Effect of Antispastic Drugs on Motor Reflexes and Voluntary Muscle Contraction in Incomplete Spinal Cord Injury

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Abstract

Objective: To investigate the effects of antispastic drugs baclofen and tizanidine on reflexes and volitional tasks.

Design: Double-blind, placebo-controlled, crossover, before-after trial, pilot study.

Setting: Research laboratory in a rehabilitation hospital.

Participants: Men with chronic (>6mo) motor incomplete spinal cord injury (N=10) were recruited for the study.

Interventions: Tizanidine, baclofen, and placebo were tested in this study. Agents were tested in separate experimental sessions separated by >1 week.

Main Outcome Measures: Reflex and strength were measured before and after the administration of a single dose of each intervention agent. Electromyographic and joint torque data were collected during assessments of plantar flexor stretch reflexes, maximum contraction during motor-assisted isokinetic movements, and maximum isometric knee extension and flexion.

Results: Reduced stretch reflex activity was observed after the administration of either tizanidine or baclofen. We observed that tizanidine had a stronger inhibitory effect on knee extensors and plantar flexors whereas baclofen had a stronger inhibitory effect on the knee flexors. The effects of these drugs on strength during isometric and isokinetic tasks varied across participants, without a consistent reduction in torque output despite decreased electromyographic activity.

Conclusions: These results suggest that antispastic drugs are effective in reducing stretch reflexes without substantially reducing volitional torque. Differential effects of tizanidine and baclofen on reflexes of flexors and extensors warrant further investigation into patient-specific management of antispastic drugs.
The effects of antispastic drugs on spinal reflexes and volitional muscle activity were assessed using a double-blinded, placebo-controlled design. Snake anterior or thoracic SCI. The purpose limb, or if grade C (4 as American Spinal Injury Association Impairment Scale as grade D (4 American Spinal Injury Association Impairment Scale grade C) and demonstrating intact flexor and stretch reflexes after cervical or thoracic SCI. The more spastic limb, or if equivalent, the right limb, was tested. All participants did not use antispastic medications for >14 days before the start of the study, verified by checking a self-report of recent medication history.

Pharmacological administration

Reflex and volitional activity was tested before and after the administration of 10mg placebo, 30mg baclofen, or 4mg tizanidine. These dosages for baclofen and tizanidine are common for single doses prescribed to patients with SCI. The placebo used in the study was an inert substance, microcrystalline cellulose. Pharmacological agents were prepared and randomized by a licensed pharmacist, overencapsulated, and coded to ensure blinding of the researcher and subject. Following initial assessments, patients were administered an agent and retested with the entire protocol after 90 to 120 minutes, equivalent to the mean half-life of either test agent (baclofen18,20 or tizanidine15,27,28). Pre- and postdrug assessments were performed at approximately the same time in the morning and afternoon for each individual subject. The participants were instructed to refrain from eating at least 2 hours before arrival at the test site to normalize drug absorption and distribution rates. Adverse effects of the drugs are reported in table 2.

Experimental setup

Participants were seated in an adjustable chair with their trunk stabilized with straps, and the test leg was secured to a footplate or a knee brace (depending on the test) mounted on a multiaxis load cell attached to an isokinetic dynamometer (Biodex Rehabilitation System 3) (fig 1). A multiaxis load cell had higher resolution and better accuracy was used to collect the data instead of the built-in load cell in the Biodex system. Torque signals from the load cell were low-pass filtered at 200Hz, and acquired at 1000Hz. The load cell was aligned to the ankle and the knee, respectively, for the ankle and knee tests.

Surface electromyogram (EMG) recordings of selected muscles were obtained through bipolar electrodes secured to the skin. Recordings obtained from tibialis anterior, soleus, medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), lateral hamstrings (HL), medial hamstrings (HM), and hip adductors of the tested extremity were amplified (×1000) and filtered (20—250Hz) online before acquisition at 1000Hz. The EMG electrodes were applied to lightly abraded skin over the muscle belly identified by palpation. The positions for electrode placement were the same as the sensor placement recommended by the SENIAM project (www.seniam.org).

Procedures

During each set of tests (pre- and postdrug administration), separate tests were performed to assess stretch reflexes at the ankle and the knee and responses to maximum volitional isokinetic and isometric knee contractions. Time did not permit testing volitional isokinetic and isometric contractions at both the ankle and the knee. The knee was selected because the larger range of motion of
the knee made it easier for subjects to complete the isokinetic tests.

**Plantar flexor stretch reflex**

Plantar flexor stretch reflexes were assessed using imposed ankle joint rotation from 30° plantar flexion to a neutral position at 120°/s similar to a previous study. Joint rotations were performed 3 times, with the ankle held at the neutral position for 10 seconds after the final perturbation. Three experimental trials were performed, with the ankle positioned at 30° plantar flexion at the start of each test. The knee joint was fully extended during all trials. To account for ankle stiffness and gravity, joint rotation was characterized as a function of the joint angle, measured from the 5°/C14°/s for 2 cycles, while the participant was instructed to relax. Then, the motor rotated the knee through the range of motion (extension and flexion) for 20 cycles at 60°/s. In the first 5 cycles, participants were instructed to relax (defined as passive cycles). In the next 5 cycles, participants were instructed to extend or flex their knee with maximal effort in the direction of movement (active cycles). Verbal encouragement was provided during the active cycles. In the last 10 cycles, the participants were again instructed to relax (passive cycles). During passive cycles, we were able to obtain a measure of the stretch reflex of the knee using torque and EMG measurements in the extensor (RF and VM) and flexor (HM and HL) muscles. In the active cycles, we measured the isokinetic extension and flexion torques and EMG activities.

**Isokinetic knee movements**

Joint torque and muscle activity were recorded during imposed knee rotations under passive conditions and during maximum volitional concentric knee extension and flexion. The leg was secured to a knee brace with the knee aligned with the motor. The range of motion was identified by extending the knee to the physiological end range and then flexing for a total range of 95°. After the range of motion was defined, the gravity of the leg and the stiffness of the knee were measured by moving the limb through the range of motion at 5°/s for 2 cycles, while the knee joint was fully extended during all trials. The knee was stabilized by securing it to the brace with the knee aligned with the motor. The range of motion was identified by extending the knee to the physiological end range and then flexing for a total range of 95°. The average size of the joint angle, measured from the 5°/C14°/s for 2 cycles, was determined via root mean square (window size=11ms). The mean EMG activity was calculated by averaging the EMG envelope in the time window of interest. All EMG measurements were based on within-session, within-subject differences between predrug and postdrug conditions. Between measurements, EMG electrodes were left in place, secured using a nonadhesive bandage wrapped around the leg.

**Data analysis**

Data were analyzed using custom scripts written in MATLAB. Torque measurements were smoothed by a 20-Hz low-pass filter. EMG signals were bandstop filtered, centered at 30 and 60Hz. The filtered EMG signal was then rectified, and the envelope of the signal was determined via root mean square (window size=11ms). The mean EMG activity was calculated by averaging the EMG envelope in the time window of interest. All EMG measurements were based on within-session, within-subject differences between predrug and postdrug conditions. Between measurements, EMG electrodes were left in place, secured using a nonadhesive bandage wrapped around the leg.

**Reflex torque** was obtained by subtracting ankle stiffness and gravitational torques from the values of the 120°/s trials. The ankle stiffness and gravity torque were characterized as a function of the joint angle, measured from the 5°/s cycles. The average

<table>
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<td>42</td>
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*NOTE:* The spasticity information was not available for subject 10. Abbreviations: AIS, American Spinal Injury Association Impairment Scale; Ashworth, Ashworth Scale, measured in the quadriceps and hamstring muscles of the test leg; LEMS, Lower Extremity Motor Score (for the test leg); ND, no data; R, right; SCATS, Spinal Cord Assessment Tool for Spastic Reflexes, extension, flexion, and clonus subscales for the test leg.

<table>
<thead>
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<th>Table 2</th>
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<td>Fatigued, somnolence</td>
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<td>None</td>
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<tr>
<td>10</td>
<td>Somnolence</td>
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ankle torque during the 10-second hold period was calculated as a measure of the stretch reflex. The mean MG EMG activity during the hold period was used as a second measure of stretch reflexes.

Active knee torque was also obtained by subtracting the passive and gravitational torques measured in the 5/s movements.

For passive cycles, we calculated the stretch reflexes as the peak knee extension torque and mean extensor EMG activity (RF and VM) during the flexion portion of the cycle and the peak knee flexion torque and mean flexor EMG activity (HM and HL) during the extension portion of the cycle. For active cycles, we calculated the isokinetic volitional activation as the peak knee torque in the instructed direction and the mean extensor and flexor EMG activity in both directions.

Strength measurements in both extension and flexion were assessed in the isometric maximum voluntary contraction protocols. Peak knee torque was measured as the maximum torque produced in the instructed direction. Mean EMG values for the knee extensor and flexor muscles (RF, VM, HM, and HL) were also calculated over the duration of contraction.

Statistical analysis

Results from the experimental protocol were compared between the predrug and postdrug tests for each drug. The difference measurements (postdrug – predrug) were used in the statistical tests. Significance was determined using a 1-way repeated-measure analysis of variance, with drug as the independent factor and significance set at P<.05. Tukey honestly significant difference post hoc tests were used for pairwise comparisons between placebo, baclofen, and tizanidine. A post hoc power analysis was performed on the analysis of variance test of the 3 primary measures: ankle stretch reflex plantar flexor torque, isokinetic knee extension torque, and isometric knee extension torque.

Results

Stretch reflexes

Stretch reflex responses of the plantar flexors elicited consistent MG activity and corresponding ankle plantar flexion torque responses (figs 2A and B). The ankle stretch reflex data were not available for 2 of the 10 subjects. Tizanidine administration produced a significant decrease in stretch reflex torque (P=.034) (fig 2C) and MG activity (P=.015) (fig 2D) than did placebo. Baclofen showed no significant difference from placebo (torque: P=.116; MG: P=.096) (see figs 2C and D).

At the knee, passive movement produced stretch reflexes that changed with the administration of the drug. The extension portion of the passive cycles activated knee flexor muscles, evidenced by increases in HM and HL EMG activities with corresponding flexion torque during the extension portion of the movements. The peak knee flexion torque during extension significantly decreased after the administration of baclofen (P<.001) compared with that of placebo but was not significantly altered after the administration of tizanidine (P=.20) (fig 3A).

The reflexive HM and HL EMG activity (figs 3B and C) significantly decreased after the administration of both baclofen (P=.026; HL: P<.001) and tizanidine (HM: P=.024; HL: P<.001) compared with that of placebo. The peak knee extension torque during the flexion movement significantly decreased after the administration of baclofen (P=.014) and tizanidine (P<.001) than that of placebo (fig 3D). The EMG activity in the RF and VM during flexion also significantly decreased after the administration...
of both baclofen (RF: $P < .001$; VM: $P < .001$) and tizanidine (RF: $P < .001$; VM: $P < .001$) compared with that of placebo (figs 3E and F).

To summarize, both the ankle and knee stretch reflex responses decreased after the administration of baclofen or tizanidine, with stronger effects of tizanidine on plantar flexors and knee extensors and stronger effects of baclofen on knee flexors.

**Isokinetic knee strength**

During isokinetic movements, joint torques were generally unchanged by antispastic drugs while EMG activities were sometimes decreased. In the extension portion of the movement, we saw no significant changes in the knee torque for both baclofen and tizanidine compared with placebo (drug effect: $P = .179$) (fig 4A). The extensor muscles (RF and VM) showed a slight decrease in EMG activity after the administration of tizanidine (RF: $P < .001$; VM: $P = .014$), but no significant changes were observed after the administration of baclofen (RF: $P = .07$; VM: $P = .99$) (figs 4B and C). The flexor muscles (HM and HL) showed a significant decrease in EMG activity after the administration of tizanidine (HM: $P = .045$; HL: $P = .012$), whereas after the administration of baclofen, only the HL muscle group showed a significant decrease ($P < .001$) (figs 4D and E).

In the flexion portion of the movement, knee flexion torque significantly increased after the administration of tizanidine compared with that of placebo ($P = .033$) (fig 5A). Interestingly, the HM showed a significant decrease in EMG activity after the administration of tizanidine ($P = .023$) (fig 5B) whereas the HL showed a decrease in activity after the administration of baclofen.
P < .001) (fig 5C). Similarly, the RF demonstrated a decrease in EMG activity after the administration of tizanidine (P < .001) (see fig 5D) and the VM demonstrated a decrease in EMG activity after the administration of baclofen (P < .001) (fig 5E).

In summary, tizanidine and baclofen did not negatively affect the participant’s ability to produce torque under isokinetic conditions. The ability to maintain torque remained despite a decrease in EMG signals.

Isometric knee strength

The effects of the administration of tizanidine and baclofen on maximal volitional isometric strength were also determined at the knee. For knee extension, there were significant increases in torque after the administration of both baclofen (P < .001) and tizanidine (P = .001) compared with that of placebo (fig 6). Unlike knee extension, subjects did not increase maximum voluntary contraction knee flexion torque with repeated contractions (see fig 6). Most participants had weak flexors, resulting in a peak knee flexion torque that was relatively small compared with extension. The changes in peak torque generated after the administration of the drug did not show a significant difference between baclofen and tizanidine compared with placebo (baclofen: P = .066; tizanidine: P = .99).

Discussion

In general, antispastic drugs reduced stretch reflexes while having little effect on voluntary torques. This study confirmed and expanded published observations that both baclofen and tizanidine significantly reduce ankle and knee stretch reflexes and showed that baclofen and tizanidine did not cause weakness. In isokinetic contractions, we did not see a significant change in torque with baclofen or tizanidine, but the overall EMG levels decreased. These results indicate that tizanidine and baclofen are good candidates for reducing excessive stretch reflexes, with little effect on strength, and give us an insight into the effect of antispastic drugs on volitional activity.

Differential effect of tizanidine and baclofen on reflexes of the flexors and extensors

In the current study, tizanidine had a stronger inhibitory effect on knee extensors and plantar flexors whereas baclofen had a stronger inhibitory effect on knee flexors. We postulate that the preferential effects on particular muscle groups are due to actions of tizanidine on noradrenergic alpha2 receptors, which are driven largely by reticulospinal pathways, originating from the locus coeruleus. Noradrenergic alpha1 receptors may have an excitatory effect on
Isokinetic extension results. Knee isokinetic extension torque (A) and EMG activity (B–E) for 10 subjects are indicated for different drug conditions. The data shown include the means and SEs for 10 subjects and 3 trials. Positive values indicate an increase in knee extension torque after the administration of the drug. Tizanidine and baclofen had no significant effect on the torque. Tizanidine reduced RF, HM, and HL EMG activity compared with placebo ($P < .05$), and baclofen reduced VM and HL EMG activity compared with placebo ($P < .05$).
Fig 5  Isokinetic flexion results. Knee isokinetic flexion torque (A) and EMG activity (B–E) for 10 subjects are indicated for different drug conditions. The data shown include the means and SEs for 10 subjects and 3 trials. Positive values indicate an increase in knee flexion torque after the administration of the drug. Tizanidine significantly increased the isokinetic flexion torque compared with placebo (P<.05). Tizanidine significantly decreased HM and RF EMG activity compared with placebo (P<.05), and baclofen significantly decreased HL and VM EMG activity compared with placebo (P<.05).
motor pools, whereas the alpha2 receptors have an inhibitory effect on extensor muscles.34-36

Given the preferential effect of baclofen on flexors and tizanidine on extensors, it might be effective to tailor drug therapies to characteristics of individual patients. It is common for spasms to have a flexor or an extensor bias.12 Flexor spasm can be triggered using an electrical stimulus, and extensor spasms are triggered by an imposed hip extension37 with the knee in an extended posture.38,39 Investigation of the effects of baclofen and tizanidine on flexor and extensor spasms and the development of patient-specific management of spasms in people with SCI might be warranted.

Effect of tizanidine and baclofen on strength

Our results showed that both tizanidine and baclofen did not negatively affect isokinetic and isometric torque. Tizanidine appeared to increase isokinetic knee flexion and isometric extension torques, whereas baclofen increased isometric knee extension. This finding occurred despite 5 of the 10 subjects reporting drowsiness and/or sleepiness as an adverse effect during the postdrug testing session for tizanidine. This torque increase could be due to reduced coactivity, as evidenced by the overall decrease in EMG activity. This seems contrary to clinical observations and patient self-reports of weakness after taking baclofen.23,40,41 It is, however, possible that patient self-reports are due to decreased motivation because of drowsiness.

The differential effect of baclofen and tizanidine on flexors and extensors was apparent in isometric tasks. Tizanidine and baclofen increased isometric extension, but no change was observed in isometric flexion, although the overall magnitude of flexion torques was smaller than that of extension. With no movements, inhibition of stretch reflex pathways is unlikely to play a major role in isometric contractions, suggesting a central mechanism. It appeared that both antispastic drugs facilitated isometric extensor but not flexor muscles.

Study limitations

The high variability of motor function of subjects with incomplete SCI presented challenges to this study. The high variability in the baseline measurements (predrug) could have masked small drug effects. Anecdotal reports from subjects’ experience with antispastic drugs also reflected high variability in efficacy. This study also limited subject recruitment to patients with SCI, with injuries classified as American Spinal Injury Association Impairment Scale grade C or grade D at the cervical or thoracic level. The results cannot necessarily be generalized to persons with complete SCI or a higher level of injury.

Drug dosing was limited in this study. We are unaware of any detailed studies of dose-response effects for baclofen or tizanidine, and the dosages used in the current study were common doses used in clinical practice. Differences in dosing make it
difficult to compare the size of the drug effects. Furthermore, we
tested only a single-dose effect of the antispastic drugs, which
may not fully represent chronic administration. Because we tested
the effects of the drugs 1 hour after the administration of the drug,
roughly the mean time of peak plasma concentration, we expect
that our results reflect the effects of the drugs in their peak condi-
tion. The difference between effects of single-dose and chronic
administration of baclofen and tizanidine remains an important
area for future study.

The nonnormalized EMG measurements made in this study
must be interpreted with caution. Differences in EMG electrode
impedance and placement preclude comparisons across muscle
groups. Similarly, comparisons of absolute EMG signal size can be
problematic. Despite these limitations, we felt that the changes in
EMG signal size within a muscle, within a session, were a
reasonable estimate of changes in muscle activity in predrug and
postdrug conditions. In general, these measurements demonstrated
relative changes in muscle activity (EMG) that were consistent with
torque measurements.

The techniques used to measure ankle and knee stretch reflexes
differed slightly because of time constraints for the study. The ankle
testing comprised 3 repeated stretches and a hold period (10s),
which quantifies the stretch reflex under conditions of
“windup.” In contrast, stretch reflexes at the knee were measured
over the course of 5 repeated stretches and were measured during
the motion. Windup also likely affected knee stretch reflex mea-
surements, but differences in the quantification procedures
necessitate caution in comparing the relative effects at the knee
and the ankle. This approach was taken because of practical time
constraints in making the measurements because we desired to
conduct the tests with similar plasma levels of the drugs and thus
limited the measurement period to under an hour.

Conclusions
Our results suggested that antispastic drugs are effective in
reducing stretch reflexes without substantially reducing volitional
torque. In our study, we observed differential effects of tizanidine
and baclofen on the flexors and the extensors. This result provides
grounds for further research into patient-specific management of
antispastic drugs.

Suppliers
a. Biodex Medical Systems, Inc, 20 Ramsey Rd, Shirley,
NY 11967.
b. Delsys, Inc, PO Box 15734, Boston, MA 02215.
c. MathWorks, 3 Apple Hill Dr, Natick, MA 01760.

Keywords
Muscle spasticity; Muscle strength; Reflex, stretch; Rehabilitation;
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