Tizanidine Versus Baclofen in the Treatment of Spasticity in Patients with Multiple Sclerosis

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ABSTRACT: Tizanidine (Sirdalud) was compared to baclofen (Lioresal) in a randomized, double-blind, cross-over trial. Each medication was introduced over a three week titration period and then maintained at the highest tolerated dose for five weeks. The two treatment phases were separated by a one week drug withdrawal and a two week washout period. Sixty-six patients entered the trial and forty-eight completed both treatment phases. At the end of the trial, neurologists and physiotherapists thought that baclofen was superior on the basis of perceived efficacy and tolerance ($p \leq 0.05$). Although the efficacy of tizanidine or baclofen was judged as good to excellent by 24 and 39% of patients respectively, this difference was not statistically significant. Muscle weakness was the most common adverse effect. This was significantly more troublesome in patients treated with baclofen. Somnolence and xerostomia were more common in patients treated with tizanidine. Both baclofen and tizanidine appear to be useful adjuncts in the treatment of spasticity in patients with multiple sclerosis. Preference of either drug is tempered principally by side-effects.

RÉSUMÉ: Tizanidine versus Baclofen dans le traitement de la spasticité chez les patients atteints de sclérose en plaques: une étude à double insu. Nous avons comparé la tizanidine (Sirdalud) au baclofen (Lioresal) dans une étude randomisée, à double insu avec permutation. Chaque médicament était introduit pendant une période de titrage de 3 semaines et la dose maximum tolérée était maintenue pendant 5 semaines. Les deux phases de traitement étaient séparées par une période de retrait progressif d'une durée d'une semaine et de retrait total d'une durée de deux semaines. Soixante-six patients ont commencé le protocol et 48 ont complété les deux phases de traitement. A la fin de l'étude, les neurologues et les physiothérapeutes étaient d'avis que le baclofen était supérieur en raison de son efficacité apparente et de son degré de tolérance ($p<0.05$). Même si l'efficacité de la tizanidine ou du baclofen était jugée d'aussi bonne à excellente par 24 et 39% des patients respectivement, cette différence n'était pas significative. L'effet secondaire le plus fréquent était la faiblesse musculaire. Ce problème était nettement plus gênant chez les patients traités avec le baclofen. La somnolence et la xérostomie étaient plus fréquents chez les patients traités avec la tizanidine. Le baclofen et la tizanidine semblent être tous deux des thérapeutiques d'appoint dans le traitement de la spasticité chez les patients atteints de sclérose en plaques. La préférence pour l'un ou l'autre de ces médicaments est fonction de leurs effets secondaires.

Can. J. Neurol. Sci. 1988; 15:15-19

Spasticity is a major complication in patients with multiple sclerosis (MS). It can be a problem in ambulatory patients and present a serious impediment to patient comfort and nursing care in more disabled patients. Therapeutic developments in pharmacology have provided us with several effective agents and the need for destructive neurosurgical procedures has been reduced. The therapeutic armamentarium includes a number of drugs which can inhibit spasticity by a variety of physiological mechanisms.[1] Baclofen appears to reduce the release of excitatory transmitters from presynaptic terminals of primary afferent fibres and diazepam potentiates presynaptic inhibition. Dantrolene sodium dissociates the electro-mechanical coupling response in both extrafusal and intrafusal skeletal muscle fibres. Their efficacy has been proven in many studies.[1] Therapeutic advantages and disadvantages are generally well recognized. One of the major side effects with these medications, especially baclofen and dantrolene sodium, is their propensity to cause weakness.[1,2]

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Received June 16, 1987. Accepted in final form October 13, 1987
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Tizanidine (5-chloro-4-[2-imidazolin-2yl-amino]-2,1,3-benzothiadiazole hydrochloride) is a newly available, centrally acting muscle relaxant with pharmacological properties somewhat different from the other agents.[3] It appears to inhibit the activity of polysynaptic pathways involved in the activation of motor units;[4] its ability to reinforce vibration inhibition of the Hoffman reflex suggests a mode of action similar to diazepam. A preliminary study has shown that it is superior to placebo in the control of spasticity in patients with MS.[5]

We have compared the therapeutic efficacy and tolerance of baclofen and tizanidine in patients with MS in a double-blind, cross-over trial.

Methods and Materials

Patients were assigned randomly to one of two groups. One group received tizanidine first and baclofen second. The other received the alternate combination. In the two weeks preceding the study, all antispasticity drugs were gradually withdrawn. In the next three weeks, the first drug was titrated on an individual basis to a maximum tolerated dose, or until a satisfactory result was obtained. This dosage was then maintained for five weeks. Drug 1 was then withdrawn over a one week period, followed by a two week "washout" period. Drug 2 was introduced then over a three week titration period and maintained for five weeks.

Patients were drawn from the MS Clinic in London, Ontario. All had clinically definite MS.[6] The patients' spasticity interfered with their activities of daily living. We chose patients in whom spasticity had been stable for at least two months.

Medications

Tizanidine was initiated at a dosage of 2 mg on the first day and 6 mg daily for the next three days. The dosage was increased by 6 mg every four days to a maximum of 32 mg/day.

Baclofen was similarly initiated at a dosage of 5 mg on the first day and 15 mg daily for the next three days. Thereafter the dosage was increased by 15 mg every four days to a maximum dosage of 80 mg/day. The dosage of either drug was increased until spasticity was adequately controlled, intolerable side effects occurred, or the maximum dosage was reached. The dosage was reduced to a lower level if there were any apparent dose related side effects. The medications were taken t.i.d. with meals or q.i.d. if the maximal dose were prescribed. Following the five week maintenance treatment the dosage was gradually reduced over a one week period.

Parameters Monitored

We performed a standard neurological examination and assessed neurological status on the Kurtzke functional scale.[7] Spasticity was measured clinically on a six point ordinal scale of muscle tone. Measurements of reflexes and clonus were performed concomitantly. Patients, investigators and physiotherapists were also asked for an overall evaluation of efficacy and tolerance. Drug safety was monitored by routine physical examination, serial monitoring of hematology, biochemistry and urinalysis, routine ophthalmological examinations, and periodic examination of visual acuity and fields. Patients were asked routinely if they had any of the recognized side effects of the medications. Each patient was serially evaluated by the same blinded neurologist and physiotherapist.

A statistical analysis to assess carry-over effects was performed at a significance level of $\alpha = 1\%$, using the results obtained at the ends of the 1st and 2nd maintenance periods. Statistically significant residual effects were observed in 3% of the cases and were therefore considered negligible. This allowed pooling of the data of the two sequences of administration for each treatment drug in order to determine the respective effects of tizanidine and baclofen. Nevertheless, in order to avoid a possible bias due to differences in the residual effect, the comparison between the two drugs was based on the difference (Δ) between the values recorded at the beginning and the end of a treatment period.

In the statistical assessment, all inferential procedures were applied to the difference between the value recorded at the beginning and at the end of the treatment. The comparisons between baclofen and tizanidine, for all data expressed in contingency tables, were performed with the Fisher Exact Probability test.[8]

Table 1: Patient Demographics*

	Mean ± S.E.M. (n) [%] (n = 62) Tizanidine - Baclofen (n = 32)	Baclofen - Tizanidine (n = 30)
SEX: Females	(15) [47%]	(16) [53%]
Males	(17) [53%]	(14) [47%]
AGE: (years)	49.7±2.0	52.5±2.2
[range]	[30-70]	[31-74]
TYPE OF DISABILITY:		
Paraparesis	29 [90%]	24 [80%]
STATUS AT ENTRY:		
Remitting	1 [3%]	0 [0%]
Progressive	8 [25%]	11 [37%]
Stable	23 [72%]	19 [63%]
NUMBER OF PATIENTS ANALYZED	28	20

*No statistically significant difference between the two groups.

Table 2: History of Spasticity*

	Tizanidine - Baclofen	Baclofen - Tizanidine
DURATION OF SPASTICITY (YEARS)		
Mean ± S.E.M. (n)	8.7±1.1	7.5±0.7
[Range]	[1-26]	[1-18]
	n [%]	n [%]
SITES AFFECTED:		
Legs only	17 [55]	21 [70]
Legs and arms	15 [45]	9 [30]
SEVERITY:		
Mild	3 [9]	3 [10]
Mild/Moderate	0 [0]	1 [3]
Moderate	20 [63]	14 [47]
Moderate/Severe	2 [6]	3 [10]
Severe	7 [22]	9 [30]
PREVIOUS TREATMENT FOR SPASTICITY (66)		
Baclofen	14	14
Diazepam	6	4
Dantrolene sodium	1	1
Cyclobenzaprine	1	0
Orphenadrine	0	1

*No statistically significant difference between the 2 groups.

https://doi.org/10.1017/S0317167100027104 Published online by Cambridge University Press

RESULTS

Patient Population

Of the 66 patients who entered the trial, four were excluded because of protocol violation or noncompliance, and 14 additional patients failed to complete one or both treatment limbs. Two were unable to complete treatment because of an exacerbation during the first phase of the trial; one was receiving tizanidine and the other baclofen at the time of discontinuation. Seven failed to complete the baclofen treatment because of weakness, often in association with other side effects. Five baclofen dropouts complained of nausea. The four patients who dropped out while receiving tizanidine complained of excessive weakness. Three patients tried both drugs and discontinued both prematurely. Forty-eight patients completed both treatment phases and these were included in the data analysis.

The patients in both treatment groups were clinically similar (Table 1). In both patient groups the spinal cord was the principal site of disease evident clinically and the nature of spasticity was similar (Table 2). Both groups had had spasticity for approximately eight years, which predominated in the legs, and which was moderately severe. Forty-two percent (28/66) of the patients who had entered the trial had received baclofen previously and fifteen percent (10/66) had been treated with diazepam. Few patients had received other treatments for spasticity.

After the eight week treatment period, the mean daily dose of tizanidine was 17.4±1.6 mg (range 2-36) and that of baclofen was 34.9±3.2 mg (range 5-80).

Neurological Function

The effect of baclofen and tizanidine on neurological status was measured on the Kurtzke functional scale. It can be seen from Table 3 that most disability scores did not change from baseline. Similar data were obtained by the physiotherapists who applied the Pedersen functional disability scale.[9] No statistical differences were seen between the two drugs in lower extremity function or personal efficiency subscores (data not shown).

Spasticity, Weakness and Deep Tendon Reflexes

The strength of various muscle groups including shoulder abductors, hip flexors, hip extensors, knee flexors, knee extensors, ankle dorsiflexors and plantarflexors were tested using a seven point ordinal scale ranging from zero to six (a score of zero indicated normal strength and a score of six indicated no movement). Data were expressed as the number of patients who changed, (deteriorated or improved) one point or more from baseline in the right and/or left side for each parameter.

There was no significant difference between baclofen and tizanidine in the incidence of increased limb weakness (Fisher exact probability test). However, these data represent a comparison between groups of patients who successfully completed both phases of the trial.

The antispasticity effect of both drugs was based primarily on changes in a six point ordinal scale which measured limb tone. Tone was assessed on elbow flexion and extension, wrist extension, pronation and supination, ankle dorsiflexion and plantarflexion, ankle inversion and eversion, knee flexion and extension, and finally hip abduction. Changes in reflexes and clonus were measured concomitantly. Again, data were expressed as the number of patients who presented a change of one or more points from baseline in the right and/or left side for each parameter.

There was no significant difference (Fisher exact probability test) in the antispasticity effect of either drug, as measured by a blinded neurologist although the trend favoured baclofen. Similar percentages of patients improved, remained the same, or worsened. Baclofen was superior to tizanidine in improving spasticity only at the ankle ($p = 0.013$) (data not shown). Baclofen reduced the amplitude of the quadriceps tendon reflex, but no change was seen in the other reflexes (data not shown). Baclofen treatment was also associated with a slightly greater and statistically significant reduction in knee, but not ankle clonus (data not shown).

The physiotherapists' assessments showed no statistically significant differences between the two treatment groups in

Table 3: Neurological Status * (Kurtzke Functional Scale)

	TIZANIDINE		BACLOFEN	
	Improvement	Deterioration	Improvement	Deterioration
Pyramidal	2	0	2	2
Cerebellar	7	3	4	7

*Data are expressed as the number of patients who presented a change of 1 score or more from baseline [score at baseline − score at the end] (n).

Table 4: Side Effects

	TIZANIDINE				BACLOFEN				
	Titration		Maintenance		Titration		Maintenance		Comparison Between Groups
	n	(%)	n	(%)	n	(%)	n	(%)	
Muscle Weakness	18	(32)	11	(21)	33	(57)	17	(35)	**
Somnolence	18	(32)	15	(29)	7	(12)	9	(19)	**
Dry Mouth	18	(32)	12	(23)	8	(14)	7	(14)	*
Spasms	11	(20)	8	(15)	2	(3)	2	(4)	*

Comparison done on the number of patients in whom the side effects were observed during the trial. *$p \leq 0.05$; **$p \leq 0.01$. (Fisher exact probability test.)

Data are expressed as the number of patients and percentage of total population (%).

https://doi.org/10.1017/S0317167100027104 Published online by Cambridge University Press

terms of functional assessment, gait and activities of daily living (data not shown). Both drugs were shown to be effective in reducing muscle spasms, but these differences were not significant, as assessed by the physiotherapists.

Side Effects

Muscle weakness was more frequently reported by patients while they received baclofen, especially during the titration period ($p \leq 0.01$) (Table 4). Daytime somnolence and xerostomia were more commonly reported by patients when they received tizanidine. The somnolence might have been secondary to insomnia, which also was reported more frequently by patients while receiving tizanidine. More patients reported spasms during tizanidine treatment and this was statistically significant. The other side effects, listed in Table 5, occurred with approximately equal frequency in both treatment groups.

Among patients who completed the trial, adverse reactions necessitated a dosage reduction in 46% of patients treated with tizanidine and 63% of patients treated with baclofen. Moreover four patients treated with tizanidine compared to 11 treated with baclofen discontinued the trial because of intolerable side effects during the introduction or maintenance phase. Neither treatment was complicated by clinically significant changes in vital signs, or abnormalities in hematological or biochemical indices.

Overall Drug Preference

At the end of the study, patients, investigators and physiotherapists were asked to evaluate the treatments in terms of efficacy and patient tolerance (Table 6). The patients generally preferred baclofen over tizanidine but the margin was not significant. The neurologists and the physiotherapists found baclofen to be more effective ($p \leq 0.05$). Drug tolerance was similar as assessed by patients, investigators and physiotherapists.

Table 5: Other Side Effects Reported

Adverse Reaction	Tizanidine (n)	Baclofen (n)
Headaches	1	5
Dizziness	2	7
Light-headedness	3	2
Irritability	3	5
Insomnia	8	3
Nausea	2	6
Vomiting	0	4
Constipation	3	0
Bladder urgency	3	7
Leg dysesthesia	3	1

Discussion

Several conclusions can be drawn from this trial. Both baclofen and tizanidine appear to help spasticity in patients with MS. In the overall assessment (Table 6), neurologists and physiotherapists preferred baclofen but tizanidine was still perceived as a useful treatment in more than 50%. Spasticity measurement at the bedside favoured baclofen, but the differences were not statistically significant in 10/11 muscle groups examined. Baclofen was superior to tizanidine in reducing clonus at the knee. Both drugs were effective in reducing spasms. The overall tolerance of each treatment in patients who completed the trial was similar. These results support the conclusions of previous trials in which tizanidine and baclofen have been shown to have similar efficacy in relieving spasticity.[5,10,11]

The major side effect of baclofen was weakness. This was indicated by the high withdrawal rate. Seven patients failed to complete treatment with baclofen because of increased muscle weakness; four patients who received tizanidine withdrew because of weakness. Somnolence and xerostomia appeared to be a greater problem in patients who received tizanidine.

Bedside means of assessing spasticity are inadequate. A statistical analysis of changes in limb spasticity, as graded on a clinical scale, failed to show a statistically significant improvement with either drug, although both were found to have a beneficial effect in most patients, as determined by overall preference of patients and neurologists. The increasing application of electrophysiological tests to characterize spasticity might improve our ability to monitor and compare antispasticity drugs.[12]

Finally, medical treatment for spasticity is inadequate in many cases. At the conclusion of the trial, 37% of patients who received baclofen and 46% of patients who received tizanidine thought that their clinical response was poor.

Acknowledgements

This trial was funded by Sandoz Canada (Montreal, Quebec). We are indebted to physiotherapists M. Kilfoil, B. Holody, and M. Drake for serial assessments of these patients. Dr. George Carruthers kindly provided help in doing serial electrocardiography. Donna Greer provided expert secretarial assistance.

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Table 6: Overall Evaluation — Efficacy Assessment

	TIZANIDINE				BACLOFEN				Comparison
	Poor	Fair	Good	Excellent	Poor	Fair	Good	Excellent	Between Groups
Patient	25 (46%)	16 (30%)	11 (20%)	2 (4%)	19 (37%)	12 (24%)	17 (33%)	3 (6%)	N.S.
Investigator	27 (50%)	16 (30%)	10 (19%)	1 (2%)	16 (32%)	14 (28%)	16 (32%)	4 (8%)	*
Physio-therapist	23 (44%)	15 (29%)	13 (25%)	1 (2%)	14 (28%)	16 (32%)	15 (30%)	5 (10%)	*

N.S.: not significant
*$p \leq 0.05$ (Fisher exact probability test).

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