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Trazodone hydrochloride in the treatment of dysesthetic pain in traumatic myelopathy: a randomized, double-blind, placebo-controlled study

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Summary Dysesthetic pain following traumatic myelopathy is characterized by diffuse burning and tingling sensations distal to the level of spinal injury. The dysesthetic pain syndrome (DPS) can compromise performance of functional abilities and inhibit participation in rehabilitation programs. Recent laboratory evidence suggests that antidepressant medications with selective inhibition of serotonin reuptake in the brain may be associated with superior analgesic effect compared to such non-selective agents as amitriptyline. Trazodone hydrochloride is a potent presynaptic serotonin reuptake blocker with few anticholinergic and cardiovascular side effects. This study was a randomized, double-blind, placebo-controlled trial of trazodone hydrochloride for the treatment of DPS. Following a 2-week placebo lead-in period, patients were randomized to a 6-week course of 150 mg trazodone hydrochloride/day or placebo. Evaluations of pain quality and intensity were performed at 2-week intervals, utilizing the McGill Pain Questionnaire, Sternbach Pain Intensity Scale, and Zung Pain and Distress Index. Neurologic examination and assessment of side effects were performed at each evaluation session. No significant changes were noted in reported pain measures between patients allocated to the active drug group and those given placebo during the course of the protocol. However, significantly more patients randomized to trazodone complained of side effects and prematurely terminated their participation in the study. The results of this investigation are consistent with those of other earlier trials which indicate that such antidepressant medications as trazodone hydrochloride which selectively inhibit presynaptic reuptake of serotonin, may not be effective in the control of certain pain syndromes. These results do not preclude the possible utility of these agents in the treatment of other pain syndromes or at higher doses than previously studied.

Key words: Spinal cord injury; Pain; Tricyclic antidepressants

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Introduction

Pain is a frequent complication of traumatic myelopathy [5,30] and was extensively reviewed by Burke [8] and Donovan et al. [11]. Pain syndromes following SCI have been classified into 5 major groups: myofascial pain at or above the level of spinal injury, psychogenic pain, visceral pain, radicular pain and diffuse dysesthetic pain distal to the level of injury [11].

Reported treatments of pain following SCI have included transcutaneous nerve stimulation [4], epidural electrical stimulation [34], cordectomy [28], rhizotomy [12], ablation of the dorsal root entry zone [29,36] and psychotropic medications [18,25]. Studies designed to evaluate the efficacy of these interventions have been limited by two fundamental methodologic flaws: these studies failed to precisely identify the types of pain syndromes under treatment and these protocols generally did not use reliable established measures of pain quality and intensity.

There have been many reports of the therapeutic efficacy of tricyclic antidepressant (TCAD) medications in the treatment of pain syndromes [9,22,39]. Two reports suggested TCAD medications were effective in the treatment of radicular and dysesthetic pain following traumatic myelopathy [18,25]. Most studies testing the efficacy of TCAD medications in the treatment of pain have used amitriptyline, which interferes with the reuptake of serotonin and norepinephrine in a 1 : 2.8 ratio [35]. The work of Akil, Mayer, Liebeskind and associates [1,24,26] has provided data to support the use of TCAD medications in the treatment of pain syndromes. They reported that analgesia induced by electrical stimulation of the nucleus raphe magnus in rats was enhanced by administration of 5-hydroxytryptamine (serotonin) and reduced by norepinephrine administration. An agent with more selective inhibition of presynaptic serotonin reuptake than amitriptyline would thus be expected to provide superior analgesia, but 3 previous reports failed to demonstrate efficacy of serotonin reuptake blockers in the treatment of chronic pain syndromes [3,14,20].

Trazodone hydrochloride is a new antidepressant medication which selectively inhibits serotonin and norepinephrine reuptake in a ratio of 25 : 1 [35]. It was anticipated that this high specificity for serotonin might promote analgesia in a select group of patients with a well-defined pain syndrome. The present study was a randomized, double-blind, placebo-controlled trial to test the efficacy of trazodone hydrochloride in the treatment of function-limiting dysesthetic pain secondary to traumatic myelopathy.

Methods

Subjects

The study group consisted of inpatients and outpatients at the Rehabilitation Institute of Chicago (RIC), Northwestern University Medical School, Chicago, IL who developed dysesthetic pain following traumatic myelopathy. Patients were referred to one of the physician-investigators (E.R.), who performed an initial

screening evaluation of each subject. Patients who met study criteria were invited to participate in the study.

Patients were excluded if they were under 18 years of age, lacked English fluency or had a history of recent ethanol or substance abuse. All patients met the following criteria:

(a) A history of dysesthetic pain of at least 1 month duration, and initial onset within the first post-injury year;

(b) Failure to respond to conventional treatment, including therapeutic exercise, physical modalities, non-prescription analgesics, non-steroidal anti-inflammatory agents or narcotics; and

(c) Pain-induced functional impairment, defined as the presence of one or more of the following: (1) disturbance of sleep–wake cycle; (2) inability to perform self-care activities; or (3) inability to fully comply with a therapeutic exercise program.

A thorough review of potential risks and benefits of participation was performed by one of the physician-investigators. All patients gave informed written consent. This study was approved by the Institutional Review Board, Northwestern University Medical School, Chicago, IL, and by the Food and Drug Administration, Washington, DC.

Procedure

This investigation consisted of a randomized, double-blind, placebo-controlled trial of trazodone hydrochloride in the treatment of patients with dysesthetic pain secondary to traumatic myelopathy. At the time of enrollment, general medical history and review of systems were elicited and physical and neurological examinations were performed. Determinations of motor and sensory levels and degree of completeness of injury were made according to the American Spinal Injury Association criteria [2]. A complete blood count with differential, urinalysis and chemistry profile was obtained at enrollment and termination from the study protocol. After the initial evaluation, patients were given, in a single-blind fashion, 1 placebo capsule/day for 2 weeks. Following this placebo lead-in period, patients were prescribed, in a double-blind fashion, 1 capsule/day of randomized medication for 3 days, 2 capsules/day for the next 4 days, and 3 capsules/day for the remaining 5 weeks of the study. Patients were evaluated in the clinic by a physician-investigator every 2 weeks until the patient completed the 8-week protocol or terminated participation in the study. Adverse reactions, orthostatic blood pressure measurement, heart rate and neurologic examination results were recorded at each follow-up clinic visit. Compliance was determined by review of patient drug diaries and pill counts at each evaluation session. At the completion of the 8-week protocol, patients were offered the opportunity to continue the use of the same medication in double-blinded fashion. These patients were re-evaluated at monthly intervals until they discontinued participation in the study. At termination, physicians and patients completed subjective global assessments of medication efficacy.

The following instruments for pain assessment were administered at the time of enrollment and every 2 weeks until termination of each patient's participation in the study protocol.

McGill Pain Questionnaire (MPQ) [27]

The MPQ generated information concerning affective, sensory and evaluative aspects of pain [27]. Three types of measures were obtained from the MPQ: The pain rating index (PRI) was based on the rank value of pain descriptors chosen from a 20-category word list. A trained research assistant administered the MPQ to each patient, who selected the word in each category that best described his or her pain at the time of evaluation. The number of words chosen (NWC) from the same 20-item inventory also was recorded. The present pain intensity (PPI) indicated the magnitude of pain on a 5-point scale. Previous authors have reported the MPQ to be a valid, reliable and reproducible instrument for pain assessment [15,23,27,31,32].

Sternbach Pain Intensity (SPI) [37]

The patient was asked to rate his or her pain intensity on a scale of 1–100, in which a score of zero represented no pain, and a score of 100 was equivalent to pain so severe that the patient would commit suicide. SPI ratings were obtained for the day of assessment (SPI-day) and for the week prior to clinic visit (SPI-week). Sternbach demonstrated that the scale was valid for assessing neurogenic and myofascial pain syndromes [37].

Zung Pain and Distress Index (PAD) [40]

Each patient responded by indicating the extent to which he or she agreed with statements describing mood and behavioral changes associated with pain. This self-administered 20-item questionnaire has been shown to be a valid and reliable index of pain and accompanying emotional distress [40].

Data analysis

Frequency distributions for sex, neurologic level, completeness of spinal lesion, surgical stabilization and etiology of injury were generated for drug and placebo groups. Significant differences in these frequencies were determined using the normal approximation of the binomial distribution to obtain confidence intervals. Student's t test was employed to compare age, duration of pain symptoms and baseline pain measures between drug and placebo groups.

A repeated measures analysis of variance and covariance [10] was performed on the pain variables derived from all patients' responses at 3 periods: (1) time of enrollment (initiation of placebo lead-in); (2) randomization to drug or placebo (week 2); and (3) termination from protocol.

Two null hypotheses were tested: (a) there were no significant differences in pain measures of both treatment groups over time; and (b) there were no significant differences in pain measures between drug and placebo groups.

Sample size calculations were determined based on a one-sided t test of the differences in pain scores between groups at entry into and termination from the

protocol [8]. Using $\alpha = 0.05$, $\beta = 0.20$, and a sample size of 9 for each group, a 30% difference in pain scores between groups could be detected.

Frequency distributions were determined for side effects and for global assessments of efficacy. Significant differences in these frequencies were evaluated using the normal approximation of the binomial distribution to obtain confidence intervals.

Results

Nineteen subjects participated in the study protocol. One patient failed to return for randomization to active drug or placebo. Characteristics of the patient sample are noted in Table I. The only statistically significant difference between the drug and placebo groups was the allocation of more sensory incomplete SCI patients to the drug group ($P < 0.05$). There were no significant baseline differences between groups for PRI, NWC, PPI, SPI-day, SPI-week and PAD (Table II).

Eight patients of the nine in the placebo group returned for all clinic visits following randomization (Table III). All patients in the drug group returned for at least one clinic visit following randomization. Compared to the placebo group, a significantly smaller number of patients randomized to active drug completed the 8-week trial (8 vs. 4; $P < 0.01$). Although most patients terminated their participa-

TABLE I

PATIENT CHARACTERISTICS

Item	Trazodone	Placebo
Sample size	9	9
Age (years)	39.4 ± 4.6	38.8 ± 2.4
Duration (months)	47.6 ± 9.8	51.0 ± 19.2
Sex		
Male	8	8
Female	1	1
Neurologic level		
Cervical	1	2
Thoracic	6	5
Lumbosacral	2	2
Complete motor	5	5
Complete sensory [a]	1	4
Etiology		
Road traffic accidents	1	1
Falls	2	2
Gunshot wounds	5	4
Sports	0	1
Other	1	1
Surgical stabilization	3	3

[a] Denotes a significant difference between groups at $P < 0.05$. $\bar{x} \pm 2$ S.E.M.

TABLE II

BASELINE PAIN MEASURES [a]

Items	Trazodone	Placebo	*P*
PRI	33.0 ± 5.5	34.7 ± 4.4	N.S.
NWC	13.2 ± 1.9	13.9 ± 1.5	N.S.
PPI	2.1 ± 0.3	2.4 ± 0.3	N.S.
SPI-day	57.9 ± 11.1	55.7 ± 10.4	N.S.
SPI-week	69.7 ± 8.7	65.6 ± 9.6	N.S.
PAD	56.9 ± 4.6	59.0 ± 4.9	N.S.

[a] All values are given as $\bar{x} \pm 2$ S.E.M.

TABLE III

PATIENT COMPLIANCE WITH PROTOCOL

Group	Baseline	Week 2	Week 4	Week 6	Week 8 [a]
Drug	9	9	9	8	4
Placebo	9	9	8	8	8

[a] Denotes a significant difference between groups at $P < 0.01$.

TABLE IV

SIDE EFFECTS

Side effects	Trazodone	Placebo
Any [a]	4	1
Drowsiness [a]	4	1
Dry mouth	2	0
Dizziness	2	0
Urinary tract infection	2	0
Increased spasticity	2	0
Urinary retention	1	0
Constipation	0	0
Priapism	0	0

[a] Denotes a significant difference between groups at $P < 0.05$.

TABLE V

GLOBAL ASSESSMENT OF EFFICACY

Assessment of efficacy		Trazodone	Placebo	*P*
Physician	Yes	5	2	N.S.
	No	4	7	N.S.
Patients	Yes	4	3	N.S.
	No	5	6	N.S.

TABLE VI

PAIN MEASURES AT PROTOCOL TERMINATION

Items		Trazodone	Placebo
PRI	Enrollment	33.0 ± 5.5	34.7 ± 4.4
	Randomization	33.2 ± 6.9	31.2 ± 6.4
	Termination	33.5 ± 2.4	32.1 ± 3.5
NWC	Enrollment	13.2 ± 1.9	13.9 ± 1.5
	Randomization	12.0 ± 1.7	12.3 ± 1.5
	Termination	14.0 ± 1.0	13.2 ± 1.5
PPI	Enrollment	2.1 ± 0.3	2.4 ± 0.3
	Randomization	2.9 ± 0.6	2.1 ± 0.3
	Termination	2.6 ± 0.2	1.7 ± 0.2
SPI-day	Enrollment	57.9 ± 11.1	55.7 ± 10.4
	Randomization	58.2 ± 9.4	56.6 ± 8.7
	Termination	61.7 ± 6.8	63.4 ± 8.4
SPI-week	Enrollment	69.7 ± 8.7	65.6 ± 9.6
	Randomization	63.8 ± 7.0	62.6 ± 8.8
	Termination	73.9 ± 4.7	68.3 ± 6.9
PAD	Enrollment	56.9 ± 4.6	59.0 ± 4.9
	Randomization	55.1 ± 4.6	55.8 ± 4.4
	Termination	67.2 ± 3.8	53.0 ± 3.2

All values given as $\bar{x} \pm 2$ S.E.M.

tion at the end of the full 8-week protocol, a small number elected to continue for up to 3 months. There was a statistically significant difference in reported side effects between the drug and placebo groups (Table IV). The most common complaints among patients on active drug were (in descending order): drowsiness, dry mouth, dizziness, increased spasticity and urinary retention.

A global assessment of efficacy was completed by a physician and the patient at the termination clinic visit (Table V). Review of results obtained from the physician assessments indicated that 5 of 9 patients randomized to trazodone and 2 of 9 patients randomized to placebo had improvement of their pain syndrome, a difference which was not statistically significant. Review of the patient global assessments suggested that four of the patients on active drug and three of the patients receiving placebo reported significant improvement in pain symptoms. None of these subjective observations was reflected in the analysis of the pain measures, which showed no significant changes over time from baseline recordings (Table VI). Consequently, the two null hypotheses were accepted at $P > 0.05$: there were no significant differences in the pain measures over time and there were no significant differences in pain measures between drug and placebo groups.

Discussion

In the past decade, animal studies have demonstrated that an increase in the cerebral concentration of serotonin enhances analgesia [1,24,26], an effect which is antagonized by agents which inhibit serotonin synthesis and transmission [1,38].

These findings suggested that antidepressant medications which selectively block brain serotonin reuptake may be associated with superior analgesic effect compared to that induced by such non-selective agents as amitriptyline, doxepin and imipramine. Trazodone hydrochloride, a new antidepressant medication, is a potent presynaptic serotonin reuptake blocker with few anticholinergic and cardiovascular side effects [6,13,19,33,35]. Because of this high selectivity for serotonin reuptake inhibition and low toxicity, it was expected that trazodone hydrochloride would prove to be a rational choice for pharmacologic therapy of the dysesthetic pain syndrome (DPS) following traumatic SCI.

Disabling denervation dysesthesias occur in a significant number of patients with traumatic myelopathy [5,8,11,30]. This DPS is characterized by diffuse burning, stinging and tingling sensations distal to the level of spinal injury. DPS can compromise functional abilities and inhibit participation in rehabilitation programs. The utility of tricyclic antidepressant (TCAD) medications in the treatment of chronic pain syndromes has been extensively investigated [3,9,14,16–18,20–22,25,39]. Amitriptyline is efficacious in the prophylaxis of migraine [8], and in the treatment of post-herpetic neuralgia [39] and tension headache [22]. Imipramine has been shown to relieve dysesthesias resulting from painful diabetic neuropathy [20].

Two previous investigators utilized TCAD medications in the treatment of DPS associated with spinal cord injury with equivocal results. Using an open design, Heilporn [18] studied 11 inpatients with dysesthetic pain. The patients received a combination of 150 mg of melitracin and 3 mg of flupenthixol daily. Several patients received transcutaneous nerve stimulation as an adjunct to therapy. Three patients reported lasting relief and five had some improvement. There was no description of follow-up. In another published report, Maury [25] recommended the use of TCAD and neuroleptic medications for the treatment of radicular and dysesthetic pain following traumatic SCI, but provided no rationale and reported no data with regard to efficacy. The present study used a randomized, double-blind, placebo-controlled design to determine the efficacy of trazodone hydrochloride for the treatment of this syndrome.

Comparison of demographic data, neurological status and pretreatment pain rating values revealed no significant differences between drug and placebo groups other than a larger number of patients with incomplete sensory myelopathy. This was not expected to bias the results of treatment in this group, since there was no significant difference in the baseline assessments for each group in this study. Evaluation of changes in the measures of pain quality and intensity was performed at 3 points: (1) enrollment; (2) randomization; and (3) exit interview. Differences in pain measures between points 1 and 2 were examined in an effort to determine the effect of placebo upon pain measures (Table VI). Differences between pain scales at points 2 and 3 were used to evaluate the effect of drug administration (Table VI). Separate analyses were conducted to determine the extent to which changes in pain ratings resulted from drug effect. Because duration of participation varied, the exit interview was chosen as the time for final outcome determination. It was assumed that patients required at least a 2-week trial of trazodone hydrochloride to perceive any therapeutic effect, and that premature termination was the result of either intolerable side effects or lack of therapeutic efficacy.

No significant changes were noted in reported pain measures during the course of the treatment protocol between patients allocated to active drug and those allocated to placebo. However, significantly more patients randomized to trazodone hydrochloride complained of side effects and terminated participation in the study prematurely (1 patient terminated at week 4, and 3 others terminated at week 6). It is possible that a higher maintenance dose of trazodone hydrochloride might have proven efficacious in the treatment of this pain syndrome. However, the dosage used was equipotent to that of other TCAD medications used for the treatment of pain syndromes [9,10,16,17,21,22,39]. Monitoring of serum drug levels might have yielded information concerning dose–response relationships between study drug concentration, therapeutic efficacy and side effects.

Three groups of investigators have previously examined the efficacy of serotonin reuptake inhibitors in the treatment of pain states and found equivocal results. Johansson et al. [20] randomized 40 patients with chronic organic and psychogenic pain to a 5-week trial of either placebo or zimelidine, a potent serotonin reuptake inhibitor. There was a dramatic change in visual analog scale (VAS) pain ratings for patients allocated to the drug group compared to those of the placebo group following treatment. However, the VAS pain ratings of the placebo group before and after treatment were not significantly different from the VAS values of the drug group at the end of the trial. The lack of comparability between treatment groups may have resulted in regression to the mean of the VAS values for the zimelidine group. In another study, Gourlay et al. [14] studied 19 patients in a double-blind, placebo-controlled, cross-over study of 300 mg of zimelidine daily for 6 weeks. There were no significant differences in objective pain measures between active drug and placebo. Likewise, Andersen et al. [3] reported a double-blind, cross-over study of 26 patients with chronic pain utilizing citalopram (a serotonin reuptake blocker) and flupenthixol (a potent neuroleptic medication), in which no differences in VAS pain scores between the drug and placebo groups were noted.

This investigation represents the first systematic trial of an antidepressant medication for the treatment of function-limiting dysesthetic pain following traumatic myelopathy. Despite animal models demonstrating the importance of the neurotransmitter serotonin in central pain control mechanisms [9,22,38,39], results of this investigation support the findings of previous authors [3,14,20] that antidepressant medications which selectively inhibit presynaptic reuptake of serotonin may not be effective in the control of certain pain syndromes. Although these results do not preclude the possibility of employing these agents for the treatment of other pain syndromes or at higher doses than previously studied, there is no evidence at this time to support the use of trazodone hydrochloride for the management of DPS following SCI.

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