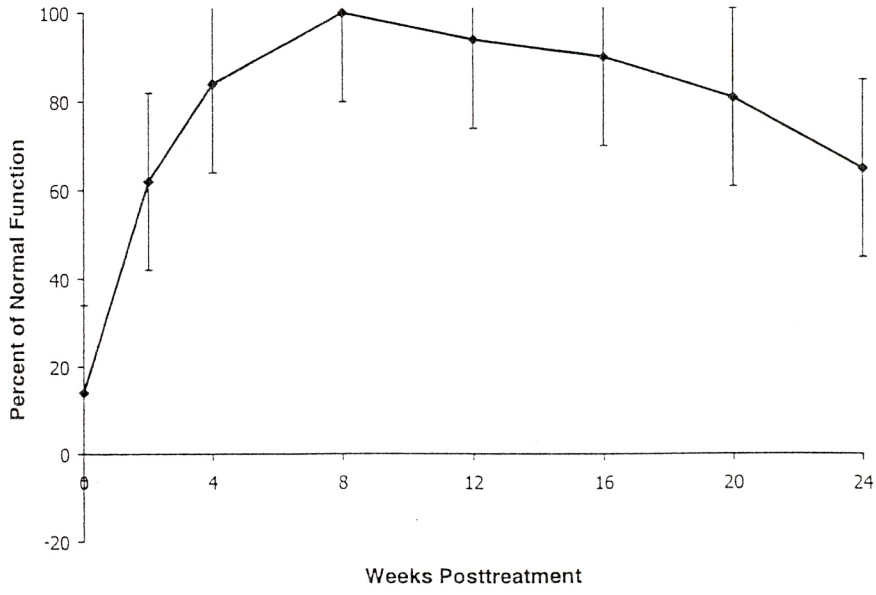

Figure 4: Effect of botulinum toxin type A on functional ability, which was rated by the patient as a percentage of normal function.

in relieving the signs and symptoms of spastic toes adds further support to the expanding literature on the usefulness of BTX-A in treating spasticity resulting from stroke,[4,7] traumatic brain injury,[8] and cerebral palsy in children.[9] In many cases, BTX-A treatment also decreases pain. It is my personal observation that patients receive greater benefit from their physical therapy regimen once their spasticity has been reduced by BTX-A. The lack of any significant adverse effect is also typical of BTX-A treatment.

Spasticity can be a significant functional problem in the management of patients with upper motor neuron lesions. The mainstay of conventional treatment for limb spasticity consists of systemic medication combined with physiotherapy. However, systemic antispastic medication may cause drowsiness and unwanted generalized muscle weakness,[1] which may further increase disability by destabilizing the patient during standing and walking. Although local treatments such as phenolic nerve and motor point blocks avoid these systemic effects, they may cause dysesthesia and local tissue necrosis.[2] Consequently, these treatments are currently not recommended for spasticity in situations in which sensation is preserved and at least some functional recovery is possible.[2]

Intramuscular BTX-A injection offers the benefit of local treatment of spasticity and selective action on motor nerves. In the present study, BTX-A treatment produced long-lasting decreases in spasticity, pain, and functional disability in patients with spastic toes, without any significant adverse effects. In conclusion, the present study has shown that BTX-A treatment using doses adjusted for spasticity severity seems to be a safe and effective treatment for spastic toes, although optimal dosing has yet to be determined.

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Self-Assessment Exam Questions

CME Article Number 10: *A. Suputtitada, et al.*

1. In the treatment of spastic toes, the dose of botulinum toxin required for a successful response ranged from:
   A. 5 to 25 units per muscle.
   B. 25 to 95 units per muscle.
   C. 95 to 100 units per muscle.
   D. 150 to 300 units per muscle.

2. In this study, one factor that determined the amount of botulinum toxin required for a successful response was:
   A. The duration of spasticity.
   B. The etiology of spasticity, stroke *vs.* traumatic brain injury.
   C. The degree of initial spasticity (on the Ashworth scale).
   D. Patient age.

3. Mean improvements in muscle tone, pain, and functional ability scores after botulinum toxin injection were maximum at:
   A. 8 weeks.
   B. 8 days.
   C. 8 months.
   D. 8 hours.

4. Twenty-four weeks after treatment with botulinum toxin functional ability
   A. Was worse than pretreatment levels.
   B. Returned to pretreatment levels.
   C. Remained at peak level response.
   D. Remained above 60% improvement.

5. In this study, the duration of response to botulinum toxin treatment for spastic toes ranged from
   A. 1 to 2 months.
   B. 2 to 3 months.
   C. 3 to 5 months.
   D. 5 months to more than 2 years.