ACRM
AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Physical Medicine and Rehabilitation

journal homepage: www.archives-pmr.org

Archives of Physical Medicine and Rehabilitation 2014;95:622-32

ORIGINAL ARTICLE

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

Virginia Way Tong Chu, PhD,[a] Thomas George Hornby, PhD, PT,[a,b] Brian David Schmit, PhD[a,c]

From the [a]Sensory Motor Performance Program, Rehabilitation Institute of Chicago, Chicago, IL; [b]Department of Physical Therapy, University of Illinois at Chicago, Chicago, IL; and [c]Department of Biomedical Engineering, Marquette University, Milwaukee, WI.

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.

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Although antispastic drugs are commonly used to manage spasticity in patients with spinal cord injury (SCI), the relative effects of these agents on spastic reflexes and voluntary muscle contraction are still poorly understood. Spasticity is a common secondary condition, affecting approximately 65% to 78% of the people with an SCI.[1] The perceived effect of spasticity on function, care, and comfort has led to the prescription of antispastic drugs. Two of the most common of these drugs are (1) baclofen, a gamma-aminobutyric acid B agonist with potential inhibitory effects on monosynaptic and polysynaptic reflex pathways,[2-5] and (2) tizanidine, an alpha$_2$ adrenergic agonist that diminishes spasticity through depression of polysynaptic reflexes and increases presynaptic inhibition to spinal interneurons.[6,7] Both agents are widely prescribed for the treatment of spasticity following an SCI, although their precise effects on motor pathways are uncertain.

The mechanisms by which baclofen and tizanidine alter motor function have been established primarily by demonstrating their

Preliminary results presented as a poster to the Society for Neuroscience, November 13-17, 2010, San Diego, California.

Supported by the National Institutes of Health (grant no. NS062982).

No commercial party having a direct financial interest in the results of the research supporting this article has conferred or will confer a benefit on the authors or on any organization with which the authors are associated.

0003-9993/14/$36 - see front matter © 2014 by the American Congress of Rehabilitation Medicine
http://dx.doi.org/10.1016/j.apmr.2013.11.001

effects on spinal reflexes. In general, spasticity has been associated with stretch reflex hyperexcitability[1,8-11] although in an SCI, muscle spasms linked to other types of spinal reflexes have been implicated in the spastic syndrome.[12-14] Both baclofen and tizanidine reduce spinal reflexes, muscle tone, spasticity, and spasms.[1,15-17] The antispastic action of baclofen and tizanidine has been quantified using the reflex response to passive stretch,[18,19] and these types of stretch reflex measurements have been proposed for titrating the dosage of baclofen in patients with intrathecal pumps.[20,21] However, the benefits of these drugs depend on how much they alter volitional and reflexive activity during functional movement. Antispastic drugs have the potential to improve motor function by reducing spastic reflexes, but these could have detrimental effects through an overall reduction in volitional activity. For example, baclofen has been associated with increased weakness,[17,22,23] despite reported reductions in coactivation,[24] while tizanidine is associated with reduced weakness and possibly increased strength.[15,16,25] The effect of each agent on multiple spastic reflex responses and volitional activation after an SCI is still unclear.

The objectives of the current study were to identify the effects of a single dose of baclofen and tizanidine on reflex and volitional muscle activity in people with an SCI. Using a double-blinded, placebo-controlled design, alteration in the excitability of stretch reflex pathways and volitional strength was determined before and after the administration of either agent or placebo. The simultaneous measurement of reflex and volitional muscle activity provided a combined assessment of the relative effects of baclofen and tizanidine on motor control in human SCI.

Methods

Study design and ethics approval

The effects of antispastic drugs on spinal reflexes and volitional muscle activity were assessed using a double-blinded, single-dose, placebo-controlled study. All subjects participated in 3 separate sessions involving testing before and after the oral administration of baclofen, tizanidine, or placebo, separated by >7 days. The test sequence of the 3 conditions was randomized and blinded from both experimenters and study participants. All study procedures were conducted in accordance with the Declaration of Helsinki and with approval from the Northwestern University and Marquette University institutional review boards. Written informed consent was obtained before enrollment and participation in the study.

Participants

Characteristics of the 10 study participants with chronic (>6mo) motor incomplete SCI who completed all tests are shown in table 1. All the participants were men, with 6 of 10 classified by the American Spinal Injury Association Impairment Scale as grade D (4 as 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.

List of abbreviations:

EMG	electromyogram
HL	lateral hamstrings
HM	medial hamstrings
MG	medial gastrocnemius
RF	rectus femoris
SCI	spinal cord injury
VM	vastus medialis

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 (baclofen[18,26] or tizanidine[7,27,28]). 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[a]) (fig 1). A multiaxis load cell with 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[b] 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