Effects of Two Different Doses of Eperisone in the Treatment of Acute Low Back Pain

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ABSTRACT

Objectives: to evaluate efficacy and tolerability of two different dosages of eperisone (150 and 300 mg/day) in comparison with those of diazepam 15 mg/day, orally given for seven days.

Methods: Spontaneous and provoked pain, muscular contracture and its impact on working capacity as well as "hand-to-floor" distance and degree of lumbar tract flexion were assessed in a randomised double-blind trial on 90 patients with acute muscle contractures. Adverse effects were also monitored.

Results: Diazepam and eperisone 150 mg/day had comparable efficacy, but the incidence of adverse effects and drowsiness was significantly lower in eperisone— than in diazepam-treated patients. Moreover, eperisone 300 mg/day was superior to diazepam in reducing muscle contracture and impairment of working capacity.

Conclusions: Eperisone represents a significant advancement among the centrally active muscle relaxant agents both in terms of efficacy and safety. A daily dosage of 300 mg appears to be effective for management of patients with acute painful spinal muscle contracture.

INTRODUCTION

Acute low back pain (LBP) is a very common symptom affecting up to 90% of all adults at least once in their life. Most of cases are represented by an LBP episode or a nonspecific lumbago, which is usually self-limited without any serious underlying pathology, but sometimes the LBP may be the spy of an underlying severe disease, such as cauda equina syndrome, cancer, infection or fracture[1].

Among patients with acute nonspecific mechanical LBP, the most frequent pharmacological approach is the administration (or self-administration) of

paracetamol, nonsteroidal anti-inflammatory drugs (NSAID) and skeletal muscle relaxants. The rationale for using muscle relaxants is that spine muscles contraction may produce clinical disability by interfering with posture, motor capacity, nursing or daily living activities. In these cases, the distribution of muscle over-activity can be limited by the use of drugs that modulate neurotransmitters acting at the cortico-spinal level, such as Á-aminobutyric acid (GABA), glycine, glutamate, noradrenaline and serotonin[2].

Sometimes, centrally acting drugs such as baclofen, tizanidine and diazepam, could be preferred in the muscle contracture of spinal origin, whereas dantrolene sodium, due to its primarily peripheral mechanism of action, may be preferable in spasticity of central origin (stroke and traumatic brain injury) where sensitivity to sedating effects is generally higher[3]. However, most of these treatments have recently been recently questioned by the Cochrane group[4]; thus, an interest exists for new centrally active muscle relaxant agents without detrimental effects on the central nervous system (CNS).

Eperisone hydrochloride is a novel antispastic agent, which has been developed in Japan and is now marketed in Japan, India and the Far East under the brand name Myonal®. It works by relaxing both skeletal muscles and vascular smooth muscles, thus demonstrating a variety of effects such as reduction of myotonia, improvement of circulation, and suppression of the pain reflex. The drug inhibits the vicious cycle of myotonia by decreasing pain, ischemia and hypertonia in skeletal muscles, thus alleviating stiffness and spasticity, and facilitating muscle movement[5-7].

Results obtained with compounds belonging to the same pharmacological class, such as tolperisone, support the view that blockade of sodium channels may be a major component of the action of tolperisone-type centrally acting muscle relaxant drugs; moreover, tolperisone, eperisone and silperisone[8] had also a marked effect on voltage-gated calcium channels. These data suggest that eperisone and its analogues exert their spinal reflex inhibitory action predominantly via a presynaptic inhibition of the transmitter release from the primary afferent endings via a combined action on voltage-gated sodium and calcium channels[9].

In addition, it has been reported that the effects of eperisone in patients with chronic LBP could be mediated by an activity on the paraspinal muscle hemodynamics with improved intramuscular oxygenation during lumbar extension and flexion[10].

In spite of it's large clinical use, published evidences of the efficacy of eperisone are limited to the treatment of patients with myelopathy or tropical spastic paraparesis[11], neurogenic bladder[12], increased muscular tone after stroke[13], and muscle cramps from liver diseases[14]; in addition, a double-blind, randomized, placebo-controlled trial has shown a clear benefit of eperisone on pain in the nuchal region, back pain, pain in arms and shoulders, stiffness and other symptoms in patients with cervical spondylosis[15].

On the contrary, there areis no controlled comparative clinical trials in the treatment of patients with LBP; thus, we wanted to investigate the efficacy and the tolerability of two escalating dosages of eperisone (150 mg and 300 mg daily), in comparison with those of diazepam 15 mg daily.

MATERIALS AND METHODS

Ninety patients of both sexes aged over more than 18, were selected among those visiting the Orthopaedic and Traumatology Divisions of our hospitals for medical advice because of LBP. Criteria for inclusion were a clinically

Table 1. Effects of the different treatment on pain at rest and on palpation, muscular contracture, working capacity and "hand-to-floor" distance (see text for methods of assessment). Statistically significant difference: * p<0.01 *vs.* eperisone 50 mg t.i.d.; ° p<0.01 *vs.* diazepam 5 t.i.d.

	Day	diazepam 5 mg tid	Eperisone 50 mg tid	Eperisone 100 mg tid
Pain at rest	0	1.57 ± 0.73	1.73 ± 0.74	1.65 ± 0.63
	3	1.10 ± 0.72	1.25 ± 0.65	0.91 ± 0.59*
	7	0.52 ± 0.63	0.77 ± 0.71	0.36 ± 0.49*
Pain at palpation	0	2.00 ± 0.64	2.07 ± 0.64	2.04 ± 0.72
	3	1.34 ± 0.67	1.46 ± 0.64	1.17 ± 0.49*
	7	0.79 ± 0.77	0.96 ± 0.77	0.59 ± 0.59*
Muscular contracture	0	2.17 ± 0.59	1.76 ± 0.69	1.73 ± 0.53
	3	1.34 ± 0.67	1.36 ± 0.62	1.00 ± 0.52*°
	7	0.76 ± 0.74	0.71 ± 0.69	0.48 ± 0.60*
Impaired working capacity	0	1.90 ± 0.48	1.93 ± 0.69	1.65 ± 0.49
	3	1.52 ± 0.51	1.61 ± 0.57	1.52 ± 0.59*°
	7	1.31 ± 0.47	1.31 ± 0.47	1.09 ± 0.43*°
Hand-to-floor distance	0	35.17 ± 13.44	37.43 ± 16.21	28.92 ± 13.96
	3	23.11 ± 14.89	27.61 ± 14.62	15.61 ± 9.82*
	7	13.48 ± 13.36	18.73 ± 16.15	7.38 ± 6.37*

relevant acute LBP arisen oversince less than 48 hours, and a muscular contracture of mild to severe intensity. Criteria for exclusion were: a) history of hypersensitivity to benzodiazepines; b) any anti-inflammatory and/or analgesic drug given in the last 24 hours; c) pregnant or nursing mothers; d) disturbances of nociception and/or proprioception that could negatively affect neuronal reflexes and motility; e) severe cardiovascular diseases; f) history and/or presence of any hepatic or renal disease, or other conditions which could affect the drugs' absorption and disposition; g) ongoing infective diseases; h) chronic rheumatic diseases; i) neoplasias of the vertebral column.

According to the Helsinki Declaration and the recommendations of the Spanish Medical Deontological Codex ("Codigo Deontologico Medico Espaniol"), before any trial-related activity the investigator informed the patient about the nature and purposes of the study, and any possible risk that might have occurred during the treatment. Patients were also informed that they could suspend the trial at any moment without any justification.

According to a randomization sequence, the patients were allocated to a double-blind oral treatment with either diazepam 5 mg three times daily (t.i.d.) (DIA), eperisone 50 mg t.i.d. (EPE150) or eperisone 100 mg t.i.d. (EPE300), for seven consecutive days. The investigational medicinal products were manufactured in a way to guarantee the full blindness for both patients and investigators.

The efficacy of the treatments was evaluated by the physicians according to the following parameters: a) intensity of pain in rest position and on palpation measured by means of a 4-point scale (0

= none; 1 = mild; 2 = moderate; 3 = severe); b) intensity of muscular contracture by a 5-point scale (0 = none; 1 = minimum; 2 = mild; 3 = moderate; 4 = severe); c) the impact on muscular contracture on working capacity by a 4-point scale (1 = no limitation of activity; 2 = partial limitation, but able to perform usual activities; 3 = not self-sufficient, needs help; 4 = bedridden).

The muscle relaxant activity of the two medications was also evaluated by the investigators who asked the patients to bend forward and try to touch the floor with their fingers; the remaining distance between fingers and ground ("hand-to-floor") was measured by means of a ruler (cm). In addition, the limitation of the lumbar motility was measured by the degree of side flexion of the spinal column that the patient could reach towards both sides (as degrees).

The patients were evaluated by the investigators at the screening/enrolment visit (basal) and after 3 (intermediate) and 7 days (end) of treatment. At each visit the patients were asked to report any occurred adverse effect to medications, as well as any treatment was needed for its relief, and taking note of them on the case report form. At the basal control visit any concomitant disease was noted together with any concomitant pharmacological treatment; then, at each visit the patients were asked to report the presence of any new concomitant disease.

The statistical analysis was performed by an independent subject (Europharma 2000 s.r.l. Firenze, Italy) by means of the SPSS-PC Version 9.0.1 package. Descriptive statistics areis reported as data ± standard deviation or frequencies as appropriate.

Initially, the Kolmogorov-Smirnoff test was applied on the quantitative variables to verify whether they followed a normal distribution; then, the Bartlett test was used to confirm the homogeneity of the variances. Afterwards, the most appropriate parametric tests (post-hoc Bonferoni test) were used for normally distributed variables, while the non-parametric tests were used for the other variables.

For non- parametric tests the homogeneity of qualitative variables was initially evaluated; then, the Friedman and Wilcoxon tests were used for intragroup comparative analysis, while the Kruskal-Wallis and Mann Whitney U tests were used for comparison between groups. The level of significance for all the statistical decisions was of $p < 0.01$ for studies of two tails.

RESULTS

The three groups of patients proved to be homogenous at the enrolment visit in terms of demographic characteristics. Thirty patients were fully evaluated in the DIA (18 M / 12 F; mean age: 39.27 ± 13.35; range: 19-74) and in the EPE150 (15 M / 15 F; mean age: 45.40 ± 13.74; range: 24-65) groups, while the third EPE300 group was formed by 26 fully evaluated patients (11 M / 15 F; mean age: 35.69 ± 11.89; range: 18-67) since four patients were lost at follow-up (these patients were unable to come back at visits and, when contacted by phone, they reported that reasons for withdrawal were independent from the medications).

The radiological examinations performed at the enrolment showed eleven cases of pre-existing lumbar diseases (four cases each in the DIA and EPE150 groups and three in the EPE300 group); all of them were of mild severity. The neurological examination showed no abnormal findings in any patient.

All the tested medications exerted a statistically significant analgesic effect in terms of "pain at rest" (Table 1). While no difference was observed among the

three groups at the basal visit, DIA, EPE150 and EPE300 reduced the "pain at rest" by 30%, 28% and 45%, respectively, after three days of treatment, and by 66%, 56% and 79%, respectively, after seven days of treatment. The intergroup comparison showed that, both after 3 and 7 days of treatment, the reduction of "pain at rest" observed in the patients treated with EPE300 was significantly higher than that achieved with EPE150 ($p<0.01$).

The treatment with diazepam and eperisone achieved also a significant reduction of "pain on palpation". The pain was reduced by 33%, 29% and 45%, respectively, with DIA, EPE150 and EPE300, after three days of treatment, and by 60%, 53% and 71%, respectively, after seven days of treatment. Similarly to "pain at rest", the statistical analysis showed a significantly higher efficacy of EPE300 *vs.* EPE150 both after 3 and 7 days of treatment ($p<0.01$ at both times).

The "muscular contracture" was significantly and progressively reduced by the treatments; the intergroup comparison showed a statistically significant difference of EPE300 *vs.* EPE150 both after 3 and 7 days of treatment ($p<0.01$ at both times), and a significant difference between EPE300 and DIA after three days of treatment ($p<0.01$).

The evaluation of the "impaired working capacity" as a result of the muscular contracture, showed that a significant improvement was achieved in the patients treated with DIA both after 3 and 7 days of treatment, while in the patients treated with EPE150 the difference was significant only at the visit performed at day 3. The patients treated with EPE300 obtained a significant improvement in the working capacity after seven days of treatment. However, the comparison between groups showed that both on day 3 and day 7 the improvement achieved with EPE300 was significantly better than that obtained with EPE150 ($p<0.01$). It is noteworthy that the score observed with EPE300 was also significantly better than that with DIA both at day 3 and day 7 of treatment ($p<0.01$).

The treatment with DIA increased the lateral flexion to right by 17% and 43%, respectively, after 3 and 7 days of treatment, and the lateral flexion to left by 18% and 37% at the two control visits; at the same times (day 3 and day 7), the improvement achieved with EPE150 in the lateral flexion was of 19% and 49% towards the right side, and 21 and 54% towards the left side, while the improvement achieved with EPE300 was of 24% and 55% towards right and 23% and 52% towards left. The statistical analysis showed a statistically significant difference ($p < 0.01$) in the right side flexion between the EPE150- and EPE300-treated patients on day 3; the difference continued to be significant on day 7 (data not shown).

Similar results were obtained in the hand-to-floor distance. In the patients treated with DIA the distance significantly decreased by 34% and 62%, respectively, after 3 and 7 days of treatment; the improvements observed at the same times with EPE150 were of 26% and 50%, and those with EPE300 were of 46% and 74%. Once more, the response achieved with EPE300 was significantly better than that obtained with the lower dosage of eperisone ($p<0.01$) (Table 1).

Finally, in the DIA-treated group 23 patients (77%) reported the following adverse reactions: somnolence (19) associated with depression in one case, and with epigastric pain in the other one; tachycardia with vertigo (1), epigastric pain (2) and diarrhoea (1). Somnolence, as well as the depression and vertigo, were of moderate-severe intensity, being the remaining symptoms of mild intensity.

Among the EPE150-treated patients, only 5 adverse reactions (17%) were reported, i.e. epigastric pain of severe intensity (3) occurring after about four days of treatment, and associated in one case with dyspnoea; somnolence of moderate intensity (1) and headache of mild intensity (1).

In the group of patients treated with EPE300 mg, the reported adverse reactions were six (23%): somnolence of slight intensity (2), epigastric pain of severe intensity (1), vertigo (1) and urinary retention (1) with a doubtful relationship to the medication since the patient had a history of nephritic colic, and slight anorexia (1).

DISCUSSION

Clinical trials of eperisone in the treatment of LBP are relatively few. A Medline search at the time of trial planning looking for "back pain" and "eperisone" has shown only a double-blind, randomized, placebo-controlled trial reporting a benefit of eperisone in patients with cervical spondylosis, with reduction of pain in the nuchal region, back pain, pain in arms and shoulders, and stiffness[15].

More recently, a randomized controlled trial has been published reporting the effects of eperisone in patients with chronic LBP. VAS for pain was significantly reduced after 4 weeks of treatment compared to controls; moreover, the relative change of oxygenated hemoglobin during lumbar extension at 4 weeks was significantly higher in the eperisone group compared to control (no treatment) and McKenzie therapy alone. Thus, administration of eperisone for 4 weeks significantly affected both the VAS pain and the muscle hemodynamics, and improved the intramuscular oxygenation during lumbar extension and flexion in patients with chronic LBP[10].

The results achieved in our clinical experience confirm the efficacy of eperisone as muscle relaxant in patients with chronic LBP. Both "pain at rest" and "pain on palpation" were significantly reduced by all the treatments, but it is noteworthy to mention that the analgesic activity was significantly better with the highest dosage of eperisone (300 mg/day) than with the lower dose (150 mg/day) and with diazepam. The superiority of the higher dose compared to the lower dose of eperisone is confirmed also by the results on "muscle contracture", "impaired working capacity" and "hand-to-floor distance". Moreover, a statistically significant difference was also observed between eperisone at the highest dose and diazepam as far as regards "muscle contracture" and "impaired working capacity".

Although the lack of a placebo arm certainly represents certainly a weakness of the study, the significant differences we observed between the low and high doses of eperisone and, in some instances between high eperisone and diazepam as well, effectively substitute for the lack of placebo arm and show proof of efficacy of eperisone much better than if it would be simply a non-inferiority trial vs. diazepam in terms of efficacy.

On the other handway, diazepam could be considered something more than a pure "placebo" since reports have been published on the use of diazepam in the treatment of spasticity[16-17], although it's use is limited by the frequent appearance of undesired side effects caused by the concentration of the benzodiazepine in the brain[18-19].

In this regard, we would like to underline that the incidence of adverse effects was much lower in both groups of patients treated with eperisone as compared to the patients treated with diazepam. The lack of a significant effect of eperisone on attention and other cog-

nitive functions is clinically relevant with regards to the compatibility of this treatment for muscle contracture with the normal- day-life activities. In fact, it should be taken into consideration that, while a few decades ago an acute LBP almost completely prevented the subject from heavy activities related to job or normal- day-life, today such a disturbance is not incompatible with some activities performed at home, such as communication, e-mailing, etc. Thus, the maintenance of a standard level of attention and cognitive capacities is welcome.

In conclusion, our results seem to indicate that, in comparison with diazepam eperisone seems to represent a significant advancement among the centrally active muscle relaxant agents both in terms of efficacy and safety. A daily dosage of 100 mg t.i.d. appears to be appropriate for the management of patients with acute painful spinal muscle contracture.

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