

# Piroxicam fast-dissolving dosage form vs diclofenac sodium in the treatment of acute renal colic: a double-blind controlled trial

A. SUPERVÍA, J. PEDRO-BOTET, X. NOGUÉS, J.L. ECHARTE,\* S. MÍNGUEZ, M.L. IGLESIAS\* and A. GELABERT†

Departments of Internal Medicine, \*Emergency and †Urology, Hospital del Mar, Universidad Autónoma de Barcelona, Barcelona, Spain

**Objective** To assess the possible therapeutic effect of 40 mg sublingual piroxicam (fast-dissolving dosage form, FDDF) compared with intramuscular 75 mg diclofenac, as a reference drug, on acute renal colic in a randomized, double-blind controlled clinical trial.

**Patients and methods** Eighty patients were assigned to one of two treatment groups; one received an intramuscular injection with 0.2 mL distilled water and two sublingual tablets of 20 mg piroxicam FDDF, and the other received an intramuscular injection with 75 mg diclofenac sodium and two sublingual tablets of placebo. Pain intensity was evaluated by the patient using a visual analogue scale and by the observers. Vital signs at baseline and 30 min after the administration of the study drugs were also recorded.

**Results** The overall efficacy of the treatment was 81%; nine patients in the piroxicam and six in the diclofenac group (no significant difference) required rescue treat-

ment. Compared with baseline levels, the pain relief was significant ( $P < 0.001$ ) at 30 min in both groups. Twenty-two patients in the piroxicam and 25 in the diclofenac group attained complete pain relief at 30 min, as evaluated by the observer (no significant difference). Both treatments were similarly effective in decreasing vital signs, mainly systolic blood pressure, heart and respiratory rates. However, when the percentage change was compared between the groups, piroxicam significantly decreased the respiratory rate ( $P < 0.03$ ).

**Conclusion** Piroxicam FDDF is as effective as parenteral diclofenac in emergency renal colic treatment. Furthermore, its ease of self-administration increases patient compliance and potential use in general practice.

**Keywords** Diclofenac, pain score, piroxicam FDDF, renal colic, vital signs

## Introduction

Renal colic is typically caused by acute urinary tract obstruction and commonly provokes the need for medical attention in emergency departments. Stones causing ureteric obstruction are a potent stimulus for renal prostaglandin synthesis, resulting in increased renal blood flow and diuresis [1,2]. The diuretic properties of prostaglandins cause increased intrarenal pressure and the pain of acute renal colic arises from the distension of the collecting system or renal capsule [3,4]. With better understanding of the pathophysiology of renal colic [5,6], NSAIDs have been widely used [7], but the need to achieve a prompt analgesic effect usually requires the use of parenteral analgesic therapy. Piroxicam, a NSAID with a long half-life and potent analgesic activity similar to that of indomethacin [8], has recently been

developed in a new formulation as fast-dissolving tablets (fast-dissolving dosage form, FDDF), which are easily administered sublingually. The bioavailability of this FDDF preparation is similar to that of standard tablets and has not caused harmful effects in the mouth. The only difference in pharmacokinetic terms is that piroxicam FDDF achieves an earlier rise in plasma drug levels during the first 15–30 min, indicating quicker dissolution and subsequent absorption during this period [9]. Although the analgesic effect of piroxicam FDDF in several pain states, including rheumatic [10–15] and non-rheumatic conditions, e.g. pain after surgery [16], dysmenorrhea [17], headache and migraine [18], has been investigated in randomized double-blind comparative trials, no studies have evaluated the use of this drug in renal colic.

The aim of the present study was to assess the possible therapeutic effect of sublingual piroxicam FDDF compared with parenteral diclofenac, as a reference drug, on acute renal colic.

Accepted for publication 17 September 1997

## Patients and methods

Patients of both sexes, aged 18–65 years, admitted to the emergency department with acute renal colic were included in a double-blind, controlled trial. The diagnosis was confirmed by clinical signs and symptoms, urine analysis or visualization of the calculus by abdominal radiography or ultrasonography. Patients with a history of allergy to salicylates or other NSAIDs, concomitant treatment with these drugs during the previous 24 h, oral mucosal lesions, haematological disorders, peptic ulcer or gastrointestinal bleeding, anticoagulation therapy, impaired renal function (serum creatinine concentration >20 mg/L), as well as pregnant women and nursing mothers, were excluded. The protocol was approved by the hospital ethics committee and by the Spanish Health Authority Committee (Dirección General de Farmacia del Ministerio de Sanidad, DGFPS 95/265). Informed consent was obtained from all participants.

Recruited participants were randomly assigned to one of two treatment groups; one received an intramuscular injection with 0.2 mL distilled water and two sublingual tablets of piroxicam FDDF 20 mg (Feldene flass<sup>®</sup>, Pfizer SA), and the other received an intramuscular injection with diclofenac sodium 75 mg (Voltaren<sup>®</sup>, Geigy) and two sublingual tablets of placebo. No other medication was administered during the evaluation period.

The double-blind nature of the trial was guaranteed by the 'blind observer' technique. The medication was kept in a randomly closed numbered envelope and administered by a nursing team in the absence of the physician; a medical team diagnosed and evaluated the patients.

The duration of the trial was 30 min, starting from administration of the treatment (baseline). Pain was evaluated as the main clinical variable and was assessed simultaneously by patients and observers at baseline and 30 min after administration of the study drugs. Pain intensity was evaluated by the patient according to a 10 cm divided line serving as a visual analogue scale (VAS): point 0 was qualified as 'no pain', and point 10 as 'the most excruciating pain'. The observer graded the pain experienced at each point in time as: 0, no pain; 1, mild, expressed by the patient as discomfort rather than true pain; 2, moderate, described as intense but without psychomotor agitation; and 3, severe, referred as unbearable and accompanied by psychomotor agitation. If, according to the VAS 30 min after drug administration, the pain score had not at least halved from the initial value, rescue treatment with an intramuscular injection of pethidine 75 mg (Dolantina<sup>®</sup>, Bayer) was given. Blood pressure, heart and respiratory rates were recorded at baseline and 30 min after administration of study medication. Additionally, all side-effects spontaneously men-

tioned by the patients were recorded by the observer.

A minimum number of patients was established at the outset to ensure that the statistical power of the study would be at least 80%, given an alpha and beta error of 0.05 and 0.2, respectively.

The homogeneity of the descriptive variables of the two treatment groups was examined by ANOVA. Percentage pain improvement was analysed with the chi-square test. Means of independent variables and proportions were compared using Student's *t*-test; the data are presented as the mean (SD).

## Results

Eighty non-consecutive patients suffering from acute renal colic were included during the 10-month study period and randomly assigned to one of the two treatment groups. Forty patients (23 men and 17 women, mean age 36.5, SD 14.1 years) received sublingual piroxicam FDDF and a distilled water injection; 11 of these (28%) had a history of renal colic. The remaining 40 patients (31 men and 9 women, mean age 41.5, SD 15.2 years) received diclofenac and two sublingual tablets of placebo; 17 (43%) had a history of renal colic. There was no significant difference between the groups in age, blood pressure, heart and respiratory rates on admission (Table 1).

According to the need for rescue therapy, the overall efficacy of the treatment was 81%; 15 patients, nine in the piroxicam FDDF group and six in the diclofenac group (NS), required rescue treatment. The pain intensity scores were similar at baseline for both treatment groups, at 79.8 (14.7) and 76.0 (14.2), respectively, and decreased significantly ( $P < 0.001$ ) at 30 min to 24.9 (36.1) and 15.5 (25.7), respectively. The decline was similar when patients who required rescue treatment were excluded. There were no significant differences when the percentage of decrease in pain relief was compared for the same point. When the pain relief was graded by the observer, 45 patients reached grade 0 at the end of the trial; of these, 22 were receiving piroxicam FDDF and 23 diclofenac (NS).

Both treatments were similarly effective in decreasing vital signs, mainly systolic blood pressure, heart and respiratory rates. However, when the percentage change between the groups was compared, piroxicam FDDF significantly decreased the respiratory rate ( $P < 0.03$ ; Table 1). Adverse effects occurred in only one case, i.e. dizziness in one patient of the diclofenac group, which require no medical treatment.

**Table 1** Mean (SEM) values of the vital signs before and after drug treatment

| Piroxicam | FDDF        |              |             | Diclofenac  |              |           |          |
|-----------|-------------|--------------|-------------|-------------|--------------|-----------|----------|
|           | Baseline    | 30 min       | % change    |             | Baseline     | 30 min    | % change |
| SBP       | 130.2 (3.7) | 126.4 (2.4)* | 2.1 (1.4)   | 137.8 (3.8) | 132.8 (3.1)* | 2.8 (1.4) |          |
| DBP       | 75.9 (2.3)  | 73.1 (1.4)   | 1.8 (2.1)   | 77.3 (2.2)  | 75.9 (1.8)   | 0.8 (1.7) |          |
| HR        | 78.6 (2.3)  | 75.4 (1.9)*  | 3.1 (1.4)   | 79.8 (1.8)  | 73.9 (1.4)†  | 6.7 (1.5) |          |
| RR        | 19.7 (0.7)  | 16.6 (0.3)†  | 13.7 (2.4)‡ | 17.8 (0.4)  | 16.4 (0.3)†  | 7.0 (2.1) |          |

SBP, Systolic blood pressure (mmHg); DBP, Diastolic blood pressure (mmHg); HR, Heart rate (b.p.m); RR, Respiratory rate (breaths/min). \* $P < 0.05$  and † $< 0.001$  compared with baseline; ‡ $P < 0.03$  compared with diclofenac group.

## Discussion

Urolithiasis is a common disorder, affecting 1–5% of the population in industrialized countries, with a lifetime risk of 20% in white men and 5–10% in women [19]. In the USA, opioids are the primary means of controlling pain in patients with renal colic. However, since the late 1970s, NSAIDs have been widely used outside the USA to treat renal colic and many studies have confirmed their efficacy [20–27]. In a recent meta-analysis, Labrecque *et al.* [7] concluded that parenteral NSAIDs were more effective than placebo and at least as effective as analgesic agents (primarily opioids) in the emergency treatment of acute renal colic. NSAIDs are as effective as these agents when given parenterally, but this route has the disadvantage of requiring either admission or the presence of medical staff before pain is relieved. NSAID suppositories have been proposed as an alternative to the parenteral form in the treatment of renal colic [28–30]. However, a better alternative would seem to be sublingual administration, which has fewer disadvantages than other routes.

The present study is the first to compare two NSAIDs, one sublingual and the other intramuscular, in a randomized, double-blind design. According to the main criterion for evaluating the efficacy of the drugs used, i.e. the need or not for rescue treatment, there was no significant difference between the treatment groups and the overall efficacy (81%) agrees with that from previous studies [20,23]. Thus, both sublingual piroxicam FDDF 40 mg and intramuscular diclofenac sodium 75 mg were effective in the treatment of acute renal colic. Furthermore, there were no severe adverse effects.

From a haemodynamic perspective, there was a correlation between pain relief and improved blood pressure, heart and respiratory rates which suggests that the stress of the painful condition clearly influences vital signs. Conversely, piroxicam FDDF induced a greater decrease in hyperventilation status compared with diclofenac and, therefore, this could be interpreted as a better clinical objective response to pain reduction, although there

were no significant differences in terms of satisfactory pain relief.

Other clinical benefits of interest which may be associated with this quick-dissolving formulation of piroxicam include: (i) ease of use, which may improve patient compliance; (ii) self-administration, which renders it useful in hospital and particularly in general practice, and for patients familiar with the symptoms of renal colic; and (iii) because it is not a controlled drug, piroxicam FDDF can be administered by all nursing staff, which is of practical importance in a busy ward.

The efficacy of piroxicam FDDF will require confirmation by future multicentre trials, but that patients responded positively to piroxicam FDDF compared with parenteral diclofenac appears to offer new possibilities in the treatment of acute renal colic.

## Acknowledgements

The authors thank the staff physicians, housemen, and nursing team of the Emergency Department of the Hospital del Mar and Miss C. O'Hara for English review of the manuscript.

## References

- 1 Johnston H, Herzog J, Laurel D. Effects of prostaglandin E2 on renal hemodynamic sodium and water excretion. *Am J Physiol* 1967; **213**: 939–46
- 2 Olsen U, Magnussen M, Eilertsen E. Prostaglandins, a link between hydro and haemodynamic in dog. *Acta Physiol Scand* 1976; **97**: 369–76
- 3 Holmlund D. Ureteral stones: an experimental and clinical study of the mechanism of passage of arrest of ureteral stones. *Scand J Urol Nephrol* 1968; **1** (Suppl. 1): 1–80
- 4 Holmlund D, Sjodin J. Treatment of ureteral colic with intravenous indomethacin. *J Urol* 1978; **120**: 676–7
- 5 Holmlund D. The pathophysiology of ureteral colic. *Scand J Urol Nephrol* (Suppl) 1983; **75**: 25–7
- 6 Van Laecke E, Oosterlinck W. Physiopathology of renal colic and the therapeutic consequences. *Acta Urol Belg* 1994; **62**: 15–8

- 7 Labrecque M, Dostaler LP, Rouselle R, Nguyen T, Poirier S. Efficacy of nonsteroidal anti-inflammatory drugs in the treatment of acute renal colic. A meta-analysis. *Arch Intern Med* 1994; **154**: 1381–7
- 8 Brodgen RN, Heel RC, Speight TM, Avery GS. Piroxicam: a review of its pharmacological properties and therapeutic efficacy. *Drugs* 1984; **28**: 293–323
- 9 Ronca F, Palmieri L, Ronca G. Effetto della formulazione e della via di somministrazione sulla velocità di assorbimento del piroxicam. *Basi Raz Ter* 1994; **24**: 1–6
- 10 Franchin F, Capozzi M, Commessati P, Bancheri C, Gospodinoff L, Pipino F. Piroxicam compresse sublinguali a rapida dissoluzione vs diclofenac nel trattamento delle affezioni acute dell'apparato muscolo-scheletico. *Minerva Ortop Traumatol* 1993; **44**: 387–94
- 11 Minisola G, Bancheri C, Bogliolo A *et al.* Clinical experience with the use of piroxicam in fast-dissolving sublingual capsules in acute recurrent osteoarthritis. *Clin Ther* 1993; **143**: 519–29
- 12 Consoli G, Covelli M, Di Matteo L *et al.* Piroxicam compresse sublinguali a rapida dissoluzione versus naprossene nel trattamento dell'osteartrosi riacutizzata. Ricerca clinica policentrica. *Minerva Med* 1994; **85**: 89–96
- 13 Montecucco C, Caporali R, Ronchetti A, Rossi S, Comaschi E. FDDF (fast dissolving dosage form) piroxicam for sublingual administration in the treatment of rheumatoid arthritis. *Minerva Med* 1994; **85**: 633–8
- 14 Auvinet B, Crielaard JM, Mantfeuffel GE, Müller P on behalf of the Multicenter piroxicam FDDF European Study Group. A double-blind comparison of piroxicam fast-dissolving dosage form and diclofenac enteric-coated tablets in the treatment of patients with acute musculoskeletal disorders. *Curr Ther Res* 1995; **56**: 1142–53
- 15 Englert R, Fontanesi G, Muller P, Ott H, Rehn L, Silva H. Piroxicam fast-dissolving dosage form in the treatment of patients with acute low back pain. *Clin Ther* 1996; **18**: 843–52
- 16 Dolci G, Ripari M, Pacifici L. Piroxicam compresse sublinguali. Valutazione clinica. *Dental Cadmos* 1993; **8**: 48–56
- 17 Ragni N, Ciccarelli A. La terapia della dismenorrea primaria con piroxicam sublinguale. *Minerva Ginecol* 1992; **45**: 365–75
- 18 Nappi G, Micieli G, Tassorelli C, Viotti E, Altavilla T. Effectiveness of a piroxicam fast dissolving formulation sublingually administered in the symptomatic treatment of migraine without aura. *Headache* 1993; **33**: 296–300
- 19 Balaji KC, Menon M. Mechanism of stone formation. *Urol Clin North Am* 1997; **24**: 1–11
- 20 Miralles R, Camí J, Gutiérrez J, Torné J, Garcés JM, Badenas JM. Diclofenac versus dipyron in acute renal colic: a double-blind controlled trial. *Eur J Pharmacol* 1987; **33**: 527–8
- 21 Kinn AC, Elabarouni J, Seideman P, Sollevi A. The effect of diclofenac sodium on renal function. *Scand J Urol Nephrol* 1989; **23**: 153–7
- 22 Sanahuja J, Corbera G, Garau J, Pla R, Carre MC. Intramuscular diclofenac sodium versus intravenous Baralgin in the treatment of renal colic. *DICP* 1990; **24**: 361–4
- 23 Collaborative Group of the Spanish Society of Clinical Pharmacology. Comparative study of the efficacy of dipyron, diclofenac sodium and pethidine in acute renal colic. *Eur J Pharmacol* 1991; **40**: 543–6
- 24 Marthak KV, Gokarn AM, Rao AV *et al.* A multicentre comparative study of diclofenac sodium and pethidine in renal colic patients in India. *Curr Med Res Opin* 1991; **12**: 366–73
- 25 Muriel C, Ortiz P. Efficacy of two different intramuscular doses of dipyron in acute renal colic. Cooperative Study Group. *Methods Find Exp Clin Pharmacol* 1993; **15**: 465–9
- 26 Al-Waili NSD. Intramuscular tenoxicam to treat acute renal colic. *Br J Urol* 1996; **77**: 15–6
- 27 Cordell WH, Wright SW, Wolfson AB *et al.* Comparison of intravenous ketorolac, meperidine, and both (balanced analgesia) for renal colic. *Ann Emerg Med* 1996; **28**: 151–8
- 28 Thompson JF, Pike JM, Chumas PD, Rundle JSH. Rectal diclofenac compared with pethidine injection in acute renal colic. *Br J Med* 1989; **299**: 1140–1
- 29 Nissen I, Birke H, Olsen JB *et al.* Treatment of ureteric colic. Intravenous versus rectal administration of indomethacin. *Br J Urol* 1990; **65**: 576–9
- 30 Cordell WH, Larson TA, Lingeman JE *et al.* Indomethacin suppositories versus intravenously titrated morphine for treatment of ureteral colic. *Ann Emerg Med* 1994; **23**: 262–9

## Authors

- A. Supervía, MD, Senior Resident.  
 J. Pedro-Botet, MD, PhD, Professor Clinical Medicine.  
 X. Nogués, MD, PhD, Associated Professor.  
 J.L. Echarte, MD, Emergency Consultant.  
 S. Mínguez, MD, Senior Resident  
 M.L. Iglesias, MD, Emergency Consultant.  
 A. Gelabert, MD, Professor and Head.
- Correspondence: Professor J. Pedro-Botet, Department of Internal Medicine, Hospital del Mar, Passeig Marítim, 25–29, 08003 Barcelona, Spain.