

Efficacy and safety of eperisone in patients with low back pain: a double blind randomized study

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Abstract. – Eperisone hydrochloride (4'-ethyl-2-methyl-3-piperidinopropiophenone hydrochloride) is an antispastic agent used for treatment of diseases characterized by muscle stiffness and pain.

The aim of this research was to investigate the efficacy of eperisone in patients with acute low back pain and spasticity of spinal muscles.

The study design was a randomized, double-blind (double-dummy) study in 160 patients with low back pain and no Rx finding of major spinal diseases, randomly assigned to a treatment with oral eperisone 100 mg three times daily (t.i.d.) or thiocolchicoside 8 mg twice daily (b.i.d.) for 12 consecutive days.

Analgesic activity was evaluated by scoring "spontaneous pain" (VAS) and pain on movement and pressure (4-digit scale), while muscle relaxant activity of the medication was evaluated by means of the "hand-to-floor" distance and the Lasegue's manoeuvre. All the measures were done at the inclusion day and after 3, 7 and 12 days of treatment.

The two medications had comparable analgesic and muscle relaxant efficacy. Spontaneous pain and pain on movement/pressure were significantly reduced by both treatments. Moreover, both eperisone- and thiocolchicoside-treated patients showed a clinically evident muscle relaxation as proved by a progressive reduction in the "hand-to-floor" distance and increase in the articular excursion (Lasegue's manoeuvre). Only 5% of eperisone-treated patients showed minor gastrointestinal side effects, while the incidence of side effects in the thiocolchicoside group was 21.25%. Moreover, in the thiocolchicoside-treated patients also diarrhoea was present, which reached a moderate intensity in some cases.

In conclusions, eperisone represents a valuable and safer alternative to other muscle relaxant agents for treatment of low back pain.

Key Words:

Eperisone hydrochloride, Muscle relaxant, Back pain, Spinal muscle spasticity.

Introduction

Acute low back pain is a leading reason for primary care visits with a generally favourable short-term prognosis. Medications with good evidence of short-term efficacy include non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and centrally active skeletal muscle relaxants. However, evidence is insufficient to identify one medication as offering a clear overall net advantage because of complex tradeoffs between benefits and harms. Therefore, an understanding of mechanisms underlying the pain is essential for any physician who sees and treats patients with acute low back pain¹.

The rationale for use of centrally acting muscle relaxants in back pain is supported by evidence of a spinal muscle spasm in these patients². In fact, nociception usually results from a secondary inflammation and muscle spasm after acute injury of different structures of the spine, such as muscle, tendon, ligament, disc or bone³. In clinical practice, muscle relaxants of short and intermediate duration of action should be preferred, since such agents carry the least risk of residual neuromuscular block⁴.

New muscle relaxants are available today. The centrally acting muscle relaxants reduce the increased muscle tonus and inhibit the hyperactive reflexes by antagonizing the receptor activation coupled to the excitation of motor functions or by acting on the receptors related to inhibitory functions. According to a prospective cohort study, muscle relaxants are used by 49% of patients with low back pain, and by 64% of those who sought care from doctors⁵. In another health examination survey of the U.S. civilian population, an estimated 2 million American adults reported muscle relaxant use. While virtually all

patients (94%) used individual muscle relaxants rather than fixed combination muscle relaxant analgesics, two thirds took an additional prescription analgesic and 85% of users took muscle relaxants for back pain or muscle disorders⁶.

Eperisone hydrochloride (4'-ethyl-2-methyl-3-piperidinopropiophenone hydrochloride) (Figure 1) is widely used for treatment of diseases with associated muscle stiffness and pain. In a trial involving 200 patients with myelopathy or spastic paraparesis, motor disability was significantly improved in 69.5% of patients by oral prednisolone and in 50% by eperisone hydrochloride⁷. In addition, eperisone has been successfully employed in patients suffering from neurogenic bladder due to different reasons⁸.

With specific refer to painful rheumatic conditions, a randomized, double-blind, clinical trial in Asian Far East patients with cervical spondylosis has shown that eperisone (50 mg t.i.d.) has a clear benefit with regard to pain in the nuchal region, back pain, pain in arms and shoulders, stiffness and other symptoms of cervical spondylosis, while the tolerance of the treatment was optimal⁹. Moreover, eperisone was found to be comparable to physiotherapy in reducing the spasticity in patients after stroke and improved the grade of tone¹⁰, and in reducing muscle cramps during chronic liver diseases¹¹.

Since there is no information on the efficacy of eperisone in the treatment of low back pain, we wanted to investigate the compound in patients with acute low back pain due to spasticity of spinal muscles, which is a major reason for medical advise in orthopaedics, in rheumatology and mostly in general medical practice.

Patients and Methods

According to a multicenter, randomized, double-blind and double-dummy, experimental design, a total of 160 patients of both sexes with low back pain, were enrolled in our centre. Pa-

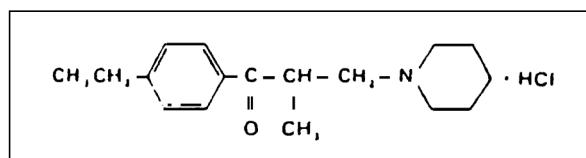


Figure 1. Molecular structure of eperisone hydrochloride.

tients were selected and enrolled among those seeking for medical advise and healthy assistance because of back pain. Main criteria for inclusion were acute or relapsing low back pain, moderate to severe, with no finding of severe spinal diseases at a Rx examination of lumbar spinal tract, such as spondylitis, fractures, cancers, severe arthritis and osteoporosis. Muscular diseases such as myositis, polimyositis, muscular dystrophy and myotonia, were considered criteria for exclusions, as well as any other severe disease affecting the neurological or cardiovascular systems, liver and kidneys.

After the patients have given their consent to taking part into the trial, they have been evaluated by the investigator for the intensity of pain and of muscle contracture. The "spontaneous pain" has been scored by means of a 100-mm visual analogue scale (VAS) reported on a patient's diary card; the patients were asked to score the by ticking off the scale between 0 (no pain) and 100 (unbearable pain); in addition, the pain on movement and the pain on pression of the lumbar tract were also scored by the patients by means of a 4-digit scale (0 = no pain; 1 = minimum; 2 = moderate; 3 = severe).

The muscle contracture has been evaluated by the investigators who asked the patients to bend forward and try to touch the floor with the fingers; the remaining distance between fingers and ground ("hand-to-floor") was measured by means of a rule (cm). Moreover, the Lasegue's manoeuvre was performed in a supine position by stretching the leg and measuring the articular excursion (degrees) the patient was able to stand before inducing pain.

Then, the patients have been randomly assigned to a treatment with eperisone hydrochloride 100 mg three times daily (t.i.d.) or with thiocolchicoside 8 mg twice daily (b.i.d.). The double-blind conditions were guaranteed by the administration of a double placebo (i.e., eperisone placebo in patients treated with thiocolchicoside, and thiocolchicoside placebo in patients treated with eperisone). Medications were given at 6:00 a.m., 2:00 p.m. and 10:00 p.m. As a "rescue" analgesic medication, the patients were allowed to take piroxicam whenever the pain was felt as unbearable. However, they were asked to carefully report the dose and time of intake on a patient diary card. In addition, other non-analgesic medications were allowed during the study for the management of specific diseases, but their dosage had to remain unchanged for all duration of the trial.

Table 1. Demographic characteristics and baseline evaluation of the patients enrolled into the clinical trial. No significant difference between the two groups was observed at the baseline evaluation.

	Eperisone	Thiocolchicoside
N° patients (M/F)	80 (28/52)	80 (21/59)
Age (years)	47.43 ± 10.94	48.49 ± 11.75
Weight (kg)	64.34 ± 9.46	65.36 ± 13.86
Disease		
Lumbar discopathy	20	28
Arthrosis	36	33
No Rx-evident abnormality	24	19

The analgesic activity of the two medications has been evaluated during medical visits performed after 3, 7 and 12 days of treatment, by asking the patients to score again the “spontaneous pain” as well as the “pain on movement” and the “pain on pression”; at the same times, the investigators repeated the evaluation of muscle contracture by means of “hand-to-floor” distance and the Lasegue’s manoeuvre.

At the end of the study, a full lab examination (haematology, 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 4-digit scale (nil; light; moderate; good efficacy).

Demographic and baseline data have been described for each treatment group. The homogeneity of the two experimental groups, with respect to the basal values, was evaluated by means of a Student’s t test for independent data in the case of continuous variables normally distributed; by means of the Mann-Whitney’s U test for independent data in the case of non-parametric variables; and by means of the χ^2 test of the Fischer’s exact test for non-continuous or nominal variables. In the comparison between the two groups of patients, the analysis of variance was used for parametric variables with repeated measures. For the non-continuous variables or variables distributed not normally, the comparisons within treatments at the different observation times were evaluated with the Friedman’s test for multiple comparisons and with the rank test of Wilcoxon when comparing the data with basal values.

Results

A total of 160 patients (49 males and 111 females) were enrolled into the study and random-

ly assigned to a treatment either with eperisone or thiocolchicoside. Among them, 48 patients showed Rx findings of lumbar discopathy and 69 of arthritis, while the Rx exam was negative for major abnormality in the remaining 43. The statistical analysis showed no significant difference between the two groups in terms of demographic data and baseline evaluation (Table I).

The effects of the two medications on spontaneous pain are reported in Figure 2. The VAS score decreased from an average value of 51.73 at the baseline evaluation to 35.93 at the end of the treatment in patients receiving eperisone ($p < 0.001$ vs. basal); the analgesic effect was similar to that observed in patients treated with thiocolchicoside, whose VAS score dropped from 51.89 at baseline to 35.68 after 12 days of treat-

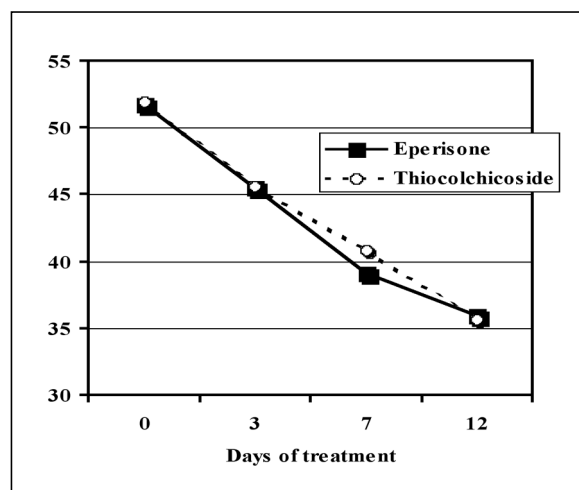


Figure 2. Effects of a 12-day treatment with eperisone 100 mg t.i.d. or thiocolchicoside 8 mg b.i.d. on the spontaneous pain in patients with acute low back pain; pain was evaluated by means of 100-mm VAS. No statistically significant difference was observed between the two groups of patients at any time.

ment ($p < 0.001$ vs. basal). No statistically significant difference was observed between the two groups of treatment.

Similar results were obtained in the evaluation of stimulated pain. The percent of patients who were free from pain on movement in the eperisone-treated group raised from 6.2% at baseline, to 11.5% after 7 days of treatment and to 20.3% at the trial end ($p < 0.001$ vs. basal), while in the thicolchicoside-treated group the percent of pain-free patients increased from 2.5% to 3.8% and 13.8% at the same times ($p < 0.05$ vs. basal). A higher value of pain-free patients was observed in the eperisone- than in the thicolchicoside-treated group at the days 7 and 12 of treatment, although the difference failed to reach the statistical significance (Table II).

The percent of patients who showed to be pain-free at the pain on pressure examination was 13.8% and 13.9% at the baseline examination, respectively, in the eperisone- and thicolchicoside-treated groups; a similar increase in the percent of pain-free patients was observed in the two groups with no statistically significant difference between treatments (Table II).

Both the medications exerted a significant effect on the "hand-to-floor" distance because of the muscle relaxing activity of both eperisone and thicolchicoside, which appeared to be superimposable. The distance decreased from 20.31 cm to 13.86 cm (-31.8%) during treatment with eperisone ($p < 0.001$ vs. basal), and from 19.88 cm to 15.53 cm (-21.9%) during the treatment with thicolchicoside ($p < 0.001$ vs. basal). Although the results achieved with eperisone were slightly better than those with thicolchicoside, no statistically significant difference was observed between the two groups at any time (Figure 3).

The muscle relaxant activity of eperisone is confirmed by the results at the Lasegue's ma-

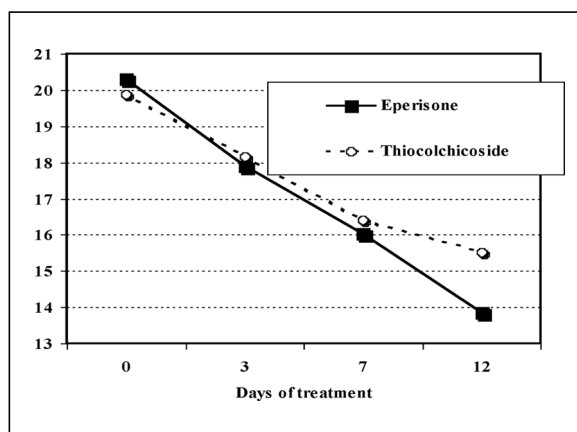


Figure 3. Effects of a 12-day treatment with eperisone 100 mg t.i.d. or thicolchicoside 8 mg b.i.d. on the "hand-to-floor" distance (cm); no statistically significant difference was observed between the two groups of patients at any time

noeuve. The articular excursion that the physician could perform before inducing pain, was on average 77.12° at baseline and increased to 82.43° at the end of the treatment with eperisone ($p < 0.01$ vs. basal), while in the patients treated with thicolchicoside the excursion increased from 74.55° at baseline to 80.19° at the end of the treatment ($p < 0.01$ vs. basal) (Figure 4).

During the trial, 10 out the eighty patients (12.5%) under treatment with eperisone needed piroxicam as a "rescue medication", while the patients treated with thicolchicoside who needed piroxicam because of unbearable pain, were 12 (15.0%); no statistically significant difference between the groups was found.

Finally, the judgment of efficacy by the physicians confirmed the good results achieved with both the medications. The efficacy was scored as "good" for 31% of the eperisone- and

Table II. Evolution of pain on movement and pain on pressure in patients treated with eperisone 100 mg t.i.d. or thicolchicoside 8 mg b.i.d. for 12 consecutive days. Data are expressed as percent of patients free from pain. Statistically significant difference: * $p < 0.05$ vs. thicolchicoside at the same observation time

Treatment		Basal	3 day	7 day	12 day
Pain on movement	Eperisone	6.2%	6.3%	11.5%	20.3%
	Thiocolchicoside	2.5%	2.5%	3.8%	13.8%
Pain on pressure	Eperisone	13.8%	12.7%	15.4%	18.9%
	Thiocolchicoside	13.9%	12.8%	17.7%	22.8%

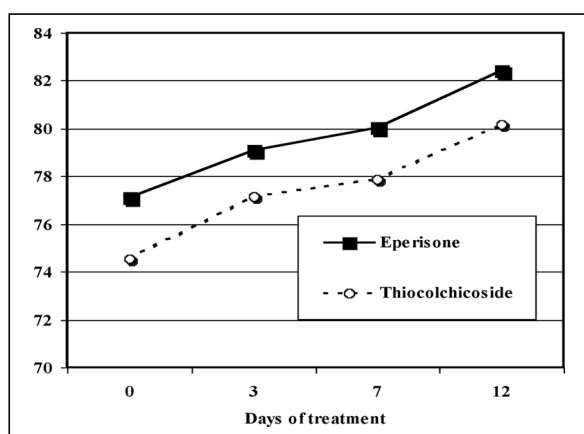


Figure 4. Effects of a 12-day treatment with eperisone 100 mg t.i.d. or thiolcolchicoside 8 mg b.i.d. on the Lasegue's manoeuvre (expressed as degrees); no statistically significant difference was observed between the two groups of patients at any time.

17% of the thiolcolchicoside-treated patients, with similar percentages observed for the other grades ("nil" to "moderate"). No statistically significant difference was observed between the groups (Figure 5).

The analysis of the adverse drug reactions occurring during the trial showed a statistically significant better tolerability in favour of eperisone. In fact, only four patients out of 80 (5.00%) treated with eperisone manifested gastrointestinal side effects during the study, represented by nausea, epigastric discomfort and vomitus, while the number of patients showing side effects in the thiolcolchicoside-treated groups was 17 (21.25%). Moreover, in the thiolcolchicoside-treated patients also diarrhoea was present, which reached a moderate intensity in some cases.

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

Discussion

Our results indicate that eperisone is an effective muscle relaxant agent with potency similar to that of other compounds, such as thiolcolchicoside, which are currently used in the management of low back pain due to a contraction of spinal muscles.

Thiolcolchicoside is a spinal GABA-agonist compound with a consolidated clinical use in the ambulatory treatment of painful contracture of the skeletal muscles; its efficacy in the treatment of acute low-back pain has been demonstrated by several randomized, double-blind, placebo-controlled trials^{12,13}. In these studies, a statistically significant improvement in spontaneous pain was achieved with thiolcolchicoside within one week of treatment, as well as a significant reduction in the hand-to-floor distance and spinal muscle spasm determined by palpation. Also a significant difference was observed in thiolcolchicoside-treated patients in the total analgesic medication (paracetamol) consumption. Other studies have also shown that thiolcolchicoside is at least as effective as tizanidine in patients complaining of acute low back pain, while it appears devoid of any sedative effect in contrast to tizanidine. These data confirm the analgesic and spasmolytic activities observed in our trial in the thiolcolchicoside-treated patients.

Eperisone is a new muscle relaxant compound with a pattern of activities slightly different from that of thiolcolchicoside. Actions of eperisone on several organs have been characterized by an inhibition of mono- and multisynaptic reflexes in relation to the inhibitory action on α - and γ -efferent neurons in the spinal cord and supra-spinal structures¹⁴. In healthy volunteers, eperisone 150 to 300 mg suppressed remarkably the frequency of spontaneous afferent discharges of muscle spindle, and the dynamic and static responses of

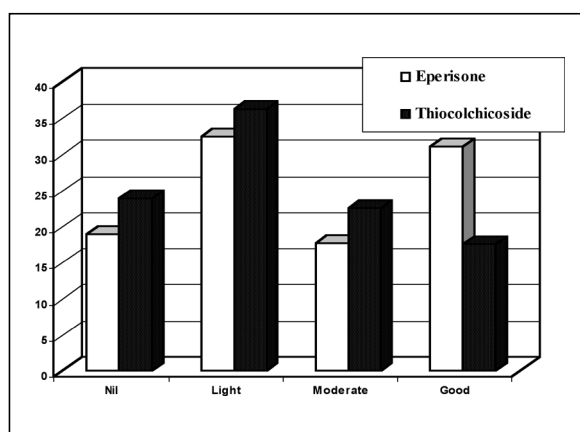


Figure 5. Evaluation by the physician about the efficacy of a 12-day treatment with eperisone 100 mg t.i.d. or thiolcolchicoside 8 mg b.i.d. in patients with back pain; no statistically significant difference was observed between the two groups of patients at any time

muscle spindle to stretch. It also suppressed the dynamic responses of muscle spindle in the de-contraction phase of electrically-induced twitch contractions of the receptor-bearing muscle. Based on these results, it is thought that eperisone suppresses the static and dynamic activities of muscle spindle in man, as a consequence of modifications of descending influences from central structures on the static and dynamic gamma motoneurons that innervate the muscle spindle¹⁵. However, an elevation of the electrical threshold required for generation of the action potential and a Ca²⁺ antagonistic activity in the smooth muscle cells of the basilar artery, have been also observed¹⁶, suggesting an activity of eperisone on local blood flow. In vitro, eperisone attenuated the contractions induced by norepinephrine and serotonin in the arteries and those by clonidine and phenylephrine in the veins. Moreover, eperisone inhibited angiotensin II-induced relaxations, mediated possibly by endogenous prostacyclin. These findings indicate that eperisone may block the postjunctional α_1 - and α_2 -adrenergic, muscarinic, serotonergic receptors and prejunctional α_2 adrenoceptors, and reduce the prostacyclin synthesis via a mechanism other than cyclooxygenase inhibition¹⁷. In healthy volunteers, a single dose of 300 mg of eperisone has shown a sympatho-suppressive action in resting skeletal muscles, without any effect on the microneurographically recorded muscle sympathetic nerve activity in actively contracting muscles, e.g. standing, hand-gripping. The sympatho-suppressive effect of eperisone could be related to the drug-induced increase of blood flow in the resting skeletal muscles¹⁸.

Since the deep tissue pain can be related to reduced muscle blood flow, which comprises the metabolic demand under muscle work¹⁹, it has been suggested that one factor leading to low back pain in some cases might be various degrees of ischemia of the extensor muscles in the lumbar spine²⁰. In these conditions, because of its effects on local blood flow, eperisone could be a valuable and appropriate alternative to other muscle relaxant agents in the treatment of low back pain.

Another consistent advantage of eperisone over thiocolchicoside and other muscle relaxant agents is represented by tolerance; in our experience, the adverse effects were restricted to the gastrointestinal tract, their severity was moderate and the total incidence of side effects was lower than 5% of the treated patients.

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