Cochrane
Library

Cochrane Database of Systematic Reviews

Single dose dipyrrone for acute renal colic pain (Review)

Edwards J, Meseguer F, Faura C, Moore RA, McQuay HJ, Derry S

Edwards J, Meseguer F, Faura C, Moore RA, McQuay HJ, Derry S.
Single dose dipyrrone for acute renal colic pain.
Cochrane Database of Systematic Reviews 2002, Issue 4. Art. No.: CD003867.
DOI: [10.1002/14651858.CD003867](https://doi.org/10.1002/14651858.CD003867).

www.cochranelibrary.com

TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	4
DISCUSSION	7
AUTHORS' CONCLUSIONS	7
ACKNOWLEDGEMENTS	8
REFERENCES	9
CHARACTERISTICS OF STUDIES	11
ADDITIONAL TABLES	22
APPENDICES	24
WHAT'S NEW	24
HISTORY	24
DECLARATIONS OF INTEREST	25
SOURCES OF SUPPORT	25
INDEX TERMS	25

[Intervention Review]

Single dose dipyrrone for acute renal colic pain

Jayne Edwards¹, Fuensanta Meseguer², Clara Faura³, R Andrew Moore⁴, Henry J McQuay⁴, Sheena Derry⁴

¹Training Team, UK Cochrane Centre, Oxford, UK. ²Reanimación y Tratamiento del Dolor, Hospital Reina Sofía, Murcia, Spain. ³Instituto de Neurosciences, Universidad Miguel Hernandez, Alicante, Spain. ⁴Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Oxford, UK

Contact: Anna Erskine, Cochrane Pain, Palliative and Supportive Care Group, Pain Research Unit, The Churchill Hospital, Old Road, Oxford, OX3 7LE, UK. anna.erskine@ndcn.ox.ac.uk.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.

Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 8, 2017.

Citation: Edwards J, Meseguer F, Faura C, Moore RA, McQuay HJ, Derry S. Single dose dipyrrone for acute renal colic pain. *Cochrane Database of Systematic Reviews* 2002, Issue 4. Art. No.: CD003867. DOI: [10.1002/14651858.CD003867](https://doi.org/10.1002/14651858.CD003867).

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Renal colic pain is extremely painful and requires immediate treatment with strong analgesics. Dipyrrone is the most popular non-opioid first line analgesic in many countries but in others it has been banned (e.g. USA, UK) because of its association with blood dyscrasias such as agranulocytosis. Since dipyrrone is used in many countries (e.g. Brazil, Spain) there is a need to determine the benefits and harms of its use to treat renal colic pain.

Objectives

Assess quantitatively the analgesic efficacy and adverse effects of single-dose dipyrrone in adults with moderate to severe renal colic pain.

Search methods

Published reports were identified from electronic databases (MEDLINE, EMBASE, *The Cochrane Library*, LILACS) and additional studies were identified from the reference lists of retrieved reports. Date of the most recent search: January 2000.

Selection criteria

Inclusion criteria were: full journal publication; RCT with a double-blind design; adult patients with baseline renal colic pain of moderate or severe intensity; treatment arms which included dipyrrone (oral, intramuscular or intravenous administration) and a control; single dose data.

Data collection and analysis

Summed pain intensity and pain relief data were extracted and converted into dichotomous information to yield the number of patients with at least 50% pain relief over 15-30 minutes, 1-2 hours and six hours. The proportion of patients with at least 50% pain relief was calculated. Single dose adverse effect data were collected.

Main results

Eleven studies with 1053 patients (550 on dipyrrone) met the inclusion criteria. Unfortunately, few data were available for analysis; most analyses were based on the results of single, small trials and statistical pooling of the results was inappropriate. Efficacy estimates were calculated as the weighted mean percent of patients achieving at least 50% pain relief with the range of values from trials contributing to the analysis. However, these estimates were not robust. Commonly reported adverse effects with intravenous dipyrrone were dry mouth and somnolence, and one study reported pain at the injection site. Insufficient information was available for safety analyses.

Authors' conclusions

Limited available data indicated that single dose dipyrrone was of similar efficacy to other analgesics used in renal colic pain, although intramuscular dipyrrone was less effective than diclofenac 75 mg. Combining dipyrrone with antispasmodic agents did not appear to improve its efficacy. Intravenous dipyrrone was more effective than intramuscular dipyrrone. Dry mouth and somnolence were commonly reported with intravenous dipyrrone. None of the studies reported agranulocytosis.

PLAIN LANGUAGE SUMMARY

Single dose dipyrrone for acute renal colic pain

Renal colic pain is extremely painful and requires immediate treatment with strong analgesics. Dipyrrone is a non-opioid analgesic widely used for this purpose but not licensed in some countries (e.g., USA, UK) because of potentially fatal side effects (agranulocytosis). This review aimed to assess the effectiveness and safety of single dose dipyrrone in adults with moderate/severe renal colic pain but there were too few data to obtain clear results. The data available indicated that intravenous dipyrrone was more effective than intramuscular dipyrrone, and combining dipyrrone with antispasmodic agents did not improve its efficacy. Commonly reported side effects included dry mouth and drowsiness, and some patients experienced pain at the injection site. Agranulocytosis was not reported.

BACKGROUND

Renal colic pain is excruciating. It requires immediate and effective treatment with strong analgesics such as opioids, either alone or in combination with spasmolytic agents. Pethidine and morphine are frequently used.

Prostaglandins are thought to be involved in the pathogenesis of renal colic pain. Prostaglandin-synthetase inhibitors, such as indomethacin and diclofenac sodium, have produced beneficial results (Quilez 1984).

Phenazones, including dipyrone, are not impressive anti-inflammatory or antirheumatic agents. The inflammatory process increases the sensitivity of nociceptors in the tissue and alters the neuronal activity in the dorsal horn of the spinal cord (wind up phenomena) (Besson 1987; Foster 1992; Schaible 1985). Dipyrone appears to mediate its analgesic effects in the spinal cord, where it reduces prostaglandin production. A normalisation of the inflammation-related pain occurs producing 'wind up phenomena'. Since dipyrone does not accumulate in the tissue, it should lack the adverse gastrointestinal and renal effects associated with anti-inflammatory drugs.

Dipyrone also exhibits a pronounced spasmolytic effect (Arrellano 1990). High-doses of intravenous or intramuscular dipyrone, alone or in combination with other drugs, are commonly used (Lloret 1987a). Such therapeutic regimens have been shown to be effective (ESPSCP 1991).

Dipyrone is the most popular non opioid first line analgesic in many countries. It is currently available in Austria, Belgium, France, Germany, India, Israel, Italy, the Netherlands, Russia, Spain, South Africa, South America and Switzerland, but its use has been banned in the USA and UK because of its association with blood dyscrasias, e.g. agranulocytosis. Agranulocytosis is a rare, but serious adverse effect which can occur in the acute treatment phase. It results in a rapid depletion of granulocytes and may be fatal.

Since dipyrone is widely used, particularly in countries like Brazil and Spain, there is a need to determine how effective it is in the treatment of renal colic pain and what adverse effects it causes.

OBJECTIVES

To evaluate quantitatively the analgesic efficacy and adverse effects of single doses of dipyrone in adults with moderate or severe renal colic pain.

METHODS

Criteria for considering studies for this review

Types of studies

Reports were included if they were: full journal publications of single dose, double blind, randomised controlled trials of dipyrone in renal colic pain. Multiple dose studies were included if they provided single dose data. Study drugs needed to have been administered (by intramuscular or intravenous injection or orally) to adult patients with moderate or severe pain at the baseline assessment.

Reports were excluded if they did not clearly state that study medication had been randomly allocated or if the method of

randomisation was considered inappropriate (e.g. date of birth), or if they examined other pain conditions (e.g. biliary colic). Abstracts, review articles, case reports and clinical observations were also excluded.

Types of participants

Trials with adult patients (individuals over the age of 15) with established renal colic pain of moderate or severe intensity at the baseline assessment were included in this review. Patients entered in the trials had an episode of acute renal colic described as colicky pain in the flank and/or radiating to the homolateral hemi-abdomen and /or genitalia, with or without vegetative symptoms. Diagnosis was based on clinical signs or symptoms, with renal or ureteral calculi identified by abdominal radiography in some trials.

Types of interventions

Reports were included if they contained a treatment group allocated to either dipyrone (single dose) compared with placebo or an active control. Oral, intramuscular or intravenous routes of administration were included.

Types of outcome measures

Data were collected on the following outcomes:

- patient characteristics
- patient reported pain at baseline (physician, nurse, or carer reported pain was excluded from the analysis)
- patient reported pain relief expressed using validated pain scales (pain intensity and pain relief in the form of visual analogue scales and /or categorical scales) over 15-30 minutes, one to two hours and six hours
- time to remedication
- use of rescue medication
- withdrawals - discontinuation of treatment for any reason
- adverse effects - major and minor

Search methods for identification of studies

Electronic searches

The Cochrane Library (Issue 3 1999), MEDLINE (1966 to October 1999), EMBASE (1980 to October 1999), LILACS (January 2000), the Oxford Pain Relief Database (Jadad 1996a) and the Internet were searched to identify published reports of randomised controlled trials (RCTs) which assessed dipyrone in renal colic pain.

A broad free text search was used without language restriction to identify the maximum possible number of citations. Search terms used were a combination of those seen in [Appendix 1](#).

Information about ongoing clinical trials was sought by searching the new clinical trials site from the National Institute of Health (<http://clinicaltrials.gov>).

Searching other resources

Reference lists

Additional citations were retrieved from checking reference lists of retrieved reports.

Personal contact

Pharmaceutical companies, study authors, experts, and the Iberoamerican and Brazilian Cochrane Centres were contacted about unpublished data.

Data collection and analysis

Study selection

Two review authors (JE, FM) independently assessed studies for inclusion in this review. There was no attempt at anonymisation of the reports before assessment. A consensus meeting was held with all authors to agree the papers for inclusion.

Data extraction

Two review authors (JE, FM) independently carried out data abstraction and quality assessments. Again, a consensus meeting was held with all authors to agree the assessments for each included study.

The following items were extracted:

- (i) the number of patients treated
- (ii) dichotomous information (e.g. number of patients with at least 50% pain relief) if presented
- (iii) mean TOTPAR, SPID, VAS TOTPAR or VAS SPID
- (iv) study duration
- (v) the dose of dipyrone
- (vi) the route of administration of study drugs
- (vii) information on adverse effects

Analysis

TOTPAR (total pain relief) or SPID (summed pain intensity difference) over 15–30 minutes, one to two hours, and six hours or sufficient data to allow their calculation were extracted.

The pain outcome measures allowed for the calculation of TOTPAR and SPID were:

- a five point categorical pain relief scale with comparable wording to 'none, slight, moderate, good, complete' (scales using percentages as anchors were not permitted)
- four point categorical pain intensity scale with comparable wording to 'none, mild, moderate, severe'
- VAS 100 mm for pain intensity
- VAS 100 mm for pain relief
- patient's global evaluation using a standard 5-point scale (poor, fair, good, very good, excellent)

When dichotomous information (number or proportion of patients with at least 50% pain relief) was available this was extracted.

For visual analogue scales (VAS) pain of at least moderate intensity equates to greater than 30 mm on a 100 mm VAS (Collins 1997). When the baseline pain intensity was presented as a mean VAS score with the corresponding standard deviation, the data were only included in the analysis if the mean minus 1.96 times the standard deviation was greater than 30 mm.

A global rating of the effect of a single dose of study medication was extracted when no other information was available. Only the patient's global evaluation using a standard 5-point scale (poor,

fair, good, very good, excellent) was allowed, and dichotomous information was extracted for the top two categories (very good and excellent). Information from the top two categories of the patient global rating has been shown to produce very similar estimates of analgesic efficacy to information from standard pain relief and pain intensity measurement scales (Collins 2001).

Where pain outcomes were reported only as mean values, mean TOTPAR, SPID, VAS TOTPAR and VAS SPID values were converted to %maxTOTPAR or %maxSPID by division into the calculated maximum value (Cooper 1991). Verified equations were used to estimate the proportion of patients achieving at least 50% maxTOTPAR (Moore 1996; Moore 1997a; Moore 1997b). This was then converted to the number of patients achieving at least 50% maxTOTPAR (pain relief) by multiplying by the total number of patients in the treatment group. Because this method has been used to calculate the efficacy of a number of different drugs, this allowed the efficacy of dipyrone to be compared with other pain relief treatments.

Weighted means (by study size) were calculated.

RESULTS

Description of studies

Twenty-six studies were identified as potential randomised controlled trials of dipyrone or dipyrone plus a spasmolytic agent for the treatment of acute renal colic pain.

Of those 26, one study could not be obtained (Victorov 1978) and 14 were excluded as follows:

- eight were not double blind
- three were not randomised
- one was a duplicate publication (Muriel 1993)
- two had no extractable data.

Information on the excluded studies is provided in the 'Characteristics of excluded studies' table.

Eleven studies met the inclusion criteria. These studies enrolled a total of 1053 patients on all treatments; 550 of these were treated with dipyrone. Also assessed were a number of doses of dipyrone (alone or combined with spasmolytic agents) administered by intramuscular or intravenous routes. Details are given in the 'Characteristics of Included Studies' table as well as in Table 1 and Table 2.

Risk of bias in included studies

Each included study was scored for quality using a three-item scale (Jadad 1996b) as follows:

- Is the study randomised? If yes then 1 point
- Is the randomisation procedure reported and is it appropriate? If yes then add 1 point, if not deduct 1
- Is the study double blind? If yes then 1 point
- Is the double blind method reported and is it appropriate? If yes then add 1 point, if not deduct 1
- Are withdrawals and dropouts described? If yes add 1 point

For inclusion in this review trials had to achieve a minimum quality score of two out of the maximum of five (i.e., had to be

of randomised and double blind design). 'Consensus' scores were agreed by the authors for each study, as follows:

Quality score of 5 (maximum): [Mora-Durban 1995](#)

Quality score of 4: [Comeri 1985](#); [Martin Carrasco 1993](#)

Quality score of 3: [Lloret 1987](#); [Miralles 1987](#); [Muriel 1993](#); [Muriel Villoria 1995](#); [Sanahuja 1990](#); [Stankov 1994](#)

Quality score of 2: [Arnau 1991](#); [Lloret 1986](#)

These scores were not used to weight the results in any way.

Effects of interventions

Eleven studies with 1053 patients in total, 550 on dipyrone, met the inclusion criteria and contributed to the analysis.

Studies assessed intramuscular and/or intravenous dipyrone, given alone or in combination with other treatments. Direct comparison of intramuscular and intravenous administration was conducted in one trial ([Muriel Villoria 1995](#)), although patients given intramuscular treatments had to be excluded from the analysis because no uncontaminated single dose data were provided. None of the included studies used oral administration; all used an active control and none used placebo.

Intramuscular dipyrone

Five trials assessed intramuscular dipyrone, given alone or in combination with other treatments, and provided uncontaminated single dose data ([Arnau 1991](#); [Miralles 1987](#); [Mora-Durban 1992](#); [Mora-Durban 1995](#); [Muriel Villoria 1995](#)). Intramuscular treatments compared in the trials were:

- dipyrone 1 g or 2 g given alone
- dipyrone 2 g plus hyoscine 20 mg
- diclofenac 75 mg
- pethidine 100 mg
- flurbiprofen 150 mg

Intravenous dipyrone

Seven trials assessed intravenous dipyrone, given alone or in combination with other treatments, and provided uncontaminated single dose data ([Comeri 1985](#); [Lloret 1986](#); [Lloret 1987](#); [Martin Carrasco 1993](#); [Muriel Villoria 1995](#); [Sanahuja 1990](#); [Stankov 1994](#)). Intravenous treatments compared in the trials were

- dipyrone 1 g, 2 g or 2.5 g given alone
- dipyrone 2.5 g plus hyoscine 20 mg
- dipyrone 1 g plus pitofenon 0.4 mg plus fempiverine 0.04 mg
- dipyrone 2.5 g plus pitofenon 10 mg plus fempipramide bromethylate 0.1 mg ([Baralgin](#))
- butylscopolamine 20 mg
- diclofenac 75 mg
- hyoscine 20 mg
- ketorolac 30 mg
- tramadol 100 mg

Other comparators were intramuscular diclofenac 75 mg and sublingual nifedipine 10 mg.

A number of studies allowed patients to receive a second dose of study medication within the observation period (e.g. after 30 minutes if adequate pain relief was not achieved). From these studies we extracted single dose information collected before the time at which the second dose was allowed. The following analyses were conducted using the uncontaminated, single dose data.

Efficacy

So little patient information was provided in the included studies that it would have been inappropriate to derive estimates of relative risk, numbers-needed-to-treat or confidence intervals around efficacy estimates. Results of the efficacy analysis are presented as weighted mean percent of patients achieving at least 50% pain relief ($=50\% \times \text{maxTOTPAR}$) with the range of values from trials contributing to the analysis. These data are shown in Table 1 and Figures 1-3 which are available through the internet at: <http://www.jr2.ox.ac.uk/Bandolier/painres/diprenco/diprenco.html>

1. INTRAMUSCULAR DIPYRONE

• Dipyrone 1 g

One trial presented information for intramuscular dipyrone 1 g compared with diclofenac 75 mg or pethidine 100 mg over 30 minutes ([Arnau 1991](#)). The response rate (proportion of patients with at least 50% pain relief) with dipyrone 1 g was 62% (72/116 patients), with pethidine 100 mg it was 68% (80/118 patients) and with diclofenac 75 mg it was 68% (78/116 patients).

• Dipyrone 2 g

Two trials presented information for intramuscular dipyrone 2 g compared with diclofenac 75 mg 30 minutes ([Arnau 1991](#); [Miralles 1987](#)). One also used pethidine as an active comparator ([Arnau 1991](#)). The data were homogeneous ($P = 0.3$). The response rate (proportion of patients with at least 50% pain relief) with intramuscular dipyrone 2 g was 65% in both trials (80/124 patients). With diclofenac 75 mg the response rates were 68% and 82% (mean 70%; 100/143 patients).

• Dipyrone 2 g plus hyoscine 20 mg

Two trials presented information for intramuscular dipyrone 2 g plus hyoscine 20 mg compared with flurbiprofen 150 mg over 20 minutes ([Mora-Durban 1992](#); [Mora-Durban 1995](#)). The data were homogeneous ($P = 0.3$). The response rates (proportion of patients with at least 50% pain relief) with intramuscular dipyrone 2 g plus hyoscine 20 mg were 28% and 48% (mean 42%; 37/90 patients). The response rates with flurbiprofen 150 mg were 36% and 69% (mean 60%; 53/89 patients).

• Combination drug

One study ([Comeri 1985](#)) assessed an intramuscular injection of a combination drug made up of dipyrone 1 g plus pitofenon 0.4 mg plus fempiverine 0.04 mg. The study presented information for the combination drug compared with diclofenac 75 mg over five hours and presented the proportion of patients with at least 50% pain relief at one hour. The response rate with the combination drug was 56% (28/50 patients) and that with diclofenac 75 mg was 79% (38/48 patients).

2. INTRAVENOUS DIPYRONE

- Dipyrrone 1 g

One trial presented information for intravenous dipyrrone 1 g compared with intravenous hyoscine 20 mg over 30 minutes (Lloret 1987). The response rate with intravenous dipyrrone 1 g was 70% (16/23 patients) and with hyoscine 20 mg it was 26% (6/23 patients).

One trial presented information for intravenous dipyrrone 1 g compared with intravenous diclofenac 75 mg over six hours (Muriel Villoria 1995). The response rate with intravenous dipyrrone 1 g was 73% (23/32 patients) and with control it was 82% (18/22 patients).

- Dipyrrone 2 / 2.5 g

One trial presented information for intravenous dipyrrone 2.5 g compared with intravenous hyoscine 20 mg over 30 minutes (Lloret 1987). The response rate with intravenous dipyrrone 2.5 was 91% (23/25 patients) and with hyoscine 20 mg it was 26% (6/23 patients).

One trial presented information for intravenous dipyrrone 2.5 g compared with intravenous tramadol 100 mg or butylscopolamine 20 mg over two hours (Stankov 1994). The response rate with intravenous dipyrrone 2.5 g was 88% (32/36 patients), with tramadol 100 mg it was 67% (23/35 patients) and with butylscopolamine 20 mg it was 65% (21/33 patients).

One trial presented information for intravenous dipyrrone 2 g compared with diclofenac 75 mg over six hours (Muriel Villoria 1995). The response rate with intravenous dipyrrone 2 g (27/30 patients) was 89%. The response rate with control (18/22 patients) was 82%.

- Dipyrrone 2.5 g plus hyoscine 20 mg

One trial presented information for intravenous dipyrrone 2.5 g plus hyoscine 20 mg compared with intravenous hyoscine 20 mg over 30 minutes (Lloret 1987). The response rate with intravenous dipyrrone 2.5 g plus hyoscine 20 mg was 85% (21/25 patients) and with hyoscine 20 mg it was 26% (6/23 patients).

One trial presented information for intravenous dipyrrone 2.5 g plus hyoscine 20 mg compared with intravenous ketorolac 30 mg over one hour (Martin Carrasco 1993). The response rate with intravenous dipyrrone 2.5 g plus hyoscine 20 mg was 88% (22/25 patients) and with ketorolac 30 mg it was 88% (17/20 patients).

- Combination drug

Two studies assessed an intravenous injection of a combination drug made up of dipyrrone 2.5 g plus piriton 10 mg plus fenipramide bromethylate 0.1 mg (brand name Baralgin) compared with intramuscular diclofenac 75 mg or sublingual nifedipine 10 mg over 15-30 minutes (Sanahuja 1990; Lloret 1986). Uncontaminated single dose data was extracted over 15 minutes. The data were heterogeneous ($P = 0.02$). The mean response rate with intravenous Baralgin (30/46 patients) was 63% (58% and 67%), with nifedipine 10 mg it was 31% (8/25 patients) and with diclofenac 75 mg it was 47% (14/29 patients) over 15 minutes.

Adverse effects

(see Table at www.jr2.ox.ac.uk/Bandolier/painres/diprenco/diprenco.html)

Information on adverse effects from five trials could not be used because the data had been contaminated with further doses of analgesic. Six trials presented uncontaminated, single dose adverse effect information (Comeri 1985; Lloret 1987; Martin Carrasco 1993; Miralles 1987; Muriel Villoria 1995; Stankov 1994). Two of these studies stated that no patients reported adverse effects (Comeri 1985; Miralles 1987). Adverse effects were reported in four trials (Lloret 1987; Martin Carrasco 1993; Muriel Villoria 1995; Stankov 1994).

Single dose data

- Two trials reported numeric information for particular adverse effects but did not mention the total number of patients with adverse effects (Lloret 1987; Martin Carrasco 1993). The severity of the reported adverse effects was not mentioned in the study by Lloret 1987, and that by Martin Carrasco 1993 stated that none of the adverse effects was clinically severe. The most frequently reported adverse effects were somnolence and dry mouth in both trials, but pain at the injection site occurred frequently in the study by Lloret 1987.
- Somnolence was reported by 5/23 (22%) patients with intravenous dipyrrone 1 g, 6/25 (24%) patients with dipyrrone 2.5 g, 23/50 (46%) patients with dipyrrone 2.5 g plus hyoscine 20 mg, 6/23 (26%) with hyoscine 20 mg and 7/20 (35%) patients with ketorolac 30 mg
- Dry mouth was reported by 5/23 (22%) patients with intravenous dipyrrone 1 g, 7/25 (28%) patients with dipyrrone 2.5 g, 33/50 patients (66%) with dipyrrone 2.5 g plus hyoscine 20 mg, 11/23 (48%) patients with hyoscine 20 mg and 11/20 (55%) patients with ketorolac 30 mg.
- Pain at the injection site was reported by 3/23 (13%) patients with dipyrrone 1 g, 15/25 (60%) patients with dipyrrone 2.5 g, 11/25 (44%) patients with dipyrrone 2.5 g plus hyoscine 20 mg and 1/23 (4%) patients with hyoscine 20 mg. Pain at the injection site was reported to have resolved within a few minutes and not to have caused thrombophlebitis.

The other two studies (Muriel Villoria 1995; Stankov 1994) provided insufficient information to analyse the adverse effects:

Muriel Villoria 1995

Single dose adverse effect information was available for intravenous dipyrrone 1 g, dipyrrone 2.5 g and diclofenac 75 mg over six hours. Information for the intramuscular treatments was contaminated because patients were given a second dose of analgesic. The number of patients reporting adverse effects with the study treatments was not provided. The most frequently reported adverse effects were:

- drowsiness with intravenous dipyrrone (1 g or 2.5 g)
- dry mouth and hypotension with diclofenac 75 mg
- severe drowsiness or vomiting with intravenous diclofenac 75 mg (reported by two (2/22; 9%) patients)

Stankov 1994

Single dose information was available for intravenous dipyrrone 2.5 g and tramadol 100 mg over two hours. One (1/36; 28%) patient reported adverse effects with dipyrrone 2.5 g: moderate lightheadedness, nausea and vomiting. Four (4/35; 29%) patients reported adverse effects with tramadol 100 mg: two reported dizziness, one reported nausea and one reported blurred vision.

The 'Characteristics of included studies' table provides details of adverse events reported with multiple (contaminated) doses of study treatments in the studies that provided no single dose data.

DISCUSSION

Despite rigorous searching, checking bibliographies of retrieved articles, contact with pharmaceutical companies and authors only 11 studies could be included in this systematic review. All used an active treatment as a control, and none used placebo. Since all trials were randomised and double blind the potential for selection or observer bias should have been minimised. Trials were generally of good quality (median quality score 3). Use of rescue medication was well described in the trials but descriptions of study withdrawals were poor.

The included trials were small, assessed a number of different doses of dipyrone (alone or in combination with other treatments), and different routes of administration (intramuscular or intravenous). Few patient data were available for analysis and most analyses were based on the results of single, small trials. The estimates of analgesic efficacy generated were not robust and statistical significance of results was not tested. Figures 1 and 2 available at the website: <http://www.jr2.ox.ac.uk/Bandolier/painres/diprenco/diprenco.html>, show the percent of patients with at least 50% pain relief for the intramuscular and intravenous drugs tested, with the largest points representing the largest analyses.

The duration of assessment and outcome data collection in the trials were considered important. This analysis was hindered by contamination of single dose information in some trials as a result of the administration of a second dose (or rescue medication) before the end of the observation period. For trials in which patients re-medicated within the observation period, information was extracted for the time period before rescue medication (or a second dose) was allowed. Calculations were conducted using the evaluable single dose efficacy information at 15-30 minutes, 1-2 hours or six hours. From the data available similar proportions of patients achieved at least 50% pain relief at 15-30 minutes, 1-2 hours or six hours (see Figure 3 at the website <http://www.jr2.ox.ac.uk/Bandolier/painres/diprenco/diprenco.html>), although the comparability of information over the different time points is uncertain.

Active comparators in trials of intramuscular dipyrone were diclofenac, flurbiprofen, pethidine and indomethacin. Limited information showed similar efficacy between intramuscular dipyrone and comparator treatments (see Table 1 at the website <http://www.jr2.ox.ac.uk/Bandolier/painres/diprenco/diprenco.html>), but with slightly lower response rates for dipyrone in direct comparisons with diclofenac. There was no evidence of a dose response for efficacy with increasing dose of intramuscular dipyrone (1 g or 2 g) using indirect or direct comparisons.

For intravenous dipyrone there was some evidence of a dose-response for efficacy (see Table 1 at the website <http://www.jr2.ox.ac.uk/Bandolier/painres/diprenco/diprenco.html>). It was also more effective than intravenous hyoscine 20 mg, tramadol 100 mg, butylscopolamine 20 mg, sublingual nifedipine 10 mg, intramuscular diclofenac 75 mg and of similar efficacy to intravenous ketorolac 30 mg.

There were no direct comparisons of intravenous dipyrone against intramuscular dipyrone, although indirect comparisons showed higher response rates with the intravenous drug. Real differences between intravenous and intramuscular dose cannot be substantiated because of the paucity of information.

The addition of spasmolytic agents (e.g. hyoscine) to dipyrone did not appear to improve its analgesic efficacy.

Information on adverse effects could not be pooled in a meta-analysis. In the majority of studies the information was contaminated because further doses of study medication were administered to patients within the observation period. In this systematic review, the objective was to establish the adverse effects caused by a single dose of dipyrone in acute renal colic pain. Combining information from these studies would have confounded the information gathered on adverse effects. Uncontaminated, single dose adverse effect information could be extracted from only four studies (Lloret 1987; Martin Carrasco 1993; Muriel Villoria 1995; Stankov 1994). These assessed intravenous dipyrone (with or without hyoscine 20 mg) compared with an active control drug. None of the adverse effects reported with dipyrone was severe in nature, although one patient reported moderate lightheadedness with dipyrone 2.5 g in one trial (Stankov 1994). The most commonly reported adverse effects with dipyrone were dry mouth and somnolence (drowsiness). Pain at the injection site occurred with single doses of all study treatments in one trial (Lloret 1987). With multiple doses, pain at the injection site with dipyrone was common (Sanahuja 1990; Mora-Durban 1995).

The trials indicate that dipyrone could be of similar efficacy to other tested analgesics, possibly with the exception of intramuscular diclofenac, in the treatment of moderate to severe renal colic pain in adults. Cautious interpretation of the results is needed because most analyses were based on the results of single, small trials.

AUTHORS' CONCLUSIONS

Implications for practice

The results obtained in this analysis were not robust, because few patients were included in the analyses for the different doses of dipyrone and the different routes of administration. Intravenous dipyrone appears to be an effective analgesic for treating renal colic pain.

Pain at the injection site occurred frequently in studies which assessed multiple doses of dipyrone, and was also reported in one single dose study.

There was insufficient information of adequate quality for any safety analyses to be conducted. Dipyrone is known to cause blood dyscrasias such as agranulocytosis (an adverse effect which can occur with short-term treatment) but there was no mention of blood dyscrasias in these trials. There is a wealth of literature on agranulocytosis: the most recent, large, international study found vastly differing rates of agranulocytosis in the 11 countries where information was collected (IAAA Study 1986). There are a number of published criticisms of this study (Kramer 1988). None of these criticisms mentions the importance of size (of the population studied and the analyses) for detecting true incidence rates for rare events. Size is an important issue of study validity (Moore 1998). Recent reports from Sweden have suggested a rate

of one case of agranulocytosis in 1700 prescriptions. This rate was based on six cases in 10,000 prescriptions. Information is available on the Swedish website (<http://www.mpa.se/biverkningar/biv99/novalglin.html>). In the absence of other robust information, the Swedish data is probably the most reliable on which to base decisions.

Implications for research

The risk of agranulocytosis needs to be quantified using adequately powered studies of good methodological design. Methodologically rigorous studies would be required to establish the benefit/risk trade-off for dipyrrone, particularly if the risk of rare adverse events was to be established. Such studies would need to be large, of adequate duration, provide clear definitions of outcomes and

independent verification of cases, and provide information on exposure to treatment.

ACKNOWLEDGEMENTS

The following helped retrieve specific papers: Joan-Ramon Laporte, University of Barcelona (Spain); José Gíl, Hospital General Universitario of Murcia (Spain); Luis Miguel Torres Hospital Universitario. Puerta del Mar Cádiz (Spain); Jordi Camí Institut Universitat Pompeu Fabra, Barcelona (Spain); Vladimir Stoukov, Centre for Evidence-based Medicine (Moscow); Medical Information Unit, Aventis Pharma (UK); Pablo Ortiz, Boehringer Ingelheim, Madrid (Spain). Anna Oldman kindly translated German reports. Nicola Thornton transferred text and data for this review into RevMan.

REFERENCES

References to studies included in this review

Arnau 1991 {published data only}

Arnau JM. Comparative study of the efficacy of dipyrrone, diclofenac sodium and pethidine in acute renal colic. *Eur J Clin Pharmacol* 1991;**40**:543-6.

Comeri 1985 {published data only}

Comeri G, Radice GP, Duvia R, Manganini V, Monza G. [Efficacia e tollerabilità degli antinfiammatori non steroidei nella colica ureterale]. *Urologia* 1985;**52**(2):268-71.

Lloret 1986 {published data only}

Lloret J, Vila A, Puig X, Monmany J, Munoz J, More J. Nifedipine in the treatment of renal colic. *Methods Find Exp Clin Pharmacol* 1986;**8**(9):575-9.

Lloret 1987 {published data only}

Lloret J, Munoz J, Monmany J, Puig X, Bonastre M, Brau J, et al. Treatment of renal colic with dipyrrone. A double-blind comparison trial with hyoscine alone or combined with dipyrrone. *Current Therapeutic Research Clinical and Experimental* 1987;**42**(6):1119-28.

Martin Carrasco 1993 {published data only}

Martin Carrasco C, Rodriguez Vazquez M, Palacios Garcia R. A double-blind study of the analgesic efficacy in kidney colic of the combination of dipyrrone and spasmolytic with ketorolac trometamol. *Arch Esp Urol* 1993;**46**(9):763-8.

Miralles 1987 {published data only}

Miralles R, Cami J, Gutierrez J, Torne J, Garces JM, Badenas JM. Diclofenac versus dipyrrone in acute renal colic: a double-blind controlled trial. *European Journal of Clinical Pharmacology* 1987;**33**(5):527-8.

Mora-Durban 1992 {published data only}

Mora-Durban MJ, Extramiana J, Navarro FJ, et al. Flurbiprofen: Alternative treatment in renal colic pain. *Arch Esp de Urol* 1992;**45**(8):773-7.

Mora-Durban 1995 {published data only}

Mora-Durban MJ, Extramiana-Cameno J, Arrizabalaga-Moreno M, et al. Flurbiprofen vs dipyrrone combined with hyoscine: the analgesic efficacy in renal colic. *Arch Esp Urol* 1995;**48**:867-73.

Muriel Villoria 1995 {published data only}

Muriel Villoria C, Zungri Telo E, Diaz Curiel M, et al. Comparison of the onset and duration of the analgesic effect of dipyrrone, 1 or 2 g, by the intramuscular or intravenous route, in acute renal colic. *European Journal of Clinical Pharmacology* 1995;**48**(2):103-7.

Sanahuja 1990 {published data only}

Sanahuja J, Corbera G, Garau J, Pla R, Carre MC. Intramuscular diclofenac sodium versus intravenous Baralgin in the treatment of renal colic. *Dicp Ann Pharmacother* 1990;**24**(4):361-4.

Stankov 1994 {published data only}

Stankov G, Schmieder G, Zerle G, Schinzel S, Brune K. Double-blind study with dipyrrone versus tramadol and butylscopolamine in acute renal colic pain. *World J Urol* 1994;**12**(3):155-61.

References to studies excluded from this review

Arico 1983 {published data only}

Arico F. [Tratamento da cólica nefrética com a associação de dipirrona com brometo de fenpiverínio]. *F Med (Br)* 1983;**86**(3):181-4.

Benyajati 1986 {published data only}

Benyajati C. Comparative study of Baralgin and hyoscine-N-methyl bromide in the treatment of intestinal and renal colic pain. *J Med Assoc Thai* 1986;**69**(10):569-73.

Borelli 1984 {published data only}

Borelli A, Roversi P, Palmieri B, Saponati G, Gallo M. Medical therapy of ureteral colic. A comparative clinical study of 3 spasmolytics, 1 of which is combined with an analgesic. *Minerva Urol Nefrol* 1984;**36**(3):253-60.

Campero 1993 {published data only}

Campero J M, Susaeta R, Verbal X, Roman M, Garcia M. Treatment of renal colic [Tratamiento del colico renal]. *Bol Hosp San Juan de Dios* 1993;**40**(4):185-8.

El Sherif 1990 {published data only}

El Sherif AE, Foda R, Norlen LJ, Yahia H. Treatment of renal colic by prostaglandin synthetase inhibitors and avafortan (analgesic antispasmodic). *Br J Urol* 1990;**66**:602-5.

Galassi 1983 {published data only}

Galassi P, Vicentini C, Scapellato F, Laurenti C. Use of indomethacin and metamizole administered intravenously in renal colic. Comparative study. *Minerva Urol* 1983;**35**(4):295-300.

Indudhara 1990 {published data only}

Indudhara R, Vaidyanathan S, Sankaranarayanan A. Oral diclofenac sodium in the treatment of acute renal colic. A prospective randomized study. *Clin Trials J* 1990;**27**:295-300.

Kalil 1982 {published data only}

Kalil M. Effect of the combination of 2.5 g of dipyrrone with 0.1 mg of fenpiverinium bromide in the treatment of renal colic. *Folha Med* 1982;**85**(5-6):959-62.

Lehtonen 1983 {published data only}

Lehtonen T, Kellokumpu I, Permi J, Sarsila O. Intravenous indomethacin in the treatment of ureteric colic. A clinical multicentre study with pethidine and metamizol as the control preparations. *Ann Clin Res* 1983;**15**(5-6):197-9.

Marthak 1991 {published data only}

Marthak KV, Gokarn AM, Rao AV, et al. A multi-centre comparative study of diclofenac sodium and a dipyrrone/

spasmolytic combination, and a single-centre comparative study of diclofenac sodium and pethidine in renal colic patients in India. *Curr Med Res Opin* 1991;**12**(6):366-73.

Muriel 1993 {published data only}

Muriel C, Ortiz P, Mella G, et al. Efficacy of two different intramuscular doses of dipyrrone in acute renal colic. *Methods Find Exp Clin Pharmacol* 1993;**15**(7):465-9.

Pardo 1984 {published data only}

Pardo A, Iriarte JL, de Paolis C. Comparison of the effects of ceruletide with respect to dipyrrone and to a single infusion of physiologic serum in patients with pain due to nephritic colic [Comparacion de la actividad del Ceruletide respecto a la Dipirona y a la sola infusion de suero fisiologico en pacientes con dolor por colico nefritico]. *Arch Esp Urol* 1984;**37**(2):94-100.

Pourrat 1984 {published data only}

Pourrat JP. Treatment of renal colic with ketoprofen. *Presse Med* 1984;**13**:2125-8.

Primus 1989 {published data only}

Primus G, Pummer K, Vucsina F, Meindl N. Tramadol versus metamizole in alleviating pain in ureteral colic. *Urologe A* 1989;**28**(2):103-5.

Additional references

Arrellano 1990

Arrellano F, Sacristán JA. Metamizol: reassessment of its therapeutic role. *European Journal of Clinical Pharmacology* 1990;**38**:617-9.

Besson 1987

Besson JM, Choauch A. Peripheral and spinal mechanisms of nociception. *Physiol Rev* 1987;**67**:67.

Collins 1997

Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres?. *Pain* 1997;**72**:95-7.

Collins 2001

Collins SL, Edwards, JE, Moore, RA, Smith LA, McQuay HJ. Seeking a simple measure of analgesia for mega-trials: is a single global assessment good enough?. *Pain* 2001;**91**:189-94.

Cooper 1991

Cooper SA. Single-dose analgesic studies: the upside and downside of assay sensitivity. In: Max MB, Portenoy RK, Laska EM Eds.. *The design of analgesic clinical trials - Advances in Pain Research and Therapy* 1991;**18**:117-24.

ESPSCP 1991

Collaborative Group of the Spanish Society of Clinical Pharmacology. Comparative study of the efficacy of dipyrrone, diclofenac sodium and pethidine in acute renal colic. *Eur J Clin Pharmacol* 1991;**40**:543-6.

Foster 1992

Foster C, Magerl W, Beck A, Gersslinger G, Gall T, Brune K, Handwerker HO. Differential effects of dipyrrone, ibuprofen and paracetamol on experimentally-induced pain in man. *Agents and Actions* 1992;**35**:112-21.

IAAA Study 1986

International Agranulocytosis and Aplastic Anemia Study. Risks of Agranulocytosis and Aplastic Anemia - A first report of their relation to drug use with special reference to anaglesics. *JAMA* 1986;**256**(13):1749-57.

Jadad 1996a

Jadad AR, Carroll D, Moore A, McQuay H. Developing a database of published reports of randomised clinical trials in pain research. *Pain* 1996;**66**:239-46.

Jadad 1996b

Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**:1-12.

Kramer 1988

Kramer MS. The International Agranulocytosis and Aplastic Anemia Study (IAAAS). *J Clin Epidemiol* 1988;**41**(6):613-4.

Moore 1996

Moore A, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics. *Pain* 1996;**66**:229-37.

Moore 1997a

Moore A, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: Verification from independent data. *Pain* 1997;**69**:127-30.

Moore 1997b

Moore A, Moore O, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: Use of pain intensity and visual analogue scales. *Pain* 1997;**69**:311-15.

Moore 1998

Moore RA, Gavaghan D, Tramer MR, Collins SL, McQuay HJ. Size is everything--large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* 1998;**78**(3):209-16.

Quilez 1984

Quilez C, Perez Mateo M, Hernandez P, Rubio I. [Utilidad de un antiinflamatorio no esteroideo, diclofenac sodico, en el tratamiento del colico nefritico. Estudio compartido con un espasmolitico y un analgesico opiaceo]. *Med Clin* 1984;**82**:754-55.

Reynolds 1993

Reynolds JEF. Martindale: the extra pharmacopoeia 292-314. 30. Vol. **292-314**, London: Pharmaceutical Press, 1993.

Schaible 1985

Schaible HG, Schmidt RF. Effects of an experimental arthritis on the sensory properties of fine articular afferents units. *J Neurophysiol* 1985; 54:1109. *J Neurophysiol* 1985;**54**:1109.

Victorov 1978

Victorov I. A clinical study of dipyron (Analgin) in urologic patients. The proceedings of the dipyron symposium, Moscow 1978. Stuttgart: Schattauer Verlag, 1980.

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Arnau 1991

Methods	Randomised, double blind No placebo group Baseline PI = moderate or severe pain (80mm in VAS 0-100) Self assessment at t = 0, 15, 30 min
Participants	Patients with diagnosed renal colic pain N=451 Dipyron 1 g, n=116 Dipyron 2 g, n=101 Diclofenac 75 mg, n=116 Pethidine 100 mg, n=118
Interventions	Dipyron 1 g Dipyron 2 g Diclofenac 75 mg Pethidine 100 mg Single IM dose, 30 min. If pain after 30 min not decreased at least 25%, pethidine 100 mg was given as rescue medication. 20% per group re-medicated. 43% (193/451) patients took rescue medication
Outcomes	PI=VAS 0-100 mm, (0=no pain; 100=excruciating pain) PR=verbal scale nonstandard (0-3) 30 min SPID: Dipyron 2 g=19.87 Dipyron 1g=20 Diclofenac 75 mg=22.75 Pethidine 100 mg=21.75
Notes	AE information is 'number of events' not 'number of patients'. Multiple dose AEs: Number of AEs per group: Warm feeling & metallic taste, dryness of the mouth, sweating: dipyron 1g (10); dipyron 2g (12); diclofenac 75 mg (7); pethidine 100 mg (23). Nausea: dipyron 1g (20); QS=2

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

Arnau 1991 (Continued)

Allocation concealment (selection bias)	Low risk	A - Adequate
--	----------	--------------

Comeri 1985

Methods	Randomised, double blind, active control, No placebo group Baseline PI = moderate or severe pain (82.5 mm on a 100 mm VAS) Self assessment at t = 0, 0.5, 1 hr
Participants	N=148 Dipyrone 1 g + pitofenon 0.4 mg + fempiverine 0.04 mg, n=50 Diclofenac 75 mg, n=48 Indomethacin 50 mg, n= 50
Interventions	Dipyrone 1 g + pitofenon 0.4 mg + fempiverine 0.04 mg Diclofenac 75 mg Indomethacin 50 mg Single IM dose, 1 hr If the PI had not decreased by 50% of the initial value at 60 mins after the first dose, the patient received a second injection of the same drug in a double blind manner. Any patient not experiencing a decrease of PI after the second dose was removed from the study
Outcomes	PI (VAS 0-100 mm) PR > 50% at 30mins: Dipyrone=28/50 Diclofenac=38/48 Indomethacin = 34/50
Notes	No AEs were reported by any patient Single dose AEs: 15 patients dropped out: diclofenac (3), indomethacin (6), dipyrone (6) QS=4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Lloret 1986

Methods	Randomised, double blind, single IV & sublingual dose, 2 hrs No placebo group Baseline PI=moderate or severe pain Self assessment at t=0, 10, 20, 30, 60, 120 min
Participants	N=43 Intravenous dipyron 2.5 g + pitofenone 10 mg + fempipramide bromomethylate 0.1mg (Baralgin), n=18 Sublingual nifedipine 10 mg, n=25
Interventions	Intravenous dipyron 2.5 g + pitofenone 10 mg + fempipramide bromomethylate 0.1mg (Baralgin) Sublingual nifedipine 10 mg Remedication was allowed 15 min after the initial dose if a clear improvement was not observed. After another 15 min a third dose was given (treatment regimes were swapped so that a patient who received dipyron at the start was given nifedipine, and vice versa
Outcomes	PI: standard scale (0-3) 30 min data provided; up to 15 min uncontaminated single dose data. 15 min SPID: Dipyron=0.2785 Nifedipine=0.1749
Notes	AE information is 'number of events' not 'number of patients'. Multiple dose AEs: Number of AEs: nifedipine (1); dipyron (15) Warm feeling & metallic taste, dry mouth, sweating: dipyron (7). Nausea: dipyron (2); nifedipine (1). Dizziness: dipyron (1) Somnolence: dipyron (1) Headache: Dipyron (1) Pain at injection site - dipyron (3) QS=2

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Lloret 1987

Methods	Randomised, double blind,
---------	---------------------------

Single dose dipyron for acute renal colic pain (Review)

Lloret 1987 (Continued)

	<p>No placebo group</p> <p>Baseline PI=moderate or severe pain > 70 mm VAS</p> <p>Self assessment at t=0, 10, 20, 30 min</p>
Participants	<p>N=96</p> <p>Dipyrone 2.5 g, n=25</p> <p>Diprone 2.5 g + hyoscine 20 mg, n=25</p> <p>Dipyrone 1 g, n=23</p> <p>Hyoscine 20 mg, n=23</p>
Interventions	<p>Dipyrone 2.5 g</p> <p>Diprone 2.5 g + hyoscine 20 mg,</p> <p>Dipyrone 1 g</p> <p>Hyoscine 20 mg</p> <p>Single IV dose, 30 min</p> <p>Rescue analgesic (100 mg pethidine IV) was allowed after 30 min if PR <50%</p>
Outcomes	<p>PI by patient: 100 mm VAS (0=no pain; 100=intolerable pain).</p> <p>PI by observer : standard scale (0-3)</p> <p>30 min SPID:</p> <p>Dipyrone 2.5 g=28.49</p> <p>Dipyrone 2.5 g + hyoscine=26.58</p> <p>Dipyrone 1 g=22.49</p> <p>Hyoscine 20 mg=8.98</p>
Notes	<p>4 patients were excluded because of the lack of diagnostic criteria or inappropriate recording of data</p> <p>Single dose AEs:</p> <p>AE information is 'number of events' not 'number of patients'.</p> <p>Number of AEs:</p> <p>Warm feeling & metallic taste, dry mouth, sweating: dipyrone 2.5 g (7); dipyrone 2.5 g + hyoscine 20 mg (11); dipyrone 1 g (5); hyoscine 20 mg (11).</p> <p>Gastric discomfort: dipyrone 2.5 g (6); dipyrone 2.5g + hyoscine 20 mg (4); dipyrone 1 g (3); hyoscine 20 mg (2).</p> <p>Dizziness: dipyrone 2.5 g (3); dipyrone 2.5g + hyoscine 20 mg (4).</p> <p>Somnolence: dipyrone 2.5 g (6); dipyrone 2.5 g + hyoscine 20 mg (9); dipyrone 1 g (5); hyoscine 20 mg (6).</p> <p>Headache: dipyrone 2.5 g + hyoscine 20 mg (1); dipyrone 1 g (1).</p> <p>Local pain at injection site: dipyrone 2.5 g (15); dipyrone 2.5 mg + hyoscine 20 mg (11); dipyrone 1 g (3); hyoscine 20 mg (1)</p> <p>Skin reactions: dipyrone 2.5 g + hyoscine 20 mg (1); dipyrone 1 g (1)</p> <p>QS=3</p>

Lloret 1987 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Martin Carrasco 1993

Methods	Randomised, double blind, Baseline PI = moderate or severe pain (VAS >60 mm) Self assessment at t = 0, 30, 60 min
Participants	N=34 Dipyrone 2.5 g + hyoscine 20 mg, n=17 Ketoralac 30 mg, n=17 Patients who took rescue analgesia were excluded from the study 1 previously enrolled in the study 3 from ketoralac group 8 from dipyrone group
Interventions	Dipyrone 2.5 g + hyoscine 20 mg, n=17 Ketoralac 30 mg, n=17 single IV dose, 1hr
Outcomes	PI=100 mm VAS (0=no pain; 100=excruciating pain) PR (5 point) nonstandard scale 1hr SPID: Dipyrone 2.5 g + hyoscine 20 mg = 46.6 Ketoralac 30 mg=47.4
Notes	AE information is 'number of events' not 'number of patients'. Single dose AEs: Number of AEs: Warm feeling & metallic taste, dry mouth, sweating: dipyrone 2.5 g + hyoscine 20 mg (22); ketoralac 30 mg (11). Gastric discomfort: dipyrone 2.5 g + hyoscine 20 mg (2). Nausea: dipyrone 2.5 g + hyoscine 20 mg (1). Dizziness: Ketoralac 30 mg (1) Somnolence: dipyrone 2.5 g + hyoscine 20 mg (14); ketoralac 30 mg (7). Headache: ketoralac 30 mg (3). Local pain at injection site: dipyrone 2.5 g + hyoscine 20 mg (1) QS=4

Risk of bias
Single dose dipyrone for acute renal colic pain (Review)

Martin Carrasco 1993 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Miralles 1987

Methods	Randomised, double blind. No placebo group Baseline PI=moderate or severe pain Self assessment at t=0 and 30 min
Participants	N=50 Dipyrone 2 g, n=23 Diclofenac 75 mg, n=27 12 patients were excluded
Interventions	Dipyrone 2 g Diclofenac 75 mg Single IM dose, 30 min
Outcomes	PI=100 mm VAS (0=no pain; 100=unbearable pain) PR=100 mm VAS, (0% to 100% improvement) Improvement=<50% reduction in pain within 30 min of drug administration. Presented dichotomous data (> 50% improvement in PR) at 30 min Dipyrone=15/23 Diclofenac=22/27
Notes	12 patients were excluded. No adverse effects were reported. QS=3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Mora-Durban 1992

Methods	Randomised, double blind No placebo group Baseline PI = severe pain
---------	---

Single dose dipyrone for acute renal colic pain (Review)

Mora-Durban 1992 (Continued)

Self assessment at t = 0, 10, 20, 30, 45, 60 min

Participants	N=51 Dipyrone 2 g + hyoscine 20 mg: n=26 Flurbiprofen 150 mg: n=25
Interventions	Dipyrone 2 g + hyoscine 20 mg Flurbiprofen 150 mg Single IM dose, 1 hr Rescue medication was allowed 20 min after the first dose. 34% of patients on dipyrone and 26.9% on flubiprofen took rescue analgesia.
Outcomes	PI = nonstandard 5 point categorical scale (0-4) VAS (0-100mm) for PI Global rating of treatment effect by the patient and the physician (4 point scale) 20 min SPID: Dipyrone 2 g + hyoscine 20 mg=8.28 Flurbiprofen 150 mg=9.82
Notes	1 patient from the flubiprofen group did not meet the inclusion criteria. Adverse effects: Multiple dose AEs: Number of patients with AEs:19.2% (5 patients) dipyrone; 11.5% (3 patients) flurbiprofen Local pain at injection site: dipyrone 2 g + hyoscine 20 mg (5); flurbiprofen 150 mg (3). QS = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Mora-Durban 1995

Methods	Randomised, double blind, No placebo group Baseline PI =severe pain Self assessment at t=0, 10, 20, 30, 45, 60 min
Participants	N=90 Dipyrone 2 g + hyoscine 20 mg, n=26 Flurbiprofen 150 mg, n=64

Single dose dipyrone for acute renal colic pain (Review)

Mora-Durban 1995 (Continued)

Interventions	Dipyrone 2 g + hyoscine 20 mg; Flurbiprofen 150 mg Single IM dose, 1 hr
Outcomes	PI=nonstandard 5 point categorical scale (0-4) VAS (0-100mm) for PI Global rating by the patient and the physician (4 point scale) Rescue medication was allowed 20 min after first dose. The final assessment prior to administration of rescue analgesic was used in the efficacy analysis . Dipyrone=14/26 Flurbiprofen = 11/64
Notes	Multiple dose AEs: Number of patients with AEs: dipyrone 2 g + hyoscine 20 mg (21); flurbiprofen 150 mg (19). Local pain at injection site: dipyrone 2 g + hyoscine 20 mg (21); flurbiprofen 150 mg (19). Five patients were excluded: methodological mistake (2); did not meet the inclusion criteria (3) QS=5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Muriel Villoria 1995

Methods	Randomised, double blind, No placebo group Baseline PI >50 mm VAS Self assessment at t = 0, 10, 20, 30, 60 min & 2, 4, 6 hrs IM + IV data IM was contaminated and excluded
Participants	N=84 Dipyrone 1 g, IV n=32 Dipyrone 2 g, IV n=30 Diclofenac 75 mg IV, n=22
Interventions	Dipyrone 1 g, IV Dipyrone 2 g, IV Diclofenac 75 mg, IV Single IV doses, 6hrs Rescue analgesia (pethidine 100 mg IM) After rescue the patients dropped out of study.

Single dose dipyrone for acute renal colic pain (Review)

Muriel Villoria 1995 (Continued)

One patient on dipyrone 1 g IV took rescue.

Outcomes	<p>Assessment by patient & observer. PI (VAS 0-100mm) & standard scale.</p> <p>6 hrs SPID (VAS) taken from Fig 1</p> <p>1hr SPID: Dipyrone 2g IV=448.32 Dipyrone 1g IV=386.21 Diclofenac 75 mg IV=407.37</p>
Notes	<p>AEs: Single dose AEs. 5 patients had severe AEs.</p> <p>Diclofenac 75 mg IV: sweating (1), vomiting (1)</p> <p>QS=3</p> <p>6 patients were excluded: 9 patients, PI < 50 mm 5 patients, voluntary withdrawal 1 patient, lost ampoules</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Sanahuja 1990

Methods	<p>Randomised, double blind,</p> <p>No placebo group</p> <p>Baseline PI moderate & severe pain</p> <p>Self assessment at t=0, 15, 30, 60 & 120 min</p>
Participants	<p>n=57</p> <p>Dipyrone 2.5 g + pitofenone 10 mg + fentanyl bromomethylate 0.1mg (Baralgin) IV, n=28</p> <p>Diclofenac 75 mg IM, n=29</p> <p>Withdrawals not mentioned</p>
Interventions	<p>Dipyrone 2.5 g + pitofenone 10 mg + fentanyl bromomethylate 0.1mg (Baralgin) IV</p> <p>Diclofenac 75 mg IM</p> <p>NB: route is different but blinded properly with placebos (double dummy)</p> <p>Single IM / IV doses, 2 hrs</p> <p>Remedication allowed 30 min after first dose if pain persisted or PI>2 (same drug as first dose).</p> <p>Also was allowed a third dose 30 min after the second one (morphine) if pain persisted or PI>2.</p>

Single dose dipyrone for acute renal colic pain (Review)

Sanahuja 1990 (Continued)

Outcomes	PI (standard categorical scale) 4 point scale (0-3) 15 min SPID: Baralgin (dipyrone combination) IV=0.3095 Diclofenac 75 mg IM = 0.359
Notes	AEs: Multiple dose AEs: Dipyrone (first dose) n=1 No AEs were observed on the second dose. Sweating: Baralgin, n=1 Local pain at injection site: Baralgin, n=1 QS=3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Stankov 1994

Methods	Randomised, double blind, No placebo group Baseline PI - severe Self assessment at t=0, 10, 20, 30, 50,70, 90 & 120 min
Participants	N=104 Dipyrone 2.5 g, n=36 Tramadol 100 mg, n=35 Butylscopolamine 20 mg, n=33
Interventions	Dipyrone 2.5 g Tramadol 100 mg Butylscopolamine 20 mg Single IV dose, 2hrs Remedication was allowed after 20 min; the last available pain measurement before the second injection was carried forward to the end of the study period. Patients who remedicated during the 2 hr observation period were withdrawn from the study. Dipyrone=5 Tramadol=13

Single dose dipyrone for acute renal colic pain (Review)

Stankov 1994 (Continued)

Outcomes	<p>PI: no pain - excruciating pain (5 points) nonstandard scale and VAS (0-100 mm)</p> <p>PR: (5 point scale), almost standard wording.</p> <p>Global assessment: (5 points) standard, by patient and investigator Distinct PR >10 mm shift on VAS.</p> <p>VAS PID: SPID 2hr: Dipyrone 2.5 g IV=124.96 Dipyrone 2.5 g IV=56.86</p> <p>VAS PID: SPID 1hr: Tramadol 100 mg IV=95.46 Tramadol 100 mg IV=40.98</p>
Notes	<p>Number of patients with AEs per group: Single dose AEs: butylscopolamine (2); dipyrone (1); tramadol (4).</p> <p>Number of AEs: Blurred vision: tramadol (1)</p> <p>Nausea & vomiting: tramadol (1); dipyrone (1); butylscopolamine (1)</p> <p>Dizziness/lightheadedness: dipyrone (1); tramadol (2)</p> <p>QS=3</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

AE - adverse effect
IM - intramuscular
IV - intravenous
PI - pain intensity
PR - pain relief
QS - quality score
VAS - visual analog score

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Arico 1983	Not randomised Not blind No assessment of baseline PI
Benyajati 1986	Not randomised Not blind No data to extract
Borelli 1984	Not blind Included mild pain

Single dose dipyrone for acute renal colic pain (Review)

Study	Reason for exclusion
Campero 1993	No data to extract - used nonstandard scale PR (4 point) Assessment of PR by observer
El Sherif 1990	Not blind
Galassi 1983	Not randomised Included other pain conditions in analysis No data to extract
Indudhara 1990	Not double blind No data to extract Did not define Pain Relief
Kalil 1982	Not randomised Not blind No assessment of baseline PI
Lehtonen 1983	Single blind No assessment of baseline PI No data to extract - Nonstandard scale
Marthak 1991	Not double blind
Muriel 1993	Duplicate of Muriel Villoria 1995
Pardo 1984	Not double blind
Pourrat 1984	No data to extract
Primus 1989	Not blind

ADDITIONAL TABLES

Table 1. Patients with at least 50% pain relief with single dose dipyrrone - Intramuscular

No. of trials	Drug	Dose	Duration	No. improved	Mean % of patients
2	Dipyrrone combination	2g+hyoscine 20mg	20 minutes	37/90	42 (28 & 48)
2	Flurbiprofen	150mg	20 minutes	53/89	60 (36 & 69)
1	Dipyrrone	1g	30 minutes	72/116	62
2	Dipyrrone	2g	30 minutes	80/124	65
1	Pethidine	100mg	30 minutes	80/118	68
2	Diclofenac*	75mg	30 minutes	100/143	70 (68 & 82)

Table 1. Patients with at least 50% pain relief with single dose dipyron - Intramuscular (Continued)

1	Dipyron combination	1g+pitofenon 0.4mg+ fempiver- ine 0.04mg	1 hour	28/50	56
1	Indomethacin	50mg	1 hour	34/50	68
1	Diclofenac	75mg	1 hour	38/48	79
<p>* Baralgin: dipyron 2.5g plus pitofenon 10mg plus fempiramide bromethylate 0.1mg</p>					

Table 2. Patients with at least 50% pain relief with single dose dipyron - Intravenous

No. of trials	Drug	Dose	Duration	No. improved	Mean % of patients
2	Dipyron combination	Baralgin*	15 minutes	30/46	63 (58 & 67)
1	Sublingual nifedipine	10mg	15 minutes	8/25	31
1	Intramuscular diclofenac	75mg	15 minutes	22/29	47
1	Dipyron	1g	30 minutes	16/23	70
1	Dipyron	2.5g	30 minutes	23/25	91
1	Dipyron combination	2.5g+hyoscine 20mg	30 minutes	21/25	85
1	Hyoscine	20mg	30 minutes	6/23	26
1	Dipyron combination	2.5g+hyoscine 20mg	1 hour	22/25	88
1	Ketorolac	30mg	1 hour	17/20	88
1	Dipyron	2.5g	2 hours	32/36	88
1	Tramadol	100mg	2 hours	23/35	67
1	Butylscopolamine	20mg	2 hours	21/33	65
1	Dipyron	1g	6 hours	23/32	73
1	Dipyron	2g	6 hours	27/30	89
1	Diclofenac	75mg	6 hours	18/22	82

Table 2. Patients with at least 50% pain relief with single dose dipyron - Intravenous *(Continued)*

* Baralgin: dipyron 2.5g plus
pitofenon 10mg plus fenipramide
bromethylate 0.1mg

APPENDICES

Appendix 1. Search strategy

dipyron OR (all brand names of dipyron)
AND
(pain or analgesi*)

Relevant records were downloaded into Procite and the following search was used to detect reports on renal colic pain:
(colic or calculi or calculus or stone or stones)
AND
(renal or ureteral or ureteric)

The brand names used in the search strategy were: adolkin, afebrin, aminopyrine sulphonate, analgin, analginum, ascorfebrina, baralgin, dolemicin, dolo buscopan, huberdor, inalgon, lasain, metamizol, metamizole, metamizole sodium, methampyrone, natrium novaminsulfonicum, minalgin, neo meubrina, neu novalgin, neu novalgine, neuro-brachont, neuro-formatin S, nolotil, noramidaophenum, noraminophenazonum, norgesic, novalgina, novalgine, novamidazofen, optalgin, pirenil, pyrethane, sulpyrine, trisalgina ([Reynolds 1993](#)).

WHAT'S NEW

Date	Event	Description
21 August 2017	Amended	Contact details updated.
20 April 2011	Review declared as stable	The review authors have declared that there are unlikely to be any new RCTs to affect the conclusions of this review.

HISTORY

Protocol first published: Issue 4, 2002
Review first published: Issue 4, 2002

Date	Event	Description
26 June 2013	Amended	Contact details updated.
8 February 2011	Amended	Contact details updated.
24 September 2010	Amended	Contact details updated.
4 July 2010	Amended	Re-published with Jayne Rees reverted to Jayne Edwards to match citations of her Cochrane reviews appearing outside the Cochrane Library
28 May 2008	Amended	Converted to new review format.

DECLARATIONS OF INTEREST

Fuensanta Meseguer was supported by an unrestricted, educational grant from Boehringer Ingelheim Laboratories, Madrid, Spain. The remaining authors had no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Pain Research Funds, UK.

External sources

- Boehringer Ingelheim Laboratories, Madrid, Spain.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Inflammatory Agents, Non-Steroidal [adverse effects] [*therapeutic use]; Colic [*drug therapy]; Dipyrrone [adverse effects] [*therapeutic use]; Injections, Intramuscular; Injections, Intravenous; Kidney Diseases [*drug therapy]

MeSH check words

Humans