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ORIGINAL RESEARCH

Phenyramidol in acute conditions of lumbago, integumental pain and musculo-skeletal pain: an open label, noncomparative, multi-center study

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Objective: To assess the safety and efficacy of phenyramidol hydrochloride tablets in acute conditions of lumbago, integumental pain and musculo-skeletal pain.

Methods: This open label, noncomparative, phase IV study recruited adult patients with acute lumbago, integumental pain and musculoskeletal pain who gave written informed consent. Those with elevated liver enzymes, or on analgesics, muscle relaxants, tranquilizers, anti-coagulants, or anti-epileptics were excluded as were pregnant/lactating women. 1 to 2 tablets of 400 mg phenyramidol were given orally 2 to 3 times daily for 3 to 7 days. Safety measures included complete blood count (CBC); liver and renal function tests; electrocardiogram (ECG); global assessments and adverse events. Efficacy measures included change in numerical pain rating scale (NPRS) score and global assessments.

Results: 100 patients completed the study. There were no serious adverse events (SAEs) or deaths. The mean (SEM) reduction in the total white blood cell count [0.27 (0.13) thou/μL, $P < 0.05$] and the mean (SEM) increase in the serum glutamic pyruvic transaminase (SGPT) level [8.78 (3.40) U/L, $P < 0.05$] were not clinically significant at the end of the treatment period. Investigators' assessment of safety was: 80% – excellent, 13% – good, 7% – fair. Tolerability grading by patients was: 53% – excellent, 34% – good, 12% – fair; 1% – poor. Out of the total 12 adverse events (AEs) recorded in 11% patients, 7 were clinical, while 5 were laboratory-related pertaining to increased liver enzymes (5%). The average NPRS score showed an improvement of 68% ($P < 0.0001$). Investigators assessed 89% patients to have clinically meaningful improvement, patients' assessment of efficacy was: excellent – 43%; good – 38%; fair – 15%; poor – 4%.

Conclusion: Phenyramidol is effective and well-tolerated in acute lumbago, musculoskeletal pain and integumental pain when given for up to 7 days. However it should be used with caution in patients with liver disease and with drugs known to cause liver damage.

Keywords: phenyramidol, analgesic, liver enzymes, musculoskeletal pain, NPRS

Introduction

Musculoskeletal disorders are prevalent in millions of people worldwide and are amongst the leading causes of disability and loss of productivity in industrialized countries. Decrease in productivity of as much as 60% and accounting for up to $20 billion has been attributed to musculoskeletal conditions associated with pain and functional limitation.[1,2] Drugs routinely employed in the management of these conditions include simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), opioids and skeletal muscle relaxants. Phenyramidol hydrochloride (Fermenta Biotech Ltd, Maharashtra, India) is a moderately potent, non-narcotic muscle relaxant with concomitant analgesic activity. It works by interrupting the interneuronal and

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polysynaptic reflexes in the spinal cord and brain stem and has been found to be beneficial in musculoskeletal disorders and integumental pain both in oral and injectable forms.

Literature on phenyramidol, although available, is limited. Adverse events (AEs) such as nausea, epigastric distress and pruritus (with and without rash) have been reported in less than 3% of patients, while vomiting, dizziness, drowsiness, sleepiness, burning in mouth, weakness, constipation, heartburn and anorexia have been reported in less than 1% of patients.[3–8] Elevation of liver enzymes with subsequent normalization within a week of stopping the drug was first reported by Koksal et al in a 70-year-old male who had elevated liver enzymes during treatment with phenyramidol[9] and then again by Ergun et al[10] in 7 (18%) out of 38 patients in their double-blind, randomized placebo controlled trial on this drug. In the Ergun study, naproxen sodium was used as rescue medication.[10] Whether the increase in liver enzyme levels was due to phenyramidol or naproxen or an interaction between the two was not discussed. In this open label non-comparator trial, we studied the safety and efficacy of phenyramidol when taken orally for 3 to 7 days by 100 patients with musculoskeletal disorders, in order to contribute more data on this drug.

Methods

Administration

The trial was carried out in the private clinics of 5 physicians. Its plan was reviewed and approved by an independent ethics committee (IEC), ACEAS – an Ahmedabad-based IEC, and good clinical research practice (GCP) recommended by ICH was followed.

Patients

We recruited male and female patients, aged 18 to 60 years, with acute and sub-acute conditions of lumbago, integumental and musculoskeletal pain. We excluded patients with elevated levels of serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum alkaline phosphatase and serum bilirubin; those on analgesics, muscle relaxants, tranquilizers 24 hours before first dose of the IP, tolbutamide, anti-coagulant medication, and anti-epileptics; those with known hypersensitivity to phenyramidol; and pregnant and lactating women. All patients gave written informed consent voluntarily.

Study design

We chose an open label, non-comparator, multi-centre design for this phase IV study of phenyramidol tablets as the main objective was to evaluate the safety of phenyramidol using blood biochemical markers. Hence, randomization and blinding were not done.

Treatments

The dose for each patient was chosen depending on the severity and intensity of pain experienced by him/her. The recommended dosage was 1 to 2 tablets of 400 mg each, 2–3 times daily for 3–7 days. Sensitive patients were prescribed phenyramidol with or after meals. Patients were dispensed the study drug after performing the laboratory tests. Patients whose laboratory results did not satisfy the recruitment criteria, were termed recruitment failures and discontinued from the study.

Outcome measures

Safety variables

Safety testing was done on day 1, at the end of treatment, and at the follow-up visit (if applicable) and included: adverse events (AEs) and serious adverse events (SAEs); laboratory testing for complete blood count; erythrocyte sedimentation rate (ESR); SGOT, SGPT, serum alkaline phosphatase and bilirubin (total, direct, indirect), serum creatinine, serum urea, ECG; investigator global assessment for safety; and patient assessment of tolerability.

Investigator's global assessment of safety – was graded as: Excellent, no adverse events and no abnormal laboratory parameters; Good, mild to moderate adverse events not requiring treatment and/or clinically non-significant changes in laboratory parameters not requiring follow-up; Fair, mild to moderate adverse events requiring treatment and/or clinically significant changes in laboratory parameters requiring follow up; Poor, severe adverse events with or without clinically significant abnormal laboratory parameter values requiring treatment/follow up.

Patient's assessment of tolerability – was graded as: Excellent, no side effects experienced; Good, mild side effects experienced; Fair, moderate side effects experienced; Poor, severe side effects experienced.

Efficacy variables

Numerical pain rating scale (NPRS) score – We asked patients to indicate the intensity of their pain on a numeric pain rating scale (NPRS) with numeric indicators from 0 to 10 where 0 = no pain; 1–2 = mild pain; 3–4 = discomforting moderate pain; 5–7 = distressing severe pain; 8–9 = intensely severe pain and 10 = worst pain imaginable. This scoring had to be done by each patient at baseline (before dose 1)

and every day of the trial during the active treatment period, before consuming the first daily dose.

Patient's global assessment of efficacy: On the last day of the treatment, the patient's global assessment for efficacy was recorded based on his/her perception of the relief experienced from the pain as: Excellent, Good, Fair or Poor.

Investigator's global assessment of efficacy: On the last day of the treatment, we recorded the Investigator's global assessment for efficacy as follows:

Clinically meaningful improvement: improvement in the NPRS score by 2 or more units;

Clinically un-meaningful improvement: either an improvement in the NPRS score by less than 2 units, or no change in the score, or a worsening of the score.[11]

Data analysis

Sample size estimation

Sample size was calculated assuming the null proportion as 0.70 and alternate proportion as 0.85 (expected percentage of patients with normal or abnormal but clinically not significant liver function values). Power of the statistical test was fixed at 90% and 5% level of significance was assumed. Power procedure in SAS 9.2 was used to determine the sample size. The calculated sample size based on the above assumptions was 82. We recruited a total of 136 patients into our study.

Data from the safety and per protocol populations were analyzed. The safety endpoints were analyzed using the safety population, consisting of all patients who had taken at least one dose of the study medication and who satisfied the recruitment criteria. Efficacy endpoints were analyzed using the per protocol (PP) population, consisting of all patients who had completed the study as per the protocol and had recorded their NPRS score in their Patient Diary.

Randomization and blinding

No randomization and blinding was performed as this was an open label, non-comparator study.

Statistical methods

Primary: Normality of data was tested using Shapiro Wilk's test. Paired *t*-test was used for normal data while Wilcoxon's signed rank test was used for non-normal data. Safety analysis also included listing and classification of adverse events; and summarization of global assessments of safety by investigator and patient as counts and percentages.

Secondary: NPRS scores were summarized in terms of counts, percentages and descriptive statistics; change in end of treatment NPRS score from day 1 NPRS score was analyzed using Wilcoxon's signed rank test. Global assessments of Efficacy by investigator and patient were summarized as counts and percentages.

Results

A total of 100 patients completed the study. Therefore, the percentage of patients for each parameter denotes the number of patients.

Patient disposition – Out of the 136 patients we recruited, 100 patients completed the study. In Figure 1 which gives the patient disposition, the 27 patients who were recruitment failures had elevated liver enzymes at baseline. 5 patients were lost to follow up. We excluded 3 patients from analysis due to protocol deviations and 1 patient from the study as his blood sample at baseline was hemolyzed.

Baseline status

There was a preponderance of female patients with a 2:3 male to female ratio with 40 males and 60 females. 54% of the patients were waged while the remaining 46% comprised of housewives and students. An almost equal proportion of patients had either acute lumbago or acute musculoskeletal pain and they accounted for 95% patients in this study. 5% patients had acute integumental pain. Table 1 gives the baseline demography and laboratory values.

Efficacy analysis

Numerical pain rating scale (NPRS) score

Ninety five percent of patients had distressing severe pain to intensely severe pain at baseline (Figure 2).

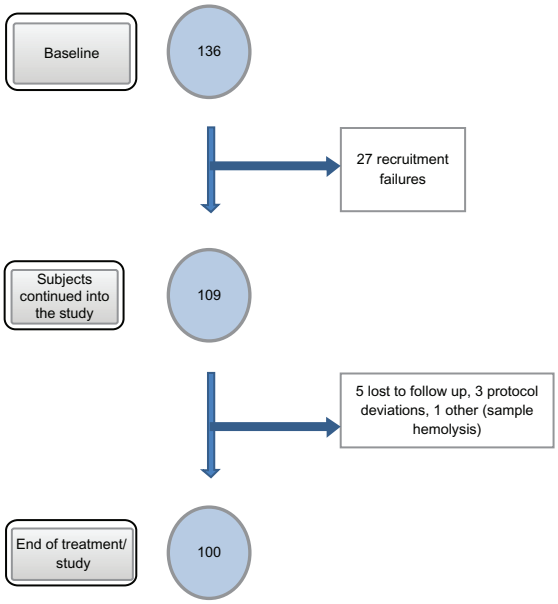

Figure 1 Patient disposition in the study depicting numbers of recruited patients and completers. Out of the 136 patients who were recruited, 100 completed the study.

Table 1 Baseline demographic and laboratory data

Variable	Mean (SEM) in study group (n = 100)
Age (years)	41.66 (1.11)
Duration of indication (days)	56.6 (5.71)
NPRS score	6.75
Total WBC count (thou/μL)	7.57 (0.17)
Hemoglobin (g/dL)	12.98 (0.18)
Platelet count (thou/μL)	273.78 (7.36)
ESR (mm at the end of 1 hr)	19.4 (1.5)
Serum total bilirubin (mg/dL)	0.45 (0.02)
SGOT (U/L)	20.24 (0.49)
SGPT (U/L)	18.88 (0.77)
Alkaline phosphatase (U/L)	74.51 (1.84)
Serum urea (mg/dL)	22.04 (0.73)
Serum creatinine (mg/dL)	0.78 (0.02)

Abbreviations: NPRS, numerical pain rating scale; WBC, white blood cells; ESR, erythrocyte sedimentation rate; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

At the end of treatment, 20% of patients were pain free, 67% had mild to moderate pain, and 13% had distressing pain while no patient had intensely severe pain. The minimum scores on day 1 and end of treatment were 4 and 0 respectively. The maximum scores on day 1 and end of treatment were 9 and 7 respectively. The average NPRS score on day 1 was 6.75 (distressing severe pain category) and average NPRS score on end of treatment was 2.19 (mild category). The percentage improvement from day 1 was approximately 68%.

Global assessment of efficacy by investigator: There was clinically meaningful improvement in 89% of patients while the improvements in 11% of patients were not deemed to be clinically meaningful.

Global assessment of efficacy by patient: Efficacy of the study drug was graded by patients either as excellent (43%), good (38%), fair (15%) or poor (4%).

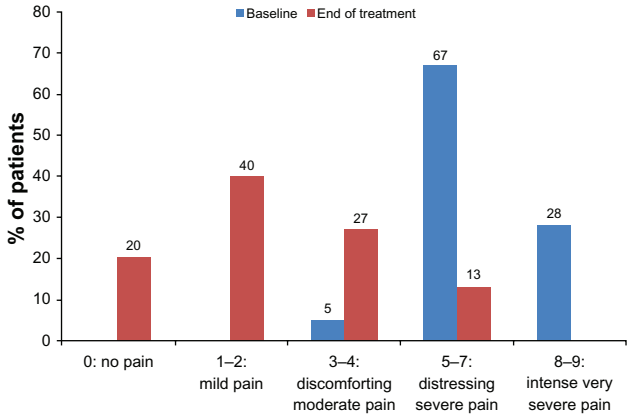

Figure 2 NPRS score at baseline and end of treatment.
Abbreviation: NPRS, numerical pain rating scale.

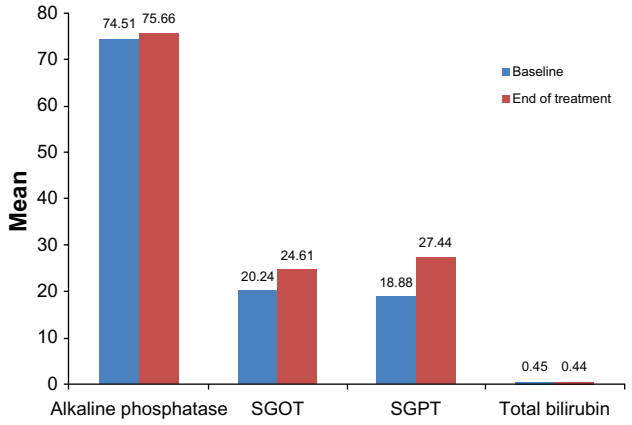

Figure 3 Mean values of liver function tests at baseline and end of treatment.

Safety analysis

There were no statistically significant changes in clinical parameters at the end of the treatment as compared to baseline. In laboratory parameters, the mean total WBC count showed a statistically significant ($P < 0.05$) but clinically insignificant reduction at the end of treatment, while the mean SGPT showed a statistically significant ($P < 0.05$) but clinically insignificant increase in the same period, being well within the normal laboratory range. The changes in the other liver function parameters (Figure 3) and other laboratory parameters were not significant.

Adverse events in the study

There were no serious adverse events (SAEs) or deaths in our study. Out of the 11 patients who had adverse events, 7 were females and 4 were males. A total of 12 adverse events (AEs) were recorded, of which 7 were clinical events while 5 were related to raised liver enzyme levels. Maximally, a 6-fold increase in SGOT and SGPT levels and a 1.5-fold increase in alkaline phosphatase levels were reported. All AEs resolved without sequelae and all raised liver function parameters returned to normal laboratory levels within 7 days of stopping the drug. Return of liver enzymes levels to normal/clinically non significant levels was also noted for the 2 patients who reported late for their follow up visit. None of the patients had to be treated except 1 patient who was given a cefpodoxime proxetil tablets for pharyngitis, which was not considered to be related to phenyramidol. All other AEs were deemed to be related possibly, probably or definitely to phenyramidol. The adverse events occurred at doses ranging from 4000 to 8400 mg. Table 2 lists the frequency of adverse events that occurred.

The body system-wise distribution of AEs showed 1 AE in ENT (Ear, Nose and Throat), 4 in CNS (Central Nervous System), 2 in GI (Gastrointestinal) and 5 in Hepatobiliary.

Table 2 Frequency of adverse events

Adverse event	Body system affected	Frequency (%)
Loose motion	GI	1
Pharyngitis (throat infection)	ENT	1
Drowsiness	CNS	1
Nausea	GI	1
Dizziness	CNS	2
Headache	CNS	1
Increase in SGOT/SGPT/ alkaline phosphatase levels at the end of treatment	Hepatobiliary	5

Abbreviations: GI, gastrointestinal; ENT, ear, nose and throat; CNS, central nervous system; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

We prescribed the study drug tailored to each patient's need based on his/her pain intensity at baseline. The frequency of patients in each dose group along with the AE frequency in each group has been tabulated in Table 3.

The AEs that occurred in this study did not show an increase in the incidence of untoward effects with increasing dose or higher dosing frequency. Hence we were unable to determine if these factors could play a role in AE causation.

Global assessment of safety by investigator – In terms of safety, we graded the drug as excellent in 80% patients, as good in 13% and fair in 7%, based upon the clinical and laboratory adverse events experienced by them.

Global assessment of tolerability by patient – Tolerability was assessed by 53% patients as excellent, by 34% as good, by 12% as fair while 1% assigned the drug poor tolerability.

Discussion

Upon analyzing the clinical and laboratory safety parameters in this study, phenyramidol demonstrated good safety and tolerability.

Table 3 Frequency of patients with adverse events in each dose group

S. No.	Dose group	Frequency (%)	No. of patients with AE
1	1 bd × 3 days	4 (4)	0
2	1 bd × 5 days	20 (20)	3
3	1 bd × 6 days	3 (3)	3
4	1 bd × 7 days	17 (17)	0
5	[1 bd × 4 days] + [2 bd × 2 days]	1 (1)	0
6	[1 bd × 5 days] + [1 tds × 2 days]	6 (6)	1
7	1 tds × 5 days	3 (3)	1
8	1 tds × 7 days	45 (45)	2
9	[2 tds × 2 days] + [1 tds × 3 days]	1 (1)	1
	Total	100 (100)	11

The adverse events due to phenyramidol pertained basically to the gastro-intestinal, hepatobiliary and central nervous systems and are in concordance with the literature available on this drug. These events are comparable to the side effects that occur in these body systems with the use of other drugs in musculoskeletal disorders. Liver damage – from elevated transaminases to fulminant hepatic failure – has been reported with NSAIDs[12–14] as well as with tizanidine,[15,16] acetaminophen,[17] chlorzoxazone[18] and oxymorphone.[19] CNS side effects of some of these drugs include headache, drowsiness and dizziness.[15,16,18–22]

The mean changes in SGPT values and total WBC count, while statistically significant, were clinically not relevant, being within normal laboratory ranges. Thus, the findings of this study reinforce the existing safety literature on phenyramidol without throwing up any fresh safety issues.

Efficacy data on phenyramidol compares well with that on oral oxycodone wherein patients had a significant decrease (57%) in pain intensity as recorded during the first week of therapy (decrease in numerical rating scale – NRS score from 7.85 ± 1.4 to 3.35 ± 1.8; $P < 0.00001$) and an overall reduction of 72.3% in NRS pain score from baseline to the end of the study, spanning 28 days which is comparable to the 68% improvement in NRS scores in our study.[23]

The NPRS has been established as valid, reliable and appropriate for clinical practice. In her study, Williamson stated that it is sensitive and able to generate statistically analyzable data for audit purposes.[24] Salaffi et al found that a numerical rating scale (NRS) change score of –2.0 and a percent change score of –33.0% were best associated with the concept of "much better" improvement.[25] Similarly, in a cohort study of patients with low back pain (LBP) receiving physical therapy, Childs et al concluded that clinicians can be confident that a 2-point change on the NPRS represents clinically meaningful change that exceeds the bounds of measurement error.[26] Hence, we have used a cut-off level of 2 or more units of improvement in the NPRS score as a measure of clinically meaningful improvement in our study.

Efficacy analysis using global assessments by the investigator and patient showed good results. However, some patients felt that the pain relieving ability of the drug was fair to poor in spite of having clinically meaningful improvement. This could be in part due to the patients' expectations regarding the performance of the drug. Hence patients expecting complete pain relief but getting only partial improvement could have assigned a lower grade of efficacy while the investigator would have assigned a grade of clinically meaningful improvement based upon an improvement of NPRS scores by

2 or more units. Nevertheless, the improvement in NPRS and global assessment efficacy scores underline phenyramidol's analgesic effects.

We included patients with concomitant health disorders so that our study population represented patients seen in day to day clinical practice, thus allowing application of our study findings in routine practice. Phenyramidol offers the modalities of skeletal muscle relaxation with concomitant analgesia with an efficacy and safety profile that is comparable with other drugs routinely employed in the management of acute painful musculoskeletal disorders. Hence, patients with such complaints can benefit from using phenyramidol without having to monitor their liver enzymes, provided it is prescribed at the dose and for the duration mentioned in this study. Monitoring liver enzyme levels, however, is advised in patients with existing liver pathology or on other drugs known to cause liver cell injury.

The limitation of our study lies in the absence of a placebo or active comparator being used as a control when the secondary (efficacy) outcome of pain relief, being a subjective measure, is prone to the placebo effect. This could have introduced an element of bias in the study. Although we calculated the sample size for our study based upon data from previous studies on this drug, it might be useful to study phenyramidol in a larger population, given the high incidence and prevalence of the study indications.

Some questions which this study did not answer pertain to the relative safety and efficacy of phenyramidol in a head to head comparison with other drugs such as chlorzoxazone, tizanidine or opioid analgesics. Similarly, the effect of phenyramidol when given for a longer duration, as might be required in patients with chronic pain, needs to be studied. Other dosage forms such as injectable phenyramidol also need to be evaluated for use in hospitalized patients who have to be put on a nil-by-mouth regimen.

To conclude, phenyramidol is an efficacious and well tolerated analgesic in the treatment of the acute conditions of lumbago, acute musculoskeletal pain and integumental pain when given at a dose of 1–2 tablets, 2–3 times a day for duration of 3–7 days. However its use in patients with liver disease or with other drugs known to cause liver cell injury is cautioned and monitoring of liver enzymes is warranted.

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Disclosure

Hitesh Shah works for Fermenta Biotech Ltd. which sponsored the study; Aliya Shakeel works as a medical writer with the CRO.

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