Spinal Cord (1997) 35, 171–175

Effectiveness of gabapentin in controlling spasticity: a quantitative study

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The purpose of this investigation was to study the effectiveness of gabapentin in controlling spasticity in persons with spinal cord injury (SCI) using a surface EMG-based quantitative assessment technique called the brain motor control assessment (BMCA). Six men from a Veterans Affairs Medical Center with spasticity due to traumatic SCI were studied as part of a multi-center, placebo-controlled, cross-over, clinical trial of gabapentin. Spasticity was evaluated using multi-channel surface EMG recordings of muscles in the lower extremities, abdomen and low back before and during treatment with oral gabapentin or placebo. Gabapentin or placebo was given orally in doses 400 mg three times daily for 48 h. Following a 10 day wash-out period subjects were crossed-over to receive the medication not received the first time. This was followed by an elective open-label extension. Group results during the controlled trial did not reach statistical significance at the dosage used. One subject demonstrated a dramatic improvement in spasticity that was apparent both clinically and with the BMCA. Other subjects demonstrated modest improvements which were seen in the BMCA but not recognized clinically. During the open label extension, the four subjects who participated experienced important clinical improvements with higher doses (to 3600 mg/day). These improvements were often in components of spasticity in which the BMCA had detected subclinical changes during the cross-over trial. A seventh subject was studied using the BMCA at doses of 1200 mg T.I.D. gabapentin, off gabapentin and 800 mg T.I.D. gabapentin and demonstrated quantitatively a dose-related effect with higher doses of gabapentin which matched clinical observations. Gabapentin at doses of 400 mg T.I.D. may be effective in controlling some features of spasticity in persons with SCI. Higher doses provide greater control of spasticity, and controlled studies using higher doses are needed to evaluate gabapentin's efficacy.

Keywords: surface electromyography; spasticity; gabapentin; Neurontin; spinal cord injury; assessment

Introduction

Spasticity and altered motor control due to upper motor neuron dysfunction are frequent and potentially function-limiting complications of spinal cord injury (SCI). Spasticity can interfere with functional mobility, activities of daily living, hygiene, sleep and quality of life. Current conventional treatments available for spasticity are often only partially effective and frequently lead to undesirable side effects at therapeutic doses.[1]

Currently there are no readily available objective, reproducible and quantitative methods for assessing spasticity.[2] We have developed a surface electromyographic (sEMG) based assessment technique for quantifying spasticity in the lower extremities of persons with SCI.[3] This technique allows a sensitive, reproducible[4] and objective measurement of the voluntary and involuntary motor activity produced during a standardized clinical examination protocol. This technique also allows a comprehensive assessment of all components of spasticity including spontaneous spasms during rest, overflow activity during reinforcement maneuvers, voluntary activity, tonic and phasic stretch reflexes, clonus, and response to plantar stimulation. Surface EMG recordings, which may be sensitive to changes not detected during the standard clinical examination, are useful for both qualitative and quantitative analysis of spasticity in this population.

Gabapentin (Neurontin), an anticonvulsant medication with chemical structure similar to gamma-amino butyric acid (GABA), but with no identified GABA receptor activity, has been anecdotally reported by one of the authors (WHO) to have antispasticity effects for

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persons with SCI and multiple sclerosis. Use of gabapentin has been reported at doses up to 3600 mg/day in studies of epilepsy.[5] The purpose of this study is to demonstrate the effectiveness of gabapentin in controlling spasticity in persons with SCI using a surface EMG-based quantitative assessment technique.

Methods and materials

Subjects

As part of a multicenter double blind, placebo controlled clinical trial of gabapentin for spasticity management in persons with SCI, six men were recruited to participate in the quantitative assessment component of the study. One additional subject was recruited after the placebo controlled trial was completed and his data is also included in this report. Subjects ranged in age from 33 to 59 years and duration of injury from 1 month to 22 years. Levels of injury ranged from C5 to T5 and degree of completeness from ASIA Impairment Scale A to D.[6] Five of the six were taking oral medication (baclofen, diazepam, and/or dantrolene sodium) for their spasticity at the time of the cross-over study. Medications were not adjusted during the trial period. Subject 2 already had severe spasticity at 1 month post-injury. He had not yet been started on other spasticity medications at the time of the trial.

Methods

After obtaining informed consent under a protocol approved by the Institutional Review Board all subjects underwent a baseline recording of their spasticity using the brain motor control assessment (BMCA), a quantitative neurophysiological evaluation of spasticity and altered motor control using sEMG recordings.

The BMCA testing methods have been extensively described elsewhere[3] but salient points are repeated here. Pairs of recessed, silver-silver chloride surface electrodes were placed with 3 cm spacing along the mid-line of the muscle bellies of the quadriceps, hamstrings, adductors, tibialis anterior and triceps surae muscles of each leg with additional pairs placed symmetrically about the mid-line over abdominal muscles at the level of the umbilicus and lumbar paraspinal muscles. The skin was lightly abraded to obtain a pair-wise electrode impedance less than 5 K Ohms. EMG signals were amplified using Grass 12A5 amplifiers (Grass Instruments, PO Box 9171 Quincy, Massachusetts 02269-9171) with a gain of 5000 and a bandwidth of 50 Hz to 800 Hz (-3 db) and were digitized at 1800 samples per second per channel with 12 bit accuracy using the AT CODAS (Dataq Instruments Inc., 150 Springside Dr., Suite B220, Akron, Ohio 44333). After calibration, data were continuously recorded for the approximately 1 h required for the electrophysiological data collection while the subject maintained a supine position on a comfortable examination table.

Data were collected in strict accordance with a protocol examination, beginning with 5 minutes relaxation followed by reinforcement maneuvers, voluntary maneuvers, passive maneuvers, tendon taps, clonus, application of vibration and finally plantar stimulation. Each maneuver was repeated three times, with the exception of tendon taps which were repeated 10 times, and vibration which was sustained for 30 s at each site but not repeated. Passive maneuvers for each side consisted of hip and knee flexion together, followed by ankle dorsi- and plantar flexion. Each phase of each maneuver was held for a minimum of 5 s. Tendon taps were applied using a hammer equipped with a piezoelectric crystal to record timing of the taps over adductor, patellar and Achilles tendons on each side. As many as 25 to 30 taps were applied if no response was observed. For purposes of analysis, the largest 10 responses were used. Clonus was manually elicited by rapid, forceful patellar displacement or by rapid ankle dorsiflexion.

After baseline assessments, subjects were begun on either gabapentin, 400 mg orally three times a day (T.I.D.), or an identically appearing placebo capsule

Table 1 Subject data

Subject number	*Age*	*Motor level*	*ASIA impariment scale*	*Duration of injury*	*Medications* (total per day)
1	56	C5	A	22 years	diazepam 30 mg baclofen 100 mg
2	59	C5	C	1 month	none
3	33	C5	A	13 years	baclofen 160 mg
4	51	C6	B	4 years	baclofen 30 mg
5	47	C7	D	4 years	diazepam 30 mg baclofen 120 mg dantrolene 150 mg
6	46	T5	A	8 years	diazepam 15 mg
7	48	C6	B	3 years	diazepam 80 mg baclofen 130 mg

T.I.D. Subjects, their physicians and the BMCA technicians did not know whether the medication being taken was active of placebo. The BMCA was repeated 48 h after beginning the trial medication. After a washout period of at least 10 days the procedure was repeated.

After the cross-over trial, subjects were given the opportunity to continue on gabapentin. Follow-up assessments were done using descriptions of self-reported improvement obtained during physician interview and routine clinical examination.

One subject, not included in the cross-over trial, was studied using the BMCA at doses of gabapentin of 1200 mg T.I.D., after tapering off gabapentin, and 800 mg T.I.D. respectively to demonstrate a dose-response effect of gabapentin.

Data analysis

BMCA data from these subjects were compared to a normative database of 52 SCI subjects with repeated studies. From the normative database a standard score (Z-score) was computed for each of the current study subjects to indicate change from base line activity as the ratio of sEMG scores from the pairs of studies. The direction of change is indicated by the sign of the Z-score (a negative number indicates reduced activity, i.e., reduced spasticity) and the magnitude of change is indicated by the distance from 0. Z-scores greater than 1.96 indicate a significant change from baseline. Z-scores were computed for relaxation, reinforcement and passive maneuvers, tendon taps and plantar stimulation for both active and placebo trials. Additionally, the Z-scores for both placebo and active medication were entered as dependent variables in a multi-variate analysis of variance.

Results

Cross-over trial

All six subjects completed the cross-over trial with complete BMCA data and had Z-scores calculated. A summary of these results is shown in Table 2, which is an enumeration of BMCA scores for the six subjects and five maneuvers which increased significantly (Z-score >1.96), decreased significantly (Z-score <-1.96) or no change ($-1.96<$Z-score$<+1.96$). As can be seen, most of the maneuvers (19 of 30) did not change significantly for either placebo or active medication. MANOVA analysis did not reveal any statistically significant differences between the gabapentin and placebo groups or interactions.

While on gabapentin at the dosage used for this study only one subject demonstrated a clinically apparent and functionally important improvement in his spasticity. This subject (subject 3) had spasticity characterized by the presence of severe phasic spasms and clonus provoked by mechanical stimulation. During the active arm of the trial he demonstrated a decrease in spontaneous activity during relaxation ($Z=-2.5$), a decrease in activity during passive stretch maneuvers ($Z=-5.2$; Figure 1), a decrease in tendon tap activity ($Z=-2.9$), and a decrease in response to plantar stimulation ($Z=-3.0$). His clonus at baseline was eliminated completely, which occurred with ($P<0.02$) in the normative database. While on placebo he also showed a decrease during tendon taps ($Z=-3.0$) and plantar stimulation ($Z=-2.5$).

This subject also reported a dramatic improvement in his spasticity while on gabapentin, but not on placebo. Gabapentin decreased his sensitivity to mechanically provoked spasms. Three subjects reported subjective improvement while on gabapentin,

Table 2 Contingency table of Z-scores

	Placebo			
	Increase	*No change*	*Decrease*	*Sub-total*
Active medication				
increase	0	1	1	2
no change	2	13	4	19
decrease	1	5	3	9
sub-total	3	19	8	

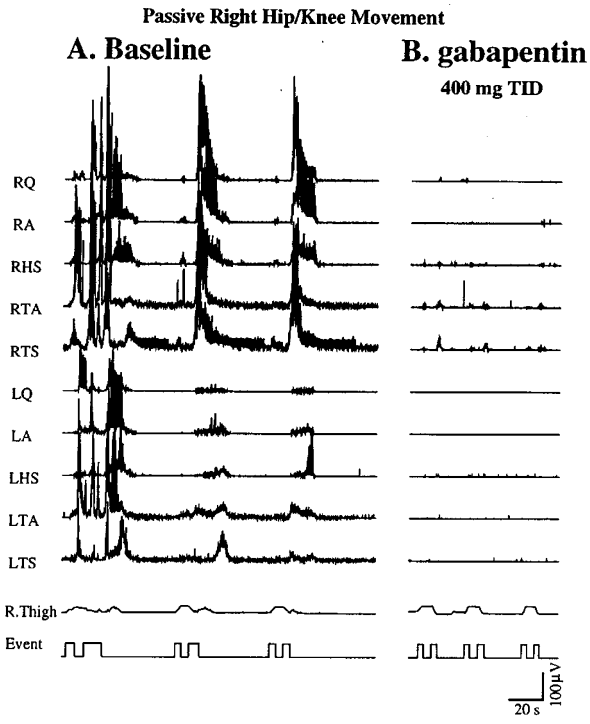

Figure 1 Passive hip/knee movement. Shown in this figure are three repetitions of passive movement of the right hip and knee. Channels display the root mean square (RMS) envelope of EMG activity from quadriceps (Q), adductors (A), hamstrings (HS), tibialis anterior (TA) and triceps surae (TS) for the right (R) and left (L) sides. (a) Maneuvers done at baseline, without medication. (b) Maneuvers done after 2 days on gabapentin at a dose of 400 mg T.I.D.

one reported improvement on both active and placebo and one reported worsening of spasticity while on gabapentin and one reported no change with either medication.

Open-label extension

Subjects were subsequently offered the opportunity to resume gabapentin. The four subjects who chose to do so were titrated to higher doses of gabapentin. *Subject 1* was titrated to 1200 mg four times a day. He achieved sufficient relief of his spasticity to avoid a destructive neurosurgical procedure that had been recommended previously. For *subject 2*, baclofen and diazepam were subsequently tried in the absence of gabapentin which resulted in minimal clinical improvement in his spasticity. Gabapentin was later added to this regimen and titrated to doses of 1200 mg T.I.D. He demonstrated marked improvement in the overflow activity seen with arm movement. This effect was observed in the BMCA results during the cross-over trial (Figure 2), but was not recognized clinically at the lower doses. The higher dose response observed (Figure 2c) was not evident with baclofen and diazepam alone, before adding 1200 mg gabapentin T.I.D. *Subject 3* had a very robust effect with gabapentin at low doses (Figure 1) and elected to continue on the medication after the clinical trial. The most functionally important improvement he reported was an increase in the stimulation required to provoke his spasms. This greatly improved his comfort and positioning in his wheelchair. He was later titrated to 800 mg T.I.D. with even greater control of his provoked spasms and was able to decrease his baclofen from 160 mg to 120 mg per day. *Subject 5* was subsequently titrated to 1200 mg T.I.D. with excellent clinical responses in all components of his spasticity. This allowed him to ambulate more effectively and safely, and he has been able to decrease use of diazepam without experiencing an increase in spasticity while on gabapentin. *Subject 4* had mild spasticity without functional interference, and felt no need to resume taking gabapentin. *Subject 6* reported a worsening of spasticity while on gabapentin and did not choose to continue the medication.

Case study

Although not available for the cross-over trial, subject 7 was treated with 1200 mg gabapentin T.I.D. for spasticity after the trial. He requested to be withdrawn from the medication because he believed it was providing little or no benefit. Prior to his withdrawal he was studied with the BMCA protocol. He was then tapered off gabapentin leaving his other spasticity medications unchanged, with a consequent, marked increase in spasticity. A second BMCA study was performed. He then requested to be restarted. After increasing the dose to 800 mg T.I.D. a third BMCA study was performed. His dose was then returned to

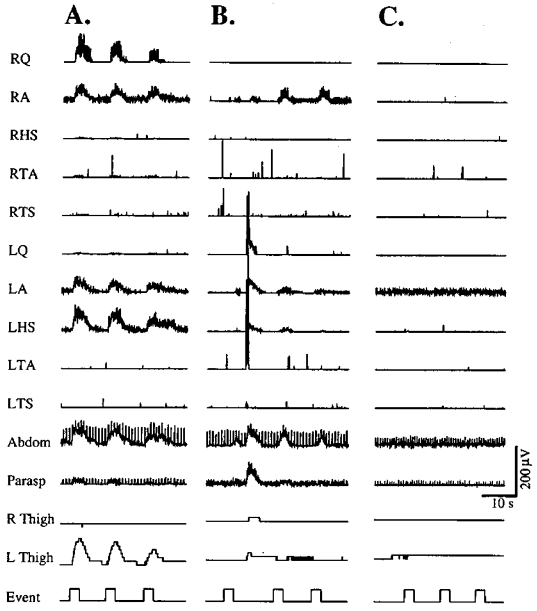

Figure 2 Reinforcement maneuvers. In this figure, the responses to efforts with non-paralyzed upper extremities, here left elbow flexion against resistance, are shown for the same channels as in Figure 1. (a) No medications. (b) 400 mg T.I.D. gabapentin. (c) 1200 mg T.I.D. gabapentin, 30 mg Q.I.D. baclofen, 10 mg Q.I.D. diazepam

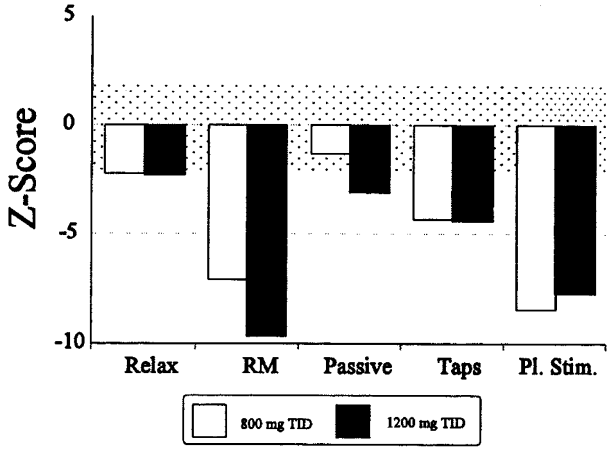

Figure 3 Summary of responses to two medication levels. In this figure are shown Z-scores for changes in sEMG activity during relaxation (Relax), reinforcement maneuvers (RM), passive maneuvers (Passive), tendon taps (Taps) and plantar stimulation (PI.Stim). Scores are calculated as the ratio of average sEMG activity from corresponding elements on studies with (numerator) and without (denominator) the indicated dose of gabapentin, transformed into a Z-score domain using normative data from a group of 52 SCI subjects compared on repeated baseline studies. The shaded area is the 95% confidence limits (± 1.96) for random changes

1200 mg T.I.D. At both 800 mg and 1200 mg T.I.D. doses he reported improvement in spasticity which was evident on clinical and BMCA examinations. His Z-scores documenting the effects of 800 mg T.I.D. and 1200 mg T.I.D. compared to his spasticity without gabapentin are summarized in Figure 3. The graph clearly illustrates the clinically apparent therapeutic effect on all five maneuvers, and is suggestive of a dose-related response as well.

Discussion

The doses chosen for the controlled clinical trial were too low to fully demonstrate the potential of gabapentin to produce clinical and functional improvements in spasticity in most subjects. Although the cross-over trial failed to demonstrate a statistically significant improvement in the group, one of the subjects had a clinically apparent and functionally important improvement on the study dose. In the open label extension, all subjects who were titrated up to as much as 3600 mg gabapentin daily had clinically important improvement in their spasticity. This experience with gabapentin has shown us that these higher doses are generally well tolerated and provide clinical and functional improvements to the patient. This was demonstrated quantitatively in Subject 7 (Figure 3). These cases illustrate the potential usefulness of gabapentin in spasticity management in combination with other antispasticity medication.

Higher doses resulted in greater clinical improvement in spasticity, often in components of spasticity where the BMCA had detected a change at a lower dose that was not clinically apparent. This illustrates one of the strengths of the BMCA – its ability to systematically document subclinical changes with interventions. These changes may have the potential for major clinical and functional importance if properly identified and maximized.

Using the BMCA we were able to quantify the changes seen with administration of both active and placebo medication and compare them with baseline recordings. This technique provides a quantitative assessment tool that can be used to document clinical changes during interventions.

Conclusions

At doses of 400 mg T.I.D., gabapentin appears to be effective in improving spasticity in some persons with SCI. However, only one subject in our cross-over trial at this dosage had clinical improvement in his spasticity. All five subjects tested open label at doses up to 1200 mg T.I.D. had reduced spasticity clinically. To validate these findings and to determine long-term efficacy and side-effects, further studies are needed.

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