The efficacy and safety of dipyrone (Novalgin®) tablets in the treatment of acute migraine attacks: a double-blind, cross-over, randomized, placebo-controlled, multi-center study

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Summary
Dipyrone, an effective analgesic drug, is widely used in the management of headache. However, few studies have evaluated its efficacy and safety in migraine. We aimed to assess the efficacy and safety of 1 g dipyrone (Novalgin®, two 500 mg tablets) on pain and related symptoms in acute migraine attacks with or without aura in a double-blind, cross-over, randomized, placebo-controlled, multi-center study design.

Seventy-three migraine with or without aura patients, diagnosed according to the IHS criteria, were randomized to receive dipyrone (for 2 attacks) and placebo (for 1 attack). Pain intensity was measured on a four-point verbal pain scale before and 1, 2, 4 and 24 hours after drug intake. Significant improvement of pain was achieved with dipyrone compared to placebo at all time points measured. Both patient and physician evaluations were significantly in favor of dipyrone. Side effects were few and trivial in both groups.

We conclude that dipyrone is an effective, safe and cost-effective option in acute migraine management.

KEY WORDS: acute treatment, dipyrone, migraine, placebo.

Introduction
Migraine, with a lifetime prevalence of at least 18% and a world population ratio of 12% (1,2), is one of the most common types of primary headache. According to a study by the World Health Organization (WHO), migraine – along with quadriplegia, psychosis, and dementia – is one of the most disabling chronic disorders (3). In the European Union alone, 1 million people have an acute migraine attack every day, and 100 million work and/or school days are lost through migraine. The high intensity of migraine pain, the associated multi-organ symptoms, and the impact of the headache on quality of life all increase the importance of effective acute treatment of migraine attacks. The influence of migraine on quality of life in Turkish patients was also investigated recently, and it was found that patients who suffer from migraine or tension-type headaches had a poorer quality of life compared to the general population (4).

Given the high numbers cited above, physicians, patients and health care providers are inevitably faced with pharmacoeconomic considerations: the cost of dipyrone is relatively low compared with that of most of the non-steroidal anti-inflammatory drugs (NSAIDs), and the possibly favorable economic impact of the drug needs to be analyzed in appropriate pharmacoeconomic studies.

Many NSAIDs have been tested for their effectiveness in the treatment of acute migraine attacks, and some were shown to be superior to placebo (5,6). The mechanism of action of NSAIDs in migraine treatment has been attributed to their analgesic and anti-inflammatory properties, which inhibit the synthesis of prostaglandins (PGs) and prevent thrombocyte aggregation, which may play a role in the pathogenesis of migraine (7-11). Dipyrone (metamizol) has been widely used in clinical practice since 1922 for its non-narcotic analgesic action (12). It is an effective analgesic, antipyretic and anti-spasmodic drug, available in oral, rectal and injectable forms. Some anti-inflammatory properties have also been recognized in pharmacological models, but it is still unclear whether this has any clinical relevance (12). Dipyrone is indicated for severe and moderate pain, particularly pain associated with smooth muscle spasm, such as gastrointestinal pain, biliary or urinary tract col...
ic. It is also useful for the treatment of fever that is refractory to other treatments (13). The strong analgesic effect of dipyrone, as well as its relatively innocuous adverse effect spectrum, availability in parenteral formulation, and low cost make it the first-choice drug for different types of pain and headache in many countries, for both pediatric and adult patients (13-15). Despite these well-known beneficial effects, few randomized clinical trials have investigated the role of dipyrone in headache management.

In this study, we aimed to assess the efficacy and safety of 1 g dipyrone (Novalgin® 500 mg tablets) on pain in acute migraine attacks, both with and without aura.

Materials and Methods

This double-blind, cross-over, randomized, placebo-controlled, multi-center study involving seventy-three migraine with or without aura patients was conducted in five centers (university headache units) in Turkey. The study was performed in accordance with the guidelines of the International Headache Society (IHS), the Declaration of Helsinki, and with local laws and regulations on the use of new and approved therapeutic agents in patients. The protocol was approved by the local ethics committees of the participating centers, and conducted according to the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines. All patients provided written informed consent before their enrollment in the study.

Subjects and inclusion criteria

Seventy-three adult male (n=14) and female (n=59) outpatients, aged 18-65 years, who had migraine headache with or without aura, diagnosed according to the 1988 IHS criteria (16), were enrolled in the study. Eligible subjects had a history of a minimum of 1 to a maximum of 6 moderate or severe migraine attacks per month.

Exclusion criteria

Patients were excluded if they presented hypersensitivity to NSAIDs or dipyrone, concomitant use of dipyrone or any other NSAID (history of peptic ulcer, gastrointestinal bleeding, raised liver enzymes, peripheral edema and acute renal failure), a history of nasal polyps, angioedema, urticaria, or reactive bronchospasm following treatment with aspirin or other NSAIDs. Patients with chronic drug use or drug abuse or under continuous treatment with prescription doses of analgesics, NSAIDs, lithium, carbamazepin, tranquilizers, and anticoagulants were also excluded. Breastfeeding women and women with confirmed or suspected pregnancy were also prohibited from entering the study.

Study design

A total of four visits was scheduled for each patient. At the preliminary visit, patients were examined in detail to ascertain their eligibility to participate in the study. At the three subsequent visits, eligible patients were twice to be given dipyrone (on each occasion 1 g in two 500 mg tablets) to treat two attacks, and once to be given placebo (two tablets) to treat one attack. The study drugs were assigned in a random order according to the randomization schema. Randomization was designed in blocks of 15 patients for each center. The investigators received the randomization list and the drugs, coded A-B-C. The randomization was organized in such a way as to result in an equal number of patients receiving placebo for the first, second and third attacks. Each center recruited their eligible consecutive patients according to this schema. To preserve blinding, placebo tablets were used that matched all but the active ingredient of the Novalgin® tablets. The drugs were sent to the centers in three separate boxes labeled “A”, “B”, and “C”. Because the placebo and the active drug were obtained from the same company (Aventis Pharma, Istanbul, Turkey), it was not possible to distinguish between the different drugs.

Therefore, in each patient, a total of three migraine attacks – there had to be an interval of at least 72 hours between subsequent attacks – were to be evaluated, two treated with 1 g of dipyrone and one treated with placebo. Patients were also requested to fill in a special "migraine pain evaluation form". Each attack was evaluated by the physician at the subsequent visit, when the study medication for the next attack was given to the patients. Rescue medicine, 1 mg ergotamine (Cafergot®) + 10 mg metochlopramide (Metpamid®), was available, to be used no sooner than 2 hours after taking the study drugs. The need for rescue medication was considered to denote lack of efficacy of the study drug.

Pain measurement

Each patient rated his/her pain intensity before the drug treatment and 1, 2, 4 and 24 hours after the medication on a four-point verbal rating scale: no pain [0], mild pain [1], moderate pain [2] and severe pain [3], according to the guidelines published by the International Headache Society Clinical Trials Subcommittee (17). Recurrence of pain was defined as the presence of headache, following total pain relief, within 24 hours of drug intake.

Efficacy assessment

The study took into consideration patients who reported headaches of moderate or severe intensity. The complete elimination of severe or moderate pain was regarded as "total pain relief", whereas the reduction of severe pain to mild or no pain, or of moderate pain to no pain was considered "pain relief". Before (0 hours), and 1, 2, 4, and 24 hours after taking the medication patients were asked to rate (and record on the "migraine pain evaluation form") the intensity of the pain, accompanying symptoms, and any drug-related side effects. Use of rescue medication and recurrence of headache were also to be noted on the "migraine pain evaluation form".

Another efficacy parameter was physician and patient evaluation of the treatment. At the end of each attack, both the patient and the physician were asked to evaluate the efficacy of the treatment on a four-point rating scale: not effective [0], slightly effective [1], effective [2], and very effective [3].
Safety assessment

Safety (scored as very good, good, moderate, and poor) was assessed both on the basis of the physician’s global evaluation, and through the monitoring of adverse events throughout the study period.

Statistical analysis

Total pain relief, pain relief, and the physician’s and patient’s evaluations of the efficacy of the treatment were analyzed using Fisher’s exact chi-square test.

Results

Seventy-three patients (59 females, 81%; 14 males, 19%) were enrolled in the study. Thirteen patients – 5 (38%) migraine with aura and 8 (62%) migraine without aura patients – did not show up at all the scheduled visits, and 4 patients – 1 (25%) migraine with aura and 3 (75%) migraine without aura – were found to have violated the study protocol. The data obtained from these patients, who either missed visits or otherwise violated the study protocol, were excluded from further analysis (Fig. 1). Thus, a total of 56 migraine with or without aura patients completed the study. The final analysis was performed on the data of 47 (84%) female and 9 (16%) male patients. The average age at final analysis was 32.7±8.7 years, and the average migraine history in these patients was 10.6±7.8 years. Eighteen (32%) of the final sample had a diagnosis of migraine with aura and 38 (68%) a diagnosis of migraine without aura. This ratio is in accordance with other epidemiological studies of migraine (18,19).

A total of 168 attacks, 112 treated with dipyrone and 56 treated with placebo, were evaluated. Average baseline pain score for both placebo- and dipyrone-treated attacks was 2.45±0.5 with a median of 2 (moderate pain). Significant improvement of pain (considering percentages of both “pain relief” and “total pain relief”) was obtained on dipyrone vs placebo at all time points measured (p<0.001) (Fig.s 2 and 3). Tables I and II (over) compare the “pain relief” and “total pain relief” responses obtained on dipyrone and placebo.

Pain recurrence and the need for rescue medication

Patients with dipyrone-treated attacks had less pain recurrence than those with placebo-treated attacks. Forty-two dipyrone-treated attacks and six placebo-treated attacks resulted in total pain relief. Of these attacks, pain recurrence (defined as the presence of headache, following total pain relief, within 24 hours of drug intake) occurred in 16.7% (7/42 attacks) and 33.3% (2/6 attacks) respectively, without the difference reaching statistical significance. However, the incidence of recurrence was too low to allow evaluation of the difference between the dipyrone- and placebo-treated attacks. The need for rescue medication was significantly less in...
dipyrone-treated (14 attacks, 12.5%) compared to placebo-treated migraine (24 attacks, 42.9%) (p<0.001). Both the patients' and the physicians' evaluations of the treatments significantly favored the dipyrone treatment (Fig. 4). Side effects were minimal and trivial in both treatments, and no serious adverse events were reported.

Discussion

There are three main classes of drugs used for the treatment of acute migraine attacks: analgesics and NSAIDs, ergot derivatives, and the triptans (serotonin 1B/1D agonists). As a rule, opiates are avoided since they seem to mask the pain without suppressing the pathophysiological mechanism of the attack, and they also lead to addiction (20). In our daily clinical practice, opiates constitute the last choice in selected cases. The strict regulations governing the prescription of opiates and the potential for misuse of these agents make these agents non-preferable. Of all the agents used, the demonstrated efficacy and good tolerability of the NSAIDs make them a first-line treatment choice for all types of migraine attack. Of the various NSAIDs, the evidence in favor of aspirin, ibuprofen, naproxen sodium, tolmetin acid, and the acetaminophen-aspirin-caffeine combination as acute

| Table I - Percentages of “pain relief” obtained 1, 2, and 4 hours after oral intake of 1g dipyrone or placebo in all attacks, and in 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd} attacks. “Pain relief” corresponded to the reduction, on a four-point verbal rating scale (no, mild, moderate, severe pain) of severe pain to mild or no pain and moderate pain to no pain. |
|-----------------|---|---|---|---|---|---|---|
|                  | n  | n  | %  | p   | n  | %  | p   | n  | %  | p   |
| All attacks      |    |    |    |     |    |    |     |    |    |     |
| Placebo         | 56 | 11 | 19.6 | <0.001 | 13 | 23.2 | <0.001 | 16 | 28.6 | <0.001 |
| Dipyrone        | 112 | 47 | 42  | 59 | 52.7 | 64 | 57.1 |
| 1\textsuperscript{st} attack | Placebo | 17 | 2 | 11.8 | 3 | 17.6 | 4 | 23.5 |
|                  | Dipyrone | 39 | 13 | 33.3 | 16 | 41.0 | 17 | 43.6 |
| 2\textsuperscript{nd} attack | Placebo | 20 | 5 | 25.0 | 5 | 25.0 | 6 | 30  |
|                  | Dipyrone | 36 | 19 | 52.8 | 23 | 63.9 | 25 | 69.4 |
| 3\textsuperscript{rd} attack | Placebo | 19 | 4 | 21.1 | 5 | 26.3 | 6 | 31.6 |
|                  | Dipyrone | 37 | 16 | 43.2 | 20 | 54.1 | 22 | 59.5 |

| Table II - Percentages of “total pain relief” obtained 1, 2, and 4 hours after oral intake of 1g dipyrone or placebo in all attacks, and in 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd} attacks. “Total pain relief” corresponded to the complete elimination of severe or moderate pain, measured on a four-point verbal rating scale (no, mild, moderate, severe pain). |
|-----------------|---|---|---|---|---|---|---|
|                  | n  | n  | %  | p   | n  | %  | p   | n  | %  | p   |
| All attacks      |    |    |    |     |    |    |     |    |    |     |
| Placebo         | 56 | 1  | 1.8 | <0.001 | 6  | 10.7 | <0.001 | 7  | 12.5 | <0.001 |
| Dipyrone        | 112 | 24 | 21.4 | 42 | 37.5 | 45 | 40.2 |
| 1\textsuperscript{st} attack | Placebo | 17 | 0 | 0.0 | 2 | 11.8 | 2 | 11.8 |
|                  | Dipyrone | 39 | 7 | 17.9 | 13 | 33.3 | 15 | 38.5 |
| 2\textsuperscript{nd} attack | Placebo | 20 | 1 | 5.0 | 2 | 10.0 | 3 | 15  |
|                  | Dipyrone | 36 | 9 | 25.0 | 15 | 41.7 | 16 | 44.4 |
| 3\textsuperscript{rd} attack | Placebo | 19 | 0 | 0.0 | 2 | 10.5 | 2 | 10.5 |
|                  | Dipyrone | 37 | 8 | 21.6 | 14 | 37.8 | 14 | 37.8 |
migraine attack treatments has emerged as the most convincing (21). The use of dipyrone in acute migraine attacks is very common in Turkey. As dipyrone has been marketed in Turkey since 1954, both patients and physicians are familiar with its efficacy and safety. Even a 500 mg dose of dipyrone is generally accepted as effective in the treatment of several headache types and is often prescribed. Despite the fact that dipyrone is widely used as a painkiller, the lack of randomized controlled trials evaluating the effectiveness of this drug constitutes a gap in modern pharmacotherapy. Moreover, the standardization of the headache patients enrolled in studies is another point to be considered. The IHS criteria for headache have been available only since 1988. Many studies conducted before this date are not comparable and do not give accurate information about the effectiveness of drugs in selected headache types. Only a few randomized clinical trials have evaluated the use of dipyrone, mostly in intravenous (i.v.) form, in headache. Recently, i.v. administration of 1 g dipyrone was found to be significantly more effective than placebo for the acute treatment of migraine both with and without aura (22). In another trial, patients with acute episodic tension-type headache receiving i.v. dipyrone showed a significant decrease in pain compared with patients receiving placebo, thus justifying its use in the emergency room setting (23). Its efficacy and safety were validated in acute migraine with aura, migraine without aura and episodic tension-type headache patients. Dipyrone was concluded to be a safe, effective and inexpensive drug for the treatment of common acute headache disorders (24). In another double-blind, placebo and active-drug (1 g aspirin) controlled study evaluating the efficacy and safety of oral administration of 0.5 or 1 g of dipyrone in moderate tension-type headache patients, the analgesic efficacy of dipyrone was found to be significantly greater than placebo at both doses. It was also noticed that dipyrone, at both doses, showed a trend towards an earlier onset of a more profound pain relief compared with aspirin (25). In the present double-blind, cross-over, randomized, placebo-controlled, multi-center study, we aimed to demonstrate the efficacy of dipyrone in acute migraine attack treatment in comparison to placebo, and to investigate the tolerability and safety of dipyrone in migraine patients. Our results are in agreement with the studies mentioned above. We found that 1 g of oral dipyrone, compared to placebo, is significantly more effective in acute migraine attack treatment. The recurrence rate in the placebo group was much higher (33%) than in the dipyrone treatment group (16.7%). However, the difference was not significant. In our opinion, the number of placebo-treated attacks resulting in total pain relief was insufficient to allow correct statistical analysis. Total pain relief was obtained in only 6 out of 56 attacks treated with placebo, and only 2 of these (2/56) had recurrence within 24 hours, whereas 42 of the dipyrone-treated attacks resulted in total pain relief and 7 of these (7/42) had recurrence (Fig. 3). Our drop-out ratio was relatively higher than that reported in other similar trials; however, this was in line with our expectations. On the basis of previous experience, we anticipated a drop-out rate of 20-30%, given that the study was conducted on outpatients and included at least four visits. Most of the drop-outs were observed after the second visit. We looked for possible correlations between the treatment of the patients with placebo versus dipyrone and the tendency to drop out of the study. Nine of the 13 patients who dropped out completed only the first attack (4 treated with placebo, 5 with dipyrone). Three patients completed two attacks, and 1 did not show up at all after the preliminary visit. We did not find any relation between treatment order or migraine type and the tendency to drop out. There are many standard analgesic drugs for headache treatment and dipyrone is a well-known agent for this purpose. Most of the patients in this study had already used dipyrone for migraine attacks before their enrollment. They had thus already formed an expectation of whether or not dipyrone would be effective. Such prior expectations may be an advantage or a disadvantage. In most new drug efficacy trials, patients have the idea that the new drug will be more effective than the older drugs. Thus, their expectations add an additional placebo effect to the efficacy of the newly discovered drugs. However, in our view this new drug-related placebo effect was not present in our study. We measured the actual efficacy of dipyrone. Our and other previously reported results provide sufficient evidence that dipyrone is a cost-effective and a safe treatment for acute migraine. However, dipyrone does present one limitation, for which it is criticized by many authors, i.e., the potential risk of agranulocytosis (26-29). One systematic trial evaluated the real risk of this (30) and found that the dipyrone-associated risk of agranulocytosis is slightly higher (1.1 cases per million users in one-week treatment) than salicylates, butazones or indomethacin (0.06, 0.2 and 0.4 per million respectively), but does not correspond to the level of risk that was reported prior to its withdrawal from the market in some countries (30). Additionally, agranulocytosis associated with the use of dipyrone presents a wide geographical variability. In regions where dipyrone was widely used, the rate ratio was very low while in regions where dipyrone usage was not common, it was higher. Many authors have discussed the risks and consequences of dipyrone usage (26-29). Baar et al. stated that blood dyscrasias, mostly associated with aminopyrine, have received much attention in the medical literature, but as discussed above, their true incidence for dipyrone is considerably lower than the often quoted incidence for aminopyrine reported more than 30 years ago. It thus emerges that dipyrone is no more dangerous than aspirin or acetaminophen and has obvious advantages for certain clinical pain conditions (31). We are in agreement with the opinions of these authors. Evaluating a risk, which is very rare, is not easy. Moreover, when the accused drug is low-cost and no longer protected by patent, it is difficult to prevent its falling victim to speculative considerations. Evaluating the safety of “a class of drugs” is also complicated. Pharmacological agents produce more than one adverse effect and the evaluation should take in the whole picture. A recent comparative study evaluating the safety of non-narcotic analgesics (dipyrone, aspirin, diclofenac and paracetamol) after their use for short periods of time showed that the excess mortality risk per million patients attributed to each of these drugs was 20 for paracetamol, 25 for
dipyrone, 185 for aspirin, and 592 for diclofenac. The authors concluded that the risk of agranulocytosis secondary to dipyrone would have to be 300 times higher for the excess mortality attributed to this drug to be comparable to that of diclofenac, and also the risk of adverse events from dipyrone is similar to that of acetylsalicylic acid, a drug widely accepted as safe (32).

In this double-blind, cross-over, randomized, placebo-controlled, multi-center study, we report that 1 g of oral dipyrone is effective, safe, and well tolerated in the acute treatment of migraine, both with and without aura. Dipyrone could be used as one of the first-line drugs in migraine attack treatment as it is safe and cost-effective. Further systematic, randomized, controlled trials are needed to address the question of which, among the drugs used in acute migraine treatment, are the safer or more effective.

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