Treatment of Spasticity with Tizanidine in Multiple Sclerosis

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ABSTRACT: Spasticity is a frequent and often disabling symptom in MS patients. Current drugs used as antispastic agents include Dantrolene Sodium, Baclofen and Diazepam. Tizanidine (5-chloro-4-(2imidazolin-2 yl amino) -2, 1, 3-benzothialdiazole) is a new antispasticity agent that has purported central action. A double blind placebo controlled trial was performed to study the efficacy of this drug in MS patients. Sixty-six patients entered an eight week therapeutic trial and fifty-nine completed the trial. Patients were assessed at 0, 2, 3 and 8 weeks of therapy for clinical effects. Electrophysiologic tests were performed at 0 and 8 weeks.

A statistically significant benefit was noted in spastic muscle groups in the legs with concomitant significant reduction in hyperactive stretch reflexes and ankle clonus. Side effects most frequently cited included dry mouth and drowsiness. Two patients developed elevated liver function test that decreased with cessation of therapy. Other clinical details, side effects and electrophysiologic data will be presented.

Tizanidine appears to reduce clinical spasticity and hyperreflexia in MS patients although no change in functional status was detected. Tizanidine may well serve as an alternate antispastic agent, alone or in combination with other agents.

RÉSUMÉ: Utilité de la tizanidine pour traiter la spasticité dans la sclérose en plaques. La spasticité est un symptôme fréquent et souvent invalidant chez les patients souffrant de SEP. Les agents antispastiques courants sont le dantrolène sodique, le baclofen et le diazépam. La tizanidine (5-chloro-4-(2imidazolin-2 yl amino)-2,1,3-benzothialdiazole) est un nouvel agent antispastique qui est censé posséder une action centrale. Nous avons procédé à un essai contrôlé en double insu afin d'étudier l'efficacité de ce médicament chez les patients souffrant de SEP. L'essai thérapeutique de 8 semaines comprenait au départ 66 patients et parmi ceux-ci, 59 ont complété le protocole. Les effets cliniques chez les patients étaient évalués après 0,2,3, et 8 semaines de thérapie. Des épreuves électrophysiologiques étaient faites après 0 et 8 semaines. On a noté un bénéfice qui était statistiquement significatif dans des groupes de muscles spastiques au niveau des jambes, avec une diminution significative simultanée des réflexes myotatiques hyperactifs et du clonus à la cheville. Les effets secondaires les plus fréquemment mentionnés étaient la sécheresse de la bouche et la somnolence. Deux patients ont présenté des épreuves de fonction hépatique perturbées qui sont revenues à la normale à l'arrêt du traitement. Nous présenterons d'autres détails cliniques, des effets secondaires et des données électrophysiologiques. La tizanidine semble diminuer la spasticité clinique et l'hyper-reflexie chez les patients atteints de SEP, même si nous n'avons pas constaté de modification de l'état fonctionnel. La tizanidine pourra probablement être utile comme médicament de relais dans le traitement de la spasticité, soit seule ou en combinaison avec d'autres médicaments.

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Spasticity is a frequent and often disabling symptom in MS patients.[1] It originates from demyelinating lesions in the cerebral, brainstem or spinal cord white matter. Current medications used as antispastic agents include Dantrolene Sodium, Diazepam and Baclofen.[2] A limited response or side effects: hepatotoxicity (Dantrolene Sodium), sedation (Diazepam and Baclofen) and varying amounts of muscle weakness (all agents) may prevent satisfactory control of spasticity in many patients. Tizanidine (Sirdalud®) is a new antispasticity agent with purported central action. It is said to preferentially inhibit the activity of polysynaptic pathways involved in the activation of motor units[3] and to abolish the tonic component of stretch reflexes.[4] A few clinical trials have already suggested that the drug can reduce muscle tone without causing undue muscle weakness in neurological patients.[5-7]

A double-blind controlled trial was undertaken to assess the efficacy of Tizanidine in MS patients with spasticity and to assess the safety and side effects related to its clinical use.

METHODS

This study was conducted under a double-blind, randomized and parallel, placebo controlled design. It involved the collaboration of 4 neurologists. The trial had a 10-week duration divided

into two consecutive phases: 1) a *washout period* lasting 2 weeks during which patients who were already treated for spasticity had all their antispastic medication withdrawn; and 2) an *active treatment period* lasting 8 weeks including a 3 weeks "*dose titration*" (individual adjustments of doses) and a *maintenance* period of 5 weeks duration.

Patients included in the study were males or females aged between 18 and 60 years with a definite diagnosis of multiple sclerosis and at least a moderate degree of spasticity, severe enough to interfere with functional performance in daily life. Their spasticity had been stable for at least two months. Patients with active infections, severe contracture or evidence of hypertension, cardiac disease, malignancy or any disease involving a major organ were excluded.

Treatment was initiated with 2 mg of Tizanidine for the first day, and 6 mg/day on the second to fifth days. Thereafter, the dose was increased by 6 mg/day at 4-day intervals until the patient's spasticity was satisfactorily controlled or intolerable side effects appeared, or to a maximum dose of 32 mg/day. The equivalent number of capsules of the same appearance but free of active medication was given to the placebo group.

Patients on other medications for various conditions were allowed to stay on them if they were judged not to interfere with muscle tone. Parameters used to assess efficacy were: 1. Neurological evaluations using a scoring system for: limb power, tone (passive stretch), deep tendon reflexes, clonus, cerebellar function and sensory function. Mental status and cranial nerves were simply reported as normal or abnormal. 2. Neurological status (Kurtzke), functional disability assessment (Kurtzke),[8] ambulation index and upper extremities index.[9] 3. Electrophysiological studies including measurements of H-maximum/M-maximum,[10] H 120/H 150, H Rest/H Jendrassick, H Rest/H Vibration 120 Hz, F-Amplitude/M-maximum.[11] All tests were done on both legs in all patients while lying comfortably with their legs supported at the appropriate angle. Studies were performed once at the end of the washout period and once near completion of the treatment period. Supramaximal square wave stimulations of 0.2 msec. duration were delivered by a DISA 1500 machine for M-max recording. H-Max was determined after applying a variable number of shocks to the tibial nerve in the popliteal fossa. Vibratory inhibition was applied manually to the Achilles tendon, using a tuning fork (frequency, 120 Hz). 4. Overall evaluation by investigators at the end of the study.

Safety was monitored by: a) Physical examination and vital signs b) Laboratory (hematology, biochemistry and urinalysis), chest x-rays and ECG tests c) Ophthalmological examinations d) Reporting of side effects.

Neurological evaluations, functional assessments and vital signs were determined on five (5) visits, from the beginning of the washout period to the end of the treatment (days - 14, 0, 10, 21, 56). Physical examinations were done on the first two visits and on the last visit. Each patient always saw the same neurologist.

Data were analyzed by using the package S.A.S.[12] Significance level for inferential tests was fixed at a = 5.0%. All referential evaluations were carried out on patients who completed the trial.

Data for limb tone, weakness and stretch reflexes were considered only for affected muscle groups. Therefore, for every muscle group, patients exhibiting normal data were excluded from the evaluation in order to truly assess the effect of the study medications. Moreover, statistical evaluations within

groups were performed only when there were seven (7) or more patients in each group. A total of 20 patients was required for performing a statistical analysis between groups.

RESULTS

Sixty-six (66) patients, (33 in each group) entered the study. Of these, fifty-nine (59) completed the study. Four (4) patients on Tizanidine withdrew because of lack of efficacy and/or unwanted effects (stiffness, gait instability and dry mouth) and 1 patient due to a relapse of Multiple Sclerosis. Two (2) patients from the placebo group prematurely discontinued the study because of intercurrent illness and unwanted effects (weakness).

Patient characteristics are presented in Tables 1 and 2. Both groups were comparable for age, sex, size and type of disease. Most patients were paraparetics. Spasticity had been present for 6 to 8 years and was generally moderate (66 and 61%) to severe (25 and 33%).

The mean daily dosage administered was 18.4 ± 1.2 mg for Tizanidine (range 4 to 24 mg) and 22.5 ± 1.2 mg for placebo (range 6 to 32 mg) (Table 3) at the end of the maintenance phase (day 56).

Neurological evaluations All patients who completed the study were free of relapse during the study period. No significant difference between the two (2) groups was observed for the following parameters: mental status, cranial nerves, cerebellar and sensory examinations from the beginning to the end of the study.

Table 1: Patient Demographics‡

	x̄ ± S.E.M. (n) [%]	
	Tizanidine	**Placebo**
SEX: Females	− (17) [52%]	− (16) [48%]
Males	− (16) [48%]	− (17) [52%]
AGE (years)	47.6 ± 1.4 (33)	43.8 ± 1.6 (33)
HEIGHT (cm)	166.0 ± 1.8 (31)	167.0 ± 1.6 (32)
WEIGHT (kg)	67.0 ± 2.8 (31)	65.0 ± 2.1 (31)

‡ No statistically significant difference between the two groups.

Table 2: History of Multiple Sclerosis‡

	Tizanidine	**Placebo**
DISEASE DURATION (mean ± S.E.M. (n))	15.2 ± 1.2 (33)	11.6 ± 1.3 (33)
SITES OF LESIONS:	n [%]	n [%]
Spinal cord	28 [90%]	31 [97%]
Brain stem	12 [39%]	13 [41%]
Optic nerve	10 [32%]	9 [28%]
Cerebellum	4 [13%]	5 [16%]
Cerebrum	1 [3%]	3 [9%]
MAJOR MOTOR DISABILITY:		
Monoparesis	7 [22%]	1 [3%]
Hemiparesis	0 [0%]	0 [0%]
Paraparesis	29 [91%]	32 [97%]
SEVERITY OF SPASTICITY:		
Mild	3 [9%]	2 [6%]
Moderate	21 [66%]	20 [61%]
Severe	8 [25%]	11 [33%]

‡ No statistically significant difference between the two groups.

The neurological status scale (Kurtzke) improved in three (3) patients of each group while it deteriorated in five (5) patients of the placebo group. However, descriptive analysis showed no significant difference between the two (2) groups.

Functional evaluations Functional scoring in the ambulation index and the upper extremity index showed a small improvement in the treated group only. (Table 4). This difference was not significant however. No change was observed in the disability status (Kurtzke) between day 0 and 56, in both groups.

Assessment of spasticity comprised limb tone, stretch reflexes and clonus. Table 5 shows that cumulative limb tone for all movements tested improved significantly in the treated group compared to the placebo. This change was most noticeable in the most spastic muscle groups; knee flexion and ankle dorsiflexion.

Similarly, a significant difference between the two groups was found for ankle tendon reflexes and total deep tendon reflexes, in favor of the Tizanidine group (Table 6). In addition, a separate analysis focusing on clonus of knee and ankle, showed a significant reduction of ankle clonus in treated patients.

Muscle strength showed a very mild improvement in both groups from day 0 to day 56. The improvement was slightly greater in the placebo group and not significant. Despite overall improvement in scores for total groups, approximately a third of the patients exhibited an increased weakness within each group.

Electrophysiological studies There was no significant change between the two groups, from day 0 to day 56 in all parameters tested.

Safety Assessment No consistent change on physical examination, including blood pressure and heart rate was seen in either group. Two patients on Tizanidine and 1 patient on the placebo did exhibit transient skin abnormalities during the treatment period but these were not considered to be related to the medication. Hematological surveys showed that one patient dropped his lymphocyte count by 25% while taking Tizanidine. He also had suffered from a viral-like illness a few weeks previously. Changes from normal to abnormal occurred in biochemical parameters in some patients. In most of these, the changes were mild, transient and were distributed in both groups.

However, there were 2 treated patients where significant SGOT and SGPT elevations occurred and resolved to normal after reduction or withdrawal of the drug. All the other parameters tested: urinalysis, ophthalmological evaluations, chest x-rays and EKG showed no drug related changes.

Side effects The most frequently reported side effects of Tizanidine were drowsiness and dry mouth. Initially, these symptoms were present in 48% and 27% of the patients respectively. These values decreased to 9 and 3% at subsequent visits, in the absence of a dose reduction in a majority of the patients. Table 7 lists the other side effects.

At the end of the study, an overall evaluation of the trial was made by the investigators based on the patient's own impression and the objective findings. Improvement was thought to have occurred in 69% on the treated patients and 38% in the placebo group. This difference is significant. It was rated as good to excellent in 27% of the Tizanidine group compared to 10% in the other group. Tolerance was considerably better in the placebo group, being good to excellent in 85% of the patients compared to 53% in the Tizanidine group.

DISCUSSION

This double-blind placebo controlled study confirms previous trials and shows Tizanidine to be effective in reducing spasticity in multiple sclerosis. This improvement of spasticity is significant only in the lower extremities. This is likely due to the high frequency of spastic paraparesis with limited arm involvement in our patients. Only some aspects of spasticity were scored namely: tone (passive stretch), myotatic reflexes and clonus. We did not retain the number of daily spasms as a measure as it was found to be reported erratically in many patients. In the three aspects measured, there was statistically significant improvement. This amelioration was not paralleled by a noticeable improvement in many of the functional indices. Interestingly, this lack of improvement in gait was not related to increased weakness, at least in most patients.

Surprisingly, no effect on any of the electrophysiological tests could be detected. It has been suggested that Tizanidine

Table 3: Mean Daily Dosage† Taken Since Last Visit

	Day 0	Day 10 (titration)	Day 21 (maintenance)	Day 56
Tizanidine (mg/day)	0.0±0.0 (32)	17.6±0.5 (33)	20.1±1.0 (31)	18.4±1.2 (28)
Placebo (mg/day)	0.0±0.0 (33)	18.0±0.3 (32)	23.4±0.5 (33)	22.5±1.2 (30)
Statistical significance between groups	N.S.	N.S.	*	*

† Data are expressed as $\bar{x}$ ± S.E.M.; values in parentheses represent the number of patients.
N.S.: Not significant, *: $p \leq 0.05$

Table 4: Functional Disability†

	TIZANIDINE‡			PLACEBO‡		
	Day 0	Day 56	Change from baseline Δ	Day 0	Day 56	Change from baseline Δ
Disability Status	5.07 ± 0.29	5.07 ± 0.28	0.00	4.90 ± 0.34	4.90 ± 0.34	0.00
Ambulation index	4.22 ± 0.40	4.11 ± 0.41	0.11	4.61 ± 0.43	4.61 ± 0.44	0.00
Upper extremity index	0.52 ± 0.14	0.48 ± 0.14	0.04	0.52 ± 0.14	0.52 ± 0.14	0.00

† Data are expressed as mean score ± S.E.M.; a **lower** score indicates less disability.

‡ No statistical significance was found within and between groups.

Table 5: Limb Tone†

		TIZANIDINE				PLACEBO			
		Day 0	Day 56	Change‡ from baseline Δ	(n)	Day 0	Day 56	Change‡ from baseline Δ	(n)
Elbow Flexion	R	3.00 ± 0.00	4.00 ± 0.00	1.00	1	1.50 ± 0.50	2.00 ± 0.00	0.50	2
	L	3.00 ± 0.00	4.00 ± 0.00	1.00	1	2.50 ± 0.50	3.00 ± 0.33	0.50	2
Elbow Extension	R	2.67 ± 0.33	3.00 ± 0.58	0.33	3	2.64 ± 0.28	**3.18 ± 0.26**	**0.54***	11
	L	2.00 ± 1.00	2.50 ± 0.50	0.50	2	3.00 ± 0.26	2.67 ± 0.21	−0.33	6
Wrist Extension	R	2.83 ± 0.17	3.33 ± 0.21	0.50	6	2.93 ± 0.16	2.86 ± 0.14	−0.07	14
	L	3.33 ± 0.33	3.00 ± 0.00	−0.33	3	3.07 ± 0.07	2.86 ± 0.14	−0.21	15
Wrist Pronation	R	3.00 ± 0.00	3.00 ± 0.00	0.00	1	3.00 ± 0.00	3.00 ± 0.00	0.00	2
	L	3.00 ± 0.00	3.00 ± 0.00	0.00	1	3.00 ± 0.00	3.50 ± 0.50	0.50	2
Wrist Supination	R	2.83 ± 0.11	**3.33 ± 0.14**	**0.50***	12	2.78 ± 0.19	2.83 ± 0.19	0.05	18
	L	2.92 ± 0.08	3.17 ± 0.11	0.25	12	2.78 ± 0.15	2.78 ± 0.17	0.00	18
Ankle DF §	R	1.93 ± 0.14	**2.36 ± 0.14**	**0.43***	28	1.87 ± 0.13	1.83 ± 0.12	−0.04	30
	L	2.04 ± 0.16	**2.43 ± 0.15**	**0.39***	28	2.03 ± 0.14	2.23 ± 0.13	0.20	31
Ankle PF	R	2.40 ± 0.40	3.20 ± 0.37	0.80	5	2.25 ± 0.25	2.75 ± 0.18	0.50	12
	L	2.33 ± 0.33	3.50 ± 0.34	1.17	6	2.20 ± 0.30	2.80 ± 0.20	0.60	10
Ankle Eversion	R	2.70 ± 0.15	**2.95 ± 0.20** (p = 0.058)	**0.25**	20	2.64 ± 0.18	2.64 ± 0.13	0.00	25
	L	2.65 ± 0.15	**3.05 ± 0.22**	**0.40***	20	2.20 ± 0.18	2.83 ± 0.15	0.63	23
Knee Flexion	R	1.89 ± 0.19	**2.42 ± 0.22**	**0.53***	19	1.85 ± 0.16	2.04 ± 0.15	0.19	26
	L	1.90 ± 0.18	**2.40 ± 0.21**	**0.50***	20	1.92 ± 0.15	2.08 ± 0.12	0.16	24
Knee Extension	R	2.61 ± 0.14	**2.96 ± 0.15**	**0.35***	23	2.50 ± 0.14	**2.92 ± 0.16**	**0.42***	26
	L	2.57 ± 0.16	2.81 ± 0.16	0.24	26	2.62 ± 0.15	**2.88 ± 0.15**	**0.26***	26
Hip Abduction	R	2.55 ± 0.13	**2.82 ± 0.17** (p = 0.054)	**0.27**	22	2.62 ± 0.14	2.66 ± 0.13	0.04	29
	L	2.65 ± 0.13	2.96 ± 0.19	0.31	23	2.64 ± 0.14	2.72 ± 0.15	0.08	25
Total Limb Tone §		23.89 ± 1.32	**27.75 ± 1.60**	**3.86***	28	29.80 ± 1.80	31.29 ± 1.74	1.49	31

† Data are expressed as mean score ± S.E.M.; a **higher score** indicates closer to normal.
‡ A negative sign (−) means deterioration.
R = Right   L = Left
*: p ≤ 0.05; (statistical significance between day 56 and day 0)
§ Statistically significant difference between the 2 groups.

Table 6: Deep Tendon Reflexes†

		TIZANIDINE				PLACEBO				Statistical Significance between the two groups (day 56)
		Day 0	Day 56	Change‡ from baseline Δ	(n)	Day 0	Day 56	Change‡ from baseline Δ	(n)	
Branchioradial	R	0.95 ± 0.13	0.95 ± 0.13	0.00	21	0.96 ± 0.04	0.92 ± 0.11	0.04	25	N.S.
	L	0.90 ± 0.10	0.75 ± 0.12	0.15	20	0.96 ± 0.04	0.88 ± 0.08	0.08	26	N.S.
Triceps	R	1.05 ± 0.12	0.95 ± 0.12	0.10	19	1.00 ± 0.06	0.96 ± 0.04	0.04	26	N.S.
	L	0.95 ± 0.08	0.81 ± 0.11	0.14	21	0.96 ± 0.04	1.00 ± 0.05	−0.04	27	N.S.
Biceps	R	1.00 ± 0.11	1.00 ± 0.12	0.00	19	1.00 ± 0.08	1.08 ± 0.11	−0.08	25	N.S.
	L	0.86 ± 0.10	0.86 ± 0.08	0.00	21	0.92 ± 0.05	0.96 ± 0.07	−0.04	26	N.S.
Knee	R	1.41 ± 0.12	1.26 ± 0.11	0.15	27	1.43 ± 0.11	1.47 ± 0.12	−0.04	30	N.S.
	L	1.37 ± 0.12	1.15 ± 0.10	0.22	27	1.34 ± 0.09	1.24 ± 0.11	0.10	29	N.S.
Ankle	R	1.92 ± 0.17	**1.65 ± 0.20**	**0.28***	26	2.10 ± 0.17	2.17 ± 0.16	−0.07	30	N.S.
	L	1.85 ± 0.17	**1.54 ± 0.19**	**0.31***	26	1.90 ± 0.18	2.13 ± 0.15	−0.23	30	*(Tizanidine)
Total Deep Tendon Reflexes		12.07 ± 0.83	**10.93 ± 0.78**	**1.14***	28	13.67 ± 0.56	13.87 ± 0.68	−0.20	30	** (Tizanidine)

† Data are expressed as mean score ± S.E.M.; a **lower score** indicates closer to normal. (see new scale in the text).
‡ A negative sign (−) means deterioration.
R = Right   L = Left
N.S.: Not significant;   *: p ≤ 0.05;   **: p ≤ 0.01

Table 7: Other Side Effects Reported

	Tizanidine (n)	Placebo (n)
Abdominal pain	2	0
Sleep disturbances	2	2
Tremor	2	0
Rash	2	2
Bladder disturbances	1	1
Dizziness	1	2
Gait disturbances	1	1
Hallucination	1	0
Muscle weakness	1	2
Pruritus	1	0
Weight gain	1	0
Constipation	0	2
Diarrhea	0	1
Dyspnea	0	1
Nausea	0	1
Nose bleeding	0	1

reinforces vibratory inhibition of H muscle response and may increase presynaptic inhibition.[10] It also lowers the ratio of H Maximum/M Maximum which measures the excitability of the motor nucleus.[10] These effects are known to be dose dependant and transient (30-60 minutes). It may be that the absence of discernible changes in our patients is due to a wearing off effect of the drug as patients were tested at different times after their last dose.

In our hands, Tizanidine appeared as a relatively safe drug. Dermatological changes consisted of sebaceous cysts in one patient, while another showed a transient papular rash which disappeared without interrupting the medication. Although a relative hypotensive effect has been reported in animals,[13] no significant reduction of blood pressure was seen in our study. The relative lymphopenia noted in one patient took place a few weeks after a viral-like illness and was more probably related to that event than to the medication. Contrariwise, we think that the increase of SGOT and SGPT in two patients was probably drug related as it persisted for many weeks and returned to normal values after reduction or interruption of the medication. Alkaline Phosphatase remained normal.

Tizanidine was easily administered, starting with lower dosages and progressively increasing to an optimal average dose of 18-24 mgm/day for maintenance. There were two main side effects: drowsiness and dry mouth. These effects improved without reduction of dose in most patients suggesting development of a tolerance. The drowsiness and dryness of mouth remained constant in only two patients respectively throughout the study. Other side effects were mild and not clearly related to the medication.

In conclusion, we can say that Tizanidine is relatively safe and well tolerated. It has a definite effect on tendon reflexes, clonus and increased tone. Tizanidine therefore may be useful alone or in combination with other agents to control these aspects of spasticity.

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