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Comparative study of the efficacy of dipyrone, diclofenac sodium and pethidine in acute renal colic

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Summary. A randomized, double-blind, multicentre clinical trial was designed to compared the analgesic efficacy of i.m. dipyrone 1 and 2 g, i.m. diclofenac sodium and i.m. pethidine in acute renal colic. The study was carried out in 451 patients in 13 Spanish hospitals. Ureteric colic was diagnosed by the clinical features, urinalysis, or when the presence of a ureteric calculus was confirmed. The severity of pain was assessed by the physicians and by patients using visual analogue scales. The main parameter of drug efficacy was the need for rescue treatment -pethidine 100 mg i.m. 30 min after the experimental treatment. Rescue treatment was required in 93 patients: they represented 24.1% of the group given dipyrone 1 g; 22.3% of those on dipyrone 2 g; 16.4% of those given diclofenac sodium; and 19.5% of those on pethidine.

The differences between the groups were not significant. In the remaining 358 patients, no difference between treatments was observed.

The results suggest that in acute renal colic the use of dipyrone 2 g is unjustified as dipyrone 1 g is equally effective. Diclofenac sodium is a valid alternative, which shows similar analgesic efficacy.

Key words: Dipyrone, Pethidine, Diclofenac, Ureteric colic, Visual analogue scale, Statistical power, analgesic efficacy, pain relief, side effects

Acute renal colic is usually treated with opiate analgesics, sometimes combined with spasmolytic agents. However, because of their side effects, opiates would best be restricted to patients who do not respond to conventional analgesics. Several non-opiate analgesic therapeutic schedules have been proposed. Recently, diclofenac sodium [1–3] and other non-steroidal anti-inflammatory agents have been used in the treatment of renal colic. Although some comparative trials of the efficacy of these agents (dipyrone, indomethacin, and diclofenac sodium) have been undertaken [4–6], the sample sizes were too small satisfactorily to establish their comparative efficacy. The use of a high dose of dipyrone, on its own or in combination with spasmolytic agents, is a common practice in Spain. There are, however, no dose-response studies of the administration of dipyrone that justify the doses in current use, which appear to have been chosen empirically. The risk of administering such high doses should be assessed in controlled studies that examine the comparative efficacy of different doses of dipyrone and other currently available therapeutic alternatives.

The comparative efficacy of different i.m. doses of dipyrone and the non-steroidal anti-inflammatory agent diclofenac sodium have been investigated, using pethidine as a reference drug. The clinical trial was done in a number of different centres in order to obtain a sufficiently large number of patients to ensure adequate statistical power.

Materials and methods

Study design

Patients were recruited from 13 Spanish hospitals that operate both a 24-hour emergency service as well as a clinical pharmacology service, which was responsible for monitoring the study. Each partici-

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pating hospital recruited at least 15 patients. The protocol was approved by the Ethics Committees of the participating centres and by the Ministry of Health (permission no. 86/147). Informed consent was obtained from all participants.

The coordinating centre carried out a simple randomization of the therapeutic schedules, which had been pre-established independently for each of the 13 participating centres. Four groups of active treatment were established: dipyrone 1 g (Nolotil^R, Europharma; $^1/_2$ ampoule); dipyrone 2 g (Nolotil^R, Europharma; one ampoule); diclofenac sodium 75 mg (Voltaren^R, Ciba-Geigy; one ampoule); and pethidine 100 mg (Dolantina^R, Química Farmacéutica Bayer; one ampoule).

The double-blindedness of the trial was guaranteed by using the "blind observer" technique: a nursing team administered the drugs, and a medical team diagnosed and evaluated the patients. All drugs were administered in a single dose by the intramuscular route. No other medication was administered during the evaluation period, except for rescue treatment in those cases in whom it proved necessary. This consisted of a single i. m. dose of pethidine 100 mg, given 30 min after beginning the treatment.

At the outset, a minimum number of patients was established so as to ensure that the statistical power of the study would be at least 80%, given an alpha error of 0.05.

Selection of patients

Patients of both sexes, aged 18 to 65 y, who had been diagnosed as having acute renal colic on the basis of presenting symptoms at least suggestive of such a condition (colicky pain in the flank and/or radiating to homolateral hemiabdomen, and/or radiating to genitalia, with or without vegetative symptoms) were selected for the study. The following were considered to be additional confirmatory criteria: more than three red cells per field in the urine sediment, passage of a calculus, and the presence of a radiopaque stone in a plain abdominal X-ray film.

Patients with any other disorder requiring special management and those with the following conditions were subsequently excluded from the original sample: known allergy to salicylates or other non-steroidal anti-inflammatory agents, peptic ulcer or gastrointestinal bleeding, mild colicky pain (graded as 0 or 1 by the observer, see below) as well as pregnant women and nursing mothers. Patients who had received treatment for renal colic prior to their admission were not excluded.

Evaluation of the efficacy of treatment

The duration of the trial was 60 min from the administration of treatment (time 0). Assessments were carried out 15, 30, 45, and 60 min after treatment.

Evaluation of pain was the main clinical parameter and it was carried out simultaneously by patients and observers. Pain was evaluated by the patient according to a visual analogue scale, consisting of straight light 10 cm long and marked in cm. Point 0 was qualified as "no pain" and point 10 as "the most excruciating pain". If, according to the scale, 30 min after initiating treatment, pain had not decreased by at least 25%, rescue treatment with pethidine was given. The need to administer pethidine was the main parameter for the overall evaluation of drug efficacy. At similar intervals and using another visual analogue scale, patients evaluated the degree of comfort. Point 0 was qualified as "the injection did not work" and point 10 as "the injection suppressed the pain".

The observer graded the pain experienced at each point in time as follows: 0, no pain; 1, mild which was expressed by the patient as discomfort rather than true pain; 2, moderate, which was described as intense but bearable and was not accompanied by psychomotor agitation; and 3, severe, which was termed 'unbearable' and was accompanied by psychomotor agitation. Blood pressure and heart rate were measured at the same times. In addition, the observer recorded all side effects spontaneously mentioned the patients.

Statistical analysis

The homogeneity of the descriptive variables of the different groups was examined by variance analysis (ANOVA). Homogeneity of variances was checked by Levene's test [7]. The chi-quare test was used for the analysis of clinical efficacy. The statistical power was calculated by the procedure of Cohen [8]. The data are expressed as mean with SD.

Results

A total of 451 patients was included in the study; 116 of them were alloted to receive dipyrone 1 g, 101 to dipyrone 2 g, 116 to diclofenac sodium, and 118 to pethidine. In each of the four treatment groups, age, sex, previous history of renal colic, previous pharmacological treatment, and self-evaluation of pain at time 0 did not differ significantly (Table 1). A total of 181 (40%) patients had received pharmacological treatment before resorting to the emergency service; 15% had received analgesics, 9% spasmolytics, 13% analgesics and spasmolytics, and the remaining 3% had received other drugs.

Efficacy of treatment

The overall efficacy of the treatment, according to the need to administer recue treatment, was 79.3%. Rescue treatment had to be given to 93 patients, 28 (24.1%) in the group given dipyrone 1 g, 23 (22.8%) in those receiving dipyrone 2 g, 19 (16.4%) in the group on diclofenac sodium, and 23 (19.5%) in the pethidine group. Differences between the four treatment groups were not significant.

The course of pain according to the visual analogue scale in the 358 patients who did not need rescue treatment is depicted in Fig. 1. There was no significant difference between the four treatment groups. Analysis of the same visual analogue scale was performed in the subgroup of patients who had not previously received any drug, and no significant difference between the finding in them and the overall results were found.

The results obtained using the visual analogue scale to evaluate the degree of comfort experienced by those pa-

Table 1. Details of the treatment groups

	Dipyr. 1 g $n = 116$	Dipyr. 2 g $n = 101$	Diclof. $n = 116$	Pethid. $n = 118$	P
Age (y)	41.2 (14.7)	42.9 (14)	40.7 (13.9)	41.4 (12.7)	0.059
Sex (males)	67	57	63	61	0.82
Prev. history Ureteric/colic	63	60	68	69	0.84
Prev. pharm. treatment	45	38	44	53	0.31
Self-evaluation of pain At time 0	7.5 (2.5)	7.5 (1.9)	7.7 (1.8)	7.6 (1.8)	0.69

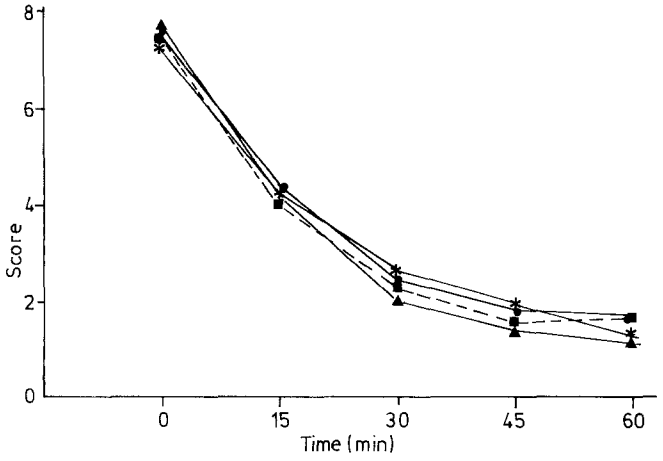

Fig. 1. Evaluation of efficacy according to the visual analogue scale for pain in the 358 patients who did not need rescue treatment

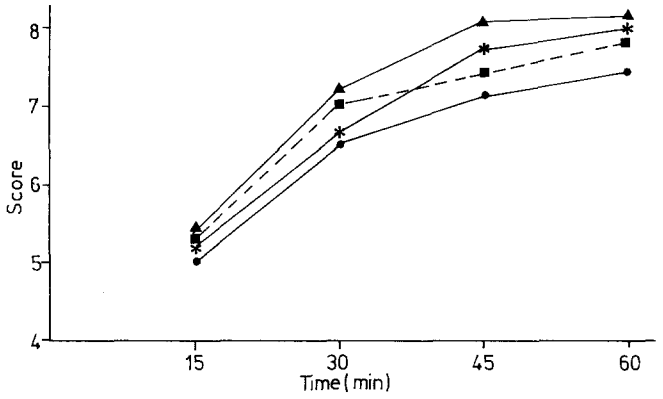

Fig. 2. Evaluation of the efficacy according to the visual analogue scale for comfort in the 358 patients who did not need rescue treatment
—•— Dipyrone 1 g ($n = 88$)
—*— Dipyrone 2 g ($n = 78$)
—▲— Diclofenac ($n = 97$)
– –■– – Pethidine ($n = 95$)

tients who did not need rescue treatment are depicted in Fig. 2. Again, significant differences between the four treatment groups were not encountered. The correlation coefficients between this scale and the pain scale at 15, 30, 45, and 60 min were 0.78, 0.84, 0.79, and 0.75, respectively ($P < 0.001$ in all cases). There were no significant differences in the course of the degree of pain according to the findings of the observer (Table 2).

The statistical power of the comparison between each pair of treatment groups was then calculated. The beta-error was acceptable for the comparison between dipyrone 1 g and dipyrone 2 g, between either of these two and pethidine, and between pethidine and diclofenac sodium (Table 3).

In the group of patients who did not need rescue treatment, the mean blood pressure showed a slight decrease [98.6 (14.7) mm Hg at time 0; 95.1 (13.4) mm Hg at 60 min] and the heart rate remained unchanged [75.9 (10.5) beats $\cdot$ min^{-1} at time 0; 74.9 (9.4) beats $\cdot$ min^{-1} at 60 min]. Significant differences between the four treatment groups were not found.

Table 2. Efficacy in the different treatment groups according to the opinion of patient (need for rescue treatment) and according to the finding of the observer

	Dipyr. 1 g $n = 116$	Dipyr. 2 g $n = 101$	Diclof. $n = 116$	Pethid. $n = 118$	All $n = 451$
N. of patients who did not require rescue treatment at 30 min (NS)	88	78	97	95	358
N. of patients with 0 or 1 pain score according to the findings of the observer at 30 min (NS)	78	70	94	90	332

Table 3. Value of beta error for each of the comparisons between different pairs of treatment

	Dipyrone 1 g		
Dipyrone 2 g	0.04		
		Dipyrone 2 g	
Diclofenac sodium	0.33	0.27	
			Diclofenac sodium
Pethidine	0.15	0.11	0.09

A total of 768 side effects were spontaneously mentioned by the patients. Their distribution in the treatment groups is shown in Table 4, including patients who needed rescue treatment.

Discussion

This multicentre clinical trial has several unique features. It was promoted by a scientific society (the Spanish Society of Clinical Pharmacology) in collaboration with a department of drug regulation (Dirección General de Farmacia y Productos Sanitarios), and it was designed to evaluate a common therapeutic practice in Spain, which had not previously been studied in depth in other controlled clinical trials.

According to the main criterion for evaluating the efficacy of the drugs used, namely, the need to administer rescue treatment, there was no significant difference between the four treatment groups, and the overall efficacy (about 80%) was similar to the results of previous studies [4–6]. There was a marked consistency between the results obtained following this criterion and those obtained using pain and comfort analogue scales and the judgement of the observer. The results suggest that there is no difference in the efficacy of the four active drugs. A common fault in reporting results of clinical trials is that the absence differences between treatments is not supported by

Table 4. Adverse effects referred to spontaneously by the patients in the four treatment groups

Side effect	Dipyrone 1 g $n = 116$	Dipyrone 2 g $n = 101$	Diclof. sodium $n = 116$	Pethid $n = 118$	Total $n = 451$
Agitation	2	2	3	1	8
Headache	5	1	2	1	9
Confusion	2	2	2	12	18
Diplopia	2	0	0	1	3
Dizziness	7	3	5	24	38
Dry mouth	21	20	15	52	108
Euphoria	0	1	0	1	2
Floating	9	11	9	46	75
Flushing	2	6	2	7	17
Hallucinations	0	0	0	3	3
Lipothymia	5	2	0	11	18
Local pain	13	19	13	4	49
Nausea	20	9	15	46	90
Orthos. Hypot.	3	2	1	14	20
Pruritus	0	0	0	2	2
Sedation	0	0	0	1	1
Somnolence	20	14	18	56	108
Sweating	9	6	8	29	52
Tremor	3	2	1	4	10
Urinary reten.	1	0	0	1	2
Vomiting	12	4	11	38	65
Warm feeling	10	12	7	23	52
Others	5	4	3	6	18
Total	151	120	115	383	768

calculation of the statistical power of the study [9]. To ensure a statistical power of 80%, the study was designed on a multicentre basis, so that the sample size was calculated a priori and a beta error of 0.2 and an alpha error of 0.05 were deemed acceptable. Of the six possible comparisons between the four therapy schedules, two, namely diclofenac sodium versus dipyrone 1 g and diclofenac sodium versus dipyrone 2 g, did not satisfy the minimal statistical power required. However, the results for those comparisons were very close (67% and 73%, respectively).

On the basis of the results, it may reasonably be concluded that there was no difference in the clinical efficacy of dipyrone 1 g and 2 g, between either of those two treatments and pethidine 100 mg, and between pethidine and diclofenac sodium 75 mg, all the treatments being administered by the intramuscular route. Any of these alternatives had acceptable clinical efficacy.

In the light of the data on adverse effects, the results have immediate practical implications. First, there is no reason to use pethidine as the treatment of first choice, as its adverse effects were comparatively common in relation to similar clinical efficacy. Some of them, such as hallucinations and/or confusion, lipothymia and/or orthostatic hypotension, and nausea and/or vomiting are clinically important. Second, the i.m. administration of dipyrone in doses higher than 1 g is unjustified. Preparations of 2 g, or 2 g plus an spasmolytic (frequently used in this country) contain too high a dose for this therapeutic use, although the adverse effects did not appear to be increased. Third, diclofenac sodium is a valid therapeutic alternative, with an efficacy similar to that of pethidine, and reasonable side effects, for this indication. The last practical implication is to confirm the possibility of effective cooperation between departments of drug regulation and scientific societies for resolving clinical problems using the most suitable methodological tool, the controlled clinical trial.

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References

1. Lundstam S, Wahlander L, Leissner KH, Kral JG (1982) Prostaglandine-synthetase inhibition with diclofenac sodium in treatment of renal colic: comparison with use of a narcotic analgesic. Lancet I: 1096–1097
2. Vignoni A, Fierro A, Morechini G, Cau M, Agostino A, Daniele E, Foti G (1983) Diclofenac sodium in ureteral colic: double blind comparison trial with placebo. J Intern Med Res 11: 303–307
3. Hetherigton JW, Philp NH (1986) Diclofenac sodium versus pethidine in acute renal colic. Br Med J 292: 237–238
4. Lehtonen T, Kellokumpu I, Permi J, Sorsila O (1983) Intravenous indomethacin in the treatment of ureteric colic. Ann Clin Res 15: 197–199
5. Comeri C, Radice GP, Duvia R, Manganini V, Monza G (1984) Efficacy and safety of non-steroidal anti-inflammatory drugs in ureteral colic. A double-blind controlled trial (Abstract n° 71) Urol Res 12: 45
6. Miralles R, Camí J, Torné J, Garcés JM, Badenas JM (1987) Diclofenac versus Dipyrone in acute renal colic: a double-blind controlled trial. Eur J Clin Pharmacol 33: 527–528
7. Dixon WJ (1985) BMDP Statistical Software. University of California Press
8. Cohen J (1977) Statistical power analysis for the behavioural sciences. Academic Press New York
9. Freiman JA, Chalmers TC, Smith H, Kuebler RR (1978) The importance of beta, type II error and sample size in the design and interpretation of the randomized control trial. N Engl J Med 299: 690–694

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