Brazilian Journal of Medical and Biological Research (2002) 35: 1139-1145
ISSN 0100-879X

Intravenous dipyrone for the acute treatment of episodic tension-type headache. A randomized, placebo-controlled, double-blind study

M.E. Bigal[1], C.A. Bordini[2] and J.G. Speciali[2]

[1]Departmet of Neurology, Albert Einstein School of Medicine, Bronx, NY, USA, and The New England Center for Headache, Stamford, CT, USA
[2]Departamento de Neurologia, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brasil

Correspondence
M.E. Bigal
The New England Center for Headache
778 Long Ridge Road
Stamford 06851, CT
USA
E-mail: marcelobigal@hotmail.com

Publication supported by FAPESP.

Received February 5, 2002
Accepted June 24, 2002

Abstract

Acute headaches are responsible for a significant percentage of the case load at primary care units and emergency rooms in Brazil. Dipyrone (metamizol) is easily available in these settings, being the most frequently used drug. We conducted a randomized, placebo-controlled, double-blind study to assess the effect of dipyrone in the acute treatment of episodic tension-type headache. Sixty patients were randomized to receive placebo (intravenous injection of 10 ml saline) or 1 g dipyrone in 10 ml saline. We used seven parameters of analgesic evaluation. The patients receiving dipyrone showed a statistically significant improvement ($P<0.05$) of pain compared to placebo up to 30 min after drug administration. The therapeutic gain was 30% in 30 min and 40% in 60 min. The number of patients needed to be treated for at least one to have benefit was 3.3 in 30 min and 2.2 in 60 min. There were statistically significant reductions in the recurrence (dipyrone = 25%, placebo = 50%) and use of rescue medication (dipyrone = 20%, placebo = 47.6%) for the dipyrone group. Intravenous dipyrone is an effective drug for the relief of pain in tension-type headache and its use is justified in the emergency room setting.

Key words
- Episodic tension-type headache
- Acute treatment
- Dipyrone
- Metamizol
- Placebo

Introduction

Although tension-type headache is the most common type of headache, with a lifetime prevalence of 78% and a yearly prevalence of 38% (1), studies concerning its acute treatment do not reflect its importance. The lower intensity of pain, the absence of associated symptoms, and the lower impact on the health system and on the quality of life when compared to migraine might be possible reasons, but, on the other hand, a highly significant number of patients with this diagnosis seek medical help in the emergency setting. A study on 6006 patients seen at basic health units in Brazil showed that this type of headache was responsible for 0.8% of all adult visits, and 7.3% of the headaches seen (2). A total of 222 visits due to tension-type headache attacks occurred at the emergency unit of a university teaching hospital over a period of one year (3).

The therapeutic arsenal available to Brazilian doctors at public health units consists

of common analgesics (paracetamol, dipyrone and others), non-steroidal anti-inflammatory drugs, corticosteroids, neuroleptics, and opioids. The drug most frequently used in such settings is intravenous dipyrone (4,5), which, however, has never been evaluated for this purpose.

The aim of the present study is to report the first randomized, placebo-controlled, double-blind trial evaluating the efficacy of intravenous dipyrone in the acute treatment of episodic tension-type headache.

Material and Methods

Study duration and setting

The study was conducted at two public health units in the towns of Ribeirão Preto and São Carlos, State of São Paulo, Brazil, from April 1, 1997 to December 31, 1999. All subjects were evaluated by the same investigator (MEB).

Inclusion criteria

The inclusion criteria were minimum age of 18 years, diagnosis of episodic tension-type headache according to the criteria of the International Headache Society (6) in the presence of a pain attack, and agreement to participate in the study by signing an informed consent form.

Exclusion criteria

The exclusion criteria were chronic tension-type headache, secondary headaches, known or reported intolerance of or contraindication for dipyrone, having taken any type of medication for that attack before seeking the health unit due to pain or any other accompanying symptoms, having presented an attack of pain that fulfilled criteria for migraine in the last 3 months, and proven or assumed pregnancy.

Study design

The patients were randomized by drawing lots (7), with 30 patients assigned to each group. The sample size was determined assuming a 25% response rate for placebo and 55% for the active drug, to work with 90% of power to detect the difference at the 5% level of significance.

We first determined how long the patient had been in pain and defined this time as T_0. We then applied scales for the evaluation of pain and of associated symptoms immediately before the administration of the study drug at T_0 and at 30 min (time 30 - T_{30}) and 60 min after its administration (time 60 - T_{60}). The patients were questioned again, by telephone, 24 h after the administration of the study drugs.

The patients were medicated in the medication room of the health unit, where they lay down and were submitted to catheterization of a peripheral vein maintained with 0.9% NaCl, 0.5 ml (10 drops) per minute. Then, according to the group to which they had been randomly assigned, they were medicated according to the following protocol: a) placebo: *iv* injection of 10 ml 0.9% NaCl, b) dipyrone: *iv* injection of 1 g (2 ml) dipyrone added to 8 ml 0.9% NaCl by one nursing attendant and administered by another one in a blind fashion.

Parameters for the assessment of pain

Analgesia was assessed according to the parameters indicated below.

Parameter 1 - primary end-point. Pain intensity measured by a 10-point verbal-analogical scale (8).

Parameter 2 - pain intensity. Measured by the traditional 4-point scale: 0 - no pain, 1 - mild pain, 2 - moderate pain, 3 - severe pain. Positive headache response was a patient's pain changing from 2 or 3 to 1 or 0 after the study drug at particular end-points.

Parameter 3 - pain free. Pain intensity

changing from 2 or 3 to 0 at a predetermined time point.

Parameter 4 - therapeutic gain (TG). TG was defined as the "active response rate - placebo response rate". We used the end-point efficacy (parameter 2) for the calculations.

Parameter 5 - number needed to treat (NNT). NNT was defined as the reciprocal of TG, i.e., 1/TG.

Parameter 6 - recurrence of pain. Recurrence was present when the patient reported to be pain free at any time after administration of the study drug, with a headache returning afterwards.

Parameter 7 - use of rescue medication. Use of rescue medication was noted if the patient used some type of analgesic medication before the reevaluation performed 24 h after the administration of the study drug.

Criteria for discharge and reevaluation

After 1 h, patients who felt better were discharged even if they had received the placebo. Those whose clinical improvement was not satisfactory, with the need for further treatment, were treated with the rescue medication (*iv* injection of 0.1 mg/kg chlorpromazine). Patients were reevaluated, by phone, 24 h after the administration of the substance under study. This reevaluation consisted of the application of the same scales as applied previously.

Statistical analysis

Data were analyzed statistically by descriptive statistics for all variables studied. The demographic variables were analyzed by the chi-square test and by contingency tables, and the efficacy of the medications was compared by the nonparametric Mann-Whitney test. $P<0.05$ was considered to be statistically significant.

The statistician responsible for the analysis worked in a blinded fashion.

The study was approved by the Research Ethics Committee of the University Hospital, Faculty of Medicine of Ribeirão Preto, USP, and the patients gave informed consent to participate.

Results

Thirty patients were assigned randomly to receive placebo. Fifty percent of them were males. Mean age was 37.6 years. The dipyrone group consisted of 30 patients, 46.7% of them males. Mean age was 44.2 years. The male:female ratio was 1.0 for the placebo group and 0.87 for the dipyrone group. The mean the patients have been in pain (T_0) was 4.1 (ranging from 92 min to 26 h) and 4.5 h (ranging from 70 min to 24 h). Although we did not consider a minimum period of pain as a requirement for inclusion, all our subjects had at least 70 min of T_0 at the time of randomization. There were no significant differences between these demographics.

Assessment of analgesia

The comparison of pain intensity evaluated by the pain scale (primary end-point, parameter 1) is presented in Figure 1. Patients who received dipyrone had significantly less pain, as indicated by this parameter, than patients randomized to receive placebo, at all times evaluated.

The group that received placebo showed the following percentages of pain reduction compared to T_0: T_{30} - 34.4%, T_{60} - 34.4%, and 24 h - 65.6%. The group that received dipyrone presented the following results: T_{30} - 57.8% ($P<0.01$), T_{60} - 78.1% ($P<0.01$), and 24 h - 90.6% ($P<0.05$).

Table 1 presents a comparison of treatment efficacy (parameter 2) and pain-free condition (parameter 3). Dipyrone was superior to placebo in both parameters at all times evaluated.

The therapeutic gain (parameter 4) of dipyrone was 30% at T_{30} and 40% at T_{60}. The

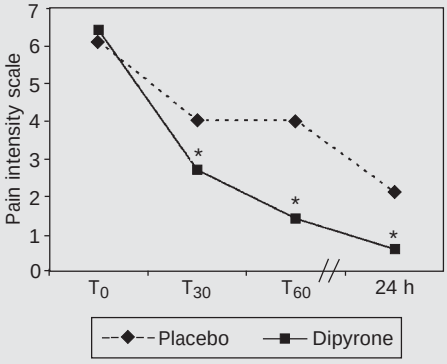

Figure 1. Time course of the reduction of headache intensity by dipyrone. Data are reported as means ± SD for 30 patients in the dipyrone and placebo groups. *P<0.05 compared to placebo (Mann-Whitney test). Standard deviation: T_0: placebo = 1.7, dipyrone = 2.1; T_{30}: placebo = 1.8, dipyrone = 2.0; T_{60}: placebo = 2.4, dipyrone = 1.8; 24 h: placebo = 2.2, dipyrone = 1.4.

Table 1. Comparison of the efficacy of the drug (parameter 2) and pain-free status (parameter 3) in patients randomly assigned to receive placebo or dipyrone.

	Placebo	Dipyrone
Efficacy (%)		
T_{30}	10.0	40.0*
T_{60}	26.7	66.7*
24 h	66.7	70.0
Pain free (%)		
T_{30}	6.7	36.7*
T_{60}	20.0	63.3*
24 h	63.3	86.7*

Data are reported as percent of patients for N = 30 in each group.
*P<0.05 compared to placebo (Mann-Whitney test).

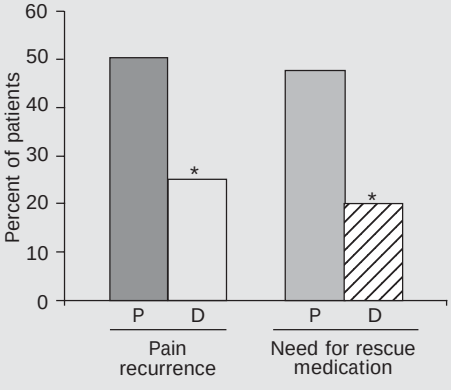

Figure 2. Comparison of dipyrone (D) and placebo (P) in terms of pain recurrence and need for rescue medication. Data are reported as means ± SD for 30 patients in the dipyrone and placebo groups. *P<0.05 compared to placebo (chi-square test).

NNT (parameter 5) was 3.3 and 2.2, respectively.

Recurrence (parameter 6) and the need for rescue medication (parameter 7) are shown in Figure 2. Patients receiving dipyrone had significantly less recurrence and need for rescue medication when compared to placebo.

Discussion

Dipyrone is an analgesic drug widely used in some countries, such as Brazil and Germany. In Spain, the estimate is that 6,460,454 pills containing dipyrone were taken just in the year of 1985 (9).

The present randomized, placebo-controlled and double-blind study shows that intravenous dipyrone (metamizol) is highly and quickly effective in episodic tension-type headache (Figure 1 and Table 1). Although frequently used in our region, until recently dipyrone had not been adequately assessed concerning the efficacy of its intravenous use in acute headache patients. We have conducted two placebo-controlled studies, a preliminary, non-randomized one (10) and a second randomized and blinded one (11), that showed the efficacy of dipyrone against pain and associated symptoms (nausea, photophobia and phonophobia) of patients with migraine with and without aura.

Oral dipyrone is effective in the treatment of episodic tension-type headache (12). The present study is the first in which intravenous dipyrone was assessed in the acute treatment of episodic tension-type headache. Another important aspect is that, as opposed to migraine, there are no specific drugs for use in the acute treatment of tension-type headache. Moreover, we do not have barbiturates, frequently used in other countries, and opioids are rarely used for this purpose in Brazil. So, we consider the rigorous evaluation of dipyrone to be essential.

Our methodology involved the assessment of pain and associated symptom inten-

sity at T_0 and at T_{30}, T_{60} and 24 h after drug administration. The fact that we limited our evaluation of efficacy to only 1 h may be criticized. However, this option was dictated by the needs of the health service where the study was conducted. Since this was a public health unit in a developing country, with overcrowding, excess demand and all the other problems of these outpatient clinics, we thought it would be inappropriate to maintain a patient under observation for more than 1 h unless his clinical condition required it. We tried to minimize this limitation by re-contacting the patients 24 h after drug administration, but we know these data must be interpreted with caution, since after 24 h there is an increase in the subjectivity with a proportional decrease in the precision of information. Although the guidelines of the International Headache Society recommend an evaluation at 2 h (13), we consider our procedure to be justified, both because of the anticipated speed of intravenous treatment and for the above stated sociologic reasons. We also guarantee that, although the methodology was not ideal, the study was conducted under the closest possible conditions of real utilization of these medications in developing countries. We also tried to minimize another bias, excluding patients with a history of migraine. If we consider this and the fact that patients were seen 4.1 to 4.5 h, on average, after the beginning of the pain, we think that the possibility of having treated the beginning of a migraine attack was considerably low.

Since the response rates observed with placebo are highly variable in different studies, two different mathematical approaches were used in an attempt to uniformize results concerning the efficacy of analgesic drugs: the therapeutic gain and the NNT. Our data show that dipyrone has a high therapeutic gain and a low NNT. If, comparatively, we consider that the therapeutic gain and NNT of 50 mg sumatriptan, a standard drug used in migraine, vary from 24 to 37 and from 2.7 to 4.2, respectively (14,15), the importance of our results with dipyrone is strongly highlighted.

In addition to the pronounced analgesic effect observed in the group that received dipyrone, the patients showed a low recurrence rate (parameter 6) and a reduced need for rescue medication (parameter 7), a fact that supports the therapeutic potential of dipyrone, which was effective and showed a low recurrence rate.

Dipyrone is a pyrazolone-derived, nonopiate analgesic drug with antipyretic and spasmolytic properties first introduced for therapeutic use in 1922. It is a highly hydrophilic compound which, when in solution, is quickly hydrolyzed to methylamino-antipyrine (MAA). Its analgesic effect reaches its peak 20 to 45 min after intravenous administration. Its active metabolites are MAA and amino-antipyrine (AA). The half-life of the MAA/AA complex is about 2.7 h. The excretion is predominantly renal (16,17). It is an effective analgesic known worldwide. Its effectiveness has been shown in several painful situations, like postsurgical pain, toothache and oncologic surgery (18-20).

It is known that there is no relationship between the analgesic effect of dipyrone and its ability to inhibit prostaglandins (21-24). The drug acts in two main ways: at the periphery, making nociceptors insensitive to pain activation (25), and centrally, acting on the periaqueductal gray matter and activating the pain inhibitory pathways (26). As the pathophysiology of tension-type headache seems to involve central hypersensitivity and peripheral triggers, we consider that dipyrone, both centrally activating the pain inhibitory system or acting on the nociceptors at the periphery, can have its mode of action explained.

The safety of dipyrone has been called into question for many years due to the possible risk of agranulocytosis. This risk was accepted to be higher than 0.1% in the seventies. However, in many countries, among

them Brazil, the drug is widely used and considered safe. More recent studies (27,28) have shown that the risk of agranulocytosis is less than 1.1 per million users and that the risk of aplastic anemia is close to zero. Unlike aspirin and other non-steroidal anti-inflammatory drugs, dipyrone is devoid of gastrointestinal tract side effects. A study comparing the risk of serious adverse effects after the use of dipyrone, aspirin, diclofenac and paracetamol for a short period of time showed that the excess mortality attributed to each of these drugs was as follows: dipyrone - 25/100 million, aspirin - 185/100 million, diclofenac - 592/100 million, paracetamol - 20/100 million. The authors concluded that the risk of agranulocytosis secondary to dipyrone would need to be 300 times higher for the excess mortality attributed to this drug to be compared to that of diclofenac (28).

We conclude that the use of intravenous dipyrone as the acute treatment of episodic tension-type headache at public health units is highly effective. Moreover, by being an inexpensive and safe drug, as shown in other studies, it is an excellent clinical option.

Acknowledgments

The authors wish to thank Dr. F.D. Sheftell and Dr. A.M. Rapoport, New England Center for Headache, Stamford, CT, USA, for a careful review of the manuscript.

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