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The efficacy, safety, and pharmacokinetics of intramuscular and oral phenyramidol in patients with low back pain in an emergency department

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Aim: To compare the efficacy, safety, and pharmacokinetics of oral and intramuscular (i.m.) phenyramidol in patients with low back pain.

Materials and methods: Consecutive patients with low back pain were recruited and randomized (5:3) to treatment with either 800 mg oral or i.m. phenyramidol. Pain was assessed by visual analogue scale every 30 min for 2 h. Blood samples were drawn at baseline and every 15 min for 2 h. A 5-point verbal global evaluation scale was performed by both patients and physicians. In addition, the need for rescue analgesics after 2 h was noted. After the acute phase, patients were re-randomized (5:3) to receive either a placebo tablet or a 400 mg phenyramidol tablet 3 times a day for 7 days. Efficacy of the long term treatment was measured by the evaluation of both patients and physicians (with a 5-point verbal global evaluation scale) and by the daily amount of naproxen sodium consumed as the rescue analgesic drug.

Results: Seventy-two patients (45F/27M) had a marked improvement in pain scores, with no significant difference between the groups. Sixty-one (39F/22M) patients completed the second phase, in which no difference in any parameter was noted. Seven of 38 patients in phenyramidol group had elevated liver enzymes at the end of the chronic treatment phase which normalized after 1 week. Only the T_{max} pharmacokinetic parameter (C_{max}, T_{max}, $t_{½}$, and AUC) was significantly but slightly different between the groups.

Conclusion: Liver enzymes should be monitored in patients taking repeated dose of phenyramidol and should not be used in combination with analgesics bearing hepatotoxicity potential, such as paracetamol.

Key words: Phenyramidol, low back pain, pharmacokinetics, emergency department

Acil servise bel ağrısı şikayeti ile başvuran hastalarda oral ve i.m. feniramidolün etkililiği, güvenliliği ve farmakokinetik özellikleri

Amaç: Bel ağrısı olan hastalarda oral ve kas içine (i.m.) feniramidol uygulamasının etkililiği, güvenliliği ve farmakokinetik parametrelerinin karşılaştırılması.

Yöntem ve gereç: Bel ağrısı nedeniyle başvuran ardışık hastalar, 800 mg oral veya i.m. feniramidol tedavisi için randomize edilerek (5:3) çalışmaya dahil edildi. Ağrı, iki saat boyunca her 30 dakikada bir görsel analog ölçek ile değerlendirildi. Kan örnekleri ilaç uygulamadan hemen önce ve iki saat boyunca her onbeş dakikada bir alındı. Etkililik, hasta ve doktorun değerlendirmesi (beş noktalı genel değerlendirme ölçeği ile) ve ilave olarak iki saat sonunda ağrı kesici gereksinimi ile tespit edildi. Akut fazın ardından hastalar 7 gün boyunca plasebo veya 400 mg feniramidol (günde 3 kez) almak üzere yeniden randomize edildi (5:3). Kronik tedavinin etkililiği hasta ve doktorun değerlendirmesi (beş noktalı genel değerlendirme ölçeği ile) ve kurtarıcı ilaç olarak kullanılan naproksen sodyumun günlük kullanım miktarı ile değerlendirildi.

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Bulgular: Yetmişiki (45K/27E) hastanın ağrısı gruplar arasında fark olmaksızın belirgin bir biçimde azaldı. Altmışbir (39K/22E) hasta çalışmanın ikinci bölümünü (değerlendirilen parametrelerde gruplar arasında fark olmaksızın) tamamladı. Feniramidol tedavi grubunda olan 38 hastanın yedisinde karaciğer enzimlerinde bir haftalık takip ardından normal düzeye dönen artış tespit edildi. Farmakokinetik parametrelerden (C_{max}, T_{max}, $t_{½}$ and AUC) yalnız T_{max} süresinde istatistiksel olarak anlamlı ancak küçük fark belirlendi.

Sonuç: Uzun süreli feniramidol kullanan hastaların karaciğer enzimleri izlenmeli ve parasetamol gibi karaciğer toksisitesi olan ağrı kesiciler ile birlikte uygulanmamalıdır.

Anahtar sözcükler: Feniramidol, bel ağrısı, farmakokinetik, acil servis

Introduction

Low back pain (LBP) is a very common medical condition, occurring in up to 90% of all adults at least once in their lives. Although most cases resolve spontaneously within a few days to weeks without sequelae, loss of productivity in the workplace can be significant (1). Many patients with acute low back pain present to the emergency department (ED) for care. Many options and routes for treatment with analgesics and/or skeletal muscle relaxant agents exist (2,3).

Phenyramidol is an aminopyridine derivative with skeletal muscle relaxant properties. It was introduced as an oral agent into clinical practice in 1960 and is still available as a tablet for oral use and as an ampoule for intramuscular (i.m.) use (4). Although it has been in use for over 45 years, limited data exist about its efficacy and safety. To date, only 3 comparative clinical trials measuring its efficacy have been performed (5-7). Other reports have found phenyramidol to be beneficial in premenstrual syndrome and various musculoskeletal conditions (8-9). Koksal et al. reported a patient who had elevated liver enzymes during treatment with phenyramidol, probably an adverse-effect of the medication (10).

In the 2 phases of this study, we investigated the efficacy and safety of phenyramidol in patients presenting to the ED with LBP. In the first phase, oral and i.m. forms of phenyramidol were compared during the first 2 hours of the patient's ED stay. In the second phase, the efficacy and safety of oral phenyramidol were compared with placebo in the same patients after they were discharged home from the ED. Finally, pharmacokinetic parameters (C_{max}, T_{max}, $t_{½}$ and AUC) after oral and i.m. administration were measured and compared.

Material and methods

This double-blind, randomized study was conducted in the ED of our tertiary-care university hospital. The study was performed in accordance with the Declaration of Helsinki and with local regulations on the use of therapeutic agents in patients. The protocol was approved by the local ethics committee of Ankara University, Faculty of Medicine, and conducted according to the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines. All patients provided written informed consent before enrolling in the study.

Subjects and inclusion criteria

Adult patients, 18-55 years old, with a primary complaint of LBP and admitting to the ED of our tertiary university hospital were evaluated for inclusion in the study. Blood was taken from the patients for the measurement of AST, ALT, BUN, and creatinine levels.

Exclusion criteria

Patients were excluded if they had abnormal levels of AST, ALT, BUN, or creatinine, pre-treatment with any skeletal muscle relaxants or analgesic drug in the previous 12 h, hypersensitivity or other contraindications to NSAIDs or skeletal muscle relaxants, any pre-existing disease or conditions, or any concomitant therapy that may interfere with the mode of action of the study drugs. Patients with any red flags, which might indicate serious spinal, sciatic nerve, pelvic or abdominal pathology, were also excluded, as were those who we thought would not comply with the study protocol. Breast-feeding women and women with proven or assumed pregnancy were also excluded from the study.

Study design

Patients and assessors were blinded to treatment as follows. All tablets and i.m. forms of phenyramidol and placebo were in original packaging. Only the serial number on each package differed from one another, and the contents were known only by one of the authors (H.E.) and kept in a big package, which was marked as "A" or "B" to preserve the blindness of investigators to the study groups. A randomization scheme was prepared and consecutive patients received their treatment according to protocol as "A" or "B" for both phases of the study. In the first phase, the efficacy, safety, and pharmacokinetics of oral and i.m. 800 mg phenyramidol were evaluated and compared during a 2-h period in the ED. In the second phase, the efficacy and safety of phenyramidol were compared with placebo over a 1-week period.

Acute phase

After an initial screening (122 patients were screened and 59% of them were enrolled), 45 patients were randomized (5:3) to receive oral (2 × 400 mg sugar-coated tablets) and 27 patients to receive i.m. (800 mg ampoule) phenyramidol. To preserve the blindness, the i.m. treatment group received identical placebo tablets and the oral treatment group the same amount (3 mL) of i.m. 0.9% NaCl. Both tablets and ampoules were donated by the Dr. F. Frik Pharmaceutical Company, the only producer of phenyramidol in Turkey.

Pain intensity was assessed by patients using a visual analogue scale (a 100 mm-long line, marked with numbers from 0 to 10) before and every 30 min after treatment for 2 h. At the same time, blood samples were drawn into K3 EDTA tubes just before ingestion or injection of phenyramidol and every 15 min for 2 h. After the 2-h observation period, patients were asked if they need any additional analgesics. At the 2-h point, patients and physicians reported pain relief as not effective, slightly effective, mildly effective, effective, or very effective, on a 5-point global evaluation scale. Blood samples were immediately centrifuged and plasma was stored at -80 °C in the dark. For analysis, samples were shipped in packages in dry ice to India and stored again at -80 °C in the dark until analyzed. The pharmacokinetic parameters, time to reach maximum concentration (t_{max}), maximum concentration of phenyramidol (C_{max}), area under the curve (AUC) elimination half-life, were calculated after fitting to the data.

Chronic phase

After the acute phase, same patients were re-randomized to receive placebo or 400 mg of phenyramidol 3 times a day for 7 days. All patients also received 20 tablets (275 mg/tablet) of naproxen sodium as rescue medication. They were instructed to take this rescue medication in case their pain was not relieved by their study medication and not to take more than 4 tablets a day. The patients were also told that they could ask for and receive another box of rescue medicine in case they finished the 20-tablet box. Patients kept a diary to record medications they had taken and the time of ingestion. Efficacy of long term treatment was measured by patients' and physicians' global evaluation score (5 point verbal scale) and daily consumption of rescue analgesia (naproxen sodium) during the 7-day period. On day 7, a blood sample was drawn 8 h after the last dose of phenyramidol for the evaluation of the steady state concentration (C_{ss}) of phenyramidol and levels of hepatic enzymes.

Analytical assay for plasma phenyramidol levels

Phenyramidol analysis was performed using liquid chromatography and mass detection by the Drug Monitoring Research Institute PVT LT Rabale, Navi Mumbai, India. Limits of detection were between 50 and 3.474 ng/mL. Biochemical analysis was as follows: each plasma sample (0.5 mL) was mixed with 20 µL metoprolol (1040 µg/mL) as an internal standard, buffered with 200 µL of 5 mM dipotassium hydrogen phosphate and extracted with 4 mL of methyl tertiary butyl ether (MTBE). After centrifuging for 2 min, 3 mL of the organic layer was transferred into an evaporating tube and evaporated under a nitrogen stream at 45 °C. The residue was reconstituted with 1000 µL of the mobile phase, and an aliquot of 2 µL was directly injected onto the HPLC column.

The HPLC system consisted of a Hypurity C18 (50 × 4.6 mm, 5 µ) column, MRM Positive detector, acetonitrile + 2 mM ammonium acetate [pH: 3.5] (v/v: 90:10) mobile phase, 0.90 mL/min flow rate with 3-way splitting. Retention times for phenyramidol and metoprolol were 0.65 ± 1 min and 1.5 ± 1 min, respectively, with a run time of 3 min.

Sample Size Estimation/Power Analysis

Sample size was estimated using the chronic phase primary parameter "average daily analgesic consumption". A decrease of daily 0.5 tablet consumption was chosen by the authors as clinically significant. This is an effect size of 0.5 with a SD ± 0.5, 5/3 randomization ratio, and a power of 95%. According to this calculation using the NCSS/PASS 2002 program, 57 (21/36) subjects were needed to detect a 0.5 tablet difference between the groups. We have estimated a 20% of drop-out rate after the initial acute phase. Therefore, the above calculated sample size was multiplied with 1.2 and corrected to be dividable to 8 (total 72 patients). The power analysis for the primary endpoint "VAS score" in the acute phase were calculated for a 10 mm ± 10 SD and 5/3 randomization ratio and found 98%.

Statistical Analysis

All data were presented as mean (±SEM), median, or percent. Groups were compared using unpaired Student's t test, Mann-Whitney U test, chi-square test, or ANOVA for repeated measures as appropriate.

Results

Acute phase

Seventy-two patients (45F/27M) completed the acute phase of the study. The i.m. (n = 27) and oral (n = 45) treatment groups were not significantly different in terms of gender (59% vs. 64% female, respectively) or mean age (36 ± 10 years vs. 38 ± 10 years, respectively). Three (11%) patients in the i.m. treatment group and 5 (11%) in the oral treatment group (n.s.) reported headache, emesis, dry mouth, or dizziness, which were all mild to moderate and did not require any treatment. Regarding the efficacy of the treatment, pain intensity decreased in both groups, with no significant difference between the groups at any time point (Figure 1). The f (time × group interaction) and P values were found 0.657 and 0.624, respectively. Rescue analgesics were needed after the 2-h observation period in 4 (15%) patients in the i.m. and 4 (9%) patients in the oral treatment group (n.s.). The median global evaluation scores of both patients and physicians were 'mildly effective' for both treatment groups.

Blood samples for pharmacokinetic evaluation were measured from 23 and 22 patients in the i.m. and oral treatment groups, respectively. Only the T_{max} value significantly but slightly differed between the groups. The remaining pharmacokinetic parameters (C_{max}, $t_{½}$, and AUC) were not significantly different between the administration routes. Five patients in each group demonstrated a second peak, which was more distinctive in the oral treatment group (Figure 2). Phenyramidol C_{ss} levels measured 8 h after the last dose of phenyramidol were mostly under the detection limit (only 5 out of 21 patients had a measurable plasma level of phenyramidol; mean of these 5 patients: 336 ± 99 ng/mL).

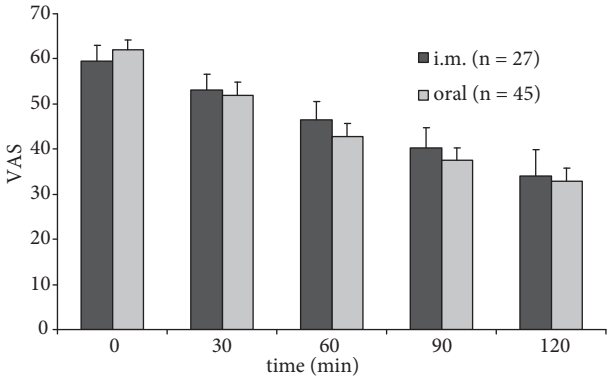

Figure 1. Pain intensity, as measured with a visual analogue scale (0-100 mm) after intramuscular or oral administration of 800 mg phenyramidol in patients with nonspecific low back pain, reported as mean ± SEM. Time 0 indicates pain intensity at baseline, just before administration of the study agent.

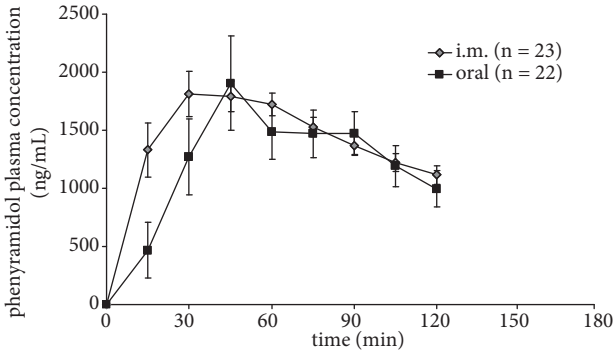

Figure 2. Time course of plasma phenyramidol concentrations in patients with nonspecific low back pain after receiving a single 800 mg dose of phenyramidol by intramuscular or oral route.

Chronic phase

Although all patients agreed to continue in the second phase of the study, only 61 (39F/22M) patients completed this phase. Two from the placebo group and 4 from the oral treatment group out of 11 patients did not show up and 2 from the placebo and 3 from the oral treatment group had protocol violations (missing doses in 4, and ingestion of disallowed medications in 1). Patients in the phenyramidol (n = 38) and placebo (n = 23) groups were not significantly different in terms of gender (68% and 56% female, respectively) or mean age (37±10 years and 38±11 years, respectively). Rescue analgesics were used less than 1 tablet/day and did not differ significantly between groups. The median patient and physician global evaluation scores were 'mildly effective' for both treatment groups (n.s.). Although not significantly different, more adverse effects occurred in the treatment group [32%, emesis, weakness, abdominal discomfort (n = 2), dizziness (n = 3), and elevated liver enzymes (n = 7)] compared to the placebo group (17%, headache, dry mouth, itching, and loss of sense of taste), but none of the adverse effects required treatment. At the end of the 1-week treatment period, 7 out of 38 patients in the phenyramidol treatment group and none in the placebo group had elevated liver enzymes. These 7 patients were checked again 1 week later, and AST and ALT levels returned to normal values in all patients.

Discussion

The aim of this study was to evaluate the efficacy, safety, and pharmacokinetics of phenyramidol when given via the oral or i.m. route. Both forms have almost the same pharmacokinetic characteristics, which agree with similar efficacy and safety of both forms of the drug in this patient population. This clinical trial is the first to compare the efficacy and safety of phenyramidol administered via 2 different routes, and we found no difference between i.m. and oral phenyramidol when given to patients with non-specific LBP in the ED. The analgesics and muscle relaxants used in many LBP patients in the ED should be cost-effective and minimally invasive. Based on the efficacy and pharmacokinetics data from this study, oral administration of phenyramidol would be a better choice if no contraindications exist.

In clinical practice, if the initial treatment for a condition is successful, many physicians continue the same treatment during the patient's outpatient course. For this reason, we re-randomized the ED patients to receive oral phenyramidol or placebo for an additional week to investigate its efficacy and safety over a longer period of time. In contrast to our expectations, no significant differences between the groups were found. However, it should be noted that the present study was limited to a specific patient population, those with low back pain in the ED who had no serious spinal pathology. In our study we have evaluated the daily analgesic consumption as the primary parameter for the second phase. Additionally, global evaluation of both patients and physicians were involved as the second efficacy parameter. It may be suggested that there are other parameters, such as evaluating the muscle spasm or physical function measures as efficacy parameters. However, due to our clinical setting it was not possible to evaluate all the patients by a single physician.

Even though the adverse effects were not serious and did not require treatment, a significant proportion (18%) of patients treated with phenyramidol for 1 week developed elevations in liver enzymes. This finding is important when considering prescribing phenyramidol to patients who have concomitant potentially hepatotoxic treatments or previous hepatic diseases. Fortunately in this study, high liver enzyme levels in all 7 patients returned to normal within 1 week after stopping the medication.

It was remarkable that the first case of elevated liver enzymes that developed during treatment with oral phenyramidol, a product that has been on the market for over 40 years, was reported in 2003 (10). In that case, the 70-year-old patient's liver enzymes returned to normal after discontinuation of phenyramidol, as in our patients. This relatively new finding of elevated liver enzymes after phenyramidol use may be explained in several ways: compliance with a prescribed regimen of analgesics may be poor in situations that often improve over time, phenyramidol may be used in many individuals with pain but who have no underlying liver disease, and the mild, asymptomatic elevations in liver enzymes associated with phenyramidol use resolve without complications when the patient stops taking the drug.

In conclusion, oral and i.m. phenyramidol did not differ significantly in their pain-relieving effects in low back pain patients during their initial 2-h treatment in the ED. After 1 week of outpatient therapy with phenyramidol, a significant proportion of patients developed asymptomatic elevations in liver enzymes, which resolved with discontinuation of the drug. Surveys regarding the adverse effects of phenyramidol should be performed in a variety of commonly encountered patient settings to define its patient safety profile.

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