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Tizanidine

An Alternative in the Pharmacologic Treatment of Spasticity

Summary

Indication: Tizanidine (Zanaflex[®], Athena Neurosciences), is indicated for the treatment of spasticity due to multiple sclerosis and spinal cord injury.

Monitoring Parameters: Patients should be monitored for resolution of symptoms of spasticity and adverse effects including hypotension and drowsiness. Liver function tests including aminotransferase levels are recommended at initiation of therapy and at 1, 3, and 6 months of therapy, then periodically based on clinical status.

Dose: The usual starting dose 2 mg by mouth once daily, titrated over 2 to 4 weeks to the maximum tolerated dose, usually 8 mg three times daily. The maximum dose is 36 mg daily in three or four divided doses.

Pediatrics: Tizanidine has not been evaluated for use in pediatric patients.

Geriatrics: Tizanidine should be used with caution in geriatric patients because of the potential for decreased clearance of the medication and increased risk of side effects, such as falls.

Pregnancy Category: C

Breast Feeding: Tizanidine is lipid-soluble. It may be excreted in breast milk.

Cost: Tizanidine is available as 4-mg tablets. The average wholesale price (AWP) is \$153.08 for a bottle of 150 tablets. The AWP for a one-month supply at a dose of 8 mg three times daily is \$183.70.

Introduction

Spasticity is a common problem among neurological rehabilitation patients. It may be due to either cerebral or spinal lesions, commonly related to multiple sclerosis (MS) or traumatic spinal cord injury (SCI).¹⁻³ The exact physiologic mechanism is not clearly defined and may in fact vary from patient to patient. Proposed mechanisms include alpha-motor neuron hyperactivity, gamma-motor neuron hyperactivity, excitatory Ia interneuron hyperexcitability, reduction in presynaptic inhi-

bitation, reduction of recurrent inhibition (Renshaw), reduction of autogenic inhibition (Ib), and reduction of reciprocal inhibition (Ia).⁴ Although spasticity may manifest itself differently based on the location and severity of the lesion, it may be generally defined as velocity-dependent, excessive activation of skeletal muscle¹⁻³ in association with the upper motor neuron syndrome.^{2,3} Spasticity is often associated with positive symptoms including flexor spasms, dystonic rigidity, and autonomic hyperreflexia. Negative symptoms may include weakness, fatigue and lack of dexterity.^{1,3}

Certain conditions may exacerbate spasticity. Any stimulus that increases nociceptive input, such as urinary tract infections, full bowel or bladder, pressure sores, fractures, ingrown toenails, and external stimuli including tight clothing, poor seating, and catheter leg bags may contribute to spasticity.^{1-3,5} Certain drugs, including non-tricyclic antidepressants such as fluoxetine and trazodone, may also increase spasticity.³

Spasticity does not inherently require therapy, and may actually be valuable to the patient in certain settings. Michaelis has discussed the differentiation between "basic" and "excess" spasticity.¹ He states that "basic" spasticity helps the patient to perform certain functions, but that excess spasticity may result in sequelae, necessitating therapy. These sequelae may include decreased functional mobility, contractures that worsen posture, and pain. Spasticity may also predispose the patient to pressure sores.²

Several therapeutic modalities exist to treat spasticity. Initial therapy includes investigation for and treatment or removal of possible exacerbating conditions. Subsequently, physiotherapy and application of heat and/or ice may be used as treatments for acute spasticity.¹⁻³ Peripheral or central nervous electrical stimulation, chemical interruption of the reflex arc with phenol or alcohol and surgical procedures have been used to change the inhibitory/excitatory balance. Oral medications are important adjunct therapies. The main agents are diazepam, baclofen and dantrolene. Unfortunately the usefulness of these agents is limited by their varying efficacy and their side effect profiles. Tizanidine (Zanaflex[®], Athena Neurosciences), a centrally acting alpha-2 adrenergic agonist,

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represents an alternative agent for the treatment of spasticity secondary to MS or SCI.

Pharmacology/Pharmacokinetics

Tizanidine is an imidazoline derivative structurally similar to clonidine.⁶ Although its mechanism of action is not clearly defined, tizanidine has several pharmacologic effects. The anti-spasticity effects of tizanidine are thought to be mediated by its alpha-2 adrenergic agonistic properties.⁵⁻⁸ In general, this results in an overall inhibitory effect on alpha motor neurons and a clinical reduction in motor reflexes. More specifically, several authors report that the primary action of tizanidine is a pre-synaptic inhibition of the release of excitatory amino acids in the spinal cord.⁵⁻⁸ Post-synaptic decreases in excitation may also occur. Furthermore, there is some evidence that tizanidine may act supraspinally to inhibit coeruleospinal reflex transmission.^{5,7,8} Tizanidine also binds to the imidazoline receptor, although it is unclear what if any role this may have in spasticity.⁸

Studies in animal models have demonstrated the antinociceptive properties of tizanidine. However, these studies were often inconsistent and showed effects only at the upper end of the dosing regimen.^{7,8} The effect appears to be modulated through alpha-2 adrenoreceptors, rather than opioid receptors. It has not been noted in any of the clinical literature reviewed in this report.

Approximately 53 to 66% of the tizanidine dose is absorbed, and absorption is not significantly affected by food.⁷ Tizanidine demonstrates linear kinetics within individual patients over the therapeutic dosing range from 1 to 20 mg.⁷ However, interpatient variability in clinical response to a given dose necessitates individualized dose titration. Peak concentrations and peak effect occur within 1 to 2 hours.^{5,6}

Bioavailability of tizanidine is approximately 21 to 40% due to extensive first-pass metabolism.^{6,7} Mean volume of distribution is 2.4 L/kg.⁷ Approximately 30% of the dose is protein-bound.^{6,7}

Metabolism of tizanidine primarily occurs through oxidation of various sections of the drug.⁷ Approximately 95% of the dose is metabolized in the liver.^{6,7} The metabolites are not known to have any pharmacologic activity.^{6,7} Roughly 60% of the dose is excreted in the urine, and 20% in the feces.⁶ The elimination half-life is approximately 2.5 hours.⁶

Clinical Trials

A multitude of trials has been performed in patients with MS. Smith, et al. conducted a 15-week randomized, double-blind, placebo-controlled trial of tizanidine for treatment of spasticity due to MS.¹⁰ The treatment groups were stratified by severity of spasticity as determined by Ashworth score at baseline into mild, moderate and severe groups. This multi-center trial analyzed a total of 220 patients through three

phases over 15 weeks. The phases included a 2-week washout period, a 3-week dose titration phase, and a 9-week plateau phase, followed by a 1-week taper and subsequent final follow-up. Tizanidine doses ranged from 2 to 36 mg/day. The primary efficacy measures were change in Ashworth scale and type and frequency of spasm based on patient diaries. At the end of the titration and plateau phases and at the study endpoint there was no significant difference between the placebo and tizanidine groups in patients who had improvement in muscle tone as measured by the Ashworth Scale (*p* values not reported). Subset analysis did not reveal any significant trends. Patient diary results, however, did show a significant decrease in daily spasms and clonus at end point for the tizanidine group as compared to placebo (*p* = 0.028). There were no significant differences during the titration or plateau phases. Of the secondary endpoints, only the global efficacy and tolerability scores were significantly better for the tizanidine group as rated by the physician/prescribers (*p* = 0.043) and the patients (*p* = 0.011). There was one patient in the tizanidine arm who developed increased liver function tests (LFTs) while on the study, which resolved after discontinuation of tizanidine.

A second multi-center, double-blind, placebo-controlled, randomized trial of 187 patients with MS was conducted by the United Kingdom Tizanidine Trial Group.¹¹ As in the study by Smith, et al, improvement in the Ashworth Scale was the primary efficacy measure and patients were stratified by baseline severity into 3 groups. The dosing schedule was also similar with washout, titration, plateau and taper periods occurring over 14 weeks. Dosing was also similar, ranging from 2-36 mg/day in divided doses, with a mean of 30 mg/day following titration. In the intent-to-treat analysis, the tizanidine group had a significantly greater reduction in the Ashworth Scale score compared to the placebo group (21% vs. 9%, *p* = 0.004). There were no clinically significant changes in laboratory values, although the tizanidine group had an increase in gamma-glutamyl transferase (GGT) from 23.1 to 27.9 IU/L (*p* = 0.05). The main adverse effects were dry mouth and drowsiness.

Several trials have compared the use of tizanidine to baclofen in the treatment of spasticity related to MS. The first, by R. Stein, et al, was a double-blind, randomized, multi-center trial involving 40 patients in nursing homes with MS to determine the optimal dose of tizanidine and to compare its efficacy and safety to baclofen.¹² The Ashworth Scale was used as a measure of muscle tone, the Kurtzke Scale was used to measure neurologic disability, and Pedersen's method was used to measure functional disability. The trial included a 5 day washout period, followed by a 2 week titration to a maximum of 20 mg tizanidine or 50 mg baclofen and a 4 week dose-optimization period, up to 36 mg tizanidine or 90 mg baclofen. The authors reported considerable interpatient variation in

response to each medication. Doses ranged from 4 to 36 mg per day (median = 24 mg) of tizanidine and 20 to 90 mg per day (median = 50 mg) of baclofen. Both drugs reduced muscle tone, although there were no significant changes in either of the disability scales.

A second study of 16 MS patients by Hoogstraten, et al. was designed as a partially blind, crossover trial comparing tizanidine and baclofen treatment with dose titration over 2 to 3 weeks and plateau for 4 weeks, with a wash-out period of at least 3 days between study medications.¹³ The results of the study demonstrated similar improvement in overall efficacy between the two medications.

Bass, et al. designed a randomized, double-blind crossover trial of 66 outpatients with definite MS.¹⁴ Dosing included a 3-week titration phase followed by a 5-week plateau phase, with a 1-week taper and 2-week washout period before crossover. The mean daily dose of tizanidine was 17 mg, and baclofen was 35 mg after the 8-week treatment period. No significant difference was noted in antispasticity effect between the medications as measured by a neurologist. A physiotherapist also noticed no significant difference in functional measures. Muscle weakness was noted more frequently in the patients receiving baclofen ($p \leq 0.01$). In assessments of overall drug efficacy, physicians preferred baclofen ($p \leq 0.05$), although patients did not demonstrate a significant preference. All groups assessed drug tolerance as similar.

Finally, Eyssette and colleagues performed a multi-center, double-blind trial over 8 weeks of 100 patients with MS comparing tizanidine and baclofen.¹⁵ Doses of the study medications were titrated over the first 2 weeks, then maintained at optimum doses for the remaining 6 weeks. A series of assessments were made to examine efficacy, including locomotor function, stretch reflex, flexor spasms, patient's state in bed and chair, clonus, muscle strength, and bladder control. Actual average doses were not reported. There were no statistically significant differences in the measures of efficacy or tolerability between the two treatment groups.

Tizanidine has also been evaluated for the treatment of spasticity due to other primary disease states. Medici, et al. performed a double-blind, randomized comparative trial of tizanidine and baclofen in 30 patients with spasticity due to cerebrovascular lesions.¹⁶ The trial was done with a 4 to 5 day washout period and a 2-week titration phase, followed by a 50-week maintenance phase. The primary efficacy parameter was improvement in muscle tone. In both groups, a significant number of patients had improved muscle tone from baseline (tizanidine = 87%, baclofen = 79%), but there was no statistical difference between the groups at any time. Only the patient's global assessment of antispasticity efficacy approached statistical significance ($p = 0.057$).

A multi-center, randomized, double-blind trial of tizanidine

and diazepam in 105 patients with spasticity related to cerebrovascular accidents or cranial trauma was done by Bes, et al.¹⁷ There was a 3 day washout period, followed by a 2-week dose titration phase. The optimum dose was then maintained for 6 weeks. Efficacy was assessed by measuring walking on flat and rough ground and by measuring contractures related to the stretch reflex in four muscle groups. The tizanidine group showed a significant improvement in the distance they were able to walk on flat ground (baseline = 572 m, last exam = 796 m, $p < 0.05$). There was no statistically significant difference in improvement in spasticity related to the stretch reflex. The investigators' assessment of overall effect relative to initial status was comparable between the treatment groups.

Nance, et al. studied tizanidine in a multi-center, double-blind, randomized, placebo-controlled trial of 124 patients with spasticity due to SCI.¹⁸ The 8-week study consisted of a 7 to 10 day washout phase followed by a 3-week titration period, a 3-week plateau period and a 1-week taper phase. Efficacy was evaluated by changes from baseline in spasticity symptoms, including assessment using the Ashworth Scale, activities of daily living, and a global evaluation of efficacy. Forty patients discontinued the trial prematurely, divided evenly between the tizanidine and placebo groups (21 vs 19). The average tizanidine dose was 19 mg per day during titration and 31 mg per day during the plateau phase, while it was 20 mg per day and 33 mg per day, respectively, for placebo. Tizanidine produced significant reductions in muscle tone (as measured by the Ashworth Scale) from baseline compared to placebo at the end of titration, plateau and taper phases ($p < 0.0001$). Although there was a trend for the tizanidine group toward better results in the global assessment, the results were not significantly different than placebo.

Tizanidine has also been evaluated for the treatment of back pain due to paravertebral muscle spasms,¹⁹ chronic tension-type headaches,^{20, 21} and trigeminal neuralgia.²² Fryda-Kaurimsky, et al. compared tizanidine to diazepam for paravertebral muscle spasms in a double-blind trial of 20 hospitalized patients over 7 days.¹⁹ They concluded that tizanidine was a comparable alternative to diazepam in safety and efficacy.

Fogelham and Murros studied tizanidine for chronic tension headaches in a randomized, double-blind, placebo controlled crossover trial.²⁰ A total of 37 women were studied for 2 6-week treatment periods with a 2-week washout period. Headache severity was assessed using a visual analog scale (VAS) (0-100 mm) and a verbal rating scale (VRS) (1-5 where 1 = no headache). Daily headaches and analgesic use were documented in a patient diary. Over the 6-week treatment periods, there was a statistically significant improvement in the tizanidine group as compared to placebo for the VAS, VRS, patient's global efficacy rating, headache-free days and analgesic use ($p = 0.018$, $p = 0.012$, $p = 0.001$, $p = 0.0003$, and $p =$

0.001). Treatment with tizanidine was initiated at 2 mg three times daily, and could be increased up to a maximum of 6 mg three times daily. The initial dose of tizanidine 6 mg per day led to a favorable response in 57% of patients, compared to 30% on placebo.

Fromm, Aumentado and Terrence have reported the results of a randomized, double blind, cross-over trial in 10 patients with trigeminal neuralgia.²² An initial dose of 2 mg (one-half tablet) three times daily for 3 days was followed by 4 mg (whole tablet) three times daily for 4 days. This was repeated for the other phase with no wash out between study medication and placebo. Daily paroxysms were recorded in a patient diary over the last 4 days of each phase. Tizanidine decreased the average daily frequency of paroxysms compared to placebo ($p = 0.02$). Two patients had increased levels of concurrent carbamazepine during the placebo phase, which the authors speculated was related to increased compliance with the prescribed regimen. The authors further reported that six patients elected to continue or resume therapy with tizanidine follow-

ing the trial. Two had recurrences of neuralgia after one month and the other 4 relapsed after 3 months.

Adverse Effects

Tizanidine has been generally well tolerated. The most commonly reported adverse effects include somnolence/drowsiness (15-67%), dry mouth (11-36%), and muscle weakness (2-47%).⁷ In two meta-analyses including patients with either MS or SCI, global assessments have shown significantly better tolerance to tizanidine than to baclofen or diazepam ($p = 0.008$ and $p = 0.001$, respectively).^{23, 24}

Interestingly, several studies have indicated that tizanidine may not affect muscle strength as much as baclofen or diazepam (see Table 1). In a comparison of baclofen and tizanidine in patients with MS, muscle weakness was noted more frequently in patients treated with baclofen ($p \leq 0.01$).¹⁴ In a cross-over comparison of baclofen and tizanidine, the authors conclude that falls related to decreased muscle strength while on treatment with baclofen were significant.¹³ However, a cross-

Table 1. Summary of comparative blinded trials investigating objective improvement in muscle strength and subjective reports of muscle weakness (adapted from reference #7).

Reference	Diagnosis	Dose (mg/day)	No. of treated (evaluable) patients	Duration (weeks)	Improvement in muscle strength (objective) ^a (patients)	Subjective muscle weakness (% of evaluable)	Patients withdrawing due to weakness (% treated patients)
Comparisons with Baclofen							
Bass, et al. ¹⁴	MS	T \leq 32 B \leq 80	Total 62 (48) ^b	8	T=B 35 ^{c**}	21 ^c 11	6
Eysette, et al. ¹⁵	MS	T \leq 24 B \leq 60	50 (41) 49 (44)	8	T=B ^d	NR (<B) 23	4 2
Hoogstraten, et al. ¹³	MS	T 12-24 B 15-60	Total 16 (14) ^b	7	T=B	29 79 ^{e*}	0 25
Medici, et al. ¹⁶	CV Lesions	T 16-20 B 50	14 (14) 14 (11)	50	T \geq B ^f	7 36	0 21
Comparisons with Diazepam							
Bes, et al. ¹⁷	Hemiplegia	T \leq 24 D \leq 30	51 (45) 54 (39)18	8	T=D	2	4 6

a: Assess using the British Medical Research Council 5-point scale. b: Crossover trial design. c: During maintenance phase. During titration phase: T 32%, B 57%. d: Muscle strength deteriorated in 33% of B recipients vs none on T by the end of the trial. e: Six patients complained of falling while receiving B vs none on T ($p < 0.05$). f: Muscle strength deteriorated in 43% of B recipients vs 33% on T by the end of the trial. Key: CV = cerebrovascular; MS = multiple sclerosis; NR = not reported “=” equivalent; “ \geq ” tendency toward superior improvement; * $p \leq 0.05$; ** $p \leq 0.01$

over effect made statistical analysis difficult (1 patient on baclofen in period I dropped out due to muscle weakness; 5 complained of weakness in period II, of which 3 dropped out). No patients on tizanidine complained of falls in either period.

In a comparison study of patients with spasticity due to cerebrovascular lesions taking either tizanidine or baclofen, 53% of patients in the tizanidine group showed improved muscle strength, and only 33% had decreased muscle strength.¹⁶ Only 21% of baclofen-treated patients had improved muscle strength and 43% had decreased muscle strength, and 3 withdrew from the study due to this side effect. These results were not statistically significant, though. Finally, a comparison of tizanidine and diazepam for spasticity in patient with spasticity due to cerebrovascular accidents or cranial trauma, there was a trend that fewer patients in the tizanidine group had decreased muscle strength compared to diazepam (2.3% vs 8.3%, no *p* value given).¹⁷

Central Nervous System Effects

Dry mouth, dizziness and drowsiness/sedation are among the most common side effects related to tizanidine. Drowsiness appears to be dose-related. In a single-dose study, 92% of patients taking tizanidine 16 mg reported drowsiness, compared to 78% taking 8 mg and 31% taking placebo.⁶ Three patients reported having hallucinations while receiving tizanidine.²³

Cardiovascular System Effects

Hypotension has been reported in 7 to 20% of patients treated with tizanidine at doses \leq 24 mg.^{6,7} The effect has usually been mild. A dose-response effect has been noted, although a decrease in blood pressure has been noted following doses of 2 mg.⁶ It has been reported in 33% of patients taking tizanidine 16 mg, 16% of patients taking 8 mg and 0% of patients taking placebo.⁶ Furthermore, a summary of three combined controlled trials noted that orthostatic hypotension was no more severe in tizanidine groups than in placebo groups.²³

Liver Effects

Several studies have commented on trends toward increased liver function tests. The first reported that although the tizanidine group had a statistically significant increase in GGT from 23.1 to 27.9 IU/L (*p* = 0.05), this was not clinically significant.¹¹ Another group noted that there was a trend toward increases of greater than 15% in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin in the tizanidine group. These changes resolved on discontinuation of the study medication, and were not statistically different than placebo.¹⁸ A third study noted a single patient who developed increased LFTs while on study in the tizanidine arm.¹⁰ Tests normalized on withdrawal of study

medication. Furthermore, there has been a case report of a patient treated with tizanidine 36 mg daily who developed serious liver injury.²⁵ Symptoms resolved and tests normalized within 6 weeks, but recurred on subsequent initiation of tizanidine 4 mg. Finally, one patient died following 2 months of therapy with tizanidine when he developed liver enlargement with multilobular necrosis.⁶ Other causes were ruled out.

Ocular Effects

Although there have been reports of retinal degeneration and corneal changes in animals, this has not been detected in most clinical trials.^{6,10,16} However, a trial of tizanidine therapy in 124 patients had three patients who developed ophthalmologic abnormalities compared to one on placebo after 8 weeks.¹⁸

Drug Interactions

There appears to be no clinically significant interaction between tizanidine and acetaminophen, although tizanidine has been shown to delay the T_{max} of acetaminophen by 16 minutes.^{6,7}

There is a case report of a patient who had an increase in serum phenytoin levels with excessive drowsiness after initiation of tizanidine 6 mg per day.^{7,26} Levels remained high despite decreases in the phenytoin dose, but returned to baseline on withdrawal of tizanidine. Drowsiness resolved as the phenytoin levels normalized.

Retrospective analysis of data has indicated that tizanidine clearance is decreased by 50% in women taking oral contraceptives concurrently.^{6,26} This may result in an increased risk of adverse effects related to tizanidine.

Drug-Food Interactions

Ethanol has been shown to increase tizanidine C_{max} and area-under-the-curve (AUC) (approximately 15% and 20%, respectively).^{6,26} This may result in an increased risk of adverse effects related to tizanidine, and CNS depression may be additive.

Cost, Dose, How Supplied

Treatment is usually initiated at 2 mg by mouth as a single dose. Over 2 to 4 weeks, the dose is titrated to an average dose of 8 mg three times daily, up to a maximum dose of 36 mg per day in divided doses. This should be reduced for patients with renal impairment.

The manufacturer supplies tizanidine as 4-mg cross-scored tablets in bottles of 150 tablets. A sustained release product is available in Europe, but is not approved in the United States. The average wholesale price (AWP) is \$153.08 per 150-count bottle. The AWP for a one-month supply at a dose of 8 mg three times daily is \$183.70. In contrast, the AWP for a one-month supply of baclofen 10 to 20 mg three times daily is \$25.87 to \$51.73 (see Table 2).

Table 2. Cost Comparison of Antispasmodics

	Baclofen	Diazepam	Dantrolene	Tizanidine
Daily dose	30-60 mg/day	10-40 mg/day	100-400 mg/day	24-36 mg/day
Cost per 30-day supply (\$)	25.87-51.73	2.79-3.19	99.37-185.17	183.70-275.54

Conclusion

Clinical trials have demonstrated that tizanidine is approximately as safe and effective as other medications used to treat spasticity due to MS or SCI, and that it is superior to placebo. Its advantages include its novel mechanism of action and its apparent lack of effect on muscle strength relative to baclofen or diazepam. However, several disadvantages also exist. As with baclofen and diazepam, multiple daily dosing is necessary to improve efficacy and decrease side effects. Like this agents, tizanidine is associated with a high degree of sedation. Careful dosing titration is needed due to interpatient variability in response.

Because it does not offer substantial clinical benefits over the current first-line therapies, its high cost, and the necessary dose titration and liver function tests on therapy initiation, tizanidine is likely to be a second-line agent. Tizanidine may be used as add-on therapy to baclofen due to its novel mechanism of action. This may result in a synergistic effect to decrease side effects and increase the antispasticity efficacy of initial baclofen therapy.

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