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ORIGINAL RESEARCH

Efficacy and Tolerability of Eperisone and Baclofen in Spastic Palsy: a Double-Blind Randomized Trial

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ABSTRACT

Introduction: Few trials have compared different central muscle relaxants in the treatment of spastic palsy. This head-to-head phase 3 trial compares oral eperisone, a central muscle relaxant with a promising activity in spasticity therapy, and oral baclofen. ***Methods:*** Patients (>18 years) with moderate to severe spastic palsy were eligible in this double-blind, randomized study; they received eperisone 300 mg/day or baclofen 60 mg/day for 6 weeks. The efficacy evaluations included: functional analysis (Pedersen's scale, muscular tone, joint range of motion, 10-meter walking time); physiological and pathological reflexes; and electromyography (Hmax/Mmax amplitude ratio and the Wartenberg test). Physicians and patients globally assessed treatment efficacy. ***Results:*** Both eperisone (n=40) and baclofen (n=40) significantly improved functionality of lower limbs versus baseline (eperisone: –9.1%, P<0.01; baclofen: –8.3%, P<0.05), but only eperisone improved this parameter in the upper limbs (–7.8%, P<0.01 vs. –6.3%, P=NS). Both drugs reduced muscular tone from week 2. Only eperisone improved the joint range of motion (–32.5%, P<0.01 vs. –14.6%, P=NS). Both treatments reduced the 10-meter walking time (eperisone: –20.2%, P<0.01; baclofen: –24.0%, P<0.01); this effect was evident at week 2 with eperisone only. Both drugs improved reflexes. Eperisone and baclofen decreased the Hmax/Mmax amplitude ratio (eperisone: –30.0%, baclofen: –18.6%; P<0.01 for both). Eperisone increased the number of leg oscillations at the Wartenberg test (P<0.05) while baclofen increased the velocity of leg falling (P<0.01). For tolerability, no differences were observed between eperisone and baclofen in any parameters. Eperisone was judged as "good" by a higher number of physicians and patients than baclofen. Eighteen adverse events, most of mild intensity, were reported with eperisone and 27 with baclofen. ***Conclusion:*** Eperisone 300 mg/day

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and baclofen 60 mg/day, administered orally, are effective and well-tolerated drugs in the treatment of spastic palsy. However, eperisone might be associated with some additional clinical benefits when compared with baclofen.

Keywords: baclofen; central muscle relaxants; double-blind; eperisone; randomized; spastic palsy

INTRODUCTION

Spastic palsy is a form of cerebral palsy, and can be defined as a velocity-dependent increase of muscle tone due to pyramidal impairment of the inhibitory afferents to the second motor neuron.[1] Patients with different conditions, such as stroke or multiple sclerosis, may experience spasticity, with important impediments to full functional recovery and social rehabilitation.

Central muscle relaxants, such as baclofen, tizanidine, diazepam, and dantrolene, reduce muscular tone and improve walking capabilities and subjective symptoms of spastic paralysis by acting on the polysynaptic reflex mechanisms.[2] These drugs could therefore represent an interesting clinical option in patients with spastic palsy.[2] In particular, baclofen is one of the most widely used central muscle relaxants;[3,4] however, only a few trials have been conducted to directly compare baclofen and other antispasticity agents.[5,6]

Eperisone hydrochloride (eperisone) is a central muscle relaxant with marked clinical effects in different conditions, such as cervical spondylosis and lower back pain.[7-11] This molecule acts on the spinal cord and supraspinal structures, reducing alpha- and gamma-efferent activities and inhibiting spinal cord activities.[12,13] Eperisone at two different doses (150 mg/day and 300 mg/day) suppresses the spontaneous contractions of muscle spindle and responses to stretch in healthy volunteers.[13] Eperisone also presents some vasodilatory activity, with a consequent increase in muscle blood flow[14-16] and provides an antinociceptive effect by inhibiting the release of P substance, a neuropeptide.[17] The results of a recent small, dose-finding, placebo-controlled trial with a crossover design suggested that oral eperisone 300 mg/day produces more marked clinical benefits in patients with spastic palsy when compared with a lower-dose regimen (150 mg/day) and with placebo.[18]

The aim of this head-to-head, randomized, phase 3 trial was to test if eperisone 300 mg/day could be as effective and well tolerated as oral baclofen in the treatment of spastic palsy of different etiologies.

MATERIALS AND METHODS

Study Design

In- and out-patients aged >18 years with clinically stabilized, moderate to severe spastic palsy of any etiology were eligible in this double-blind, randomized, phase 3 study. Patients were recruited in two Italian University Clinics and in two hospital departments specialized in the treatment of neurological diseases: Neurology Clinic Institute, University of Milan, Milan; Nervous System Diseases Institute, University of Torino, Torino; "Fondazione Clinica del lavoro" Rehabilitation Center, Veruno, Novara; and Neurophysiopathology Department, Casa Sollievo Della Sofferenza, San Giovanni Rotondo, Foggia.

Eligible patients could be mono-, hemi-, para-, or tetraparetic with spastic paralysis due to vascular accident or other cause with duration assessed from at least 6 months. Patients were not eligible for the study if they presented with concomitant neurological and/or psychiatric disorders such as epilepsy, neoplasm, remittent multiple sclerosis, or psychosis, or if they

were affected by chronic kidney disease or liver failure. Patients with known hypersensitivity to eperisone, baclofen, or similar drugs were also not eligible in the study. The study was conducted in accordance with the declaration of Helsinki. All patients signed an informed consent form, and the ethical committees of each center approved the study design.

Patients were randomized in a 1:1 ratio, according to a sequence number randomly generated by a computer (0=eperisone, 1=baclofen) to eperisone or to baclofen for 6 weeks. Both patients and physicians were blind to the treatment, and the randomization key was kept sealed in an envelope until the end of the study. Eperisone was given in 50 mg tablets and was administered orally 3 times a day for 14 days; the dose was then titrated during a period of 5 days until the full dose (six 50 mg tablets a day, given in three administrations) was reached, for a total exposure of 300 mg/day. Baclofen was given in 10 mg tablets and was administered orally 3 times a day for 14 days; the dose was then titrated during a period of 5 days until the full dose (six 10 mg tablets a day, given in three administrations) was reached, for a total exposure of 60 mg/day. Patients could follow standard physiotherapy if the program was not changed for 3 months prior to study entry; no modifications in the physiotherapy program were allowed during the study. All concomitant medications were allowed, with the exception of other muscle relaxants and benzodiazepines.

Evaluation Criteria

Patients were evaluated at baseline, after 2 weeks of treatment, and at the study end if not otherwise specified. The clinical assessment was performed by a trained neurologist; all visits were performed by the same physician at the same time of the day. The efficacy evaluations included three different types of analysis: functional analysis, physiological and pathological reflexes, and electromyography. Functional analysis included a functional evaluation using the six-item Pedersen's scale for lower and upper limbs, as well as personal efficiency, ie, making oneself independent.[17] Moreover, an evaluation of the muscular tone and of joint range of motion was performed using the Ashworth's scale.[19] The time necessary to walk for 10 meters without any external aid (10-meter walking time) was also measured. Physiological and pathological reflexes were analyzed in the upper limbs (bicipital, tricipital, styloradial, and flexors of the hand), in the lower limbs (cutaneous-plantar, Achilles tendon, patellar, and clonus foot), and at superficial abdominal level using Russell's scale.[20] In patients with lower limb spasticity, the electromyography included an analysis on femoral quadriceps with recording of Hmax/Mmax amplitude ratio and the Wartenberg test (free falling of the leg with gravity from maximum extension, with the patient seated).[18] Both tests were performed at week 2 and at study end.

At the end of treatment, physicians and patients gave an overall assessment of efficacy, using a four-item scale (good improvement, moderate improvement, slight improvement, no improvement). Tolerability was evaluated by monitoring adverse events and their potential correlation to the treatment, as well as by measuring laboratory parameters and vital signs at all visits.

Statistical Analysis

Data were analyzed by an independent statistician using descriptive statistics. The comparison between treatment groups was performed by chi-square test (categorical data) or the analysis of variance (continuous data). A P value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

In total, 40 patients per group with clinically stabilized disease were included in the study. Their spastic palsy, across both groups, was mainly of vascular (37.5%), demyelinating (27.5%), and compressive (40%) origin. The distribution of mono-, hemi-, para-, and tetraparesis was similar in both arms of the study. Two patients (5%; one for adverse event and one for personal reasons) in the eperisone group and five patients (12.5%; all for adverse events) in the baclofen group withdrew during the study period. Patient characteristics are summarized in Table 1. In total, 49 patients (61.0%) were males; the mean age was 51.7±14.6 years (±SD). Mean duration of disease was 98.5±94.9 months (±SD).

Efficacy Evaluations

The neurological assessment showed an improvement both for the upper limbs and for the lower limbs (Figure 1). At study end, both drugs had significantly reduced the Pedersen's score in the lower limbs versus baseline values (–9.1%, $P<0.01$ for eperisone; –8.3%, $P<0.05$ for baclofen), but only eperisone had significantly improved this parameter in the upper limb (–7.8%, $P<0.01$ for eperisone; –6.3% for baclofen, P=NS). No significant differences between study drugs were observed. Neither drug had a significant effect on the personal efficiency; however, an improvement (–8.6%) in this parameter was observed in the eperisone group, although the reduction from baseline did not reach statistical significance.

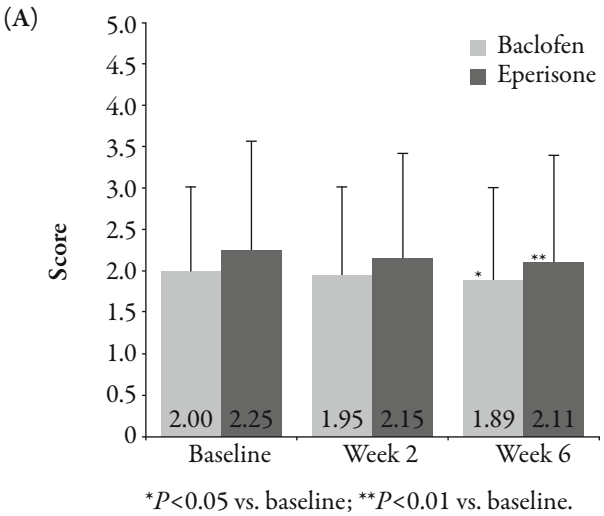
Both eperisone and baclofen significantly reduced the Ashworth's score for muscular tone versus baseline values, with the effect already being evident from week 2 (–19.0% and –46.5% for eperisone at week 2 and week 6, respectively, $P<0.01$ vs. baseline for both time points; –23.8% and –44.8% for baclofen at week 2 and week 6, respectively, $P<0.01$ vs. baseline for both time points) (Figure 2). No statistically significant differences were observed between the treatment arms. The joint range of motion was improved versus baseline in association with both drugs, but a statistical significance at study end was reached only in the eperisone group (–32.5%, $P<0.01$ for eperisone; and –14.6%, P=NS for baclofen) (Figure 2). However, there were no significant differences between eperisone and baclofen even for this parameter.

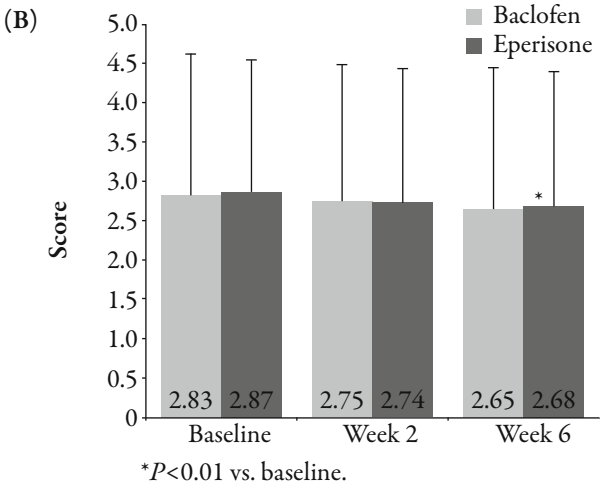
The 10-meter walking time was significantly reduced at week 6 when compared with baseline values in both treatment arms (–20.2%, $P<0.01$ for eperisone group and –24.0%, $P<0.01$ for baclofen group) (Figure 3). The onset of this effect with eperisone was already evident at week 2, whereas no statistical difference versus baseline was reported in the baclofen group at

Table 1. Baseline characteristics of patients enrolled in the study.

	Eperisone (*n*=40)	**Baclofen (*n*=40)**
Males, *n* (%)	25 (62.5)	24 (60.0)
Mean age, years, ±SD	49.8±13.8	52.4±15.1
Duration of disease, months, ±SD	111.6±99.3	93.73±90.91
Etiology of palsy, *n* (%)		
Cerebral	2 (5.0)	1 (2.5)
Compressive	7 (17.5)	9 (22.5)
Demyelinating	10 (25.0)	12 (30.0)
Degenerative	5 (12.5)	3 (7.5)
Vascular	16 (40.0)	14 (35.0)
Missing	0 (0)	1 (2.5)

Figure 1. Pedersen's score for: (**A**) lower limbs, (**B**) upper limbs, and (**C**) personal efficiency in the baclofen and eperisone groups during the study period. Histograms represent mean values; lines represent SD.





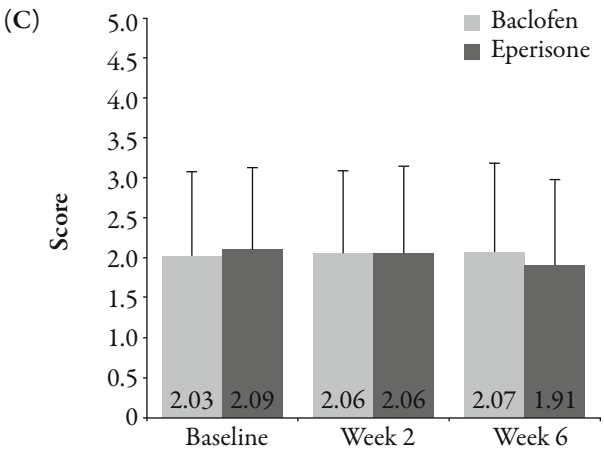
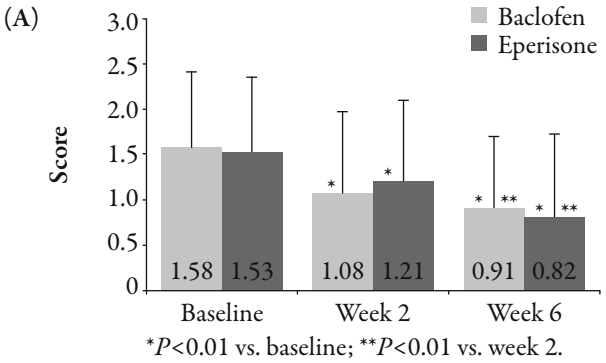


Figure 2. Ashworth's score for: (**A**) muscular tone, and (**B**) joint range of motion in the baclofen and eperisone groups during the study period. Histograms represent mean values; lines represent SD.



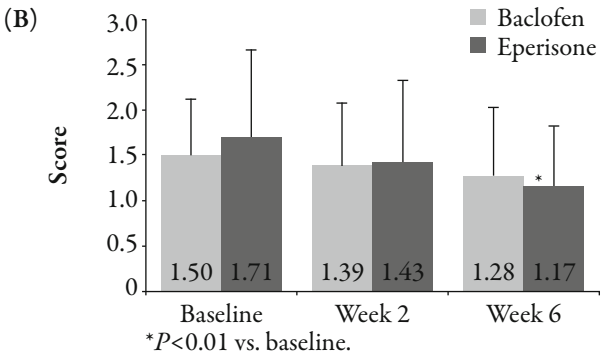


Figure 3. 10-meter walking time in the baclofen and eperisone groups during the study period. Histograms represent mean values; lines represent SD.

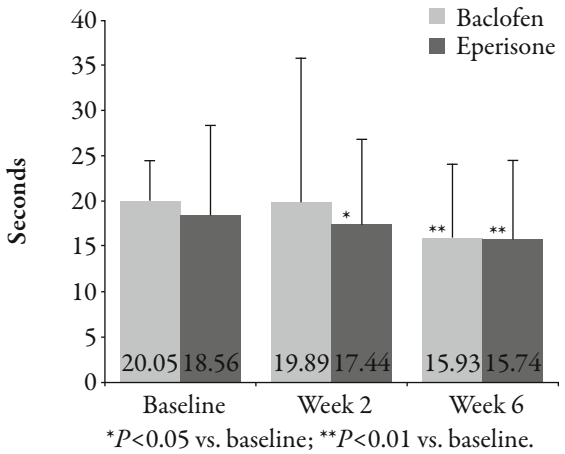
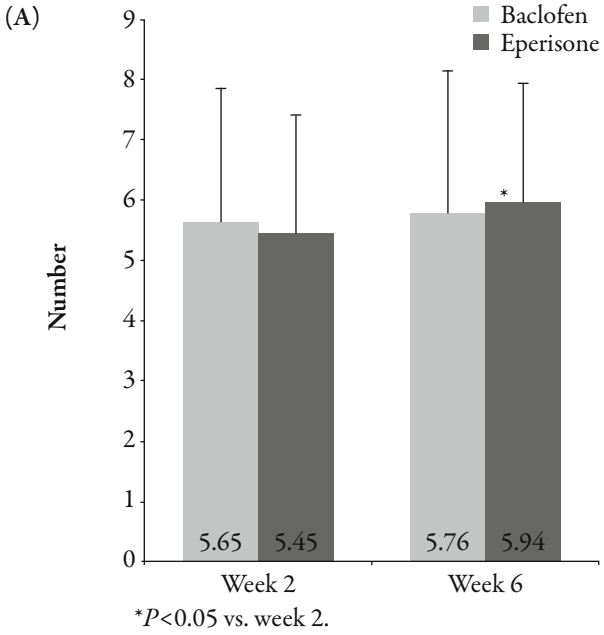
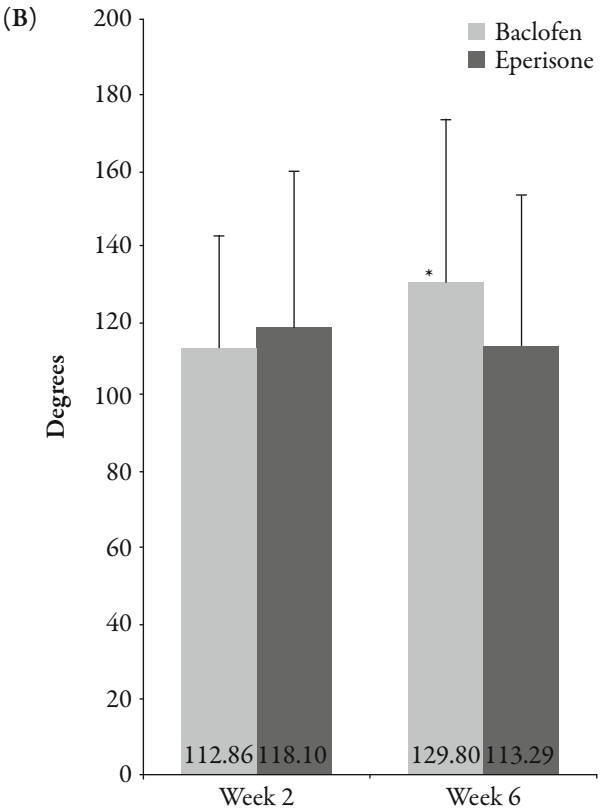


Figure 4. Results of the Wartenberg test: (**A**) number of leg oscillations; (**B**) velocity of leg falling in the baclofen and eperisone groups during the study period. Histograms represent mean values; lines represent SD.



*P<0.05 vs. week 2.



*P<0.01 vs. week 2.

week 2 (Figure 3). There were no significant differences between treatment arms.

An overall reduction in all the physiological and pathological reflexes was observed in association with both study drugs, with the exception of abdominal reflexes (data not shown).

The electromyography test showed a decrease in the Hmax/Mmax amplitude ratio between week 2 and week 6 with eperisone and baclofen (0.63±0.28 and 0.45±0.25 for eperisone at week 2 and week 6, respectively, P<0.01; 0.55±0.23 and 0.47±0.22 for baclofen at week 2 and week 6, respectively, P<0.01). This reduction was numerically greater with eperisone (–30.0%) than with baclofen (–18.6%), although statistical significance was not reached. The Wartenberg test showed a different effect for eperisone, which significantly increased the number of leg oscillations (P<0.05 for week 6 vs. week 2), and baclofen, which was associated to an increase in the velocity of leg falling (P<0.01 for week 6 vs. week 2) (Figure 4). No significant differences between the study drugs were observed.

Overall Assessment of Efficacy

The overall assessment of treatment efficacy according to physicians and patients is reported in Table 2. A higher percentage of physicians (8.1%) and of patients (21.6%) judged, more frequently, the improvement in spastic symptoms obtained with eperisone as "good" than was reported with baclofen (2.9% for both physicians and patients).

Tolerability

In total, 15 patients (39.5%) reported adverse events in the eperisone group and 17 patients (48.6%) reported adverse events with baclofen. Only one patient (2.5%) withdrew from the study for the onset of adverse

Table 2. Overall assessment of treatment efficacy according to physicians and patients.*

	Eperisone, *n* (%)		Baclofen, *n* (%)	
	Physicians	**Patients**	**Physicians**	**Patients**
No improvement	5 (13.5)	6 (16.2)	8 (22.9)	8 (22.9)
Slight improvement	18 (48.6)	13 (35.1)	13 (37.1)	10 (28.6)
Moderate improvement	11 (29.7)	10 (27.0)	13 (37.1)	16 (45.7)
Good improvement	3 (8.1)	8 (21.6)	1 (2.9)	1 (2.9)

*Eight patients' data missing, as they were unavailable for follow-up

Table 3. Adverse events reported during the study.

	Eperisone, *n* (% of patients) *n*=38	Baclofen, *n* (% of patients) *n*=35
Amenorrhea	0 (0)	1 (2.9)
Anorexia	0 (0)	1 (2.9)
Asthenia	3 (7.9)	9 (25.7)
Cramps	1 (2.6)	1 (2.9)
Dyspepsia	1 (2.6)	0 (0)
Eczema	1 (2.6)	0 (0)
Epigastric pain	2 (5.3)	1 (2.9)
Headache	1 (2.6)	0 (0)
Heat in lower limbs	0 (0)	1 (2.9)
Hypertension	1 (2.6)	0 (0)
Hypochondrial pain	0 (0)	1 (2.9)
Hyposthenia in lower limbs	0 (0)	4 (11.4)
Hypotonia	1 (2.6)	0 (0)
Insomnia	2 (5.3)	0 (0)
Itching	1 (2.6)	0 (0)
Leukocytosis	1 (2.6)	0 (0)
Nausea	0 (0)	1 (2.9)
Paresthesia	0 (0)	1 (2.9)
Sciatica	0 (0)	1 (2.9)
Shivering	1 (2.6)	0 (0)
Sleepiness	1 (2.6)	4 (11.4)
Sweating	1 (2.6)	0 (0)
Vertigo	0 (0)	1 (2.9)
Total	18 (47.4)	27 (77.1)

events (severe cephalea) in the eperisone group, while another withdrew for personal reasons, versus five patients (12.5%) in the baclofen arm (generalized asthenia and hyposthenia of lower limb). Adverse events were reported in 18 patients treated with eperisone and 27 with baclofen. The incidence of different adverse events is reported in Table 3. Asthenia was the most frequent adverse event both in the eperisone group (7.9% of patients) and in the baclofen group (25.7%). In most cases, adverse events were of mild intensity. Overall, no variations in laboratory parameters or in vital signs were reported in association with eperisone or baclofen.

DISCUSSION

This double-blind, randomized, head-to-head trial compared eperisone and baclofen by three main types of analysis: functional analysis, physiological and pathological reflexes, and electromyography. In this way, it becomes possible to evaluate different aspects of the management of spastic palsy: mobility and personal efficiency; hyper-response of deep tendon reflexes; and the degree of muscular response to electric stimuli. Moreover, the overall efficacy and tolerability of the treatment, as evaluated by physicians and patients, were assessed in this trial, which can therefore provide a complete picture of the drug effects in patients with spastic palsy of any etiology.

Evaluation of Efficacy and Tolerability

Overall, the results of this study show that both oral eperisone 300 mg/day and oral baclofen 60 mg/day provide a marked antispastic efficacy, as observed with the different functional evaluations. As expected from the mechanisms of action of eperisone and baclofen, the greatest effect was observed in the evaluation of muscular tone, which decreased almost by 50% at the end of study with both drugs, when compared with baseline. The muscle-relaxant effect was already evident after 2 weeks with both drugs. These findings can further confirm the relaxant effect of eperisone and baclofen, as seen in previous studies.[3,8-10] For instance, eperisone was at least as effective as physiotherapy in improving the muscular tone in 26 post-stroke patients,[21] and improved spasticity, functional capability, and pain during the dose-finding trial conducted in 18 patients with spastic palsy of different etiology.[18] Beside the reduction of muscular tone, eperisone and baclofen had an important effect on the other functional parameters evaluated. Although no statistically significant differences were observed between drugs, the patients in the eperisone arm reported a significant improvement in some parameters that were not affected by baclofen, such as the neurological evaluation for the upper limbs, as measured with the Pedersen's score, and the joint range of motion. A slight improvement in the personal efficiency was also reported with eperisone, but not with baclofen. Eperisone also determined a faster onset of reduction in the 10-meter walking time, even though the reduction at the end of the study was numerically greater in the baclofen arm. These findings are important in terms of allowing the patients to become self-sufficient.

The effects of eperisone and baclofen on the functional evaluations were well supported by the analysis of different reflexes, which improved in association with both drugs and, in particular, by electromyographic analysis. In fact, eperisone and baclofen improved the Hmax/Mmax amplitude ratio, as suggested in previous studies,[18,22-24] even though the muscle relaxant effect was 12% numerically greater with eperisone. Interestingly, the Wartenberg

test, which is one of the most accurate assessments currently used in the evaluation of spasticity,[25] suggested that eperisone and baclofen could exert their actions in different ways: baclofen increased the velocity of leg falling, while eperisone improved the number of oscillations. It would therefore be interesting to test if the combination of the two drugs could have an additive efficacy with better tolerability.

Since central muscle relaxants are chronically administered in the therapy of spastic palsy, the tolerability profile represents a central issue in the choice of the optimal treatment strategy. In this study, both eperisone and baclofen were well tolerated. However, eperisone was associated with a lower incidence of adverse events than baclofen, and in particular with less-severe adverse events. These findings are in agreement with other previous analyses that show a good tolerability profile for eperisone,[10,18,21] while, over time, many patients do not tolerate the side effects of oral baclofen. This is a key problem with oral baclofen and a reason behind the increasing use of intrathecal baclofen. The intrathecal route is the most commonly used for baclofen, particularly for high dosage, due to tolerance.[26] Therefore, further studies of eperisone versus intrathecal baclofen could be useful.

Strengths and Limitations

A potential weakness of the study is the relatively short follow-up time of patients. If the patients were followed up for longer, more side effects of either drug might be documented, as side effects for oral baclofen are often seen to increase over time.[27] The same may be true for eperisone. One other possible limitation of this study is the use of oral baclofen as a comparative agent. Most published studies focus on intrathecal baclofen, but the aim of the study was to directly compare oral formulations, since eperisone is not available for intrathecal administration. Another possible limitation could be identified as the lack of a placebo control, which would allow us to distinguish between therapeutic effect and spontaneous improvement of the symptoms. However, both eperisone and baclofen have been compared with placebo in several trials[18,26,27] and therefore a placebo control may not be necessary in the present head-to-head trial. Moreover, the direct comparison of two central muscle agents may represent a strong point of this analysis, since the number of similar studies in the therapy of spastic palsy is scant. Furthermore, the standard deviation of the values of the duration of the disease was very widespread, which suggests that some patients had a very short period of symptoms before treatment. The characteristics of their disease, and response to treatment, might therefore be different from those with more established spasticity.

Among the other possible strengths of this study, it is possible to suggest the use of different quantitative assessments. In fact, it has been suggested that the lack of quantitative tests might represent a confounding factor in the evaluation of the efficacy of different central muscle relaxants in a complex clinical situation like spastic palsy.[28] Another strength could be represented by the high number of patients enrolled in the study; as well as the fact that spastic palsy could be of any etiology, therefore extending the generalizability of the results.

CONCLUSION

The results of this double-blind, randomized, phase 3 trial suggest that both eperisone 300 mg/day and baclofen 60 mg/day, administered orally, are effective and well-tolerated drugs in the treatment of spastic palsy. However,

eperisone might be associated, at least preliminarily, to some additional clinical benefits when compared with baclofen. This study further confirms the muscle-relaxant efficacy of eperisone in similar therapeutic contexts. Taken together, these findings suggest that eperisone 300 mg/day might represent a possible effective therapeutic alternative in the treatment of spastic palsy of any etiology.

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