THE EFFECTS OF CLONIDINE ON CLINICAL SPASTICITY
AND IN MODULATION OF THE LOCOMOTOR PATTERN
IN SPASTIC SPINAL CORD PATIENTS

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ⓒ Jennifer E. Stewart
THE EFFECT OF CLONIDINE ON SPASTICITY AND SPASTIC PARETIC GAIT
ABSTRACT

This double blind cross-over study investigated the effects of the noradrenergic agonist clonidine on spasticity and in modulation of the locomotor pattern in 6 paraplegics and 3 paraparetics. Clinical measures of spasticity included evoked tonic stretch reflex (TSR), ankle clonus, and a visual analog scale (VAS) recording patients' perceived level of spasticity. Electromyographic (EMG), footswitch and video recordings were made as the patients walked on a treadmill at 0.26 ms\(^{-1}\) supported by an overhead harness. Overground locomotion was also assessed in the paraparetics.

With clonidine, 4/9 patients had a reduction in ankle TSR, 3/9 had diminished ankle clonus, while 4/9 patients recorded lower VAS scores. Of those completing daily diaries of spasticity, 2/4 reflected a diminution of spasms and 4/5 in clonus. Those with medical lesions (3/9) had more severe side-effects and less reduction of spasticity. 1/3 paraparetics demonstrated a marked improvement in locomotor function, gaining the ability to take independent steps. The other 2 paraparetics showed some modification of EMG profiles and timing, and of joint angular excursion. Clonidine did not affect the paraplegics' locomotor ability. 1/6 paraplegics and 2/3 paraparetics reported functional improvement.
Une étude à double insue a été effectuée pour étudier l'effet modulateur de la clonidine sur la spasticité et sur le patron locomoteur chez 6 patients paraplégiques et 3 patients paraparétiques. La spasticité a été mesurée cliniquement par le réflexe d'étirement et par le clonus alchiléen. La perception de la spasticité par les patients a été mesurée à l'aide d'une échelle visuelle analogue. La fonction locomotrice a été évaluée sur tapis roulant à une vitesse de $0.26 \text{ m.s}^{-1}$ chez tous les patients et sur trottoir chez les patients paraparétiques seulement.

La clonidine produit une diminution du réflexe d'étirement chez 4/9, du clonus alchiléen chez 3/9 et une diminution de la perception de la spasticité chez 4/9. 2/4 des patients ont observé une diminution du nombre de spasmes et 4/5 une diminution du nombre épisodes spontanés de clonus. Les patients avec une étiologie médicale 3/9, présentaient des effets secondaires importants et une moins grande diminution de spasticité. Chez 1/3 des patients paraparétiques, une remarquable amélioration de la marche a été observée alors que chez les 2 autres, un changement du patron électromyographique et cinématographique a été mesuré. La fonction locomotrice n'a pas été modifiée chez aucun des patient paraplégiques. 1/6 patients paraplégique et 2/3 paraparétiques ont reporté une amélioration fonctionnelle.
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STATEMENT OF AUTHORSHIP

I certify that I am the primary author of all manuscripts contained in this thesis. I also claim full responsibility for the content and style of all texts included herein.
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CHAPTER ONE: INTRODUCTION

Spinal cord lesions will completely or partially section neuronal tracts which are descending through the spinal cord, thus releasing the spinal or segmental structures from supraspinal control. As a result, injury of the spinal cord typically results in spasticity and paresis below the site of the lesion. Frequent manifestations of spinal spasticity include hyperreflexia, hypertonus, spasms and clonus. These symptoms of spasticity can affect the expression of motor actions such as locomotion. Spastic paraparetic gait can be characterized by abnormal EMG timing and profiles (Knutsson, 1983, Conrad et al., 1983), reduced angular excursion at hip knee and ankle (Knutsson, 1983), reduced balance and the presence of protective gait mechanisms (Conrad et al 1983, 1985), and decreased temporal distance factors such as stride length, cadence and velocity (Conrad et al., 1985, Barbeau et al., 1988).

Spinal spasticity and spastic paraparetic gait have increasingly become a focus of investigative research in the past decade, as there is a large population of patients with spinal cord injuries (SCI) within the North American population. In the United States, an incidence rate of 8,000 - 10,000 new SCI cases annually was estimated by the National Institute of Handicapped Research in 1981. The majority of SCI occurs in males in the 19 - 35 year age bracket (Eisenberg and Tierney, 1985), and involves an incomplete lesion (Yashon
1978). This would indicate a large population in the prime of life who are handicapped by the paresis and spasticity which typically accompany partial spinal cord transections. Thus, a treatment strategy which could reduce hyperactive reflexes as well as improve the underlying motor control mechanisms might provide beneficial to these patients.

Recent studies using a chronic spinal cat (CSC) model have revealed that the noradrenergic alpha$_2$ agonist, clonidine reduces hyperactive spinal reflexes (Rossignol et al., 1986). In addition, clonidine has been shown to trigger rhythmic stepping in acute spinal kittens, apparently stimulating a central spinal pattern generator (Forssberg and Grillner, 1973, Grillner and Zangger, 1979). In adult chronic spinal cats (CSC) who have been trained to walk independently on a treadmill, the injection of clonidine has a modulatory effect on the locomotor pattern affecting both EMG timing and kinematics. These effects are thought to reflect the action of clonidine on the interneurons which are involved in the central spinal level generation of the locomotor pattern (Grillner, 1981).

Clinical studies (Naftchi 1982, Tuckman et al. 1982, Maynard 1986, Nance et al. 1985) investigating the effects of clonidine in spinal cord patients have also reported a reduction of clinical spasticity with clonidine. However, these studies have tended to be largely qualitative and descriptive in nature.
Therefore, in light of the animal studies revealing the effects of clonidine in modulating locomotor function and spinal reflexes in CSC, and the clinical trials demonstrating a role for clonidine as an antispastic medication, it was the purpose of the present study to further investigate the potential effect of clonidine in modulating the locomotor pattern in spinal cord patients, and its action on spinal spasticity.
1.1 OBJECTIVES OF THE STUDY

The general objective of this study was to determine the modulatory effects of clonidine on the locomotor pattern and clinical symptomatology of spasticity in spastic spinal cord patients. Specifically:

1. To contrast the effects of clonidine and placebo on spastic paraparetic gait by comparing temporal distance factors such as: the cycle duration, percentage stance phase, velocity, and percentage total double support time. Kinematic variables such as: total angular excursion for the hip, knee, and ankle as well as maximal swing angles across the step cycle were also compared, as were the timing, and activation profiles of EMG recordings for lower extremity muscles involved with locomotion.

2. To investigate the potential effects of clonidine on the expression of the locomotor pattern in paraplegic patients during assisted locomotion on the treadmill.

3. To assess overground locomotion as the paraparetics walk between parallel bars at their natural cadence, obtaining qualitative and quantitative details on parameters of gait such as velocity, cadence, and stride length.

4. To clinically evaluate the effects of clonidine on the spasticity of paraplegic and paraparetic patients, by
measuring the degree of ankle clonus and tonic stretch reflexes evoked during the clonidine and control assessment sessions. Additionally, to determine the effect of clonidine on the patients' perception of spasticity through the use of a visual analog scale each session, and by having the patient maintain a diary of daily episodes of spasms and clonus.
CHAPTER TWO: LITERATURE REVIEW

Noradrenaline (NE), and the noradrenergic agonist clonidine, are involved in the modulation of sensory, autonomic and spinal motor functions (Marshall, 1983). This paper will focus on the role of NE and clonidine in the modulation of spinal motor function. Although the exact mechanisms of clonidine’s action are not fully understood, it is known to be a noradrenergic agonist, acting primarily on alpha₂ adrenergic receptors (Feldman and Quenzer, 1984).

Extensive study of NE neuropharmacology (Marshall, 1983), and the effects of NE and its agonists on segmental reflexes and motor control have been conducted in animals (Forssberg and Grillner, 1973, Barbeau et al., 1987), however such research has been limited in humans. Accordingly, in the proceeding sections, primarily animal results will be presented; human parallels will be drawn where possible. This literature review will focus on the synthesis and distribution of NE, as well as the effects of NE and clonidine on spinal neurons, reflexes and locomotion. Subsequently, the effects of spinal cord lesions on motor function, and the effects of NE and clonidine on spinal motor function will be addressed.

2.1 Distribution of the Noradrenergic System

Within the brainstem, nuclei designated by Dahlstrom and Fuxe (1964) as A1, A2, A3, A5, A6 (locus coeruleus), and A7 are the major sources of NE cell bodies. It has been
determined with histofluorescent techniques that the majority of NE neurons project rostrally, through the central and ventral tegmental tracts as well as the dorsal longitudinal fasciculus, to innervate the cortex, thalamus, hypothalamus, and limbic system. A fourth tract also courses from nucleus A6 to the cerebellum (Feldman and Quenzer, 1984). Descending NE tracts have further been identified, projecting from pontine nuclei A1, A2, A5, the ventral portion of A6, and the subcoeruleus nucleus (Satoh et al., 1977, Dahlstrom and Fuxe, 1965, Jones and Yang, 1985). The neuronal tracts descend from these nuclei in two main bundles, within the ventral funiculus and the ventral portion of the lateral funiculus, and terminate in the dorsal and lateral horns of the spinal cord (Dahlstrom and Fuxe, 1965). The ventral pole of A6 is the origin of most fibers implicated in somatic motor function. These fibres decussate at the spinal level and project to laminae 6, 7, and 9 in the ventral horn, lamina 10 in the intermediate grey area, and laminae 4, 5, and 6 in the ventral half of the dorsal horn (Commissiong, 1981a, Commissiong et al., 1978, Nygren and Olsen, 1976).

Haggendal and Dahlstrom (1973) demonstrated that within 14 days following spinal transection, over 90% of NE was eliminated caudal to the lesion in rats, suggesting an almost complete absence of NE cell bodies in the spinal cord. Thus, destruction of the descending NE tracts appears to remove the primary source of NE influence on spinal neurons, and
consequently on spinal motor functions, such as reflexes and locomotion.

2.2 Pharmacology of Noradrenaline

NE is synthesized in the soma and terminals of NE neurons. Tyrosine, an amino acid circulating in the bloodstream, is hydroxylated to form dopa in the soma of all catecholaminergic neurons. Dopa is then decarboxylated to dopamine, which is both a precursor for NE, and a neurotransmitter on its own. Dopamine is converted to NE through the action of enzyme DBH, which is only present in NE and adrenergic neurons. In NE neurons, the dopamine-containing vesicles are transported from the soma to the terminal bouton, where NE synthesis is completed. In adrenergic neurons, NE is further metabolized by enzyme PNMT into adrenaline (Feldman and Quenzer, 1984). The synthesized NE is stored in vesicles within the terminal boutons, pending a nerve impulse triggering their release into the synaptic cleft. Once released, the NE may transverse the cleft to bind with receptor sites on the post-synaptic membrane, and/or with autoreceptors on the presynaptic membrane (U’Pritchard 1984). Residual NE in the cleft may be re-uptaken into the terminal bouton for subsequent re-release, or it can be catabolized by enzymes circulating in the vicinity of the synaptic cleft, such as catechol-O-methyl transferase or monoamine oxidase.

Receptors are identified by their neurotransmitter
sensitivity, by their linkage to a second messenger, by rank order of binding potency, and by their location (Marshall, 1983, Ruffalo, 1983). Adrenoceptors have been categorized into alpha and beta types, based on pharmacological action. As beta type receptors are not involved with the action of clonidine, they will not be further described here. Alpha receptors have been subdivided morphologically into alpha_1 and alpha_2 subtypes (Ruffolo, 1983). The NE agonist clonidine appears to act primarily at alpha_2 receptors, either presynaptically to inhibit NE release (Feldman and Quenzer 1984), or post-synaptically to mimic NE action (Anderson and Stone, 1974, Anden et al., 1970).

2.3 Noradrenergic Effects on Spinal Neurons and Spinal Reflexes

Histofluorescent analysis has shown that descending NE fibres in the intermediate zone have varicosities in the vicinity of interneurons while those projecting to lamina 9 in the ventral horn terminate close to spinal motoneurons (Jones and Yang, 1985). Their findings suggest that noradrenergic action at the spinal level is probably mediated by both interneurons and motoneurons.

NE and clonidine have been reported to have primarily an inhibitory effect on spinal neurons in both spinalized and decerebrate cats (Bergmans and Grillner, 1968, Engberg and Ryall, 1966, Engberg and Marshall, 1971, Jordan et al., 1977).
Cutaneous excitability was reduced in spinal cats following injection of clonidine, such that the threshold for a single shock eliciting the flexor reflex was double that of the control condition (Barbeau and Rossignol, 1987, Rossignol et al., 1986). In spinal rabbits, injection of the NE precursor dopa also consistently depressed the flexion response (Viala et al., 1974). Supporting the role of NE in this response was the finding that toxic destruction of NE neurons prior to spinalization in rats markedly reduced the subsequent flexion response to dopa. Furthermore, the introduction of clonidine caused an exaggerated flexor response, suggesting denervation supersensitivity of post-synaptic adrenoceptors as a result of the neurotoxic destruction of the NE neurons (Nygren and Olsen, 1976).

In conjunction with this inhibition of the flexion reflex, a prolonged (>500 msec), long latency (200 msec) dorsal root potential (DRP) occurred, involving both ipsi- and contra-lateral flexor and extensor Ia afferents (Anden et al., 1966b). Accompanying this DRP in the rabbit was a characteristic sequence of alternating discharges in the flexor and extensor nerves, yielding an electroneurographic (ENG) activation pattern comparable to that recorded during locomotion (Viala et al., 1974). It has been hypothesized that the basis of this action is a depression of the short latency arcs from the flexor reflex afferents, concomittant with a disinhibition of alternate pathways, producing longer

It has been suggested that the induced discharges following either dopa or clonidine injections are similar to the EMG activation pattern observed during spinal locomotion (Vidal et al., 1979, Grillner and Rossignol, 1978). However, Rossignol et al. (1986) did not observe these long latency discharges following electrical stimulation, either preceding or proceeding clonidine injections in their chronic spinal cats (CSC), yet these CSC had been trained to walk on the treadmill with a near-normal gait pattern. Thus, the presence of the late discharges would not seem to be an essential component of spinal locomotion. The precise neuronal circuitry for the generation of locomotion has yet to be elucidated.

2.4 Noradrenergic Effects on Locomotion

There is considerable evidence based on animal research supporting the existence of a spinal locomotor generator, which functions in association with a mesencephalic locomotor region (MLR) (Shik and Orlovsky 1976, Grillner, 1981, Shefchyk and Jordan, 1985). Electrical stimulation of the MLR elicits a monosynaptic response in descending reticulospinal neurons, which triggers rhythmic stepping movements of the hindlimbs of decerebrate cats (Shik and Orlovsky, 1976). The reticulospinal tracts involved are postulated to include some noradrenergic fibres, as the injection of clonidine produced
stepping movements similar to those induced by MLR stimulation (Forssberg and Grillner, 1973, Grillner, 1975). In addition, stimulation of the MLR produced prolonged late DRPs in the Ia afferents while suppressing short latency flexor responses similar to those produced by NE agonists and precursors (Grillner and Shik, 1973). However, MLR activation is not essential for initiation or maintenance of locomotion, as animals with bilateral MLR lesions (Shik and Orlovsky, 1976), or extensive destruction of descending monoaminergic tracts (Steeves et al., 1980) can still walk. Moreover, spinalized cats are capable of walking with a near-normal gait pattern (Forrsberg, 1982). These findings support the existence of a spinal level locomotor generator which can be influenced by descending tracts, but can function without their input.

To further elucidate the role of noradrenaline in locomotor function, Rossignol et al. (1986) investigated the effects of clonidine on the gait pattern of a stable walking preparation (CSC). The findings indicated that clonidine had a modulatory effect, involving an increased burst duration in both flexor and extensor muscles. The resultant prolongation of the flexor bursts was particularly associated with an increased step cycle duration (Rossignol et al. 1986, Barbeau and Rossignol, 1987). The stride length also increased, in association with increased hip, knee and ankle joint excursion, during the step cycle. These effects were reversed by the injection of NE alpha_{2} antagonist, Yohimbine (Rossignol
et al., 1986, Barbeau and Rossignol, 1987).

In summary, it would seem that a spinal locomotor generator system may underlie the expression of the locomotor program, based on innate motor programming. NE, while not essential to trigger spinal locomotion, seems to have a modulatory effect on the locomotor pattern.

2.5 The Hypothesis of a Spinal Locomotor Pattern Generator in Humans

It is of interest to consider the concept of the spinal locomotor generator in the context of humans, as the presence of such a mechanism might hold implications regarding the potential for recovery of locomotor function in spinal cord injured patients. A comparable neural substrate between quadrupeds and bipeds is suggested by similarities in locomotor movements and EMG patterns (Grillner, 1981), and by the common presence of a step cycle, subdivided into a stance phase, which shortens with increasing speed, and a swing phase, which stays relatively constant in duration (Grillner, 1981, Forssberg, 1982). Although there exist these elementary similarities, there are many characteristics which are different. Bipedal gait is unique in its combination of pelvic rotation, pelvic tilt, knee flexion in early stance phase, hip flexion, knee and ankle coupling, plantigrade foot placement, and lateral pelvic displacement (Basmajian, 1986). These characteristics serve to smooth the sinusoidal
displacement passage of the body’s centre of mass during ambulation, adding to the efficiency of upright locomotion (Inman, 1981).

Despite these differences, it has been proposed that a spinal level locomotor generator could exist in humans, which is modulated by descending supraspinal control in normal adults (Forssberg, 1982). It has been suggested that while such a generator would control the stereotypic locomotor movement pattern, supraspinal centres would act to initiate, maintain, modify, and terminate the locomotor activity (Forssberg, 1982). This is supported by the archaeological finding that hominids walked with a plantigrade bipedal gait before brain expansion, thus reflecting subcortical control of bipedal locomotion (Forssberg, 1986). Moreover, anencephalic neonates demonstrate strong rhythmic stepping despite their lack of functional supraspinal structures (Forssberg 1982, 1985). Normal infants also demonstrate a reflex-induced stereotypic neonatal stepping. Following the neonatal period, this pattern of stepping disappears for several months then re-emerges, with the child having more voluntary control over initiation and cessation of the movement. Throughout this time the stepping pattern remains essentially the same (Forssberg, 1986, Thelen and Cooke, 1987). Over the first 18 months, the infant’s locomotor pattern remains immature, with absence of pelvic rotation, no heelstrike or push-off, and primarily flexion-extension
patterns of the legs in stepping. Within the following year, the infant's locomotor function becomes progressively integrated with postural control and adaptive behavior, in association with the emergence of a plantigrade gait pattern. These findings have been suggested to reflect the existence of a basic spinal locomotor generator which is progressively influenced by supraspinal structures as cortical development and myelinization of the descending tracts occurs (Forssberg 1986).

In spinal cord injured (SCI) patients, involuntary rhythmic flexor and extensor movements of the legs in a stepping pattern were observed in 4 soldiers who had sustained traumatic lesions to the high lumbar region (Holmes 1915). Holmes suggested that this phenomenon, resembling movements seen in spinal dogs, was a manifestation of a vestigial spinal locomotor generator (Holmes 1915). More recently, Zomlefer (1986) attempted to elicit treadmill-induced stepping in SCI subjects. He reported no spontaneous stepping, although regular EMG bursting occurred during manually assisted locomotion. He ascribed this to either the action of a spinal stepping generator or to alternating stretch reactions (Zomlefer, 1986).

Thus, it appears that a spinal level locomotor generator could exist in humans, but is modulated by descending supraspinal control in normal adults. In light of the research on animal models indicating a role for clonidine in
the modulation of spinal reflexes, locomotion, and neuronal excitability, and given the implication that a spinal level generator may possibly underlie human gait, it is interesting to investigate the effects of clonidine on the motor function of patients with complete and incomplete spinal cord lesions. It is therefore relevant to review the sequelae related to spinal cord lesions, and to explore the role of NE in the process.

2.6 Spinal Cord Lesions

2.6.1 Spinal Spasticity

Lesions of the spinal cord can be caused by a variety of pathological processes including cancer, congenital malformations, multiple sclerosis, and spinal infections. They may also be caused traumatically, most commonly by motor vehicle accidents, falls, and sports injuries. Although pathological lesions can occur at any level, traumatic lesions are most common at low cervical (C5-6) and low thoracic (T12-L1) levels, which are the areas of greatest vertebral mobility (Yashon 1978). Approximately 60% of all spinal cord patients have incomplete transections (Yashon, 1978). Indeed, many patients with apparently complete spinal transections do actually have some residual intact descending tracts (Dimitrijevic et al., 1983). Following spinal transection, there is an initial one to three week period of spinal shock, characterized by flaccidity and absence of motor response.
Subsequently, over the proceeding month, spasticity and residual voluntary movements progressively emerge (McDowell, 1981). Clinically, such spinal spasticity is manifested by hyperreflexia, the presence of clonus and spasms, and hypertonus (Chapman and Weisendanger, 1982).

Although the exact mechanisms of neural reorganization following transection are not fully understood, it is suggested that the initial period of flaccidity is associated with the massive degeneration of the terminal segments of descending tracts (Yashon, 1978). The resulting elimination of supraspinal influences allows peripheral or segmental afferent excitation of the motoneurons to occur without inhibition (Bishop, 1977, Young and Delwaide, 1981).

Based on the animal findings, degeneration of the descending fibres results in a disinhibition or unmasking of latent synaptic connections, previously suppressed by the descending neurons (Dostrovsky et al., 1976, Nelson et al., 1979). Over the weeks following the lesion, a denervation supersensitivity of the post-synaptic receptor sites develops, characterized by an increased affinity for the neurotransmitter or its agonists (Salzman et al., 1987), and often associated with a proliferation of receptor sites (Menkes et al., 1983, Korczyzn, 1975). Axonal sprouting, also occurring within weeks of the lesion, results in the formation of new viable synapses (Murakami et al., 1976). These may affect not only the discharge pattern of the postsynaptic
neuron, but also the reorganization of neuronal circuits, thereby resulting in an alteration of behavioral response patterns (Steward et al., 1977). It has been suggested that axonal sprouting may be triggered by environmental demands (Mendell, 1984), such that functional connections may be facilitated by appropriate training or therapy programs following the lesion (Goldberger and Murray, 1974, Bach-y-Rita, 1981). Dietz (1987) has also suggested that chronic spasticity could result in a dysfunction of the interneuronal systems associated with motor activity, and may in addition alter the structural properties of spastic muscles to create a predominance of type I fibre (slow twitch). It therefore appears that neural plasticity and resultant neuromuscular changes can either contribute to the development of clinical signs of spasticity or result in a functional adaptation of the damaged system to meet environmental demands (Korczyzn, 1975).

The presence of spasticity may severely limit the level of functional motor control in patients with incomplete lesions. Frequently, a patient with sufficient strength to carry out a motoric activity such as ambulation, may be restricted from doing so by the overriding features of spasticity (Yashon, 1978), as well as by the difficult task of supporting and balancing his body weight (Conrad et al., 1983). As a result of the manifestations of spasticity, there are certain characteristic features which are commonly seen
in the gait of spastic paraparetics.

2.6.2 Spastic Paraparetic Gait

Spastic paraparetic gait has been characterized by hyperreflexia, abnormal muscle timing and activation patterns, as well as difficulty with bearing weight, and coping with balance (Barbeau et al., 1988). As a result of these problems, such deviations as reduced angular excursions of the hip, knee and ankle, poor foot placement, reduced speed, cadence and stride length, increased base of support, and prolonged stance phase and percentage total double support time (% TDST) are common (Conrad et al., 1983, 1985). EMG activity typically shows abnormal timing of muscle activation, prolongation of the muscle bursts, presence of clonus, and coactivation of flexors and extensors (Barbeau et al., 1988). It has been hypothesized that these gait abnormalities stem from a disturbance in the normal supraspinal modulation of polysynaptic and monosynaptic reflexes (Dietz, 1987), resulting in hyperactive stretch reactions evoked as the muscle lengthens (Beneke and Conrad, 1986), and in stretch and loading reactions, related to weight-bearing (Knutsson, 1983). These influences may contribute to the prolongation of the EMG recruitment period, and to the abnormality of the EMG profile which thus alters with ongoing changes in stretch and load.

A treatment approach which could address problems of clinical spasticity such as hyperactive reflexes, spasms and
hypertonia, as well as the disturbance of underlying motor control mechanisms would be of great benefit to this patient population.

2.7 Treatment of Spasticity

Both surgical and pharmacological approaches have been used to treat spasticity. Among the surgical interventions, selective ventral or dorsal rhizotomy to interrupt the reflex arc is the most commonly performed (Yashon, 1978). Although surgery is still recommended in severe chronic spasticity, the irreversibility of the surgery, frequent complicating side effects, and inconsistent benefits have made pharmacology the treatment of choice in many cases (McDowell, 1981).

The most commonly used drugs in the treatment of spinal spasticity are: baclofen/Lioresal (R), diazepam/Valium (R), and dantrolene sodium/Dantrium (R). Baclofen, a Gabaergic derivative, acts presynaptically to interfere with the release of excitatory transmitters from spinal afferents. Diazepam, a benzodiazepine compound primarily prescribed for its anxiolytic effects, increases the affinity of postsynaptic gabaergic receptors for that inhibitory neurotransmitter. Dantrolene sodium suppresses calcium release from the sarcoplasmic reticulum (McDowell, 1981, Young and Delwaide, 1981). Dantrolene sodium and diazepam are of approximately equal efficacy (Young and Delwaide, 1981), however a major side-effect of dantrolene sodium is muscle weakness, while
Diazepam is addictive, and causes drowsiness. Baclofen, the most commonly used drug for spinal spasticity, reduces involuntary spasms, but has relatively little effect on clonus and hyperreflexia (McDowell, 1981, Young and Delwaide, 1981) or on stretch reactions (Knutsson, 1983). Baclofen also has some sedative side-effects. Thus, although these drugs do affect various components of spasticity, they have undesirable side-effects and do not provide generalized relief.

Consequently, in attempting to more effectively manage spinal spasticity and maximize motor control, researchers have begun to investigate the potential contribution of the monoamines which have been implicated in motor function. Serotonergic (5-HT) antagonists have been shown to decrease hyperactive reflexes, clonus and spasms, (Banna and Anderson, 1965, Barbeau et al., 1981) as well as to modulate the locomotor pattern in spinal animals (Rossignol et al., 1986). In spinal cord patients, recent studies have revealed improved gait characteristics and a reduction of spontaneous spasms and clonus with the 5-HT antagonist cyproheptadine (Barbeau et al., 1982, Wainberg et al., 1986, Fung et al., 1988).

Clonidine was also qualitatively reported to have an antispasmodic effect in over 30 subjects with transverse cervical or thoracic myelopathy, however no quantitative data was included (Naftchi, 1982). Tuckman et al. (1982) reported a decreased level of spontaneous EMG activity and fewer involuntary spasms in the two C5-6 quadriplegic patients.
investigated, after the first dose of clonidine. Moreover, their spasticity continued to decrease over several weeks of treatment, allowing both patients to benefit from physical therapy. Maynard et al. (1986) reported that 2 of the 12 spinal cord patients in his clinical trial experienced "some reduction" in their spasticity, 5/12 experienced "excellent reduction" on a short term basis, while 3 reportedly continued on the medication with "excellent results" for between 3-19 months. No details as to the criteria for judging improvement were provided. Nance et al. (1985) reported reduction of clinical spasticity in all 4 spastic spinal cord patients following the initiation of a clonidine treatment regime. However, only 2 of the 4 continued on the medication due to problematic side-effects.

Unfortunately, quantitative measurements and analytical data were lacking in all these studies, as was specific information on methodology and no definition of outcome variables. Sample populations were small, and included a wide variety of ages, types of lesion, and degrees of chronicity. Moreover, in none of the studies was there any attempt to limit experimental error or researcher bias through use of a cross-over design, placebo treatment, or double-blind technique. Additionally, despite animal findings suggesting a role for clonidine in the modulation of locomotion (Grillner, 1975, Forssberg and Grillner, 1973, Barbeau et al., 1987), no studies have yet assessed the effects of clonidine
on the locomotor pattern of spinal cord patients.

2.8 Measures of Locomotion and Spasticity

In order to effectively measure the effects of clonidine on spastic paraparetic gait, quantification of locomotor function is necessary. Recent studies investigating the reliability of objective gait analysis using a checklist format have reflected a rather low inter-rater agreement in recording kinematic gait deviations (Krebs et al., 1985). This reinforces the need for use of quantitative measures such as EMG, video, and footswitch recordings to supplement observations for detailed, accurate gait analysis. Use of a treadmill permits analysis of gait in a controlled setting, allowing systematic interventions such as speed adjustments. Moreover, recent studies have indicated generally comparable kinematic and EMG measures in treadmill and over-ground locomotion (Arsenault, 1986, Murray et al., 1985). Use of the treadmill in gait analysis thus allows effective recording of angular displacement, muscle activation, and temporal features of the step cycle. Clinical assessments of over-ground walking, involving footprint analysis, can generate supplementary information on velocity, cadence, stride and step length (Robinson, 1977), as well as asymmetries and foot placement (Shores, 1980). Use of these measures will allow repeated, reliable assessment of changes in all aspects of gait.
At present, there is no single definitive measure for spasticity, however tests of ankle clonus and tonic stretch reflex are frequently used clinically. Sustained ankle clonus, characterized by a rhythmical spontaneous discharge, occurs in the presence of hypertonia following lesion of the lateral corticospinal tract. It is thought to be triggered by a stretch reflex, with the subsequent synchronous bursts programmed by a central generator (Dimitrijevic et al., 1980). Clonus is elicited by briskly dorsiflexing the ankle and sustaining the pressure (Yashon, 1978). It can be quantified in terms of the EMG activity in triceps surae and by the duration of the bursts. Thus, it provides a fast and effective clinical measure of one aspect of spasticity.

A velocity-dependent increase in the tonic stretch reflex elicited by passive lengthening of the muscles is described as another characteristic feature of spasticity (Taylor et al., 1984). The underlying mechanisms are yet to be elucidated, however a disturbance in the activation of Group III and IV afferents has been suggested (Rymer et al., 1979). To quantify this reflex as a spasticity measure, the resistance elicited by passive flexion and extension of the knee or ankle joint at a constant velocity can be rated on a numerical scale. Thus, a reduction in the degree of the tonic stretch reflex would result in a lower TSR score. It would be important to maintain constancy of velocity and examiner, to maximize test-retest reliability.
2.9 Conclusions

This literature review has demonstrated that clonidine, acting as a NE alpha<sub>2</sub> agonist, can modulate locomotion and decrease hyperactive spinal reflexes in a variety of animal models. Clinical trials involving spinal cord patients have qualitatively shown antispastic effects; no studies to date have investigated the effect of clonidine on human paraparetic locomotion. Thus, a controlled research project is warranted, to quantitatively and qualitatively examine the effects of clonidine: a) in the modulation of spastic paraparetic gait, both on the treadmill and overground, b) on the expression of locomotor pattern in paraplegics, and c) on clinical symptoms of spasticity including hyperreflexia, clonus and spasms.
CHAPTER THREE: METHODOLOGY

3.1 Population

Twelve subjects were selected for participation in this research study. Of these, 9 completed the protocol (Table 3.1). All potential subjects were screened by a neurologist. Selection was based on the following inclusion criteria: presence of a spinal cord lesion, clinical symptoms of spasticity including ankle clonus, spasms and hyper-reflexia, absence of lower extremity pathology, age in the range of 18 - 65 years, and absence of cardiovascular problems. Subjects were all volunteers.

3.2 Research Design

Figure 3.1 provides a schematic overview of the research design protocol for the main study, involving the double blind crossover format. On the patient's initial visit to the Gait Laboratory, he was oriented to the lab, informed verbally as to the details of the study, and had a complete neurological examination by the consultant neurologist. The subjects then signed the informed consent (see Appendix 1A, 1B), and began the orientation assessment session. This included a series of treadmill locomotion trials, an over-ground locomotion trial for the paraparetics, and clinical tests of spasticity. These measures were repeated at the beginning and end of each subsequent post-medication assessment session.

The patient returned the following week for the second
Table 3.1. Demographic details of the patients. NVA: motor vehicle accident, CA: SURGERY: lesion secondary to surgery for cancer, KYPHOSCOL: kyphoscoliosis resulting in progressive paralysis, TRAUMA: fall resulting in SCI. Frankel’s classifications: B: incomplete sensation, no motor function below the lesion, C: incomplete sensation, no useful motor function below lesion, D: incomplete sensation, some useful motor function below lesion
**TABLE 3.1**

**DEMOGRAPHIC DATA**

<table>
<thead>
<tr>
<th>NAME</th>
<th>AGE (yrs.)</th>
<th>SEX</th>
<th>ETIOLOGY</th>
<th>LESION LEVEL</th>
<th>LESION CHRONICITY (yrs.)</th>
<th>DAILY DOSAGE (mg.)</th>
<th>FRANKELS CATEGORIES (A-D)</th>
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<tr>
<td>S.Q.</td>
<td>25</td>
<td>M</td>
<td>MVA</td>
<td>T4</td>
<td>2</td>
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<td>D</td>
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<td>M.H.</td>
<td>33</td>
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<td>CA:SURG.</td>
<td>T10</td>
<td>4</td>
<td>0.20</td>
<td>D</td>
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<tr>
<td>S.H.</td>
<td>24</td>
<td>M</td>
<td>MVA</td>
<td>C7-T1</td>
<td>0.75</td>
<td>0.50</td>
<td>C</td>
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<tr>
<td>E.P.</td>
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<td>MVA</td>
<td>T7</td>
<td>1</td>
<td>0.20</td>
<td>B</td>
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<tr>
<td>J.C.</td>
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<td>MVA</td>
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<td>E.C.</td>
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<td>CA:SURG.</td>
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<td>B</td>
</tr>
<tr>
<td>J.P.D</td>
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<td>M</td>
<td>MVA</td>
<td>T7</td>
<td>2</td>
<td>0.15</td>
<td>B</td>
</tr>
<tr>
<td>F.L.</td>
<td>25</td>
<td>M</td>
<td>MVA</td>
<td>T7</td>
<td>1</td>
<td>0.20</td>
<td>B</td>
</tr>
<tr>
<td>M.F.</td>
<td>37</td>
<td>M</td>
<td>KYPHOSCOL.</td>
<td>C7-T1</td>
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<td>0.10</td>
<td>B</td>
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</table>

**WITHDREW:**

<table>
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<th>NAME</th>
<th>AGE (yrs.)</th>
<th>SEX</th>
<th>ETIOLOGY</th>
<th>LESION LEVEL</th>
<th>LESION CHRONICITY (yrs.)</th>
<th>DAILY DOSAGE (mg.)</th>
<th>FRANKELS CATEGORIES (A-D)</th>
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<td>G.T.</td>
<td>45</td>
<td>M</td>
<td>TRAUMA</td>
<td>T8-10</td>
<td>14</td>
<td>-</td>
<td>B</td>
</tr>
<tr>
<td>R.S.</td>
<td>37</td>
<td>M</td>
<td>MVA</td>
<td>T8-9</td>
<td>20</td>
<td>-</td>
<td>B</td>
</tr>
<tr>
<td>R.L.</td>
<td>57</td>
<td>M</td>
<td>MVA</td>
<td>T11</td>
<td>1.75</td>
<td>-</td>
<td>D</td>
</tr>
</tbody>
</table>
Figure 3.1 Schematic representation of the study design. The orientation assessment session (1) allowed baseline measures to be obtained, and familiarized the subject with the lab. Assessment sessions 2 and 4 were premedication, while sessions 3 and 5 measured the patients' function while on medication.
RESEARCH STUDY DESIGN

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tr>
<td>MEDICATION PERIOD</td>
<td>WASHOUT</td>
<td>MEDICATION PERIOD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>PERIOD</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4 weeks)</td>
<td>(2 weeks)</td>
<td>(4 weeks)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1: Orientation assessment session
2: Premedication (A) assessment session
3: Postmedication (A) assessment session
4: Premedication (B) assessment session
5: Postmedication (B) assessment session
assessment session, after which he was given a tablet of medication A. To detect possible severe side-effects, the patient remained in the laboratory for an hour following the administration of the medication, with his blood pressure monitored first in supine then sitting position every 15 minutes. None of the patients demonstrated hypotension or other side-effects in this first hour. Following this, the subject was provided with a four week supply of the medication, with the prescribed titration protocol (Table 3.2). The random allocation of placebo and clonidine to medication periods A or B was conducted by Boehringer-Ingelheim Co. prior to the onset of the study; only one research assistant was informed as to the order of the medications. As the subject began each medication period, the informed research assistant contacted the local public health nurse and a referral was made. The nurse visited the patient every third day, during the periods of dosage increase and decrease, monitoring vital signs, using the standard form attached (see Appendix 2A, 2B), to monitor the patient's status for the presence of adverse side-effects. The research assistant contacted the nurse to record the results of each assessment, and also called the patient himself every third day during dosage increase and decrease periods, to monitor his condition. At the end of the medication period (A), the patient returned for the third assessment session, followed by a two week washout period. A fourth assessment session
TABLE 3.2 Clonidine Titration Procedure. This protocol for increasing and decreasing the dosage of clonidine (Dixarit (R)) was provided to each patient in both medication periods.
Table 3.2

**CLONIDINE TITRATION PROCEDURE**

**INCREASING DOSAGE**

DAY 1-3:  0.05 mg/day  (1 tablet b.i.d. = 2 tablets/day)
DAY 4-6:  0.10 mg/day  (2 tablets b.i.d. = 4 tablets/day)
DAY 7-9:  0.15 mg/day  (3 tablets b.i.d. = 6 tablets/day)
DAY 10-12: 0.20 mg/day  (4 tablets b.i.d. = 8 tablets/day)
DAY 13-28: 0.25 mg/day  (5 tablets b.i.d. = 10 tablets/day)

* dosage is increased every 3 days, as this allows for manifestation of peak period effects

**DECREASING DOSAGE**

DAY 29-31: 0.15 mg/day  (3 tablets b.i.d. = 6 tablets/day)
DAY 32-34: 0.05 mg/day  (1 tablet b.i.d. = 2 tablets/day)

* medication is stopped on the 35th day. The following 8 days of the washout period allows residual drug to be eliminated from the body.

* placebo dosage increase and decrease followed the same protocol to assist in maintaining the double blind format.

* tablets are 0.025 mg, therefore when taken b.i.d., the basic daily dosage is 0.05 mg/day.
immediately preceeded the final 4 week medication period (B). and the fifth assessment session at the end of period B concluded the study.

3.3 Treatment Intervention

To minimize the possibility of adverse side-effects, the titration procedure, involving twice daily (b.i.d.) oral administration of the medications, was established in consultation with Dr. Allen Davis of Boehringer-Ingelheim Co., and was strictly followed for all patients (Table 3.2, appendix 3A, 3B). The program was based on the fact that peak blood plasma level for clonidine occurs within 3 hours following oral administration, with a cumulative peak period of 3 days (Arndts et al., 1983). Hence, the medication was increased every third day, following a visit by the public health nurse. In this manner, the dosage was gradually increased from an initial level of 0.05 mg/day to the optimal dosage of 0.25 mg/day (as tolerated) over the first 12 days of the clonidine medication period.

Optimal dosage is defined as the highest dose level of medication within the titration range producing minimal or no side-effects. Secondary effects most commonly associated with clonidine are: hypotension, sedation, dryness of mouth and/or eyes, dizziness, headache, and depression. However, these were thought to be minimized at the dosage ranges involved in this study. Individualized optimal drug levels were thus set
for each patient by the research assistant in conjunction with the nurse and the consultant neurologist, based on the patient's response to the medication, as determined by the nurse's assessments and the patient's own feedback. At the end of the 4 week medication period, following the assessment session, the dosage was decreased according to the titration protocol, with drug 'weaning' completed by the sixth day of the decrease period. This allowed a further week for the elimination of residual drug from the patient's body.

S.Q., a preliminary study patient, took only clonidine as he was not involved in the double-blind main study format, while each patient in the main study took both clonidine and the placebo. Both placebo and clonidine were graciously provided by the Boehringer-Ingelheim Co. The placebo and clonidine tablets were identical in appearance helping to maintain the double blind component of the study, as both the researcher and the patient were naive to the type of medication. The titration procedures for the placebo and the clonidine were also identical.

3.4 Assessments

3.4.1 Clinical Assessments (Appendix 4)

a) Overground Locomotion: The paraparetic patients walked between an 8 foot long parallel bars along a series of rubber mats with powder coating the soles of their shoes, such that each step left a residual footprint of powder. EMG,
footswitch, and video recordings were also taken. Measurements were made from the residual footprints to determine bilateral stride length, cadence and velocity.

b) Visual Analog Scale: Before each assessment session, the patients were asked to rate the severity of their current level of spasticity, using a visual analog scale. On the patient's side, there were two points on the scale, one corresponding to the maximum spasticity they had ever experienced, and the other to the minimum amount of spasticity within their experience. The opposite side was demarcated on a 10 point scale to provide the researcher with a numerical score corresponding to the patients' response. Additionally, patients were asked to keep a daily record of the frequency of clonus and spasms over the weeks they participated in the study. (Appendix 5)

c) Tonic Stretch Reflex (TSR): The right and left ankle were slowly dorsiflexed with the knee supported in extension, and then again with the knee in flexion. The strength of the TSR was recorded on a 5 point scale (0:normal resistance, 1:minimal resistance, 2:moderate resistance, 3:strong resistance, 4:maximum resistance). Passive flexion and extension of the knee were also conducted.

e) Clonus Test: Evoked ankle clonus test was conducted with the patient seated comfortably with hips in 90°. The patient's ankle was briskly dorsiflexed and maintained in dorsiflexion until cessation of clonus, first with the knee
extended (0°) and repeated with the knee in flexion (90°). The degree of clonus was recorded, using a 4 point scale (0: no clonus, 1: one to two beats, 2: more than two beats, 3: sustained clonus).

3. 4. 2. Assessment of Treadmill Locomotion

As shown in figure 3.2, the subjects walked on a motor-driven treadmill (W.E. Collins #101), while comfortably supported in a custom built overhead modified Tyrolean harness, and with 1 hand on the horizontal railing extending the length of the treadmill. The treadmill speed was set at 0.26 m sec⁻¹ for all subjects. A weight calibration system which adjusted the height of the harness to take a greater or lesser percentage of the body weight, was utilized to provide body weight support (BWS). For those paraparetics capable of locomotion, this BWS system provided the support necessary to allow them to walk without having to support their total body weight or to maintain postural control. For those unable to stand or walk, the system lifted the patient from their wheelchair into a standing position, and supported their body weight in stance and during assisted locomotion. The BWS system has been reported in detail (Barbeau et al., 1987). For the paraplegics, all locomotor trials were at 100% BWS, while for the paraparetics, treadmill locomotor trials were conducted with BWS varying from 0% - 50%. For those unable to walk independently, research assistants positioned on
Figure 3.2  Lateral (A) and posterior (B) views of the body weight support system (BWS) and treadmill. The subject is supported in a harness while walking on the treadmill. Transducers are used to quantify the BWS provided; a gauge indicates the ongoing percentage of BWS. (from: Barbeau et al., Description and application of a system for locomotor rehabilitation, Med. and Biol. Eng. Comp., 25, 341-344, 1987.)
either side of the treadmill belt manually guided the patient's legs to simulate a locomotor pattern. When specifically assessing the ability to step independently, assistance would be provided to one leg while the patient attempted to step with the contralateral limb.

The trials of treadmill locomotion were adapted to suit the capacity of each subject. Blood pressure and heart rate readings were taken by the researcher at the commencement of the first trial, and at the end of each trial. The trials were 2 - 5 minutes in length, followed by rest periods of at least 5 minutes. Trials were terminated immediately if signs of fatigue were observed, or if other signs of discomfort were noted. Although the treadmill was controlled by the researcher, the patient had a safety button with which he could stop the treadmill immediately, in case of emergency.

As the patient walked on the treadmill, surface EMG electrodes recorded muscle activity, bilateral footswitches provided temporal parameters of each step cycle, a video camera recorded movements of the patients lower limbs in the sagittal plane, and an audio channel recorded the researcher's comments. To synchronize the EMG and kinematic data, a time code generator (Skotel: TCG-80) produced time codes which were recorded on both the video tape and the FM magnetic tape.

a) Electromyography: EMG recordings of activity in the 5 main lower extremity muscle groups were obtained by placing disposable, bipolar, surface electrodes (silver-silver
chloride Meditrace pellet electrodes), after appropriate skin preparation, over the bellies of the following muscles of both legs: Vastus Lateralis (VL), Medial Hamstrings (MH), medial head of Gastrocnemius (GA), Tibialis Anterior (TA), and the right Gluteus Maximus (GM). Skin preparation and electrode placement was carried out according to Basmajian’s text (Basmajian 1982). An acupuncture point finder (MEA WQ-10C) was used supplementarily to verify the location of each motor point. EMG signals were pre-amplified before being further amplified and bandpassed (10Hz - 1kHz). Subsequently, EMG and footswitch signals were simultaneously displayed on a 16 channel oscilloscope (Nikon-Kohen VC-680) and recorded on FM tape by a 14 channel magnetic FM tape recorder (Honeywell #101) at 3.75 i.p.s. (frequency response of 2500 Hz). The raw signals were full wave rectified and linear enveloped (second order Butterworth filter low pass cut-off 3.0 Hz) before being digitized by the PDP 11/34 at a 1 KHz sampling rate.

b) Footswitch Recordings: Footswitches (Tapeswitch System of America) were attached to the patients’ shoe directly under the base of the great toe, fifth metatarsal, and heel of the foot. Each footswitch has a distinct voltage activated by pressure, such that weight borne through the heel, ball, or toe of the foot has a characteristic configuration in the recorded trace. Thus, critical events of the step cycle (foot floor contact, foot flat (midstance), toe off) could be
Figure 3.3 The right (CONR) and left (CONL) footswitches and EMG activity for the right MH of a normal subject walking at 0.97 ms\(^{-1}\) on the treadmill at 30% BWS. Heel contact (HC), foot-flat (FF), and toe-off (TO) are indicated on the CONR trace. Stance and swing phases of the gait cycle, double support period (DS) and total cycle duration (CYCLE) are shown. (from: Barbeau et al., Description and application of a system for locomotor rehabilitation, Med. and Biol. Eng. Comp., 25, 341-344, 1987.)
identified through the foot switch recording trace, and temporally linked to muscle activation patterns (fig. 3.3). Duration of step cycle, stance/swing ratios, and percentage total double support time (% TDST) could also be determined from the footswitch recordings.

c) Video recordings: To allow recording of kinematic characteristics in the sagittal plane, the subject had adhesive-backed reflective markers attached to the shoulder, greater trochanter, knee joint line, and lateral malleolus of the right leg, as well as on both shoes at the heel, fifth tarsal-metatarsal joint, and toe. Two 1000 watt quartz lamps (Acme Lite Co. 710SL) provided direct illumination of the treadmill area. Additional markers on an L-shaped reference frame gave absolute horizontal and vertical coordinates for subsequent video analysis. Sagittal movements of the patients' trunk and lower extremities were filmed with a rotary shutter video camera (Sony: RSC-1010) placed 4 meters from and perpendicular to the treadmill, and set at an exposure time of 1/500 sec. The trials were viewed on a video monitor (Panasonic: WV-5470), and recorded on 3/4" video tape (video cassette recorder Panasonic: NV-9240) at 60 fields/sec. Subsequent kinematic analysis involved measurement of angular displacements of hip, knee and ankle joints.

3.5 DATA ANALYSIS

The linear enveloped EMG and footswitch signals were
displayed on the computer terminal (Transiac 1024), and cursors indicating the initiation and termination of EMG burst activity of every muscle for several consecutive step cycles were manually inserted. Subsequent computer analysis provided information on temporal aspects of the muscle activity, as well as on the EMG activation profile. Representative and consecutive gait cycles were normalized to each step cycle duration, with consecutive heelstrikes occurring at 0% and 100%. The EMG was averaged over 0.4% of the gait cycle, yielding a within subject ensemble average profile for each muscle. Amplitudes were determined in terms of microvoltage, as well as in percentage of ensemble average peak amplitude (100%) over the step cycles chosen.

Temporal distance gait characteristics including: % double support, step cycle duration, % stance, and cadence, were also determined using manually inserted arrow markers on the footswitch traces at the initiation and termination of stance and swing phases for each of the step cycles analysed. Both EMG and temporal step cycle characteristics were normalised to the step cycle.

Kinematic data was analysed directly on the video monitor. Angular displacements of the trunk, hip, knee, and ankle joints were measured at 5% intervals through representative step cycles. To provide a comparative reference, EMG and kinematic data were also recorded as a normal subject walked at a comfortable speed on the treadmill.
(1.36 ms\(^{-1}\)) at 0\% BWS in the overhead harness.

Additionally, the footprints from the over-ground locomotion trials were manually measured to determine stride length, cadence, and velocity as described by Shores (1980) and Robinson (1977).

T-tests were used to compare such aspects of locomotor function as cycle duration, \% stance, stride length, and \% total double support time between the placebo and clonidine sessions.
CHAPTER FOUR: RESULTS AND DISCUSSION

I. THE EFFECTS OF CLONIDINE IN THE MODULATION OF THE
   LOCOMOTOR PATTERN IN SPASTIC PARETICS: A PRELIMINARY STUDY
   (to be submitted to: Journal of Neurology, Neurosurgery, and Psychiatry)

II. THE EFFECTS OF CLONIDINE IN THE REDUCTION OF SPASTICITY
    IN SPINAL CORD PATIENTS: A PRELIMINARY STUDY
    (To be submitted to: Journal of Neurology)
I. The Effects of Clonidin in the Modulation of the Locomotor Pattern of Spastic Paretics: a Preliminary Study" 

This paper describes the effect of clonidine on the locomotor pattern in 3 paraparetic and 6 paraplegic patients participating in this double-blind crossover study. EMG, footswitch, and video recordings were made while the patients walked on the treadmill at 0.26 ms\(^{-1}\), while supported in an overhead harness system. Where necessary, research assistants manually moved the patients' lower extremities to simulate a walking pattern. Overground locomotion between parallel bars was also assessed in the paraparetic patients.

1/3 of the paraparetics experienced a significant improvement in locomotor function, gaining the ability to take independent steps while on clonidine. The other 2/3 paraparetics experienced some modification of EMG profile and timing, and kinematics, associated with a reduction in locomotor spasticity. The effect of clonidine among the paraplegics was to decrease tonic stretch reactions, spasms and clonus without altering their locomotor ability.
THE EFFECTS OF CLONIDINE IN THE MODULATION OF THE LOCOMOTOR PATTERN OF SPASTIC PARETICS: A PRELIMINARY STUDY

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Key Words: locomotion, clonidine, spastic paretic gait, spasticity
Spastic paraparetic gait has been characterized by an alteration in the timing, duration, profile and variability of EMG activity (Knutsson 1983), as well as by changes in hip, knee and angle kinematics, and a prolongation of both stance phase and percentage total double support time (% TDST) (Conrad et al. 1983, 1985). Furthermore, difficulty in coping with increased speed has also been reported in spastic paraparetics during treadmill walking (Barbeau et al. 1988).

It has been hypothesized that these gait abnormalities stem from a disturbance in the normal supraspinal modulation of polysynaptic and monosynaptic reflexes (Dietz 1986), resulting in hyperactive stretch reactions evoked as the muscle lengthens (Knutsson and Richards 1979), and in stretch and loading reactions related to weight-bearing (Knutsson 1985).

A treatment strategy which could address these problems would be of considerable benefit for the spastic paraparetic population. Recent clinical trials have explored the antispastic effects of the noradrenergic alpha₂ agonist clonidine on spastic spinal cord patients. Clonidine was reported to decrease muscular hypertonus (Maynard 1986, Nance 1985, Tuckman 1982), spontaneous spasms (Nance 1985, Tuckman 1982) and to a lesser extent, clonus (Maynard 1986). However, all of these were qualitative, descriptive studies investigating clinical spasticity, with little objective quantification of results and minimal reference to effects in functional motor activities such as locomotion.
The effect of clonidine in modulating locomotion and spinal reflexes has been investigated in the chronic spinal cat (CSC) (Rossignol et al. 1986, Barbeau et al. 1987). In this animal model, clonidine decreased the flexion reflex and abolished the fast paw shake reflex (Rossignol et al. 1986, Barbeau et al. 1987). Moreover, clonidine has been shown to trigger rhythmic stepping in acute spinal kittens (Grillner and Zangger 1979) and modulate the locomotor pattern in CSC (Rossignol et al. 1986, Barbeau et al. 1987). These modulatory effects are thought to reflect the action of clonidine on the spinal neuronal circuitry which has been implicated in the generation of the locomotor pattern (Grillner and Zangger 1979, Grillner 1981).

In light of these findings, clonidine appears to have potential as an effective antispastic medication for spinal cord injured patients. Moreover, based on animal studies, clonidine has been demonstrated to have a modulatory effect on spinal locomotion. The purpose of this study was therefore to investigate the effects of clonidine on the locomotor function of patients with incomplete chronic spinal cord lesions and to explore the possibility of clonidine initiating locomotor activity in patients with clinically complete spinal cord lesions.

METHODOLOGY

Table 4.1.1 summarizes demographic information for the
Table 4.1.1. Demographic details of the patients. MVA: motor vehicle accident, CA: SURGERY: lesion secondary to surgery for cancer, KYPHOSCOL: kyphoscoliosis resulting in progressive paralysis, TRAUMA: fall resulting in SCI. Frankel's classifications: B: incomplete sensation, no motor function below the lesion, C: incomplete sensation, no useful motor function below lesion, D: incomplete sensation, some useful motor function below lesion.
## DEMOGRAPHIC DATA

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<th>SEX</th>
<th>ETIOLOGY</th>
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<th>DAILY DOSAGE (mg.)</th>
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<th>DAILY DOSAGE (mg.)</th>
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patients participating in this study. Six of the nine patients who completed the study had lesions of traumatic origin, two developed the lesion secondary to surgery for cancer, and one had a progressive kyphoscoliosis which caused paralysis five years previously. Furthermore, six had incomplete sensation and no motor function below the site of the lesion (Frankels category B). Two had incomplete sensation and some useful motor function (Frankels category D), and one had incomplete sensation and no useful motor function due to excessive spasticity (Frankels category C) (Frankel, 1972). For the purpose of this study, patients in categories C and D will be further designated as paraparetics, because of their residual motor function; those in category B will be designated as paraplegics, reflecting their lack of motor function below the lesion. The lesion chronicity ranged from 8 months to 10 years. The three patients who did not complete the study, withdrew for reasons of illness or poor compliance with the protocol.

This double-blind crossover study involved two 4 week medication periods separated by a 2 week washout period. The order of clonidine and placebo was randomly assigned. Clonidine and placebo were administered per oris on a b.i.d. basis. The basic dose per tablet was 0.025 mg.; the initial daily dosage was 0.05 mg/day. The daily dosage was then systematically increased over the proceeding two weeks until an optimal level was reached for each patient. The optimal
dosage level was defined as the maximum level of medication within the titration range which caused minimal side-effects. The titration protocol was developed in collaboration with Boehringer Ingelheim, establishing optimal dose levels within the 0.05 - 0.25 mg range which was below the range prescribed for hypotensive effects. All of the patients were stabilized within this range except S.H., who independently raised his daily dosage level to 0.50 mg despite instructions. S.Q. was a preliminary subject, therefore he did not receive the placebo medication, and his results were taken from a pre-medication session and a clonidine medication session.

Following an initial orientation, assessment sessions preceded and proceeded each medication period to evaluate treadmill and overground locomotion, as well as clinical spasticity, including tonic stretch reflex of the ankle and knee, ankle clonus, and measurement of the patient’s perceived levels of spasticity using a visual analog scale. The results of the clinical spasticity tests are reported elsewhere (Stewart, Barbeau and Gauthier, in prep.). During the treadmill locomotion trials, the subjects walked on a motor-driven treadmill (W.E. Collins #101), while comfortably supported in a custom-built overhead harness, with one hand on the side railing. A weight calibration system, which adjusted the height of the harness to take a percentage of the body weight, was utilised to provide body weight support (BWS) as required for the paraparetic patients who could not walk
at full weight. For the paraplegics, the BWS system was used to lift the patients from the wheelchair to the standing position, and to support their weight during assisted locomotion. This system has been described previously (Barbeau et al. 1987). All patients walked on the treadmill at the minimal speed of 0.26 ms$^{-1}$; for those unable to advance their lower limbs independently, research assistants manually guided the legs to simulate walking. When the ability to step independently was being specifically investigated in the paraplegics, manual assistance would be provided to one leg while the patient attempted to advance the other.

Overground locomotion was assessed as the paraparetics walked between a set of parallel bars 8 feet in length, with powder under their shoes. The resulting footprints were then measured to determine velocity, cadence, and stride lengths.

Surface EMG, video and footswitch recordings were made during treadmill and overground locomotion trials to measure muscle activation pattern, kinematic data, and temporal distance aspects of each gait cycle. Bipolar surface EMG electrodes were used to detect the activity of nine muscles involved in locomotion: right Gluteus Maximus (GM), right and left Medial Hamstrings (MH), Vastus Lateralis (VL), Tibialis Anterior (TA), and the medial head of Gastrocnemius (GA). Signals were preamplified before being further amplified and bandpassed. The high pass filter was set at 10 Hz, the low-pass filter at 1 KHz. EMG and footswitch recordings were
displayed on an oscilloscope (Nihon Kohden V.C.-680G) and recorded by a 14 channel magnetic FM tape recorder (Honeywell #101) at 3.75 i.p.s. (frequency response at 2500 Hz). Additionally, the researcher’s observations were recorded on an audio channel onto both the FM and video tapes. A time code generator (Skotel: TCG-80) was also recorded on both tapes to synchronize the video and EMG data. For subsequent analysis, raw signals were full wave rectified and linear enveloped (second order Butterworth filter low pass cut-off 3.0 Hz) before being digitized at a 1 KHz sampling rate with a PDP 11/34. Subsequent computer analysis provided information on temporal aspects of the muscle activity, as well as on the EMG activation profile. To allow between-session and between-subject comparisons, consecutive representative gait cycles were normalised to the gait cycle duration, with consecutive heelstrikes occurring at 0 and 100%. The EMG was averaged every 0.4% of the gait cycle, yielding a within-subject ensemble average EMG profile for each muscle. The amplitude of the EMG profile was also normalised to the ensemble average peak amplitude (100%). Kinematic characteristics of the patients’ gait were recorded on video, using reflective markers attached to landmarks at the shoulder, hip, knee, and ankle joints. Reference markers gave absolute coordinates for subsequent video analysis. Movements of the patients’ lower extremities in the sagittal plane were filmed with a rotary shutter video camera (Sony:
Trials were simultaneously viewed on the video monitor (Panasonic WV5470) and recorded on 3/4" videotape at 60 fields/sec. Angular excursion of the lower extremity joints were subsequently measured at 5% intervals across a representative step cycle. To determine joint angles, measurements were taken directly from the video monitor, using a goniometer.

To provide a comparative reference, EMG and kinematics were also recorded from a normal subject walking on the treadmill while in the overhead BWS harness, at a comfortable walking speed (1.36 ms⁻¹) and at 0% BWS.

In comparisons of gait characteristics between assessment sessions for S.Q. and M.H., the EMG, kinematic and temporal data presented reflect their gait patterns on the treadmill at the minimal speed of 0.26 ms⁻¹ and the lowest level of BWS at which they can walk independently in both sessions (S.Q.: 0% BWS, M.H.: 40% BWS). EMG, kinematic and temporal distance data are presented for S.H. walking overground, as this was his only means of independent locomotion. T-tests were used to compare the effects of placebo and clonidine on temporal distance factors cycle duration, percentage stance and percentage total double stance time (% TDST).

RESULTS

Overground Locomotion:

The three paraparetic patients (S.H., S.Q., M.H.) had
Figure 4.1.1. Paraparetic S.H. walking overground during placebo (upper row) and clonidine (lower row) sessions. Shown are foot floor contact (A,F), midstance (B,G), toe-off (C,H), midswing (D,I), and subsequent foot floor contact (E,J). Note the changes in trunk posture as well as hands, hip knee and ankle positions between the two sessions.
quite different functional locomotor capabilities at the onset of the study. S.H., the most severely spastic patient, could take 2-3 laborious, spastic steps within a 4 minute period, as illustrated in Figure 4.1.1 A-E. S.H.'s posture was characterized by hip adduction and extension, knee extension, and ankle plantarflexion, resulting in toe standing (fig. 4.1.1 A,B,E). Substantial weight-bearing through the hands occurred, as evidenced by the shoulder girdle fixation and tightly fisted hands (fig. 4.1.1 A,B,D,E). He also used flexion manoeuvres of the trunk (fig. 4.1.1 B,C,D) to initiate advancement of the legs (fig. 4.1.1 D). Cadence and velocity of locomotion could not be calculated, as S.H. could not take consecutive steps, requiring postural readjustments after each of the three steps. With clonidine, a modification in locomotor function was noted, such that he no longer utilised the previous trunk flexion manoeuvres, demonstrating instead a more erect trunk posture (fig. 4.1.1 F-J). He also had more frequent and sustained heel and metatarsal contact with the floor in midstance (fig. 4.1.1 G), improved ability to advance each leg independently (fig.4.1.1 F-J), and reduced weight-bearing through the upper extremities, as suggested by the relaxed position of his hands (fig. 4.1.1 G-J) He was able to take several independent consecutive steps with a cadence of 6.05 steps/min and a velocity of 0.03 m/sec.

Figure 4.1.2 provides the raw EMG activity of the right muscles and footswitch as well as the kinematics for the step
Figure 4.1.2 A and B depict the EMG and footswitch recordings of S.H. walking overground. Note the generalized co-activation of the muscles in the placebo session (left) which is replaced by a more phasic activation pattern in the clonidine session (right). Stance/swing transition occurred at 70% ± 22% (placebo) and 84% ± 7% (clonidine) of the gait cycle. The hip (C,F), knee (D,G) and ankle (E,H) joint angular excursions for a representative gait cycle of S.H. walking overground during the placebo (left) and clonidine (right) sessions are also presented. Points represent every 5% of the step cycle. Arrows indicate TO for each gait cycle.
cycles illustrated in figure 4.1.1. The EMG activity of the right GM, MH, TA, and GA as well as the footswitch recordings revealed some marked changes across the assessment sessions. During the placebo session, a pattern of excessive co-contraction between antagonistic muscles was observed (fig. 4.1.2 A), such that all muscles were co-activated from late swing through stance and early swing phases. In contrast, during the clonidine session, there was a more normal muscle activation pattern relative to the step cycle (fig. 4.1.2 B). GM, VL, and GA were active from late swing through stance to toe-off (TO), while MH showed a main burst of activity during swing and an occasional secondary burst just prior to TO. TA had an unusual activation profile, being biphasically active from mid stance through swing phase. The footswitch recordings also reflected the more regular and slightly shorter gait cycle durations (R: 15000 ± 6788 (n=3) to 12300 ± 1294 (n=5)). This was not a significant alteration, however (p > 0.05). In conjunction, there was more sustained complete heel contact during stance on clonidine. There was no change in % stance (R: 83.4 ± 4.1 % to 84.7 ± 8.0%) (p > 0.05). Stride lengths increased slightly with clonidine (R: 23.63 ± 6.56 cm to 28.89 ± 6.47 cm, L: 24.53 ± 6.91 cm to 25.73 ± 2.00 cm). None of these changes in temporal distance factors were significant (p > 0.05).

Kinematically, the hip (fig. 4.2.2 A), knee (fig. 4.2.2 B) and ankle (fig. 4.2.2 C) angular displacements were
characterized by a gradual increase in flexion across the gait cycle on placebo. On clonidine, coincident with the marked changes in the phasing of muscle activation, both hip (fig. 4.2.2 F) and knee (fig. 4.2.2 G) angular excursion profiles reflected extension occurring in stance, and flexion primarily during swing phase. The total angular excursion of the hip increased with clonidine (placebo: 10° to 30°, clonidine: -4° to 30°), due to an increase in extension in stance. However, the total angular excursion of the knee did not alter markedly (placebo: 15° to 46°, clonidine: 12° to 44°), and excessive knee flexion at foot floor contact (FFC) persisted. Ankle plantarflexion at FFC also continued, however this was followed by a more normal profile, with less plantarflexion position through early/mid stance, and plantarflexion proceeding T.O. (fig. 4.1.2 H). Thus, at 20% of the gait cycle, the ankle position was -15° on placebo, and 2° on clonidine, moreover at T.O. it was at 8° on placebo and at -11° with clonidine. The total angular excursion decreased for the ankle (placebo: -15° to 13°, clonidine: -15° to 3°).

The other 2 paraparetics were capable of walking the length of the parallel bars independently. S.Q., a moderately spastic paraparetic, walked at a velocity of 0.10 m/sec., a cadence of 18.00 steps/min., a right stride length of 80.98 ± 7.31 cm, and a left stride length of 81.13 ± 3.43 cm (n=6). M.H., mildly spastic and quite paretic, could walk at a velocity of 0.14 m/sec. and a cadence of 27.3 steps/min., with
a right stride length of 58.96 ± 17.8 cm and a left of 64.27 ± 7.5 cm (n=6). In comparison with normal subjects walking overground at natural rates (107 ± 8.8 steps/min) (Winter 1987), the cadence and velocity were significantly decreased. The paraplegics were incapable of walking overground, except with long leg braces and a swing-through gait.

With clonidine, M.H. and S.Q. did not demonstrate significant alteration in cadence, velocity or stride length in overground locomotion. However, M.H. did show a consistent albeit non-significant (p > 0.05) trend towards decreased percentage stance (R: 73.5 ± 9% to 69.5 ± 6%, L: 75.4 ± 8% to 78.6 ± 5%) and % TDST (50.2 ± 9% to 41.9 ± 10%) (placebo:n=6, clonidine:n=8). There was no change in the paraplegics' inability to walk overground.

Treadmill Locomotion

On the treadmill during the placebo session, S.H. could not walk independently, even with maximum BWS. He was, however, able to step with each leg for several consecutive steps with 50% BWS and manual assistance to the other leg. With clonidine, S.H. still required manual assistance to one leg in order to step with the other independently. On placebo, M.H. could not step at all at 0% BWS, but could walk with occasional manual assistance to the left leg at 40% BWS. With clonidine, M.H. developed the ability to walk at 0% BWS with occasional slight assistance to the left leg. Premedication, S.Q. could walk independently at 0% BWS with
Figure 4.1.3. Overlapped ensemble averages of the EMG activity of MH and VL (A) and TA and GA (B) for a normal subject walking on the treadmill at a comfortable walking speed of 1.36 ms$^{-1}$. Muscle activity is normalized to mean peak amplitude (Y axis) and to gait cycle duration (X axis). Averages represent 5 gait cycles. The average swing/stance transition occurs at 63.7% for these cycles. The hip (C), knee (D), and ankle (E) joint angular excursion for a representative gait cycle are also portrayed, with each point representing 5% of the gait cycle. The arrow indicates TO for the gait cycle represented.
a Klenzac brace on the left leg to maintain the ankle in neutral position, this was maintained on clonidine. Among the paraplegics, none were able to walk independently on the treadmill at any level of BWS on placebo. Their functional locomotor abilities did not change with clonidine. The EMG and joint angular profiles for the normal subject during treadmill walking (fig. 4.1.3) provides a reference for comparison with that of spastic paraparetic gait. As seen in figure 4.1.3 A, VL becomes active in early stance during the loading of the lower extremities to maintain knee stability during single limb support. VL activity terminates as soon as the centre of gravity passes forward over the shank. MH activates in late swing, just prior to VL, to decelerate the forward swinging leg and to facilitate the erect posture of the trunk. MH activity continues until midstance to assist hip extension and upright trunk posture during stance. Thus, co-contraction occurs between VL and MH for the first 20% of the step cycle. In figure 4.1.3 B it can be seen that TA shows a biphasic activation pattern, with the largest peak occurring in early stance for eccentric control of the deceleration of plantarflexion following HS. The smaller peak in early swing is related to the increased dorsiflexion following TO. GA is active primarily through the period of single limb support (SLS) from 20 to 70% of stance period, acting to propel the body forward, and ceasing activity at TO. Thus, TA and GA reflect a mutually reciprocal pattern of
Kinematically, the hip becomes increasingly extended through stance, reaching maximum extension (-20°) at TO, and subsequently flexing through swing, with maximum flexion (26°) occurring just prior to HS (fig. 4.1.3 B). The knee is fully extended at heelstrike, after which it flexes approximately 20 degrees as the body passes over the support leg. Following the initial flexion period, the knee extends again briefly during SLS before again flexing as the heel lifts prior to TO. The maximum swing angle (62°) occurs in mid-swing (fig. 3 C). The ankle is in neutral position at HS, plantarflexes briefly for foot-flat, then dorsiflexes as the centre of gravity passes forward, plantarflexes for push-off, and finally dorsiflexes to the neutral position for the remainder of the step cycle. Maximal dorsiflexion (20°) occurs in mid-stance, with maximal plantarflexion (30°) occurring after TO (fig. 4.1.3 D).

The EMG and kinematic profiles of S.Q. and M.H. demonstrate several deviations from the gait pattern of the normal subject. Premedication, S.Q. showed abnormal VL/MH co-activation, with VL contracting through middle and late stance, and MH active through much of swing (fig. 4.1.4 A). Moreover, GA was active throughout stance, while TA was tonically active in both stance and swing phases, with a similar pattern of activation to GA in stance (fig. 4.1.4 B). Kinematically, the hip remained in flexion, never reaching
Figure 4.1.4. Overlapped ensemble averages of the EMG activity of MH and VL (A,C) as well as TA and GA (B,D) for paraparetic S.Q. walking on the treadmill at 0% BWS. Muscle activity is normalized to mean peak amplitude (Y axis) and to gait cycle duration (X axis). Averages represent 10 and 7 gait cycles for the placebo and clonidine sessions, respectively. Maximum peak amplitudes: premedication: MH: 45.02 uv, VL: 105.32, TA: 64.82, GA: 109.72, clonidine: MH: 61.58, VL: 87.80, TA: 71.08, GA: 53.64. The average stance/swing transition for these gait cycles occurred at 69% ± 4% (placebo) and 74% ± 4% (clonidine) of the gait cycle. Hip (E,H), knee (F,I), and ankle (G,J) joint angular excursions for a representative gait cycle are also portrayed, with each point representing 5% of the gait cycle. Arrows indicate TO for the gait cycle represented.
neutral (fig. 4.1.4 E), and the maximum swing angle of the knee was abnormally high (71°) (fig. 4.1.4 G). Moreover, the ankle was forced into dorsiflexion throughout stance as a consequence of the excessive hip and knee flexion, with only a brief period of plantarflexion in early swing phase. On clonidine, a distinct phasic burst of MH activity occurred in early stance, while VL activity initiated slightly later than previously. Both VL and MH became relatively silent through swing. As a result of these changes, there was a slight reduction of the co-contraction period between MH and VL (fig. 4.1.4 C). Some decrease in TA activity during swing phase, as well as in the level of tonic activation was evident for S.Q., however GA demonstrated an unusual biphasic pattern, apparently secondary to the knee sagging with weight acceptance (fig. 4.1.4 D). However, the second burst which occurred just prior to TO, appears to be a functional burst related to push-off.

Kinematically, there was an increase in maximum hip extension (from 18° to 0°) (fig. 4.1.4 F). Total angular excursion of the hip also increased (27° to 39°), with clonidine. The maximum swing angle for the hip decreased slightly from 45° to 39°. Knee flexion persisted at FFC; moreover a pronounced sag into flexion occurred during SLST, as the loading became maximal. Knee total angular excursion was unchanged, although maximum extension increased slightly (44° to 40°) and maximum swing angle decreased slightly (69°
Figure 4.1.5. Overlapped ensemble averages of the EMG activity of MH and VL (A,C) as well as TA and GA (B,D) for paraparetic M.H. walking on the treadmill at 40% BWS. Muscle activity is normalized to mean peak amplitude (Y axis) and to gait cycle duration (X axis). Averages represent 12 and 11 gait cycles for the placebo and clonidine sessions respectively. Maximum peak amplitudes: Clonidine: MH:10.98 uv, VL:54.42 uv, TA:34.04 uv, GA:26.66 uv. Placebo: MH:14.06 uv, VL:32.10 uv, TA:53.78 uv, GA:23.80 uv. Swing/stance transition occurred at 66% ± 10% (placebo) and 64% ± 6% (clonidine) of the gait cycle. Hip (E,H), knee (F,I), and ankle (G,J) joint angular excursions for a representative gait cycle are also portrayed, with each point representing 5% of the gait cycle. Arrows indicate TO for the gait cycle represented.
The ankle reflected a decrease in the imposed dorsiflexion, with an increase in plantarflexion prior to T.O. (fig. 4.1.4 J). Thus, ankle angular excursion increased slightly ($9^\circ$ to $13^\circ$), with an increase in the maximum plantarflexion angle ($-7^\circ$ to $-18^\circ$) and decreased dorsiflexion ($16$ to $5^\circ$).

The mean cycle duration for S.Q. was unchanged (R: $3296 \pm 256$ to $3238 \pm 145$ ms, L: $3288 \pm 362$ to $3302 \pm 419$ ms), while % stance increased on the right and decreased on the left (R: $69.1 \pm 4.0\%$ to $76.9 \pm 2.9\%$, L: $77.9 \pm 5.0\%$ to $66.6 \pm 7.0\%$) and % TDST decreased ($45.8 \pm 7.0\%$ to $40.9 \pm 8.0\%$) (pre-medication: n=10, clonidine: n=7). Of these changes, the decrease in right % stance and increase in left % stance were significant ($p < 0.05$).

As illustrated in figure 4.1.5 A, M.H. demonstrated almost complete VL and MH co-activation throughout stance. TA was tonically active throughout the step cycle, with GA activity initiating in swing and persisting throughout stance (fig. 4.1.5 B). Moreover, as with S.Q., the pattern of activation for TA and GA was similar in stance.

Kinematically, the hip total angular excursion was within the normal range ($-10$ to $24^\circ$) (fig. 4.1.5 E), however his knee locked into extension during stance, concurrent with simultaneous activation of VL, MH, and TA (fig. 4.1.5 A,B,F). The ankle remained in neutral position after plantarflexion in early stance, until the next plantarflexion phase occurring
with TO (fig. 4.1.5 I).

With clonidine, there was a marked reduction in the duration of the MH main burst, and more appropriate relative VL/MH timing (fig. 4.1.5 C). Moreover, TA/GA activation profiles more closely approached the normal reciprocal relationship, with GA active across stance and TA during swing phase (fig. 4.1.5 D). Kinematically, M.H. showed a reduction in the previously noted knee hyperextension (fig. 4.1.5 H), and a sag into flexion was evident across stance. Total knee angular excursion increased from 37° to 44°, with a decrease in the maximum extension (−6° to 0°), and no change in the maximum swing angle. Little change was noted in the hip profile (fig. 4.1.5 F), other than the slight sag into flexion in late stance concommitant with knee flexion. The total angular excursion, maximum extension, and maximum swing angle of the hip were unchanged across the two sessions. The ankle remained in dorsiflexion throughout the step cycle, probably secondary to the increase in knee flexion (fig. 4.1.5 J). As a result, the total angular excursion of the ankle decreased from 23° to 13°, with a decrease in maximum plantarflexion (−16° to 0°) and increased dorsiflexion (8° to 13°). The mean cycle duration decreased (R:3140 ± 468 to 2651 ± 371 ms, L:3238 ± 445 to 2583 ± 259 ms), while % stance increased (R:59.4 ± 16.0% to 64.5 ± 6.0%, L:65.3 ± 7.0% to 66.8 ± 6.0%), and % TDST decreased (49.4 ± 13.0% to 30.0 ± 6.0%) (placebo: n=12, clonidine: n=11). Of these changes, only the decrease
Figure 4.1.6. EMG activity in right muscles for paraplegic F.L. during assisted treadmill locomotion in the premedication session. Downward arrows indicate FFC, upward arrows TO, and horizontal lines reflect stance phase. Arrow A indicates when verbal instructions were given to prepare to step with the right foot, arrow B shows when the examiner released F.L.'s leg. The dashed line indicates the period during which F.L. attempted to initiate stepping. The subsequent period before the next FFC coincides with the dragging of his foot backwards by the treadmill, and the manual assistance of the examiner to bring the leg forward again.
Thus, all 3 paraparetics demonstrated prolonged and abnormal EMG recruitment profiles during the premedication or placebo sessions. With clonidine, more phasic MH profiles emerged. The degree of co-activation between VL and MH as well as TA and GA was reduced for all patients. Kinematically, the changes in locomotor strategy demonstrated by all paraparetics were manifested by modifications in hip and knee profiles especially. Some kinematic deviations, notably knee flexion at FFC and increased knee stance flexion, persisted in all paraparetics.

B. Paraplegics

Among the paraplegics, none were able to initiate independent stepping, resulting in a passive dragging, by the treadmill, of the leg not manually assisted. The EMG activity associated with this often reflected a widespread clonic discharge. Figure 4.1.6 provides an example of the strong clonic activity evident in all muscles of F.L. as he attempted to advance his right leg. The rhythmically phasic VL and MH activity observed during the assisted locomotion was replaced by a marked clonic activation both preceding and concomittant with the dragging of the foot when independent stepping was attempted, as indicated by the footswitch.

During assisted locomotion for the paraplegics, regular EMG bursts were characteristically seen in the medial hamstring muscles, as well as regular clonic discharge in the
Figure 4.1.7. Bilateral MH EMG activity and footswitch traces for paraplegic E.P. during assisted treadmill locomotion are presented for the placebo (A) and clonidine (B) sessions. Recordings of left MH EMG during passive knee extension for the placebo (C) and clonidine (D) sessions are also presented. The examiner attempted to maintain a constant speed of passive flexion and extension within and between sessions (note durations of knee extension indicated). Horizontal bar indicates 1 second, vertical bar reflects calibration of 100 uv.
TA and GA muscles. Figure 4.1.7 A depicts right and left MH EMG activity for a paraplegic, E.P., during assisted locomotion while on placebo. Both right and left MH showed a consistent step-to-step activation from midswing to midstance (fig. 4.1.7 A), which was no longer present during the clonidine session (fig. 4.1.7 B). The timing of this burst was consistent with the stretch applied to the hamstrings in mid/late swing, when the knee was passively extended as the leg was drawn forward by the experimenters, in preparation for heel strike. Moreover, during passive flexion and extension of the knee with E.P. seated, a TSR was evoked in MH in the placebo session (fig. 4.1.7 C) which was completely suppressed with clonidine (fig. 4.1.7 D). Furthermore, during assisted locomotion while on clonidine, the experimenters reported a reduction in the resistance previously felt when pulling the lower leg forward. This reduction in stretch reactions in MH during locomotion was demonstrated in 4/6 paraplegics (F.L., E.P., J.C., J.P.D.) on clonidine.

Figure 4.1.8 A illustrates clonic activation in TA and GA which was evoked during assisted locomotion in F.L. on placebo. The clonus initiated at heelstrike, and persisted until early swing phase as the muscles were loaded and lengthened. On clonidine, the clonus was reduced to less than 1 to 2 beats (fig. 4.1.8 B). Consistent with the diminution of clonus during locomotion, the sustained clonus evoked in
Figure 4.1.8. Right TA and GA EMG activity of paraplegic F.L. during assisted treadmill locomotion are depicted for the placebo (A) and clonidine (B) sessions. Downward arrows indicate FFC, while upward arrows indicate TO. Evoked ankle clonus is reflected in the TA and GA EMG activity for the placebo (C) and clonidine sessions (D). Horizontal bar indicates 1 second, vertical bar reflects 100 uv.
PLACEBO

A TARI

GARI

CONR

C TARI

GARI

CLONIDINE

B TARI

GARI

CONR

D TARI

GARI
sitting with the hip and knee at 90° position while on placebo (fig. 4.1.8 C) was abolished with clonidine (fig. 4.1.8 D).

DISCUSSION

The paraparetic subjects demonstrated several characteristic features of spastic paraparetic gait as described previously, namely abnormal timing of muscle activation, prolonged burst duration with abnormal EMG activation profiles, muscle weakness or paresis, spontaneous flexor spasms, and excessive tonic background EMG activity especially in the flexor muscles such as MH and TA.

S.H. demonstrated a very abnormal pattern of muscle activation with great inter-step variation. While standing upright, his extensor muscles manifested marked hypertonia, which could be relaxed only by assuming extreme trunk flexion. Thus, such a pattern of spasticity resembled the clasp-knife reflex, which has been described as a common feature of spinal spasticity and associated with the activity of high threshold group III and IV muscle afferents (Rymer et al., 1979).

A relationship was observed between the EMG activation profiles of M.H. and S.Q. and lengthening and stretch activation of the muscles. This was especially evident for the two bi-articular muscles GA and MH, with GA most active during concommittant knee extension and ankle dorsiflexion, and MH during simultaneous hip flexion and knee extension. Alternatively, VL showed a prolonged activation for all patients across the stance phase, with peak activation
occurring between 0 - 25% gait cycle, when the muscle is relatively shortened but loading is maximal. The notion that the VL recruitment period may reflect some reaction to load is further supported by the consistent termination of activation with the initiation of hip and knee flexion before T0 in both S.Q. and M.H.. These hyperactive stretch reactions and the response to loading both contributed to the prolongation of the EMG burst duration.

The TA activation profile for M.H. and S.Q. was biphasic, with the timing of the first burst closely associated with that of GA, while the second peak paralleled the muscle lengthening on ankle plantarflexion. Herman et al. (1973) also described a marked coactivation of calf extensors and flexors in paraplegic subjects, ascribing the phenomenon to either increased muscle afferent discharge or decreased activity in the Ia inhibitory interneurons. This may be a plausible explanation for the first burst of TA activation in S.Q. and M.H. The second burst appears to be more related to the normal pattern of TA activity during swing which serves to clear the foot from the ground.

In addition to the stretch-induced activations associated with muscle lengthening and loading, a high level of tonic background activity was evident for all paraparetics, especially in the flexor muscles. This reflects the elevated resting level of EMG activity underlying the hypertonus which characterizes spastic spinal cord patients. The
neurophysiological mechanisms underlying this phenomenon have yet to be elucidated, although a disturbance in the alpha-gamma linkage involved with muscle activation and reciprocal inhibition has been postulated (Yanigisawa, 1980).

Associated with these EMG abnormalities were various kinematic deviations. With S.H., the result of the flexor maneuvers of the trunk caused a gradual increase in flexion in all lower extremity joints, as the flexor pattern began to dominate. In the case of M.H., the paretic lower extremity muscles were apparently insufficient to dynamically stabilize his knee (M.H. EMG mean peak amplitude for clonidine session: MH: 14.06 uv, VL: 32.10 uv; normal mean peak amplitude MH: 183.6 uv, VL:201.10 (Winter, 1987)). Therefore, the knee tended to snap into extension at the beginning of SLST, and remained locked in full extension or hyperextension until just before TO. His leg also tended to externally rotate through stance, with some circumduction occurring in swing, resulting in a reduced degree of knee flexion. S.Q. demonstrated decreased hip, knee, and ankle extension in stance, reflecting muscle weakness which was associated with difficulty coping with load. The predominant knee flexion sag immediately after FFC and again in midstance may be linked to the same difficulties.

With clonidine, there was a dramatic alteration in the timing of all muscles for S.H., with a phasic pattern of activation replacing the previous tonic activity evident in
all muscles. This, in turn, permitted the expression of a more functional locomotor pattern. For M.H. and S.Q., the primary effect of clonidine was an alteration in the activation profiles of the flexor muscles especially, as reflected by changes in the timing and main burst duration of MH, as well as in the degree of tonic activation in TA. Another notable change for S.Q. was the occurrence of a transient but consistent break in the VL and GA EMG activity around the initiation of SLST, concomittant with a marked flexor sag in the hip, knee, and ankle. This may be associated with a diminution in the "crutch spasticity" (Knutsson 1983), which had allowed weightbearing through a knee stiffened by the hyperactive stretch reactions. M.H. also demonstrated increased knee instability, reflected by the occurrence of midstance flexion in all 3 joints. This may be linked to a decrease in the early GA stretch activation which had exerted a posterior thrust on the tibia, causing knee hyperextension. The MH burst which coincided with this may have also reflected a stretch reaction, as it disappeared with the alleviation of the knee hyperextension. This reduction of hyperactive stretch and loading reactions as well as tonic background activity revealed the underlying muscle weakness in both paraparetics, resulting in gait patterns which reflected more paresis than spasticity. As a consequence, with clonidine both became candidates for a supplementary muscle strengthening and locomotor training program. Thus a
comprehensive approach, combining pharmacological intervention with interactive gait training, provides a potential for improving locomotor function (Fung et al., 1988).

The contrast between the striking effects on S.H.'s overground locomotor function and the relatively mild changes noted in S.Q. and M.H. may be related to several factors. S.H. was much less chronic (8 mos. post-lesion) than the other two paraparetics (S.Q.: 2yrs., M.H.: 5 yrs.), and it has been suggested that in the presence of a chronic lesion, physiological changes can result both centrally and at the muscular level (Dietz 1987). Moreover, S.H. was at a much higher dosage level than the other patients, and had a more severe degree of spasticity. S.Q.'s spasticity had already been partially controlled by other medications which he had been taking for the past year, and M.H. had less spasticity in general. With such a small and heterogeneous sample any conclusions have to be drawn with caution, and further investigation is warranted.

It was noted that consistent spontaneous stepping was not initiated in any of the paraplegics during assisted locomotion on the treadmill at this speed, whether on or off clonidine. Indeed, the primary effect of clonidine on the paraplegic patients' locomotion was to diminish the clonus and stretch reactions, thereby reducing the EMG activity seen rather than inducing or enhancing it. This is in contrast to the animal findings that locomotion could be modulated by clonidine in
spinal animals (Rossignol et al., 1986, Barbeau and Rossignol, 1987). The existence of a spinal level locomotor generator has been proposed in primates, however Eidelberg et al. (1981) were unable to induce treadmill stepping in spinalized macaque monkeys, even with the administration of dopa or clonidine. These authors suggest that supraspinal influences may be required to activate the CPG in monkeys, or alternatively, that the environmental demands have not reinforced the need for a locomotor CPG in these primates (Eidelberg 1983). In humans, it has been suggested that a CPG may mediate the stereotypic locomotor movements, while supraspinal centres act to initiate, maintain, modify, and terminate locomotor activity (Forssberg 1986). This hypothesis is supported by the fact that anencephalic neonates demonstrate strong rhythmic stepping despite their lack of functional supraspinal structures (Forssberg 1982), and the fact that neonates demonstrate stereotypic automatic stepping which is modified as myelination and encephalization occurs (Forssberg, 1985, Thelen et al., 1987). Zomlefer (1986) attempted to elicit treadmill-induced stepping in SCI subjects. He reported no spontaneous stepping, although regular EMG bursting occurred during manually assisted locomotion. He ascribed this to either the action of a spinal stepping generator or to alternating stretch reactions. In the present study, independent stepping on the treadmill was not induced in the paraplegics either. The notion that the EMG bursts seen in
our patients reflected stretch reactions was supported by the fact that the regular EMG bursting during assisted locomotion was replaced by a generalized clonus when assistance was withdrawn, and abolished by clonidine. The expression of the spinal CPG was not evident in this study, perhaps due to the neurophysiological differences between the mechanisms of the CPG in man and lower mammals, or in the chronic states of these patients. It may also be true that different stimuli, such as cutaneous or proprioceptive, is required. Intensity of stimulus, such as electrical, could also be important. Moreover, a higher dosage of medication may be necessary to facilitate the expression of the locomotor pattern, although the presence of side effects is an important limiting factor.

Conclusions

The results of this study provide evidence supporting the role of clonidine as a modulator of locomotor function in paraparetic patients. A further study investigating the effects of various dosage levels of clonidine on clinical spasticity and in the modulation of the locomotor pattern in a larger and more homogenous sample of patients with incomplete lesions and severe spasticity is warranted. Moreover, further investigation into the neurophysiological mechanisms underlying the action of clonidine is necessary.
II The Effect of Clonidine in the Reduction of Spasticity in Spinal Cord Patients: A Preliminary Study

This paper describes the effect of clonidine on the clinical spasticity of 3 paraparetic and 6 paraplegic patients, as measured by the evoked tonic stretch reflex (TSR), ankle clonus, a visual analog scale (VAS), and daily diaries of spasms and clonus.

In comparing the control sessions (premedication, placebo sessions) with the clonidine session, 4/9 patients demonstrated a reduction in ankle TSR, 3/9 had reduction in ankle clonus, and 4/9 experienced a subjective decrease in their perception of spasticity levels. Episodes of daily spasms were reduced for 2/4 patients recording these, while episodes of clonus diminished for 4/5. Side effects were experienced by 8/9 patients, but only those with medical lesions found these to persist following dosage decrease. One of the six paraplegics and 2/3 paraparetics reported functional improvement with clonidine.
THE EFFECT OF CLONIDINE ON THE REDUCTION OF SPASTICITY
IN SPINAL CORD PATIENTS: A PRELIMINARY STUDY

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key words: spasticity, spinal cord injury, clonidine
Introduction

Spinal cord injury (SCI) typically results in paresis, and spasticity below the level of the lesion. The SCI patient may demonstrate such manifestations of abnormal reflex activity as sustained ankle clonus, velocity-dependent stretch reactions, hypertonus and hyperactive reflexes (Bishop 1977).

The presence of spasticity has a markedly deleterious effect on the functional capabilities of both complete and incomplete SCI patients. Those with complete lesions (paraplegics) find the severe spasms limit their ability to carry out transfers, to sit comfortably in the wheelchair, and to carry out other activities of daily living. Additionally, for those with incomplete lesions (paraparetics) having residual motor control, spasticity may interfere with their functional abilities such as locomotion.

In the pharmacological treatment of spinal spasticity, the most frequently used medications are bacofen, diazepam, and dantrolene sodium. However, each of these drugs only addresses certain features of spasticity, and side effects such as sedation (baclofen, diazepam), muscle weakness (dantrolene sodium) are common (Young and Delwaide, 1981, McDowell, 1981). Thus, a comprehensive pharmacological intervention which can effectively reduce the spasticity without producing excessive side effects has yet to be identified. Recently, the potential contribution of clonidine, a noradrenergic alpha-2 agonist, has been
investigated. In patients with spinal cord lesions, a qualitative reduction in clinical spasticity has been reported after the administration of clonidine. Naftchi (1982) reported an antispasmodic effect of clonidine in over 30 subjects with transverse cervical or thoracic myelopathy. Tuckman et al. (1982) reported a decreased level of spontaneous EMG activity and fewer involuntary spasms in two C5-6 quadriplegic patients, after the first dose of clonidine. Moreover, their spasticity continued to decrease over several weeks of treatment, allowing both patients to benefit from physical therapy. Maynard et al. (1986) reported that the majority of his spinal cord patients experienced some degree of spasticity reduction with clonidine. Nance et al. (1985) also reported qualitatively a reduction of clinical spasticity in all 4 spastic spinal cord patients with clonidine, however, only 2 of the 4 continued on the medication due to problematic side-effects. However, these clinical trials are quite descriptive, with little quantitative data, and little information on the effects of the medication on such aspects of the patients' motor function as locomotion.

In light of the results of these clinical trials, it was the objective of the present study to further quantitatively investigate the antispastic effects of clonidine on chronic spinal cord patients, and to determine the effects on the patient's motor function.
Table 4.2.1. Demographic details of the patients. MVA: motor vehicle accident, CA:SURGERY: lesion secondary to surgery for cancer, KYPHOSCOL: kyphoscoliosis resulting in progressive paralysis, TRAUMA: fall resulting in SCI. Frankel's classifications: B: incomplete sensation, no motor function below the lesion, C: incomplete sensation, no useful motor function below lesion, D: incomplete sensation, some useful motor function below lesion
## DEMOGRAPHIC DATA

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Methodology

Table 4.2.1 summarizes the demographic information related to the 12 patients who participated in this study. Six of the patients had traumatically induced lesions, 2 developed lesions secondary to surgery for cancer, and one has a progressive kyphoscoliosis which caused paraplegia 5 years prior to the onset of the study. The lesion chronicity ranged from 8 months to 10 years. According to Frankel's functional classification of SCI, 8/12 patients fell within group B (incomplete sensory-no motor function), 4/12 were in group C (incomplete sensory-no useful motor function) and 3/12 were in group D (incomplete sensory-useful motor function). The 3 subjects who withdrew did so for personal reasons and not as a result of medication effects.

Three spastic paraparetics and 6 spastic paraplegics completed this double-blind crossover study, which involved two 4 week medication periods separated by a 2 week washout period. The order of clonidine and placebo was randomly assigned for each patient. To minimize the possibility of adverse side-effects, the titration procedure involving twice daily (b.i.d.) oral administration was established in consultation with Boehringer-Ingelheim Co.. The titration procedure for the placebo and the clonidine were identical. The basic dose per tablet was 0.025 mg.; the initial daily dosage was 0.05 mg/day. Peak blood plasma level for clonidine occurs within 1-3 hours following oral administration, with
a cumulative peak period of 3-4 days (Arndts et al., 1983, Anavekar et al., 1982). Based on this, the patient was given a tablet of the medication immediately following the pre-medication assessment session and, to detect possible severe side-effects, had his blood pressure monitored in supine and sitting position every 15 minutes for the next hour. None of the patients showed adverse reactions during the first hour. Subsequently, the medication was increased every 3rd day following a visit from the public health nurse, who was blind to the medication type. The nurse visited the patient during the periods of dosage increase and decrease, assessing vital signs and monitoring for presence of adverse side-effects. Secondary effects most commonly associated with clonidine are: hypotension, sedation, dryness of mouth and/or eyes, dizziness, headache, and depression. However, the titration range was designed to minimize the risk of these effects. The research assistant, who was the only member of the research team informed as to the medication types, recorded the results of the nurse’s assessments and monitored the patient’s status every third day during dosage increase and decrease periods. In this manner, the dosage was systematically increased from the initial level towards the optimal dosage of approximately 0.25 mg/day (as suggested by Boehringer Ingelheim) over the first 12 days of the clonidine medication period. Optimal dosage is defined as the maximum level of medication within the titration range which caused minimal side-effects.
Optimal dosages for each patient were established by the research assistant, based on the nurse's assessments and the patients' own feedback. All of the patients were stabilized within the 0.10 - 0.25 mg. range with the exception of S.H., who independently raised his dosage level to 0.50 mg/day despite instructions. Patients were all stabilized at their optimal level for a minimum of 2 weeks before returning for the postmedication session. Following this assessment session, the dosage was decreased according to the titration protocol, with drug 'weaning' completed by the sixth day of the decrease period. This allowed a further week for the elimination of the drug from the patient's body before reassessment. S.Q. was a preliminary subject, therefore he was not included in the double-blind crossover format. His results are taken from a premedication session, the clonidine medication session, and a post-clonidine washout session, while for the other patients the results of a placebo session are also presented.

After an initial orientation, assessment sessions preceded and proceeded each medication period. Included in these sessions were clinical tests of spasticity as well as evaluation of locomotion. Detailed results of the locomotor assessments will be reported elsewhere (Stewart and Barbeau in prep.). The clinical assessments of spasticity included a visual analog scale (VAS) measure of spasticity, tests of ankle and knee tonic stretch reflexes (TSR), and test of
evoked ankle clonus. Additionally, the patients were asked to keep a daily diary of spasms and clonus.

Before each assessment session the patients were asked to rate the severity of their current level of spasticity, using the visual analog scale, in the context of the range of spasticity they had ever experienced. On the scale, only the two extremes of the range were marked on the side that the patient saw, while the other side provided the researcher with a numerical score corresponding to the patients subjective response (0: no spasticity to 10: intolerable spasticity). In measuring the TSR, the right and left ankles were dorsiflexed at a constant speed by the examiner. This test is conducted first with the knee in extension (0°), and then repeated with knee flexion (90°). In both cases, the strength of the TSR was recorded on a 5 point scale (0: normal resistance, 1: minimal resistance, 2: moderate resistance, 3: strong resistance, 4: maximum resistance). Passive flexion and extension of the knee at a constant speed were also conducted, to determine the knee TSR. Ankle clonus test was done with the patient seated with the hip and knee in 90° flexion; the patient's ankle was briskly dorsiflexed and maintained in dorsiflexion until cessation of clonus, first with the knee extended and then repeated with knee flexion. The degree of clonus for right and left was recorded, using a 4 point scale (0: no clonus 1: one to two beats, 2: more than 2 beats, 3: sustained clonus). Overground locomotion was assessed in
the paraparetics as they walked between parallel bars at their own pace.

Surface electrodes were used to detect the EMG activity of right and left Medial Hamstrings (MH), Vastus Lateralis (VL), Tibialis Anterior (TA), and the medial head of Gastrocnemius (GA). Signals were buffered and preamplified before being further amplified and bandpassed between 10 Hz - 1 KHz. EMG and footswitch recordings were displayed on an oscilloscope (Nihon Kohden V.C.-680G) and recorded by a 14 channel magnetic FM tape recorder (Honeywell #101) at 3.75 i.p.s. (mid band recording level 2500 Hz). Locomotor trials were filmed with a rotary shutter video camera (Sony: RSC1010), and recorded on 3/4" videotape at 60 fields/sec.

Results
A. Clinical Spasticity

To measure the antispastic effect of clonidine, comparison was made between the results of the clinical tests of spasticity in the placebo, and the clonidine sessions for the patients as a group. Individual results are also presented, comparing the premedication, placebo, and clonidine sessions. Right and left scores are combined for a total score for TSR and clonus test results for each patient. A change of at least 1 point (TSR:20%, VAS:10%, clonus:25%) is considered an improvement or deterioration for the results of the spasticity tests.
Figure 4.2.1. Comparison of the patient's scores on clinical spasticity tests between the placebo and clonidine sessions (S.Q.: pre-medication and clonidine sessions). For the ankle TSR, clonus and VAS measures, all 9 patients are included; for the knee TSR, the 7 patients tested are represented; for the diary of spasms and clonus the 4 and 5 patients, respectively, completing the diaries are presented. Right and left values are combined for the TSR and clonus tests. Improvement implies a reduction of $\geq 1$ point; deterioration means an increase of $\geq 1$ point.
SPASTICITY TESTS:

PLACEBO/CIONIDINE WITHIN-GROUP COMPARISON

![Graph showing the number of patients with different spasticity measures (ANKLE, KNEE, VAS, CLONUS, DAILY SPASMS, DAILY CLONUS) comparing placebo and cionidine.]
In figure 4.2.1, the group trends are presented for each spasticity test, showing the antispastic effects of clonidine relative to the placebo period. Five of the 9 (55%) patients showed a reduction in ankle TSR, with 2/9 (22%) patients having an increase, and 2/9 (22%) with no change. The TSR reaction to passive knee flexion and extension was also reduced in the majority of patients tested (5/7:71%) and unchanged in the rest (2/7:28%), with no patient showing an increased knee TSR. In figure 4.2.2 A and B, an example of the effect of clonidine on the TSR is presented. The consistent stretch activation elicited in MH on passive knee extension during the placebo session (fig. 4.2.2 A) can be noted to disappear with clonidine for paraplegic E.P. (fig. 4.2.2 B).

As depicted in figure 4.2.1, 6/9 (66%) patients recorded a reduction in their overall spasticity level, while only 1/9 (11%) felt his spasticity to be higher, as recorded on the VAS. Two patients registered negligible change. For the test of ankle clonus, while 5/9 (55%) patients demonstrated no change between the 2 sessions, 3/9 (33%) showed a reduction of at least 1 point, and 1/9 (11%) demonstrated an increase of at least on point in the degree of clonus evoked. Among the patients who completed diaries of daily spasms (n=4) and clonus (n=7), 2/4 (50%) reported a reduction in daily spasms and 4/5 (80%) a reduction in daily clonus, while 2/4 (50%) and 1/5 (20%) recorded no change in spasms and clonus.
Figure 4.2.2. MH EMG activity during passive extension and flexion of the knee (TSR), with paraplegic E.P. sitting, during placebo (A) and clonidine (B) sessions. Note the consistent activation concommittant with knee extension during the placebo session which is absent on clonidine. A constant speed of passive flexion and extension was attempted by a consistent examiner both within and between sessions. (Note the duration of knee extension indicated)

TA and GA EMG activity evoked by quick dorsiflexion of the right ankle, with paraplegic F.L. seated, during the placebo (C) and clonidine (D) sessions. Note the sustained clonus evoked during the placebo session, which is abolished with clonidine. Horizontal bars indicate 1 sec., vertical bars indicate 100 uv.
respectively. No patients reported an increase in the frequency of daily spasms or clonus. In summary, the degree of evoked TSR, daily occurrence of clonus and the patients' own perception of spasticity levels showed a trend towards a decrease with clonidine, while evoked ankle clonus was minimally affected.

Individual results are presented in figure 4.2.3; the patients' right and left TSR and clonus values were combined in a total score displayed for the placebo, premedication and clonidine sessions. As reflected in figure 4.2.3 A, 4/9 patients (S.Q., J.P.D., F.L., J.C.) showed a reduction in ankle TSR with clonidine as compared to both placebo and premedication sessions, while 1/9 (E.C.) reflected a decrease in the TSR on placebo, with the clonidine and premedication values remaining the same. 2/9 (M.H., E.P.) demonstrated no change in TSR when clonidine is compared to one of the control sessions. Two of the nine (S.H., M.F.) had no change in the degree of tonic stretch reflex across the three sessions.

As depicted in figure 4.2.3 B, 4/9 (S.Q., S.H., E.P., J.D.) showed a marked decrease in the VAS score on clonidine, as compared to either one of the control values. 2/9 (F.L., J.C.) showed a decrease in the VAS from premedication to clonidine, but negligible change from clonidine to placebo. 2/9 (M.H., E.C.) showed minimal change in their VAS scores, indicating no change in their perceived spasticity levels. 1/9 (M.F.) registered an increase in spasticity on comparing
Figure 4.2.3 A. Comparison of the patients' individual scores between the premedication, clonidine, and placebo sessions (S.Q.: post clonidine washout session) for the TSR. The right and left ankle scores have been combined into a total score. Range: 0: normal degree of resistance bilaterally to 10: hyperactive response bilaterally.
TONIC STRETCH REFLEX

TOTAL TSR SCORE

S.Q. M.H. S.H. E.P. J.C. E.C. J.D. F.L. M.F.

PREMEDICATION
CLONIDINE
PLACEBO (S.Q.: WASHOUT)
Figure 4.2.3 B. Comparison of the patients' individual scores between the premedication, clonidine, and placebo (S.Q.: post clonidine washout session) sessions for the VAS test. VAS scores range from 0: least spasticity ever experienced to 10: maximum spasticity ever experienced.
VISUAL ANALOG SCALE

S.Q. M.H. S.H. E.P. J.C. E.C. J.D. F.L. M.F.

- - - - PREMEDICATION
- - - - CLONIDINE
- - - - PLACEBO (S.Q.: WASHOUT)
Figure 4.2.3 C. Comparison of the patients' individual scores between the premedication, clonidine, and placebo (S.Q.: post clonidine washout session) sessions for the ankle clonus test. The right and left ankle scores have been combined into a total score. Range: 0: no clonus to 6: sustained clonus bilaterally.
EVOKED ANKLE CLONUS

TOTAL CLONUS SCORE

S.Q. M.H. S.H. E.P. J.C. E.C. J.D. F.L. M.F.

- PREMEDICATION
- CLONIDINE
- PLACEBO (S.Q.: WASHOUT)
the premedication and clonidine scores, but no change between clonidine and placebo.

As figure 4.2.3 C indicates, evoked ankle clonus changed little across the sessions for 5/9 patients (S.H., E.P., J.C., E.C., M.F.), while 3/9 (S.Q., J.D., F.L.) showed a decrease in clonus on clonidine, as compared to both control sessions. Only 1 patient (M.H.) showed increased clonus on clonidine. As an example, figure 4.2.2 C depicts the sustained ankle clonus which was evoked in F.L. during the placebo session and which is almost completely abolished with clonidine (fig. 4.2.2. D).

It is notable that the largest reductions in perceived spasticity levels were not always accompanied by a decrease in clinical spasticity measures. Of the patients reporting the greatest reduction in perceived spasticity levels, only S.Q. and J.D. showed a consistent reduction in evoked clonus and TSR. S.H. demonstrated no reduction in either clonus or TSR, and E.P. had less ankle TSR on clonidine while clonus was unchanged. Moreover F.L., who showed a consistent reduction in clonus and TSR, indicated only a small diminution in his perceived severity of spasticity. M.H., who had consistent increases on the spasticity tests, registered a reduced level on the VAS. Of those patients who completed the daily diaries, M.H., E.P., J.D. and J.C. all reported a reduction in the incidence of daily episodes of spasms and clonus; 3/4 of these also registered a decrease on the VAS.
Table 4.2.2. Relationships between antispastic effects and level of lesion (A), lesion etiology (B), and dosage levels (C), as well as between etiology and secondary effects (D) for the clinical measures ankle clonus, TSR, and VAS, on comparison of placebo and clonidine sessions. Only those with improvement or deterioration are included in Tables A-C. I: improvement (≤ 1 point on scale), D: deterioration (≥ 1 point). Table 2 D: Transient symptoms: appear on dosage increases and disappear spontaneously, Moderate: disappear with a decrease in dosage, Severe: persist despite dosage decrease.
A. RELATIONSHIP BETWEEN EXTENT OF LESION & ANTISPASTIC EFFECTS:

<table>
<thead>
<tr>
<th></th>
<th>GLOMUS</th>
<th>ANKLE TORSION</th>
<th>VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COMPLETE</strong></td>
<td>2/6</td>
<td>0/6</td>
<td>2/6</td>
</tr>
<tr>
<td>(n=6)</td>
<td>(33%)</td>
<td>(0%)</td>
<td>(33%)</td>
</tr>
<tr>
<td><strong>INCOMPLETE</strong></td>
<td>1/3</td>
<td>0/3</td>
<td>2/3</td>
</tr>
<tr>
<td>(n=3)</td>
<td>(33%)</td>
<td>(0%)</td>
<td>(66%)</td>
</tr>
</tbody>
</table>

B. RELATIONSHIP BETWEEN ETIOLOGY & ANTISPASTIC EFFECTS:

<table>
<thead>
<tr>
<th></th>
<th>GLOMUS</th>
<th>ANKLE TORSION</th>
<th>VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEDICAL</strong></td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
</tr>
<tr>
<td>(n=3)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0%)</td>
</tr>
<tr>
<td><strong>TRAUMATIC</strong></td>
<td>3/6</td>
<td>0/6</td>
<td>4/6</td>
</tr>
<tr>
<td>(n=6)</td>
<td>(50%)</td>
<td>(0%)</td>
<td>(66%)</td>
</tr>
</tbody>
</table>

C. RELATIONSHIP BETWEEN DAILY DOSAGE & ANTISPASTIC EFFECTS:

<table>
<thead>
<tr>
<th></th>
<th>GLOMUS</th>
<th>ANKLE TORSION</th>
<th>VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BELOW 0.16 mg</strong></td>
<td>1/3</td>
<td>0/3</td>
<td>1/3</td>
</tr>
<tr>
<td>(n=3)</td>
<td>(33%)</td>
<td>(0%)</td>
<td>(33%)</td>
</tr>
<tr>
<td>0.21 mg *</td>
<td>2/4</td>
<td>0/4</td>
<td>2/4</td>
</tr>
<tr>
<td>(n=4)</td>
<td>(50%)</td>
<td>(0%)</td>
<td>(100%)</td>
</tr>
<tr>
<td><strong>ABOVE 0.21 mg</strong></td>
<td>0/2</td>
<td>0/2</td>
<td>1/2</td>
</tr>
<tr>
<td>(n=2)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(50%)</td>
</tr>
</tbody>
</table>

D. RELATIONSHIP BETWEEN ETIOLOGY AND SIDE EFFECTS:

<table>
<thead>
<tr>
<th></th>
<th>DRYNESS</th>
<th>LETHARGY</th>
<th>HYPOTENSION</th>
<th>CONSTIPATION</th>
<th>CARDIOVASCULAR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEDICAL ETIOLOGY</strong></td>
<td>2 - 1</td>
<td>1 - 2</td>
<td>1 - 1</td>
<td>2 - 1</td>
<td>2 - 1</td>
</tr>
<tr>
<td>(n=3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TRAUMATIC ETIOLOGY</strong></td>
<td>1 4 1</td>
<td>3 3 1</td>
<td>2 5 2</td>
<td>6 6 6</td>
<td>6 6 6</td>
</tr>
<tr>
<td>(n=6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL PATIENTS</strong></td>
<td>1 6 2</td>
<td>4 3 2</td>
<td>3 5 1</td>
<td>8 6 1</td>
<td>8 6 1</td>
</tr>
</tbody>
</table>

N: no symptoms
T: transient symptoms
M: moderate symptoms
S: severe symptoms
To investigate the relationship between the anti-spastic effects and the lesion etiology, extent of the lesion, and dosage levels, Table 4.2.2 classifies the patients accordingly. In comparing the paraparetics and paraplegics (Table 4.2.2 A), the only inter-group difference was a slight trend towards greater reduction of ankle TSR among those with complete lesions.

In exploring the effect of lesion etiology (Table 4.2.2 B), those with medically-based lesions showed no improvement on any of the spasticity tests, with 1/3 showing more severe clonus. This is in contrast to the group of patients with traumatic lesions, in which at least 50% had a reduction in spasticity for each test and none showed deterioration in any of the spasticity tests with clonidine. Thus as a group, those with traumatic lesions had a better response to the medication, while those with medical etiologies were more likely to show either no change or increased spasticity.

In terms of the dosage effect (Table 4.2.2 C), there was a trend towards greater improvement in the perceived spasticity levels among the patients within the medium and higher dosage ranges, However, a consistent dose-response relationship was not seen for any of the tests of clinical spasticity.

Side effects were experienced by 8/9 patients to some degree, during dosage increases, although for most these symptoms were transient. As shown in table 4.2.2D, the side
Effects experienced included dryness of the eyes and mouth, lethargy, hypotension, constipation, and cardiovascular problems, with dryness of the eyes/mouth being the most common. Among those with medically based lesions, M.H. experienced moderate lethargy and severe constipation, E.C. had moderate lethargy and severe bradycardia, and M.F. reported moderate to severe dryness of eyes and mouth and demonstrated moderate hypotension. Transient side-effects disappeared spontaneously, while moderate side-effects subsided with a reduction of the dosage. Severe side-effects diminished with dosage reduction, but were not eliminated.

Among those with traumatic lesions, only 1 patient experienced even a moderate degree of side-effects, while for most the effects were transient. Thus, the majority of those with traumatic lesions (mean dosage level: 0.26 mg/day) experienced either transient or negligible side effects, while those with medically based lesions (mean dosage: 0.17 mg/day) experienced both moderate and severe side effects. A dose-response relationship in the severity of side-effects was not demonstrated within the dose range utilized, nor was there a consistent threshold for side effects. However, there was a significant relationship between etiology and side-effects. All of the medically-based cases complained of severe or moderate secondary effects, while the traumatic cases largely found the side effects to be negligible or transient.
B. Functional Abilities

Functionally, 2/3 of the paraparetic patients (S.Q., M.H.) were capable of ambulation in the placebo or premedication session. S.H. required supervision and occasional assistance to transfer safely. He was unable to take consecutive steps, due to severe spasticity. This can be observed in figure 4.2.4 A-F, depicting his overground locomotion on placebo. S.H. demonstrated a stiffly extended posture at heelstrike, supporting his body weight on his toes and through his hands (fig. 4.2.4 A). He utilised a trunk flexion maneuver to initiate stepping (fig. 4.2.4 B), demonstrating hip adduction in conjunction with poor dissociation of the legs (fig. 4.2.4 C).

With clonidine, he was able to take independent and consecutive steps within parallel bars, with a more erect trunk posture, better foot-flat weight bearing, and independent movement of the lower extremities (fig. 4.2.4 D-F). He was also able to transfer independently, thus altering his functional level from a "C" to "D" level. S.Q. experienced a marked reduction in spasticity following clonidine, resulting in initial difficulty in bearing weight during overground locomotion. With this reduction in spasticity, S.Q. became a candidate for subsequent muscle strengthening and locomotor training program. M.H., with little change in his spasticity, reported no improvement in functional abilities. However, this patient was more limited
Figure 4.2.4. Paraparetic S.H. walking overground on placebo (A–D) and clonidine (E–H). Shown are: heel strike (A, E), midstance (B, F), toe-off (C, G) and midswing (D, H). Note the change in trunk posture as well as hip, knee, and ankle joint angles between the two sessions.

Premedication, the paraplegics could all transfer independently, but were hampered by their spasticity. Many also reported that spontaneous spasms disturbed their sleep. With clonidine, 1/6 reported an improvement in such functional abilities as transfers (J.P.D.), and 2 others reported a decrease in daily spasms experienced (E.P., J.C.).

Discussion

The majority of our patients demonstrated a diminution of tonic stretch reactions as well as spontaneous clonus and spasms, both in the wheelchair and during ambulation. Some reduction in evoked clonus was also evident, but only in a minority of the patients. Most patients also reported a reduction in their perceived levels of spasticity with clonidine, although the decrease did not always reflect the changes in clinical spasticity measures. Of the three patients recording a markedly decreased VAS score (>40%) on clonidine as compared to either control sessions (S.Q., S.H., E.P.), only S.Q. showed a similarly marked decrease in the spasticity tests. However, 3 of the 4 patients reporting the least reduction in spasticity on the VAS (M.F., E.C., M.H.) also demonstrated the least changes on the clinical measures.
of spasticity. It would thus appear that, when the patients experienced no change or a deterioration in clinical spasticity tests, their VAS score reflected this status. However, in the presence of some reduction of clinical spasticity, the VAS score was less closely associated with the results of the clinical measures. It may be, as suggested by Young and Weigner (1987), that static tests of spasticity do not necessarily reflect the functional abilities of the patient. This was evident for S.H., who progressed from being non-ambulatory to being able to take steps with the medication, although the clinical spasticity revealed negligible changes. Among our patients, three of the four with the highest improvement in VAS scores (S.H., S.Q., J.P.D.) did also subjectively report an improvement in such functional motor activities as locomotion and transfers. Hence, the VAS appears more sensitive to functional changes in dynamic motor activities such as locomotion and transfers than to alterations in the more passive and static classical spasticity tests. The validity and reliability of this visual analog scale should be further explored in future studies, with comparisons made with both static and dynamic measures.

The difference between the 2 control sessions was \( \leq 1 \) point for 6/9 patients on the ankle TSR, for 4/9 on the VAS, and for 9/9 on the clonus test. There may be two possible explanations for the fact that the control session values were not always equal. Firstly, in the case of those patients
having clonidine first, changes caused by the medication may have altered the degree of spasticity from control levels. This is supported by the finding that S.H., who could not take steps on placebo, retained the ability to step after the clonidine washout period, suggesting that some persistent changes had occurred with clonidine. This might explain the reduction in VAS placebo values seen for S.H., F.L. and J.C., and in the TSR placebo values for E.P. and J.C. since all of these patients had placebo in medication period B. Secondly, the variation between control sessions for VAS may reflect the fact that this was a single measure taken only once at the initiation of each assessment session, and therefore may not fully reflect the within- and between-session variations. Daily recordings on the VAS throughout the medication periods, as well as multiple recordings during various aspects of the assessment session would yield VAS average scores rather than a single score; this may be more representative of the patients' overall levels of spasticity.

Both S.H. and S.Q. experienced a functional improvement in their locomotor abilities. The specific effects of clonidine on locomotion in these patients are reported in detail elsewhere (Stewart and Barbeau, in prep.).

A relationship between dosage and antispastic effects was reported by Nance et al. (1985) and Maynard (1986), the latter also suggesting a therapeutic threshold dose of 0.30 mg/day. In the present study, a dose-response relationship was not
evident relative to the antispastic effects. In fact, the patients with the greatest decrease in spasticity were in the 0.15 - 0.25 mg/day range, well below the 0.30 mg/day threshold suggested by Maynard (1986). However, the minimal effects experienced by M.F. suggest that his dosage level may have been too low for therapeutic effects. This would need to be confirmed in a more extensive study, investigating specific dose-response relationships within individual patients.

In the animal model, dosage has been found to be an important factor relative to the action of clonidine. At low dosages in spinal rats (0.06 - 0.10 mg/kg), clonidine was found to reduce motoneuronal excitability and spontaneous EMG activity in the flexor and extensor muscles (Tremblay and Bedard 1986) and to depress tonic tail flick reflex discharges (Kawasaki et al. 1978). In contrast, at higher doses (0.50 mg/kg) it had less of an inhibitory effect on spontaneous EMG activity (Tremblay and Bedard 1986) and even potentiated the tonic reflexive reaction to tail pinching (Kawasaki et al. 1978). This has been postulated to reflect two different sites of action for clonidine: alpha_2 receptor sites at low doses (Kawasaki et al. 1978, Tremblay and Bedard 1986), and alpha_1 at high dose ranges (Yaksh 1985). These hypotheses were supported by the finding that the alpha_2 antagonist Yohimbine reversed only the inhibitory effects of clonidine (Kawasaki et al., 1978). The dosages in the present clinical trial were much lower than those reported in the animal
studies. In light of this, the inhibitory effects on hyperactive stretch reactions and spasms experienced by some patients may support alpha₂ mediation. However, further investigation is required to clarify the actual site of clonidine action in this patient population.

A therapeutic dose-response relationship may not have been evident in the present study as the dosage levels were too low, with side-effects being a limiting factor. Additionally, the small sample size may have obscured the dose-response relationship. Moreover, it is also difficult to draw strong conclusions as to the dose-response relationship regarding side effects, as the severity of side effects was one of the variables used in establishing optimal dosage levels. As a result, those with a predisposition for secondary effects, tended to be stabilised at lower dose levels. In future studies, the inclusion of blood-plasma level sampling and alternative methods of medication administration to ensure the maintenance of more constant blood plasma levels of the medication may allow higher dosages with less side-effects.

Within the limited sample size, the present results did not support a relationship between therapeutic effect and the lesion completeness. However, all 3 patients with medically-based lesions responded more poorly than those with traumatic lesions, suggesting a relationship between etiology and therapeutic effect. Both M.H. and E.C. had been on
oncological radiation and chemotherapy within the last 5 years; this may have caused some neurotoxic pathology. Moreover, both of these patients and M.F., who had a progressive kyphoscoliosis, likely had compression related nerve damage rather than trauma induced nerve lesions; the effect of this type of damage on the neurons may have influenced their reaction to clonidine.

Conclusions

The results of this study provide evidence supporting the role of clonidine as an antispastic agent in both paraplegics and paraparetics, which appeared to be more effective for patients with traumatic lesions. Moreover, the main antispastic effect was to diminish the tonic stretch reactions, as well as the spontaneous clonus and spasms, with less effect on evoked clonus. Among the paraplegics, only 1/6 reported a functional improvement on clonidine, while 2/3 of the paraparetics reported improvement, primarily associated with locomotor function. The majority of patients, however, did subjectively experience less spasticity on the medication.

The mean daily dosage was 0.20 mg., and the doses ranged from 0.10 - 0.50 mg. A dose-response trend was not obvious within these dose ranges for either therapeutic benefits or severity of side effects. Side-effects were present to some degree in almost all patients, most severely among those with lesions which were medically based. On the basis of the side-
effects and the relatively inconsistent antispastic effects, clonidine would not seem to be the medication of choice for the paraplegics with lesions of medical etiology. In those patients with traumatic lesions demonstrating severe spasticity in conjunction with some active movement (Frankel grade C-D), clonidine appears to have considerable potential in improving functional level. This should be further investigated in an extensive trial involving this patient population, and using dynamic as well as static measures of spasticity.
CHAPTER FIVE: CONCLUSIONS

This research project has investigated the effects of the noradrenergic agonist clonidine on the locomotor pattern and clinical spasticity of patients with complete and incomplete spinal cord lesions. In this chapter, results will be summarized. As well, limitations to the study and an outline of future directions for related research will be presented.

A. Locomotion

One paraparetic who was initially non-ambulatory gained the ability to take independent steps with clonidine, demonstrating marked improvement in EMG profile and timing as well as in joint angular excursion during overground locomotion. The remaining 2/3 paraparetics, already ambulatory at the onset of the study, did not demonstrate a marked change in cadence, velocity, or stride length during overground locomotion.

For all paraparetics, clonidine was associated with more phasic medial hamstrings activity, less tonic background activity generally, and a reduction of TA/GA coactivation. Coincident with these changes were some individual alterations in kinematics, although all continued to demonstrate characteristic gait deviations such as knee flexion at foot floor contact, and deficient hip extension during stance.
phase. 2/3 paraparetics experienced a reduction in spasticity during treadmill locomotion, allowing both to walk at 0% BWS at the speed of 0.26 ms\(^{-1}\).

The paraplegics were unable to step independently, with either placebo and clonidine. The main effect of clonidine for these patients was to reduce the tonic stretch reactions and ankle clonus evoked by the manual manipulation of the patient's legs to simulate the locomotor pattern.

Clinical Spasticity

The greatest reduction in spasticity was in the TSR, episodes of spontaneous clonus and spasms, and in the patient's perceived levels of spasticity. No relationship between antispastic effects and lesion level, chronicity, completeness were noted. Moreover a dose-response relationship was not evident for therapeutic effectiveness or degree of side-effects. However, the patients with traumatic lesions had less severe side-effects and better reduction of spasticity than patients with medically-based lesions.

LIMITATIONS OF THE STUDY

- The heterogeneity of the sample size was a limitation in this study, as neither paraplegic or paraparetic, nor the traumatic or medical etiology groups were large enough to allow statistical analysis and the drawing of stronger conclusions.

- Given the static nature of these tests of clinical
spasticity, the results may not necessarily reflect functional change, as function frequently involves voluntary activity.

- The basal treadmill speed of 0.26ms⁻¹ was considerably faster than the natural cadence of all three paraparetics, thus improvements may have been evident at slower speeds which were not present at this speed.

- Within the double blind design, the rigid titration protocol precluded the chance to explore dose-response relationships more fully, also the dosage range of the protocol may have been too low for some patients, as S.H. experienced positive effects at a dose level well above the prescribed range.

- The generation of a locomotor pattern in the paraplegics was perhaps not evident due to insufficiently high clonidine dosages, or the chronicity of the patients' lesions.

FUTURE DIRECTIONS FOR RELATED RESEARCH PROJECTS

It would be important to conduct a subsequent research study to investigate the effects of this medication on a larger sample of patients with incomplete, traumatic lesions.

Moreover, the tests of spasticity should include such electrophysiological measures as the flexion and H reflex, as well as more dynamic measures such as tracking tasks to monitor TSR, and measures of spasticity during functional motor tasks such as locomotion.

A study specifically investigating the combined effects
of clonidine with peripheral stimulation, such as cutaneous or proprioceptive, on the locomotor function of paraplegics would also be interesting.

Additionally, systematic investigation of the dose-response relationships for both antispastic and side-effects is warranted. Alternative methods of drug administration should be explored.
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APPENDICES

1A and B  Consent Forms (English & French versions)
2A and B  Patient Assessment Form (Public Health Nurse)  
          (English and French versions)
3A and B  Clonidine Titration Procedure (English & French  
          versions)
4        Clinical Evaluation (Clinical Spasticity Tests)
5        Daily Record of Spasms and Clonus
CONSENT FORM FOR PARTICIPATION IN THE RESEARCH STUDY

"LOCOMOTOR AND CLINICAL ASSESSMENT OF THE EFFECTS OF CLONIDINE/CATAPRES ON SPASTIC PARAPARETIC PATIENTS"

I, ____________________________, consent to participate in a research study on the effects of Catapres on spasticity and spastic paraparetic gait.

Purpose and Design of the Study

The purpose of this study is to investigate the effects of Catapres on the symptoms of spasticity, and on spastic paraparetic gait. There will be a 4 week medication period involving Catapres, and a 4 week medication period involving a placebo; a 2 week washout period will separate the medication periods. The order of the placebo and Catapres will be randomized, neither the researcher nor the participants will be aware of which medication is taken during the two periods. Assessment sessions will be conducted to measure the effects of the medications on locomotor function and symptoms of spasticity.

Participation in this study will involve the taking of Catapres tablets twice daily over the 4 week period, and the placebo pills for another 4 weeks. It will also involve participation in five 2-1/2 hour assessment sessions at the Human Gait Laboratory in the School of Physical and Occupational Therapy at McGill University.

Assessment sessions will take place on the participant's initial visit, and at the start and finish of each medication period. These will include measurements of walking on the treadmill and the floor, tests for ankle clonus and tonic stretch reflex, and a scale measure of spasticity.

The tests are non-invasive and painless. Surface electrodes and reflective skin markers will be taped to the participant's legs, and footswitches taped to the soles of the shoes to allow measurement of muscle activity and limb movement during the treadmill locomotion. For the floor walking assessment, the participant will walk along a paper pathway with paint on his/her shoes, making footprints which will later be analyzed.

... /2
The clonus and tonic stretch reflex tests will be conducted once on each foot, as the participant sits in a chair. The spasticity scale test involves the participant indicating on a sliding scale the current severity of his/her spasticity.

In addition to these assessments, the participant will be requested to keep a daily diary of episodes of spontaneous spasm and clonus. The participant's involvement in the study will span 10 weeks.

Transportation costs will be provided by the researchers. Results of the study may be used in scientific publications, or for educational purposes, however the participant's anonymity is ensured at all times.

Disadvantages to Participation in the Study

The disadvantages in participating in the study involve the possibility of side effects including drowsiness, dryness of mouth, and the lowering of blood pressure. However the risk of these side-effects occurring is minimized by the slow rate of dosage increase.

The inconvenience of the 5 visits to the Gait Laboratory and the home visits of the nurse may also be a disadvantage.

Advantages to Participation in the Study

Participants may find that Catapres helps decrease their symptoms of spasticity, and improves their ability to walk.

Participants are not restricted from continuing on with any external therapy or medication throughout the study, providing it is not pharmacologically contraindicated, and there is no change in the dosage or program over the period of the study.

Moreover, information obtained in this study will increase the current level of knowledge regarding methods of alleviating spinal spasticity, and improving motor function in patients with partial spinal cord lesions.

Effects of Participation on Treatment

Any treatment received by the participant will in no way be affected by the participant's decision to participate or not in this study.
Enquiries Concerning the Study

Any questions or enquiries regarding the study that the patient may have will be answered promptly. Jennifer Stewart, the researcher, will be reachable at telephone numbers provided at any hour. Dr. Barbeau and Dr. Gauthier will also be available for consultation as well.

Withdrawal from the Study

Participation in the study is voluntary; participants may withdraw at any time without any prejudice to themselves.

I, the undersigned, understanding the procedures, advantages, disadvantages, and effects of participation and withdrawal involved with this research study, and aware that any enquiries that I may have will be answered by the researchers and medical consultant, agree to participate in this research study.

Dated, the ___ day of _____________, 198__.
Signed by ________________________________________________
Witnessed by ______________________________________________

I hereby certify that I have fully explained to the above named participant the nature of this research study, and the known risks involved with the study, and that the patient has the right to withdraw from the study at any time.

Signed ________________________________________________
Dated ________________________________________________
CONSENTEMENT A PARTICIPER A UNE RECHERCHE SUR
"L'EFFET DE LA CATAPRES(R) DANS LA SPASTICITE ET LA
FONCTION LOCOMOTRICE CHEZ DES PATIENTS PARAPARETIQUES

Je, soussigné(e) __________________________, consens à participer à une
recherche sur les effets de la Catapres dans la spasticité et la fonction
locomotrice chez des patients paraparétiques.

But et protocole de l'étude

Le but de cette étude est d'examiner les effets de la Catapres sur les symptômes
de spasticité et de fonction locomotrice chez des patients paraparétiques.

Quiconque consent à participer à cette étude devra prendre les comprimés Catapres
2 fois par jour pour une période de 4 semaines et le placebo pour 4 autres semai-
nes. Il devra aussi participer à 5 sessions d'évaluation d'une durée de 2½ heures
chacune au Laboratoire de Locomotion de l'Ecole de physiothérapie et d'ergothérapie
de l'Université McGill.

Ces sessions d'évaluation se tiendront lors de la première visite du (de la)
participant(e) et au début et à la fin de chaque période de médication. Elles
incluront des mesures de la locomotion sur le sol et sur tapis roulant, ainsi
que des tests cliniques évaluant les réflexes, le clonus et la spasticité.

Les procédures d'évaluation sont sûres, indolores et non-invasives. Des élec-
trodes de surface et des marqueurs cutanés réfléchissants seront attachés aux
jambes, ainsi que des interrupteurs de contact qui seront attachés aux semelles
des chaussures, afin de mesurer l'activité musculaire et les paramètres de
marche lors de la locomotion sur tapis roulant. L'évaluation de la locomotion
sur le sol sera évaluée d'après les empreintes laissées par les semelles des
chaussures (celles-ci seront peinturées), lorsque le (la) participant(e) marchera
sur un trajet de papier. Ces empreintes seront analysées plus tard.

Les évaluations de clonus et de réflexes seront faites une fois pour chaque pied,
lorsque le (la) participant(e) sera assis(e). Afin d'évaluer la spasticité, on
demendra au (à la) participant(e) d'indiquer, selon une échelle graduée, la
sévérité de sa spasticité.

En plus de ces évaluations, le (la) participant(e) devra tenir un journal quoti-
dien de ses épisodes de spasmes musculaires et de clonus. La durée de la parti-
cipation à cette étude sera de 10 semaines.

Postal address  3654 Drummond Street, Montreal, PQ, Canada  H3G 1Y5
CONSENTEMENT (CATAPRES) - 2 -

Les coûts de transport des participants(es) seront défrayés par l'Ecole de physiothérapie et d'ergothérapie. Les résultats de cette étude pourront paraître dans les revues scientifiques ou serviront pour fin éducationnelle. L'anonymat de chaque participant(e) est assuré en tout temps.

Désavantages de la participation à cette étude

Le médicament Catapres peut causer des effets négatifs secondaires tels que la somnolence, une bouche sèche et l'abaissement de la tension artérielle. Toutefois, le risque de ces effets est minime car l'augmentation de la dose de la Catapres est lente.

Autres désavantages: l'inconvénient des 5 visites au Laboratoire ainsi que les visites à domicile d'un(e) professionnel(le) de la santé.

Bénéfices découlant de votre participation

Le médicament Catapres peut s'avérer bénéfique en diminuant votre spasticité et en améliorant votre fonction locomotrice.

Le participant n'est pas restreint de continuer d'autres traitements ou médicaments en dehors de cette étude, à condition qu'il n'y ait aucune contre-indication pharmacologique et/ou aucun changement de dosage ou de programme pendant la période de l'étude avec nous.

De plus, les résultats obtenus suite à cette étude contribueront à l'amélioration des connaissances actuelles concernant les méthodes pour diminuer la spasticité et améliorer la fonction locomotrice chez les patients ayant une lésion incomplète de la moelle épinière.

Effets de la participation sur le traitement

Le traitement suivi ne sera affecté en aucune façon par ma décision de participer ou non à cette étude.

Renseignements concernant l'étude

Toutes questions ou renseignements concernant l'étude seront fournies aux participants(tes) avec promptitude. Vous pourrez communiquer avec Jennifer Stewart aux numéros indiqués, en tout temps. Drs Barbeau et Gauthier seront disponibles pour consultation.

Retrait de l'étude

Votre participation à cette étude est tout à fait volontaire et vous pouvez vous en retirer n'importe quand, sans qu'il vous en soit porté préjudice.

... /3
CONSENTEMENT (CATAPRES) - 3 -

Je, soussigné(e) _______________, comprends les procédures, avantages, désavantages et effets de ma participation ou de mon retrait relatifs à cette étude, et sachant que la chercheuse ainsi que les conseillers médicaux répondront à mes questions, je consens à participer à cette étude.

Daté le _______ jour de _____________, 19__.

Signé ___________________________________________________________________

Témoin __________________________________________________________________

Je, soussigné(e) _______________, certifie avoir bien expliqué au (à la) participant(e) mentionné(e) ci-haut la nature de l'étude projetée et ses risques, et le fait qu'il (elle) a le droit de se retirer de l'étude n'importe quand.

Signé ___________________________________________________________________

Date ____________________________________________________________________
PATIENT ASSESSMENT FORM

PATIENT'S NAME: ________________________________

DATE of VISIT: ________________ TIME of VISIT: ________

TIME of PATIENT'S LAST MEDICATION INGESTION: ________________

PATIENT STATUS:

Blood Pressure: __________ mm/hg
Pulse Rate: __________ beats/minute

POSSIBLE ADVERSE SIDE EFFECTS OF CATAPRES:
-indicate presence and severity (0, +, ++, +++)

Bradycardia: yes ___ no ___ Sedation: yes ___ no ___
Dryness of mouth: yes ___ no ___ Skin Pallor: yes ___ no ___
Dizziness: yes ___ no ___ Depression: yes ___ no ___
Dryness of eyes: yes ___ no ___ Nausea: yes ___ no ___

NOTES:

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signed: ____________________________
EVALUATION DES PATIENTS

NOM DU PATIENT: ____________________________________________

DATE DE LA VISITE: _______ HEURE DE LA VISITE: _______

HEURE DE LA DERNIERE INGESTION DU MEDICAMENT: ___________

*******************************************************************************

ETAT MEDICALE DE PATIENT:

Pression Sanguine: __________ mm/Hg
le Pouls: _______________ pulsations/minute

EFFETS SECONDAIRES NEGATIFS DU MEDICAMENT,
- indiquez la presence et la severite (0, +, ++, +++)

Bradycardie: oui non ______
Secheresse de bouche: oui non ______
Sedation: oui non ______ Peau Pale: oui non ______
Vertige: oui non ______ Depression: oui non ______
Nausee: oui non ______
Secheresse des yeux: oui non ______

NOTES: _________________________________________________________

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__________________________________________________________________

Signee: ___________________________ R.N.

Postal address: 3654 Drummond Street, Montreal, PQ, Canada H3G 1Y5
CATAPRES TITRATION PROCEDURE

INCREASING DOSAGE

DAY 1-3: 0.05 mg/day (1 tablet b.i.d. = 2 tablets/day)
DAY 4-6: 0.10 mg/day (2 tablets b.i.d. = 4 tablets/day)
DAY 7-9: 0.15 mg/day (3 tablets b.i.d. = 6 tablets/day)
DAY 10-12: 0.20 mg/day (4 tablets b.i.d. = 8 tablets/day)
DAY 13-28: 0.25 mg/day (5 tablets b.i.d. = 10 tablets/day)

* dosage is increased every 3 days, as this allows for manifestation of peak period effects

DECREASING DOSAGE

DAY 29-31: 0.15 mg/day (3 tablets b.i.d. = 6 tablets/day)
DAY 32-34: 0.05 mg/day (1 tablet b.i.d. = 2 tablets/day)

* medication is stopped on the 35th day. The following 8 days of the washout period allows residual drug to be eliminated from the body.

* placebo dosage increase and decrease followed the same protocol to assist in maintaining the double blind format.

* tablets are 0.025 mg, therefore when taken b.i.d., the basic daily dosage is 0.05 mg/day.
PROTOCOLE DE CHANGEMENT DE DOSE

(tel que suggéré par Dr A. Davis de Boehringer-Ingelheim (Canada) Ltée)

AUGMENTATION DE LA DOSE

Jour 1-3  Prendre 1 comprimé le matin et 1 comprimé le soir
Jour 4-6  Prendre 2 comprimés le matin et 2 comprimés le soir
Jour 7-9  Prendre 3 comprimés le matin et 3 comprimés le soir
Jour 10-12  Prendre 4 comprimés le matin et 4 comprimés le soir
Jour 13-28  Prendre 5 comprimés le matin et 5 comprimés le soir

Le 29e jour, vous devrez revenir au laboratoire pour une réexamination; ce sera le dernier jour de la dose complète.

DIMINUTION DE LA DOSE

Jour 29-31  Prendre 3 comprimés le matin et 3 comprimés le soir
Jour 32-34  Prendre 1 comprimé le matin et 1 comprimé le soir

Vous aurez terminé la dose prescrite au 35e jour; s'il reste des comprimés dans la bouteille, veuillez ne pas les prendre.

Une infirmière diplômée vous rendra visite tous les 3 jours, durant l'augmentation et la diminution de la dose, pour s'assurer que cette drogue n'a pas de résultat secondaire. Elle vous posera quelques questions, mesurera votre rythme cardiaque et votre tension artérielle. Elle nous tiendra continuellement au courant de votre réaction à ce médicament.

Si vous avez des questions ou quelque inquiétude que ce soit, n'hésitez pas à communiquer avec:

JENNIFER STEWART (le jour) à 392-5949, (le soir) à 937-6938
ou
DR HUGUES BARBEAU (le jour) à 392-5949.
CLINICAL EVALUATION

PATIENT NAME: __________________________________________________________

DATE: _________________________________________________________________

COMMENTS: ____________________________________________________________

ASSESSMENT RESULTS:

A. CLONUS

   no response (0):

   one to two beats (1):

   more than two beats (2):

   sustained response (3):

B. TONIC STRETCH REFLEX

   normal response (0):

   minimal response (1):

   moderate response (2):

   strong response (3):

   hyperactive response (4):

C) OVERGROUND LOCOMOTION

   velocity (cm/sec):

   cadence (steps/min):

   stride length (cm):

D) LEVEL OF SPASTICITY (VAS): ________________________________
## DAILY RECORD OF SPASMS AND CLONUS

**NAME/NOM:** ________________________________

**WEEK of/SEMAINE de:** ___________ to/au: ___________ 198_

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<th>DAY/JOUR</th>
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