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ORIGINAL RESEARCH

Open Experience with a New Myorelaxant Agent for Low Back Pain

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ABSTRACT

Introduction: Eperisone hydrochloride has been recently proposed as a muscle relaxant for the treatment of muscle contracture and chronic low back pain (LBP) as it is devoid of clinically relevant sedative effects on the central nervous system (CNS). We tested this hypothesis by performing a study of patients with LBP and muscle contracture who were treated with full-dose eperisone.

***Methods*:** Patients with moderate to severe, acute, or relapsing LBP received eperisone 100 mg three times daily for 10 consecutive days. Assessments included: spontaneous pain, pain on movement, resistance to passive movement, antalgic rigidity, and tolerability.

***Results*:** In total, 100 patients were enrolled into the study. The treatment achieved a consistent analgesic and muscle relaxant activity across all patients. Both spontaneous pain and pain on movement were significantly decreased, as was resistance encountered by the investigator to passive movements, antalgic rigidity, and muscle contracture. As a consequence, treatment with eperisone resulted in a lower rigidity of the lower back and an improved motility for patients.

Only seven adverse reactions were reported, including light-headedness (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 adverse reaction resolved spontaneously.

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***Conclusions*:** Eperisone had an analgesic and muscle relaxant effect in patients with LBP. It should be noted that while it is common practice in rheumatology to combine a pain killer with a muscle relaxant in order to achieve a satisfactory result on both symptoms, the present results with eperisone were achieved with a single drug. With an improved tolerability profile compared with nonsteroidal anti-inflammatory drugs, and a lack of significant adverse effects on the CNS, eperisone hydrochloride represents a valuable alternative to traditional analgesics and muscle relaxants for the treatment of LBP.

Keywords: analgesic; eperisone hydrochloride; low back pain; muscle relaxant

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] Approximately 45% of the adult population experience LBP annually and the direct cost for diagnosis and treatment was reported to be more than 23 billion dollars in the USA in 1990.[2] Together with knee and hip osteoarthritis, LBP is one of the leading causes of disability in European countries,[3] and is the tenth most common reason for outpatient office visits.[4]

Analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, and opioids, are the most widely used medications for the symptomatic treatment of LBP.[5] However, traditional NSAIDs are associated with: an increased risk of serious upper gastrointestinal (GI) complications, including bleeding and perforation; nephrotoxicity including edema, hypertension, and acute renal failure; congestive heart failure; and adverse reproductive outcomes.[6-8] Paracetamol is generally considered to be safer and better tolerated than NSAIDs when used at therapeutic doses, but the results of an epidemiological study seem to indicate that high doses of paracetamol may involve the same risk of upper GI complications as traditional NSAIDs.[9] Opioids, such as oxymorphone,[10] oxycodone,[11,12] tramadol,[13] or tramadol in combination with paracetamol,[14] are effective analgesics, but somnolence or other detrimental effects on the central nervous system (CNS), and constipation, are observed in 3%-20% of patients.

Centrally acting muscle relaxants are mostly used for treating muscle spasticities of neurological origin, while their use for minor complaints, such as acute LBP, has been limited by their adverse effects on the CNS.[15] Among these compounds, eperisone hydrochloride has recently emerged as an antispastic agent with an

improved safety profile compared with other drugs of the same pharmacological class; in particular, eperisone has been introduced to the market for the management of painful conditions caused by muscle contracture.[16-18]

The mechanism of action of eperisone is believed to be blockade of sodium channels,[19] and similar compounds are also reported to have a marked effect on voltage-gated calcium channels.[20] These data suggest that eperisone and its analogs may exert their spinal reflex inhibitory action predominantly via presynaptic inhibition of transmitter release from the primary afferent endings, via a combined action on voltage-gated sodium and calcium channels.[21] More importantly, eperisone appears to be devoid of clinically relevant sedative effects on the CNS, as reported in trials involving patients with myelopathy or tropical spastic paraparesis,[22] patients with neurogenic bladder,[23] and patients with muscle cramps secondary to liver diseases.[24] The lack of sedative effects, together with a lack of GI adverse effects typical of NSAIDs, represent the most important advantages of eperisone. This is especially true in patients with LBP as they are usually older and, therefore, are at high risk of NSAID-induced GI toxicity.[25]

This study was designed to investigate the safety of eperisone treatment in a preliminary series of patients with LBP and spinal muscle contracture who were treated with eperisone 300 mg daily. In particular, we assessed the incidence of adverse events of the CNS and GI system.

MATERIALS AND METHODS

We screened 100 consecutive male or female patients who visited the Service of Rehabilitation and Functional Reeducation, S. Orsola-Malpighi Hospital, Bologna, and the Division of Orthopedics and Traumatology, Hospital of Vignola, Modena, for medical advice and health assistance because of LBP. The main criteria for inclusion were moderate to severe, acute, or relapsing LBP, with no finding of severe spinal diseases on examination of the lumbar spinal tract (eg, spondylitis, fractures, cancers, severe arthrosis, and osteoporosis).

Exclusion criteria included muscular diseases, such as myositis, polymyositis, muscular dystrophy, and myotonia, as well as any other severe disease affecting neurological or cardiovascular systems, or the liver and kidneys. 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 drug absorption and disposition; and ongoing infective diseases.

The patients gave their informed consent to take part in the trial. They were then treated with eperisone hydrochloride 100 mg three times daily for 10 consecutive days; the medication was given at 6:00 AM, 2:00 PM, and 10:00 PM. Other nonanalgesic medications were allowed during the study for specific diseases, but their dosage had to remain unchanged throughout the trial.

At baseline, "spontaneous pain" and "pain on movement" (pain provoked by a passive movement induced by the investigator) were assessed by means of a 10-cm visual analog scale (VAS); the patient was asked to score the pain by marking on the scale between 0 (no pain) and 10 (unbearable pain). In addition, resistance to passive movement, antalgic rigidity, and muscle contracture were evaluated by the investigator by means of a 5-digit scale (0, absent; 1, minimum; 2, mild; 3, moderate; 4, severe) and functional impairment was scored by means of a 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 their fingers; the remaining distance between fingers and floor ("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 laboratory investigation (hematology, blood chemistry, and urinalysis) was performed, and the physicians were asked to give their judgment on the efficacy of the treatment by means of a 5-digit scale (nil; poor; moderate; good; excellent).

Demographic and baseline data were described statistically. Analysis of variance was used for "between-times" comparison, Student's *t* test was used for paired data of continuous normally distributed variables, and the Mann-Whitney *U* test was used for nonparametric variables. The χ^2 test was used for analysis of the efficacy judgment of the investigator.

RESULTS

Patients

A total of 100 patients were enrolled into the study: 40 patients at the Service of Rehabilitation and Functional Reeducation, S. Orsola-Malpighi Hospital, Bologna, and 60 patients at the Division of Orthopedics and Traumatology, Hospital of Vignola, Modena.

The patients comprised 41 males and 59 females, aged between 18 and 70 years (mean±standard error of the mean [SEM]: 47.62±1.46 years), and weighing between 48 and 100 kg (mean±SEM: 67.68±1.16 kg). The patients had suffered with LBP for no more than 24 hours before the trial began and had not been previously treated for the LBP episodes. Moreover, all the patients were eperisone-naive.

Efficacy

Treatment with eperisone provided a consistent beneficial analgesic and muscle relaxant activity across all patients. Both spontaneous pain and pain on movement significantly decreased during the study; after 3 and 10 days of treatment, the VAS values of spontaneous pain were reduced by 17% and 46%, respectively, while the values for pain on movement showed a 16% and 44% decrease at the

Table 1. Effects of 10 days of treatment with eperisone 300 mg/day in 100 patients with low back pain of sciatic origin. Results are reported as mean±standard deviation either of a 10-cm visual analog scale (spontaneous pain and pain on movement), a 5-point scale (resistance to passive movements, antalgic rigidity, muscle contracture, spine functional impairment), or centimeters (hand-to-floor distance).

Efficacy variable	Baseline	Day 3	Day 10
Spontaneous pain	6.49±0.12	5.4±0.15*	3.54±0.18‡
Pain on movement	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‡

*P<0.01 vs. baseline.
†P<0.05 vs. baseline.
‡P<0.01 vs. day 3.

same observation times (all P<0.01 for day 3 vs. baseline and day 10 vs. day 3; Table 1). Similarly, after 3 days of treatment, the resistance encountered by the investigator to passive movements, antalgic rigidity and muscle contracture, showed a 18%, 19%, and 19% reduction, respectively, while after 10 days the reductions were 45%, 48%, and 49%, respectively (all P<0.01 for day 3 vs. baseline and day 10 vs. day 3; Table 1).

The score for spine functional impairment was reduced from 2.74 at baseline to 2.24 at day 3 (–18%) (P<0.01), and to 1.54 at day 10 (–44%) (P<0.01 vs. day 3). The "hand-to-floor" distance was significantly reduced from 58.03 cm at baseline, to 48.71 cm at day 3 (–16%; P<0.05), and to 36.55 cm at day 10 (–47%; P<0.01 vs. day 3) (Table 1). Thus, the analgesic and muscle relaxant activities of eperisone resulted in a lower rigidity of the lower back and an improved motility of the patients.

According to the investigators, the efficacy treatment with eperisone was judged to be good-to-excellent in 41% of patients; moderate in 36% of patients; and nil-to-poor in only 23% of patients.

Safety and Tolerability

Only seven adverse drug reactions (ADR) were observed in the 100 treated patients (7%; Table 2). There was one case of mild light-headedness occurring from day 4 to the end of treatment, three cases of light to mild vertigo and/or loss of equilibrium, and two cases of mild somnolence. In all these cases, the ADR was considered by the investigator as probably related to the treatment, but no action was undertaken and no treatment was given for ADR. No ADR was severe enough to require withdrawal from the study, and all resolved spontaneously.

Table 2. Adverse drug reactions (ADRs) observed in 100 patients treated for 10 days with eperisone 300 mg/day.

ADR, *n*	Relationship with eperisone	Treatment withdrawal	ADR resolution	Treatment for ADR given
Light-headedness, 1	Probable	No	Yes	No
Vertigo, 2	Probable	No	Yes	No
Loss of equilibrium, 1	Probable	No	Yes	No
Somnolence, 2	Probable	No	Yes	No
Epigastric pain, 1	Probable	Yes	Yes	No

One patient stopped treatment because of epigastric pain. However, this patient had already manifested a similar symptomatology with other treatments and, therefore, the investigator decided to withdraw the patient from the study. The epigastric pain resolved after stopping treatment with eperisone. There were no abnormal laboratory values in any patient.

DISCUSSION

In our study, eperisone hydrochloride provided a consistent analgesic and muscle relaxant activity across all patients. Although our study was not controlled with placebo or active reference drug, the results we obtained in a relatively large series of patients are consistent with those reported from previous studies.[22-24,26-27]

A randomized, double-blind, clinical trial in patients with cervical spondylosis showed that eperisone had a beneficial activity on pain in arms and shoulders, stiffness, and other symptoms related to cervical spondylosis.[26] In addition, eperisone was found to be comparable to physiotherapy in reducing the spasticity in patients with cerebral stroke,[27] and the 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 those patients treated with other muscle relaxants or anti-inflammatory drugs.[22]

It is worth noting that the analgesic and muscle relaxant effects of eperisone were achieved with a single drug, while it is common practice in rheumatology to combine a pain killer (eg, paracetamol or NSAID) with a muscle relaxant (eg, tramadol, thiocholchicoside, or dantrolene), even using fixed-dose combinations,[14] in order to achieve a satisfactory reduction of both pain and muscle contracture.[28,29]

The spinal muscle contracture underlying LBP is usually complicated by reduced blood flow to the muscles, whose metabolic requirements are further increased by the contraction.[30] It has therefore been suggested that, in some instances, ischemia of the extensor muscles in the lumbar spine may be an aggravating factor leading to LBP.[31] With reference to this, preclinical studies have shown that ep-

erisone exerts several activities on the saphenous artery and veins, thus regulating the blood flow to skeletal muscles of the lower limbs.[32,33] For example, eperisone relaxes the saphenous arteries and veins previously contracted by norepinephrine, serotonin, acetylcholine, potassium, or barium.[32] Moreover, 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.[32] In healthy volunteers, a single dose of eperisone 300 mg has a sympatho-suppressive action and enhances the blood flow in resting skeletal muscles, with no effect on the sympathetic nerve activity in actively contracting muscles, eg, while standing or hand-gripping.[18] Thus, in patients with LBP, eperisone is also expected to improve the blood flow to muscles and improve the hypoxic condition.

Our study mostly focused on evaluating the safety of eperisone. In this regard, the drug was well tolerated, with a low incidence of ADRs (7% of patients) that were of minor clinical relevance. The most commonly reported ADRs were vertigo and somnolence, each occurring in two patients, but they were not severe enough for treatment withdrawal. One case of epigastric pain led to treatment withdrawal, but was not definitely related to eperisone since the patient also reported this symptom while taking previous medications.

The study has limitations that are typical of the noncontrolled design; however, the results we achieved with eperisone are particularly relevant when we consider the following: 1) traditional NSAIDs have a consistently poor GI tolerability; 2) the more recent generations of NSAIDs (eg, selective inhibitors of cyclooxygenase-2 [COX-2]) seem to have a better GI tolerability than traditional NSAIDs, but have been linked with an increased risk of cardiovascular events which led to the voluntary withdrawal of rofecoxib from the market in 2004;[33] 3) NSAIDs have an analgesic and anti-inflammatory activity, but they are devoid of muscle relaxant effects.

To conclude, eperisone hydrochloride provides both analgesic and muscle relaxant effects in patients with LBP. It represents a valuable alternative to traditional centrally acting muscle relaxants, which despite having well-documented therapeutic efficacy have limited use due to CNS adverse events, such as drowsiness.[34-36] Furthermore, eperisone hydrochloride has an improved tolerability profile compared with NSAIDs and COX-2 inhibitors. Together, these suggest that eperisone hydrochloride is a useful alternative for the treatment of LBP.

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