Artigo Original

Dipyrone for acute primary headaches: a Systematic Review

Dipirona nas cefaléias primárias agudas: Revisão Sistemática

Adriana de Souza Ramacciotti[1], Álvaro Nagib Atallah[2], Bernardo Garcia de Oliveira Soares[3]

SUMMARY

Introduction: Headaches commonly affect working-age people. Dipyrone is largely used in many countries. **Objectives:** To determine effectiveness/safety of dipyrone for adults with acute primary headaches. **Method:** Double blind randomized controlled trials systematic review. Dichotomous data were expressed as relative risks and risk differences, and continuous data as weighted mean differences. If possible, numbers-needed-to-treat were calculated. **Results:** Four studies were included (636 subjects). Meta-analysis was possible for one outcome, favouring dipyrone. Regarding episodic tension-type headache and migraine, individual studies data showed dipyrone statistically significant beneficial effect. No severe adverse events were reported. There was no statistically significant difference between dipyrone and placebo regarding mild to moderate adverse events. **Conclusion:** Dipyrone is effective in migraine and episodic tension-type headache. Conclusions about its safety and agranulocytosis can not be drawn probably due to the relatively small sample. If the results of a recent study, which is related to the incidence of agranulocytosis in Latin America, do not clarify the question, data from observational studies on dipyrone side effects should be searched to determine its safety.

Keywords: Review, Dipyrone, Headache.

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RESUMO

Introdução: A cefaléia atinge com freqüência pessoas profissionalmente ativas, e dipirona é usada em muitos países. **Objetivos:** Determinar a efetividade e a segurança da dipirona no tratamento de adultos e crianças com cefaléia primária aguda. **Método:** Revisão sistemática de ensaios clínicos controlados randomizados duplo-cegos. Os dados dicotômicos foram expressos em riscos relativos e diferenças de risco, e os contínuos, em diferenças de média ponderada. Quando possível, calcularam-se números necessários para tratar. **Resultados:** Foram incluídos quatro estudos (636 adultos). Foi possível metanálise, que favoreceu a dipirona, para apenas um desfecho. Tanto na cefaléia tensional episódica, como na migrânea, dados de estudos individuais mostraram benefício estatisticamente significante da dipirona. Não foram relatados efeitos colaterais graves e não houve diferença estatisticamente significante entre dipirona e placebo aos leves e moderados. **Conclusão:** A dipirona é efetiva na migrânea e na cefaléia tensional episódica. Não se pode chegar a conclusões sobre sua segurança e a agranulocitose devido ao tamanho da amostra relativamente pequeno. Deve-se aguardar os resultados de um estudo em andamento sobre a incidência da agranulocitose na América Latinae, se necessário, buscar estudos observacionais sobre os efeitos colaterais dessa droga

Unitermos: Revisão Sistemática, Dipirona, Cefaléia.

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1.MD. Post-Graduating student of Department of Urgency Medicine, Federal University of São Paulo, Brazil.
2.MD, PhD. Full Professor of Urgency Medicine and Evidence-Based Medicine and Director of Brazilian Cochrane Centre, Federal University of São Paulo, Brazil.
3. MD. Post-Graduated student and Co-Director of Brazilian Cochrane Centre, Federal University of São Paulo, Brazil.

Address for correspondence: Adriana de Souza Ramacciotti, Rua Pedro de Toledo, 598, São Paulo – SP – Brasil. CEP: 04039-031
E-mail: asrama@uol.com.br / asrama@gmail.com

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INTRODUCTION

Headache is a frequent complaint of inpatients and outpatients and a very common condition that affects mainly people of working age. Every year, migraine and tension-type headaches affect an estimated 10% to 12%[1] and over 38%[2] of the population, respectively. Cluster headache is less common, occurring in less than 1% of the population[3]. Although most headaches are benign, they may interfere with productivity at work, as well as with family and social relationships. Because headaches negatively affect quality of life and result in substantial lost workdays[2,4-6], their effective treatment is extremely important.

There are many different therapies for treating people with headache, which may be based on drugs or not. The most commonly used drugs include acetaminophen (paracetamol), acetylsalicylic acid, dipyrone, ergot derivatives, chlorpromazine, triptans and non-steroidal anti-inflammatory drugs. Non-pharmacological interventions include relaxation techniques, trigger point therapy, exercise therapy, acupuncture, and spinal manipulation or mobilization.

Dipyrone is a pyrazolone derivative commercially launched in Germany in 1922[7]. It is a non-opioid analgesic, most commonly administered either orally or intravenously, whose effectiveness has been said to be comparable to that of some opioid analgesics[8]. It is the most popular non-opioid analgesic in many countries, currently available in South America, several European countries, South Africa, Russia, Israel and India, and in its oral form can be purchased without a prescription in Brazil and Spain. Nevertheless, it has been banned in the United States and United Kingdom because of its potential to cause blood dyscrasias, in particular agranulocytosis, which is rare, but can lead to a rapid depletion of granulocytes and may be fatal[7,9]. Although it is clear that dipyrone causes agranulocytosis, the risk has so far not been adequately quantified[10], and there is little consensus in the literature about it. The worst-case scenario was reported as 9.0 cases per million per year[11]. The calculated risks of agranulocytosis are approximately one out of every 31,000 dipyrone-treated inpatients and one of every 1,400 dipyrone-treated outpatients according to another study[12]. The same study[12] also pointed out that most patients in the study sample who developed agranulocytosis after treatment with dipyrone had also been treated with other medications associated with agranulocytosis, complicating quantification of the risk associated with dipyrone.

Since dipyrone is widely used in some countries for treating patients with different kinds of pain (post-operative pain, colic pain, cancer pain, headache, etc.), it is necessary to conduct a systematic review to assess its benefits and harms. The objective of this review is to assess the effectiveness and safety of dipyrone for acute primary headaches (migraine, episodic tension-type headache, cluster headache, or unclassified primary headache) in adults and children.

METHOD

Systematic review of double-blind randomized controlled trials evaluating dipyrone for the symptomatic relief of acute primary headaches in children and adults. Quasi-randomised trials, in which allocation is done, for instance, by using alternate days of the week, were excluded. Studies involving secondary headache disorders (post-dural puncture headache, post-traumatic headache, headaches related to cancer, etc.) were also excluded.

Dipyrone could be compared to analgesics, non-steroidal anti-inflammatory drugs, opioids, ergot derivatives, triptans, other drugs, combination agents, non-pharmacological interventions, placebo or no intervention.

Trials were searched by the using of different sources: electronic databases — Cochrane Pain, Palliative & Supportive Care Trials Register (2004), Cochrane Central Register of Controlled Trials (Issue 1, 2004), MEDLINE (1966-2004), EMBASE (1980-2004) and LILACS (1982-2004) —; reference lists of identified studies; personal contact to pharmaceutical companies, study authors, and other experts in the area.

The three authors independently screened trials identified by the literature search, extracted data, assessed trial quality, and analyzed the results. The methodological quality of the included trials was assessed by the using of the Cochrane Handbook criteria[13], according to which trials are classified as A ("low risk of bias", when allocation concealment is adequate), B ("moderate risk of bias", when there is some doubt about the results) and C ("high risk of bias", when allocation concealment is inadequate)[13]. The internal validity of individual trials was assessed using the scale devised by Jadad et al.[14], and thus each trial received a score of 0 to 5 points, with higher scores indicating higher quality in the conduct or reporting of the trial.

Studies were assessed according to presence of intention-to-treat analysis, which means that participants were "analyzed in the groups to which they were randomized regardless of which (or how much) treatment they actually received, and regardless of other protocol irregularities, such as ineligibility"[15].

For dichotomous data, relative risks for effectiveness outcomes and risk differences for adverse event outcomes were estimated, both with 95% confidence intervals (p-value < 0.05). Because we were using relative risk as a summary measure of effectiveness, we translated 'positive' outcomes into 'negative' ones for the analysis. Thus, for instance, 'pain-free response' became 'no pain-free

response' for the purpose of calculating relative risks.

The primary effectiveness outcomes considered in the analysis were pain-free response, which could also has been described as complete resolution of headache pain or complete relief; and improvement in headache, which includes any of the following: pain relief, decreasing in pain intensity or headache response. The primary outcomes related to adverse events and tolerability were proportion of patients reporting major harm (any adverse event resulting in death or serious illness or sufficiently serious to cause withdrawal from the study); and proportion of patients reporting minor harm (any adverse event).

The following secondary effectiveness outcomes were considered in the analysis: use of rescue medication; and for migraine studies, relief of other symptoms associated with migraine, specifically aura, nausea, vomiting, photophobia and phonophobia. The primary outcomes related to adverse events and tolerability were number of withdrawals due to adverse events; number of withdrawals for any reason; and identity and rates of individual adverse events.

Other outcomes that would be considered if reported in the included studies were: patient satisfaction; absenteeism; quality of life; productivity at work; functional disability; and costs.

We anticipated that the studies to be reviewed would report effectiveness outcomes at several different time points post-intervention. Data from the various time points were analyzed separately.

The most relevant dichotomous outcome measures evaluated were no pain-free response, no improvement in headache, proportion of patients reporting major harm (any adverse event resulting in death or serious illness or sufficiently serious to cause withdrawal from the study), proportion of patients reporting minor harm (any adverse event), use of rescue medication, no relief of other symptoms associated with migraine (for migraine studies) and no satisfaction with treatment.

Results were combined, where appropriate, using a fixed-effect model. For all statistically significant effectiveness results, numbers-needed-to-treat were calculated, and numbers-needed-to-harm would also be calculated if there were statistically significant results about side effects, what did not happen. Numbers-needed-to-treat were calculated as the reciprocal of the absolute risk reduction[16].

Continuous outcomes were expressed as weighted mean differences between groups. As data on continuous outcomes are frequently skewed (the mean is not the centre of the distribution), to assess skewness the following standard were applied to all continuous data: for data with finite limits, such as endpoint scale data, the standard deviation, when multiplied by two, had to be less than the mean[17]. As skewed data are not bad data18, they were analyzed, but were discussed with care. The most relevant continuous outcome evaluated was pain relief.

Heterogeneity was statistically assessed when meta-analysis was possible.

RESULTS

One thousand and seventy one (1671) references were identified, 1669 from the electronic searches and two from hand searching. Eight of the 1671 references were selected for a careful analysis of the complete article. We have so far been unable to obtain a copy of one of these articles[19]. Three others were excluded after full-text review: a non-randomized placebo-controlled study[20], a review article[21], and a study whose assessed subject was not primary headache[22]. Authors of included studies did not provide further references and no ongoing studies were identified.

Four studies were included in the review. All of them were intention-to-treat randomized controlled trials with a parallel-group design and were classified as B according to the Cochrane Handbook criteria [(13)]. According to Jadad scale, one[23] was classified as 5, and the other three[24-26] as 4. Only one included trial[23] reported any dropouts: 4 patients (1 randomized to dipyrone 0.5 g and 3 randomized to dipyrone 1 g) were excluded from the analysis for failing to return their study diaries.

Duration of assessment ranged from 4 to 24 hours. The study that assessed outcomes over 4 hours[23] considered two episodes of headache with a 48-hour interval between them.

Three of these studies were performed in the same centers (two public health units) in Brazil by the same group of authors[24-26]. One trial[23] included 31 participating centers, and subjects were not hospitalized.

The four studies included 636 subjects (187 males), with a mean age ranging from 29.5 to 44.2 years. They used the International Headache Society structured diagnostic criteria for episodic tension-type headache[23], [24], migraine with aura[26], and migraine with or without aura[25]. No pediatric trials were identified.

All four trials compared dipyrone to placebo; two of them also compared dipyrone to other active treatments[23,26]. In three studies[24-26], dipyrone 1g was administered intravenously, whereas in one[23] oral administration of dipyrone 0.5g and 1g was evaluated. Acetylsalicylic acid[23], magnesium sulphate[26] and chlorpromazine[26] were the comparative medications evaluated. Intravenous placebo was 0.9% physiological saline solution.

Meta-analysis was possible only for one outcome: persistence of aura at 60 minutes. All other presented

results are provided from individual studies.

Migraine

Two studies[25,26] evaluated patients with migraine and provided data for meta-analysis for the outcome persistence of aura at 60 minutes[25,26]. Dipyrone 1 g intravenously showed a statistically significant beneficial effect when compared to placebo (2 studies; 84 subjects; fixed-effect model; relative risk 0.16; 95% confidence interval: 0.03 to 0.84; p-value < 0.05; number-needed-to-treat = 6). When dipyrone 1 g IV was compared to chlorpromazine and to magnesium sulphate[26], no statistically significant results were presented for the outcome 'persistence of aura at 30 minutes' and there were no events for persistence of aura at 60 minutes for dipyrone, chlorpromazine and magnesium sulphate.

For the outcomes "no improvement in headache" and "no pain-free response", data for migraine with aura and migraine without aura[25] were summed. With regards to "no improvement in headache at 30 minutes " and "no improvement in headache at 60 minutes", data were statistically significant favouring dipyrone 1g intravenously, compared to placebo: 134 subjects, relative risk 0.75 (95% confidence interval: 0.64 to 0.89; p-value<0.05), number-needed-to-treat = 5 and 134 subjects, relative risk 0.41 (95% confidence interval: 0.30 to 0.57; p-value<0.05), number-needed-to-treat = 2. For "no pain-free response" at 30 minutes, 60 minutes and 24 hours, there were statistically significant results favoring dipyrone 1g intravenously, when it was compared to placebo: 134 subjects, relative risk 0.87 (95% confidence interval: 0.78 to 0.96; p-value<0.05), number-needed-to-treat = 8; 134 subjects, relative risk 0.59 (95% confidence interval: 0.47 to 0.74; p-value<0.05), number-needed-to-treat =3; and 134 subjects, relative risk 0.57 (95% confidence interval: 0.34 to 0.97; p-value<0.05), number-needed-to-treat = 6 respectively.

Episodic tension-type headache

One study data[23] showed statistically significant results favouring dipyrone 0.5g and dipyrone 1g, both orally, when compared to placebo, for the outcomes "pain relief at 30 minutes" (dipyrone 0.5g: 173 subjects, weighted mean difference 0.26, 95% confidence interval: 0.02 to 0.50, p-value<0.05; dipyrone 1g: 183 subjects, weighted mean difference 0.38, 95% confidence interval: 0.14 to 0.62, p-value<0.05), "pain relief at one hour" (dipyrone 0.5g: 173 subjects, weighted mean difference 0.48, 95% confidence interval: 0.19 to 0.77, p-value<0.05; dipyrone 1g: 183 subjects, weighted mean difference 0.56, 95% confidence interval: 0.26 to 0.86, p-value<0.05), "pain relief at two hours" (dipyrone 0.5g: 173 subjects, weighted mean difference 0.68, 95% confidence interval: 0.30 to 1.06, p-value<0.05; dipyrone 1g: 183 subjects, weighted mean difference 0.71, 95% confidence interval: 0.36 to 1.06, p-value<0.05), "pain relief at three hours" (dipyrone 0.5g: 173 subjects, weighted mean difference 0.74, 95% confidence interval: 0.33 to 1.15, p-value<0.05; dipyrone 1g: 183 subjects, weighted mean difference 0.74, 95% confidence interval: 0.35 to 1.13, p-value<0.05) and "pain relief at four hours" (dipyrone 0.5g: 173 subjects, weighted mean difference 0.95, 95% confidence interval: 0.52 to 1.38, p-value<0.05; dipyrone 1g: 183 subjects, weighted mean difference 0.94, 95% confidence interval: 0.53 to 1.35, p-value<0.05). These results should be considered carefully, since, except for the comparison between dipyrone 1 g orally and placebo for "pain relief at two hours", data of these continuous outcomes were skewed.

According to the same trial[23] and the comparison dipyrone versus placebo, for the outcome "need of rescue medication", dipyrone 0.5g orally tended to cause a beneficial effect, but the results were not statistically significant, whereas dipyrone 1g orally showed statistically significant results favouring dipyrone: (183 subjects, relative risk 0.36, 95% confidence interval: 0.18 to 0.72, p-value<0.05, number-needed-to-treat = 6). Regarding "no satisfaction with treatment", dipyrone 0.5 g orally and dipyrone 1g orally caused a beneficial effect over placebo, with statistically significant results: 173 subjects, relative risk 0.67 (95% confidence interval: 0.47 to 0.95, p-value<0.05), number-needed-to-treat=6; and 183 subjects, relative risk 0.43 (95% confidence interval: 0.28 to 0.66, p-value<0.05), number-needed-to-treat = 4 respectively.

Another study[24] showed statistically significant results favouring dipyrone 1g intravenously, when compared to placebo, for the outcomes "no improvement in headache at 30 minutes" (60 subjects, relative risk 0.67, 95% confidence interval: 0.49 to 0.91, p-value<0.05, number-needed-to-treat = 4), "no improvement in headache at 60 minutes" (60 subjects, relative risk 0.45, 95% confidence interval: 0.26 to 0.79, p-value<0.05, number-needed-to-treat = 3), "no pain-free response at 30 minutes" (60 subjects, relative risk 0.68, 95% confidence interval: 0.51 to 0.91, p-value<0.05, number-needed-to-treat=4) and "no pain-free response at 60 minutes" (60 subjects, relative risk 0.46, 95% confidence interval: 0.28 to 0.76, p-value<0.05, number-needed-to-treat=3).

Results from comparison between two doses of oral dipyrone and acetylsalicylic acid[23] show both doses of dipyrone were statistically significantly better for the outcomes "pain relief at 30 minutes" (dipyrone 0.5g: 173 subjects, weighted mean difference 0.32, 95% confidence interval: 0.09 to 0.55, p-value<0.05; dipyrone 1g: 183 subjects, weighted mean difference 0.44, 95% confidence interval: 0.21 to 0.67, p-value<0.05) and "pain relief at one hour" (dipyrone 0.5g: 173 subjects, weighted mean difference 0.38, 95% confidence interval: 0.12 to 0.64, p-value<0.05; dipyrone 1g: 183 subjects, weighted mean difference 0.46, 95% confidence interval: 0.18 to 0.74, p-value<0.05). For "pain relief at two hours" statistically significant results favoured dipyrone 1g orally

(183 subjects, weighted mean difference 0.35, 95% confidence interval: 0.02 to 0.68, p-value<0.05). When dipyrone 0.5g and/or dipyrone 1g orally was compared to acetylsalicylic acid on the outcome "no satisfaction with treatment", statistically significant results favoured dipyrone 1g orally: 183 subjects; relative risk 0.52 (95% confidence interval: 0.33 to 0.81, p-value<0.05), number-needed-to-treat = 5.

There was no statistically significant difference between either dose of dipyrone and acetylsalicylic acid for use of rescue medication.

Side-effects and dropouts

Considering the four studies (636 subjects), 57 (8.96%) individuals were described as presenting side effects: 35 (5.5%) in one study[25] and [22] (3.46%) in another one[23].

Side effects were considered not major in one study[25] and mild to moderate in another[23]. Individual data of adverse events reported both studies[23,25] showed a non statistically significant result. When comparing dipyrone 0.5 g and dipyrone 1g orally to placebo[23], there was a non-statistically significant risk difference.

Results for dry mouth, postural hypotension, somnolence, dyspepsia, nausea and others[25] were non statistically significant when each side effect was analyzed individually or when all side effects were analyzed together.

There was a non statistically significant difference between groups for the outcome number of patients presenting mild/moderate adverse effects when dipyrone orally was compared to placebo, when dipyrone 0.5g with dipyrone 1g, both orally, were compared and when dipyrone 0.5g and/or dipyrone 1g, both orally, were compared with acetylsalicylic acid[23].

Only one study[23] reported dropouts: four patients were excluded from the effectiveness analysis for not having returned their diaries with needed information.

Details of outcomes and studies are specified in Table 1.

Table 1. *Dipyrone for acute primary headaches: characteristics of included randomised controlled trials.*

Author/Year/ Reference	Methods	Participants	Interventions
Bigal 2002a (24)	Double-blind; 24 hours duration; ITT; 2 parallel groups; randomized by drawing lots.	60 patients with ETTH (IHS criteria 1988) in the presence of pain attack and 18 years old or over. Sex: ~ 48% males Age: ~ 44.2 years (dipyrone group) ~ 37.6 years (placebo group) Setting: two public health units	Dipyrone: intravenous injection of 1g (2 ml) added to 8 ml 0.9% NaCl (n=30); Placebo: intravenous injection of 10 ml 0.9% NaCl (N=30).
Bigal 2002b (25)	Double-blind, 24 hours duration; ITT; 2 parallel groups randomized by drawing lots.	134 patients (31% males and 69% females) in the presence of moderate to severe pain with diagnosis of MA (45%) or MO (55%), according to IHS criteria; mean age ~31 years. Setting: two public health units	Dipyrone intravenous 1g in 10 ml of 0.9% physiological saline (n=74); Placebo: 10 ml 0.9% physiological saline (n=60).
Bigal 2002c (26)	Double-blind; 60 minutes duration; ITT; 4 parallel groups.	86 patients (33% males) witn MA present at evaluation and 18 years or over. MA diagnoses according to IHS criteria; mean age ~29.5 years. Setting: two public health units	Dipyrone: intravenous 1g (2 ml) in 8 ml of 0.9% physiological saline (n=21); Chlorpromazine: intravenous 5 ml/kg weight of 0.9% physiological saline, followed by 0,1 ml/kg weight in 10ml of 0.9% physiological saline in bolus (single dose) (n=23); Magnesium sulphate: intravenous 1g in 10 ml of 0.9% physiological saline (n=21); Placebo: intravenous 10 ml 0.9% physiological saline (n=21).
Martinez-Martin 2001 (16)	Double-blind (double-dummy technique); 4 hours duration (two episodes of 48h between episodes); ITT; 4 parallel groups.	417 patients (356 analysed) with moderate ETTH (IHS). Sex: 25% males Age: 18-65 years History: at least 2 episodes of ETTH/month in 3 months prior to enrolment (48 hr between episodes); successful previous pain relief with a non-opioid analgesic; first HA episode < 50 years old. Setting: 31 centres	Dipyrone 0.5 g single dose orally (n= 82); Dipyrone 1g single dose orally (n=92); ASA 1g single dose orally (n=91); Placebo single dose orally (n=91). Treatment when at least moderate headache at first episode and at 2nd episode (48h between episodes)

GLOSSARY: ITT – Intention to treat treatment; ASA - Acetyl Salicylic Acid; IHS - International Headache Society; MA - Migraine with aura; MO - Migraine without aura; ETTH - episodic tension type headache; HA – headache; U/K- Unknown.

DISCUSSION

In spite of the fact there were statistically significant results favouring dipyrone when it was compared to placebo in the meta-analysis for the outcome "persistence of aura at 60 minutes", this is not clinically important in most cases since spontaneous resolution of aura is expected to happen in one hour[26]. This result may be relevant in cases of persistent aura, thus systematic reviews and randomized controlled trials assessing this issue should be searched and conducted if necessary.

Individual data showed important results favouring dipyrone in the treatment of subjects with migraine: for the outcomes "no improvement in headache at 30 minutes" and "no improvement in headache at 60 minutes", number-needed-to-treat is respectively 5 and 2. For "no pain-free response at 30 minutes", "no pain-free response at 60 minutes" and "no pain-free response at 24 hours, number-needed-to-treat is 8, 3 and 6 respectively. The fact of having to treat 2 and 3 patients with dipyrone 1g intravenously to have one with improvement in headache at 60 minutes and pain-free response at 60 minutes respectively shows dipyrone 1 g intravenously is effective for migraine.

With regards to episodic tension-type headache, individual data of the following outcomes showed dipyrone statistically significant beneficial effect over placebo: "pain relief at 30 minutes", "pain relief at one hour", "pain relief at two hours", "pain relief at three hours" and "pain relief at four hours"[23]. However, these results should be considered carefully, since data of most of these continuous outcomes were skewed, except for the comparison between dipyrone 1g orally and placebo for "pain relief at two hours".

For the outcome "need of rescue medication", dipyrone 1 g orally was effective (number-needed-to-treat=6). For "no satisfaction with treatment", statistically significant results favoured dipyrone 0.5g orally (number-needed-to-treat=6) and dipyrone 1g orally (number-needed-to-treat=4). In other words, we should treat 6 subjects with dipyrone 1g orally to have one individual presenting no "need of rescue medication" which would not happen if these people have received placebo. We should also treat 6 subjects with dipyrone 0.5g orally and 4 subjects with dipyrone 1g orally to have one individual satisfied with treatment and this satisfaction would not happen if these individuals have been treated with placebo.

For both outcomes "no improvement in headache at 30 minutes" and "no pain-free response at 30 minutes", number-needed-to-treat is 4, whereas for "no improvement in headache at 60 minutes" and "no pain-free response at 60 minutes", this number is 3. When compared to acetylsalicylic acid, number-needed-to-treat for dipyrone 1g intravenously is 5.

Thus, this review has found evidence from individual studies that dipyrone is effective for treating adults with migraine and episodic tension-type headache.

No severe side effects were reported in any of the included trials. However, as agranulocytosis is rare (9.0 cases per million per year according to the worst-case scenario)11, the 636 patients studied are not enough to assess the safety of dipyrone and we cannot come to a conclusion on the basis of the included trials alone. Considering this drug is currently widely used in many countries, such as Brazil and Spain (among others), data from observational studies on dipyrone side effects (case-report, case series, case-control) should be searched in order to determine the risk of dipyrone-induced agranulocytosis. These issues may be clarified by a recent study, planned to be ended in August 2006, which is being conducted to assess the incidence of aplastic anemia and agranulocytosis in Latin America[27], where dipyrone is largely used.

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