Open Experience with a New Myorelaxant Agent for Low Back Pain

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ABSTRACT

Eperisone hydrochloride has been recently proposed as a muscle relaxant for treatment of muscle contracture and chronic low back pain (LBP), being devoid of clinically relevant sedative effects on central nervous system (CNS). This view has been confirmed by our experience in a series of 100 patients with LBP and spinal muscle contracture, treated with a full eperisone dose (300 mg/day) for ten consecutive days.

The treatment achieved a consistent analgesic and muscle relaxant activity across all of the patients. Both "spontaneous pain" and "pain on movement" were significantly decreased, as did the resistance encountered by the investigator to passive movements, the antalgic rigidity and the muscle contracture. As a consequence, the treatment with eperisone resulted in a lower rigidity of low back and an improved motility for patients.

Only 7 cases of adverse reactions were reported, such as lightheadness,[1] occasional vertigo and/or loss of equilibrium,[3] mild somnolence,[2] and epigastric pain.[1] In almost all cases, there was no need to interrupt the treatment, and the reactions spontaneously recovered.

It is noteworthy to mention that both the activities with eperisone, ie, analgesia and muscle relaxation, were achieved with 1 drug only, while it is common practice in rheumatology to combine a painkiller with a muscle relaxant in order to achieve a satisfactory result with both symptoms. Moreover, because of the lack of significant effects on the CNS such as drowsiness, eperisone represents a valuable alternative to the traditional centrally acting muscle relaxants, whose use has been significantly limited in recent years by their CNS adverse effects in spite of a well-documented therapeutic efficacy.

INTRODUCTION

Chronic low back pain (LBP) is one of the most common debilitating conditions reported by patients, and represents a substantial burden on the healthcare system,[1] with approximately 45% of the adult population experienc-

ing LBP annually. Direct cost for diagnosis and treatment is reported to be higher than 23 billion dollars in the U.S.A. in 1990.[2] Together with knee and hip osteoarthritis, LBP is one of the leading causes of disability in European countries[3] as well, and it is the 10th most common complaint in outpatient office visits.[4]

Analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and opioids are the most largely used medications for symptomatic treatment of LBP. However, traditional NSAIDs are associated with an increased risk for serious upper gastrointestinal (GI) complications, including bleeding and perforation; nephrotoxicity, including oedema, hypertension, and acute renal failure; congestive heart failure; and adverse reproductive outcomes[5,6,7]. Paracetamol is generally considered to be safer and better tolerated than NSAIDs when used at therapeutic doses, but the results of a recent epidemiological study seem to indicate that high doses of paracetamol may involve the same risk for upper GI complications as traditional NSAIDs.[8] Opioids such as oxymorphone,[9] oxycodone,[10,11] tramadol,[12] or tramadol, in combination with paracetamol,[13] are effective analgesics. However, somnolence or other detrimental effects on CNS, and constipation, are observed in a percentage of patients ranging between 3% and 20%.

Central muscle relaxants (CMRs) are most often used for treating muscle spasticities of neurological origin, while their use for minor complaints, such as acute LBP, has been limited by their adverse CNS effects. Among these compounds, eperisone hydrochloride has recently emerged as antispastic agent with an improved profile of safety compared to other drugs of the same pharmacological class; in particular, eperisone has been introduced on the market for the management of painful conditions sustained by a muscle contracture.[14,15,16]

According to results achieved with other compounds belonging to the same pharmacological class, the mechanism of action of eperisone is believed to be a blockade of sodium channels; in addition, these compounds, including eperisone, are reported to have a marked effect on voltage-gated calcium channels.[17] These data suggest that eperisone and its analogues may 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.[18]

More importantly, eperisone appears to be devoid of clinically relevant sedative effects on CNS, as it has been reported in trials involving patients with myelopathy or tropical spastic paraparesis;[19] patients with neurogenic bladder;[xx] and patients with muscle cramps secondary to liver diseases.[20] The lack of sedative effects, together with the lack of those GI adverse effects that are typical of traditional NSAIDs, represent the most important advantage of eperisone, keeping in mind that patients with LBP are not usually young and, therefore, at high risk for NSAID-induced GI toxicity.

PATIENTS AND METHODS

We have screened 100 consecutive patients of both sexes, among those seeking our centres for medical advise and healthy assistance because of LBP. Forty patients were enrolled at the Service of Rehabilitation and Functional Reeducation, S. Orsola-Malpighi Hospital, Bologna (Italy), and 60 patients at the Division of Orthopaedics and Traumatology, Hospital of Vignola (Modena, Italy).

Main criteria for inclusion were acute or relapsing LBP, moderate to

Table 1. Effects of a 10-day treatment with eperisone in 100 patients with low back pain of sciatic origin. Results are reported as means ± standard deviation either of a 10-cm VAS (spontaneous pain and pain on movement); a 5-point scale (resistance to passive movements; antalgic rigidity, muscular contracture, joint functional impairment); or centimetres ("hand-to-floor" distance). Statistically significant differences: * p<005 and ** p<0.01 vs. baseline; °° p<0.01 vs. day 3.

	BASELINE	DAY 3	DAY 10
Spontaneous pain (VAS)	6.49 ± 0.12	5.40 ± 0.15**	3.54 ± 0.18°°
Pain on movement (VAS)	7.28 ± 0.12	6.08 ± 0.17**	4.06 ± 0.20°°
Resistance to passive movements	2.98 ± 0.07	2.45 ± 0.08**	1.63 ± 0.08°°
Antalgic rigidity	3.18 ± 0.07	2.56 ± 0.07**	1.66 ± 0.09°°
Muscle contracture	3.17 ± 0.07	2.56 ± 0.08**	1.62 ± 0.09°°
Spine functional impairment	2.74 ± 0.10	2.24 ± 0.09**	1.54 ± 0.09°°
"Hand-to-floor" distance (cm)	58.03 ± 3.21	48.71 ± 2.58*	36.55 ± 2.44°°

severe, with no finding of severe spinal diseases at a Rx examination of lumbar spinal tract, such as spondilitis, fractures, cancers, severe arthrosis and osteoporosis. Muscular diseases, such as myositis, polimyositis, muscular dystrophia and myotonia, were criteria for exclusion, as well as any other severe disease affecting neurological or cardiovascular systems, liver and kidney. Other criteria for exclusion were history of hypersensitivity to the test compound; any anti-inflammatory and/or analgesic drug given in the last 24 hours; pregnant or nursing mothers; disturbances of nociception and/or proprioception that could negatively affect neuronal reflexes and motility; any condition that could affect drugs' absorption and disposition; and ongoing infective diseases.

The patients gave their informed consent to taking part into the trial, and then they were treated with eperisone hydrochloride 100 mg 3 times daily (tid.) for 10 consecutive days. The medication was given at 6:00 AM., 2:00 PM. and 10:00 PM. Other non-analgesic medications were allowed during the study for specific diseases, but their dosage remained unchanged for all the trial.

At baseline (day 0), the "spontaneous pain" and the "pain on movement" (pain provoked by a passive movement induced by the investigator) were assessed by means of a 10-cm visual analogue scale (VAS); the patient was asked to score the pain by ticking off the scale between 0 (no pain) and 10 (unbearable pain).

In addition, the resistance to passive movement, the antalgic rigidity, and the muscle contracture, were evaluated by the investigator by means of a 5-digit scale (0 = absent; 1 = minimum; 2 = mild; 3 = moderate; 4 = severe); the functional impairment was also scored by means of semiquantitative scale (0 = none; 1 = ≤ 25%; 2 = between 25 and 50%; 3 = between 50% and 75%; 4 = > 75%). Finally, the patients were asked to bend forward and try to touch the floor with fingers. The remaining distance between fingers and ground ("hand-to-floor" distance) was measured (cm).

All these assessments were repeated after 3 and 10 days of treatment. At these times, the patients were asked a non-leading question such as "Have you felt different in any way since starting treatment or since the last visit?" in order to identify any adverse event occurring during treatment. At the end of the study, a full lab examination (hematology, blood chemistry, and urinalysis) was performed, and the physicians were asked to give their judgment

about the efficacy of the treatment by means of a 5-digit scale (nil; light; moderate; good; excellent efficacy).

Demographic and baseline data were described statistically. The analysis of variance was used for "between-times" comparison. Then, the Student's t test and the Mann-Whitney's U test were used, respectively, for paired data of continuous normally distributed variables and for non-parametric variables. The ¯Ç test was for analysis of the efficacy judgement done by the investigator.

RESULTS

A total of 100 patients were enrolled into the study. There were 41 males and 59 females between 18 and 70 years of age (mean ± s.e.m.: 47.62 ± 1.46 years), and weighed between 48 and 100 kg (mean ± s.e.m. 67.68 ± 1.16 kg).

The treatment with eperisone achieved a consistent beneficial analgesic and muscle relaxant activity across all patients. Both "spontaneous pain" and "pain on movement" (induced by the manoeuvres of the investigators) significantly decreased during the study; the VAS values of spontaneous pain were respectively reduced by 17% and 46%, after three and ten days of treatment with eperisone, while the values for pain on movement showed a 16% and 44% decrease at the same observation times. Similarly, the resistance encountered by the investigator to passive movements, the antalgic rigidity, and the muscle contracture showed an 18%, 19%, and 19% reduction, respectively, after 3 days of treatment. At the end of the treatment, the reductions for the same 3 parameters were 45%, 48%, and 49% respectively (Table 1).

The score for spine functional impairment was reduced from 2.74 at baseline to 2.24 at day 3 (-18%), and to 1.54 at day 10 (-44%) ($p < 0.01$). Also, the "hand-to-floor" distance was significantly reduced from 58.03 cm at baseline, to 48.71 cm at day 3 (-16%) and to 36.55 cm at day 10 (-47%) ($p < 0.01$) (Table 1). Thus, the analgesic and muscle relaxant activities of eperisone resulted in a lower rigidity of the low back and an improved motility of the patients.

According to the investigators, the treatment with eperisone was very successful in 41% of patients and relatively good in other 36%. However, the most interesting findings observed with eperisone refer to its safety of use.

Only 7 adverse drug reactions (ADRs) were observed on a total of 100 treated patients (Table 2). One patient complained of minimal lightheadness from day 4 to the end of treatment. There were 3 intermittent cases of light to mild vertigo and/or loss of equilibrium, and 2 patients reported mild somnolence. In all these cases, the ADR was considered as likely related to the treatment, but no action was undertaken and no treatment was given for ADRs. More importantly, no ADR was severe enough to require withdrawal from the study, and they all abated spontaneously.

In only 1 case, the patient was obliged to stop treatment, that because of epigastric pain. However, this patient had already manifested a similar symptomatology with other treatments, so the investigator preferred to withdraw the patient from the study. Also in this case, the ADR abated after suspension of eperisone.

No finding of systemic poor tolerability was observed at the lab examination performed at the end of the trial.

DISCUSSION

Although our experience was not controlled with placebo or active reference drug, the results we obtained in a relatively large series of patients confirm the efficacy of eperisone, as it has been reported in several published reports.

A randomized, double-blind, clinical trial in patients with cervical spondylosis

Table 2. Adverse drug reactions (ADR) observed in a 100 patient-population treated for 10 days with eperisone 300 mg/day.

ADRs (n)	Relationship with Eperisone	Treatment Withdrawal	ADR Resolution	Treatment for ADR given
Lightheadness (1)	Probable	No	Yes	No
Vertigo (2)	Probable	No	Yes	No
Lost equilibrium (1)	Probable	No	Yes	No
Somnolence (2)	Probable	No	Yes	No
Epigastric pain (1)	Probable	Yes	Yes	No

N° of patients = 100
ADR incidence = 7%

has shown that eperisone has a beneficial activity on pain in arms and shoulders, stiffness, and other symptoms related to cervical spondylosis.[22] In addition, eperisone was found to be comparable to physiotherapy in reducing spasticity in patients with cerebral stroke[23] and cramps secondary to chronic liver diseases.[24] A trial involving patients with myelopathy or tropical spastic paraparesis showed that motor disability was significantly improved in 50% of patients treated with eperisone hydrochloride alone, and, to a lesser extent, in patients treated with other muscle relaxants or anti-inflammatory drugs.[25]

It is noteworthy that both activities observed in our patients, ie. analgesia and muscle relaxation, were achieved with 1 drug only (eperisone), while it is common practice in rheumatology to prescribe a pain-killer (eg, paracetamol or an NSAID) with a muscle relaxant (eg, tramadol, thiocholchicoside, dantrolene), even in fixed combinations,[26] in order to achieve a satisfactory result on both pain and muscle contracture.[27,28]

In addition, the spinal muscle contracture underlying LBP is usually complicated by a reduced blood flow to the muscles, whose metabolic requirements are further increased by the contraction.[29] It has been therefore suggested that in some cases various degrees of ischemia of the extensor muscles in the lumbar spine may represent an aggravating factor leading to LBP.[30]

In this regard, preclinical studies have shown that eperisone exerts several activities on the saphenous artery and veins, thus regulating the blood flow to the skeletal muscles of the lower limbs. It would then follow that eperisone relaxes the saphenous arteries and veins previously contracted by norepinephrine, serotonin, acetylcholine, potassium, or barium. Moreover, a treatment with eperisone attenuates the contractions induced by norepinephrine and serotonin in the arteries, as well as the contractions induced by clonidine and phenylephrine in the veins.[31] In healthy volunteers, a single dose of 300 mg of eperisone has a sympatho-suppressive action and enhances the blood flow in resting skeletal muscles of healthy volunteers with no effect on the sympathetic nerve activity in actively contracting muscles, eg, standing or hand-gripping.[32] Thus, in patients with LBP, eperisone is expected also to improve the blood flow to muscles and improve the hypoxic condition.

Our study was mostly aimed at evaluating the safety of eperisone. In this regard, the drug resulted was well tolerated. Adverse drug reactions were rare (7%), and of minor clinical relevance. In particular, there were only 2 reports of somnolence, and they were not severe enough to oblige the patients to cease

treatment. On the other hand, only 1 case of epigastric pain was reported, but it was not certainly related to eperisone, since it was reported by the patients with other medications as well.

These findings are noteworthy, if we keep in mind that traditional NSAID have a consistently worse tolerability; also the more recent generations of NSAIDs, such as the selective inhibitors of cyclooxygenase-2 (COXIB), which seemed to have a better GI tolerability than traditional NSAIDs, have been reported to be responsible of an increased risk for cardiovascular accidents and withdrawn from the market in 2004[33]. Moreover, NSAIDs have an analgesic and anti-inflammatory activity, but they are devoid of muscle relaxant effects.

In conclusion, because of lack of significant CNS-related effects uch as drowsiness, eperisone represents a valuable alternative to traditional CMRs, whose use has been significantly limited in the last years because of their CNS adverse effects in spite of a well-documented therapeutic efficacy.[34,35,36,37]

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