Intramuscular Etofenamate versus Diclofenac in the Relief of Renal Colic
A Randomised, Single-Blind, Comparative Study

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Abstract

Objective: To compare the efficacy and adverse effects of intramuscular etofenamate and intramuscular diclofenac in the relief of acute renal colic.

Patients and methods: A multicentre, randomised, single-blind study was performed in 119 patients admitted to the emergency room for renal colic. Patients were assigned to treatment with either etofenamate 1000mg or diclofenac 75mg, both administered intramuscularly. Pain was self-assessed using a 4-point verbal rating scale (VRS) and a visual analogue scale (VAS) just before drug administration and 30, 60, 120 and 240 min later.

Results: The two groups were similar with regard to baseline characteristics. The percentages of patients who reported an improvement in the VRS at 60 min post-administration (primary variable) were 84.5% with etofenamate and 83.3% with diclofenac (p = 0.73). At the other timepoints (30, 120 and 240 min), the proportions of patients improved were, respectively, 69.5%, 82.6% and 79.3% in the etofenamate group, and 75.0%, 81.7% and 80.0% in the diclofenac group. The VAS score showed a statistically significant improvement in both groups, but no differences between groups were found.

Analgesic rescue medication was required by 11 (18.6%) patients in the etofenamate group and by 12 (20.0%) patients in the diclofenac group. Mild to moderate adverse events were reported by 3.4% of patients receiving etofenamate and by 5.0% of patients receiving diclofenac.

Conclusion: Etofenamate and diclofenac were similarly effective and tolerated in the relief of acute renal colic.
Renal colic has an annual incidence of approximately 16 per 10,000 individuals, and a lifetime incidence of 2–5%,[1] and is mainly caused by nephrolithiasis. The passage of stone through the ureter is a common mechanical cause of urinary tract obstruction. When the obstruction is acute, pain is the predominant clinical symptom and is due to the distension of the collecting system or renal capsule. The pain begins gradually but increases over time to become so severe that it is often described as the worst pain a patient has ever experienced, justifying the urgent prescription of rapid and effective analgesia even before diagnostic confirmation.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and narcotic analgesics are the most commonly used drugs in the acute relief of renal colic, and both groups have been shown to be effective in randomised, prospective studies.[2,3] However, narcotics can cause excessive sedation.[4] The inhibition of cyclo-oxygenase by NSAIDs decreases prostaglandin production and, consequently, the smooth muscle activity of the ureteral and renal pelvis, oedema and inflammation. The reduction in local oedema and inflammation can have a positive influence in stone progression.[5]

Etofenamate is a NSAID of the flufenamic acid derivative group and possesses strong anti-inflammatory and analgesic activity. In clinical practice, it is only administered by cutaneous and intramuscular routes because it has poor oral bioavailability.

The present study aimed to compare the efficacy and adverse effects of intramuscular etofenamate and diclofenac in the relief of acute renal colic. Diclofenac was chosen as the reference product because its use has been established in the treatment of renal colic.[6-8]

**Patients and Methods**

**Study Design and Ethical Approval**

This was a multicentre, comparative, parallel group, randomised, single-blind study carried out at emergency care units. The study was conducted according to the principles of the current revision of the Declaration of Helsinki and according to Good Clinical Practice guidelines. An independent Ethics Committee revised and approved the study protocol and the information provided to the patients in each centre. Written informed consent was obtained for each patient prior to enrolment in the study.

**Study Population and Procedures**

Patients with moderate to severe pain suggestive of a clinical diagnosis of acute renal colic, who had not taken any analgesic or antispasmodic drugs in the previous 2h, were selected. To confirm the diagnosis of renal colic, patients were observed for spontaneous voiding of a calculus, and an abdominal x-ray, ultrasonography or urography was performed. Other procedures, such as urinalysis or blood tests, were performed when needed, according to the investigator’s judgement. Subjects with pain symptoms lasting more than 12h, any condition that could constitute a contraindication to NSAIDs, evidence of drug addiction, unavailability for completing the pain self-assessment scales, pregnant or lactating women or women of childbearing potential not using effective contraception were excluded.

Eligible patients were randomly assigned to treatment with a single intramuscular dose of etofenamate (1000mg/2mL, Reumon® IM, Laboratorios Bial, S. Mamede do Coronado, Portugal) or diclofenac (75mg/3mL, Voltaren® IM, Novartis, Sintra, Portugal). A single-blind procedure was followed: patients were unaware of which treatment they had received.

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1 The use of tradenames is for product identification purposes only and does not imply endorsement.
### Table I. Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Etofenamate (n = 59)</th>
<th>Diclofenac (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex [n (%)]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>40 (67.8)</td>
<td>36 (60.0)</td>
</tr>
<tr>
<td>female</td>
<td>19 (32.2)</td>
<td>24 (40.0)</td>
</tr>
<tr>
<td><strong>Age (y) [mean ± SD (range)]</strong></td>
<td>47.4 ± 17.0 (21–80)</td>
<td>45.0 ± 14.7 (20–73)</td>
</tr>
<tr>
<td><strong>Height (cm) [mean ± SD (range)]</strong></td>
<td>167.6 ± 8.1 (152–182)</td>
<td>165.3 ± 8.5 (140–180)</td>
</tr>
<tr>
<td><strong>Weight (kg) [mean ± SD (range)]</strong></td>
<td>75.0 ± 10.8 (55–105)</td>
<td>72.8 ± 11.5 (51–100)</td>
</tr>
<tr>
<td><strong>VRS pain score [n (%)]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe</td>
<td>37 (62.7)</td>
<td>36 (60.0)</td>
</tr>
<tr>
<td>moderate</td>
<td>22 (37.3)</td>
<td>24 (40.0)</td>
</tr>
<tr>
<td><strong>VAS score (mm) [mean ± SD (range)]</strong></td>
<td>80.1 ± 17.7 (30–100)</td>
<td>78.5 ± 16.5 (42–100)</td>
</tr>
</tbody>
</table>

**VAS** = visual analogue scale; **VRS** = verbal rating scale.

been assigned to; blinding of the healthcare personnel was considered to be unfeasible because of the different characteristics of the two products (volume, colour and viscosity).

Pain intensity was self-assessed by the patients using a 4-point verbal rating scale (VRS) [0 = absence of pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain] as described elsewhere,[8] and a 100mm visual analogue scale (VAS), in which the left end represented “absence of pain” and the right end represented the “most painful situation you can imagine”. Pain intensity was assessed just before product administration and 30, 60, 120 and 240 min later. Patients were allowed to receive rescue medication when required, according to the investigator’s judgement.

All adverse events spontaneously reported by patients during the study were characterised and recorded.

### Statistical Analysis

The primary efficacy parameter defined in the protocol was the proportion of patients reporting an improvement in the VRS after 60 min. According to published data and assuming that 85% of diclofenac-treated patients will improve, a sample size of 60 patients per group will detect differences between treatments, with a level of significance of 5% and a power of 80%. The secondary efficacy variables were the proportion of patients reporting an improvement in the VRS in the 30-, 120- and 240-min assessments, the evolution of the VAS score during the study period, and the proportion of patients requiring rescue medication. All statistical tests were two-tailed with a 5% level of significance.

All patients who were administered medication were considered for adverse event analysis. The statistical package used was Statistica 5.5 (StatSoft, Inc., Tulsa, OK, USA).

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**Fig. 1.** Percentage of patients reporting improvement in the verbal rating scale from baseline after administration of either etofenamate or diclofenac in patients with renal colic.
respectively. VAS scores remained not significantly different at 120 and 240 min. Analgesic rescue medication was required by 11 (18.6%) patients in the etofenamate group and by 12 (20.0%) patients in the diclofenac group (figure 3). The decision to administer rescue medication was based on the investigator’s judgement, taking into account the severity of pain. Drugs and doses used were decided according to the centre protocols for treatment of acute renal colic in clinical routine. Pethidine (n = 13), with or without metoclopramide, was the most used rescue analgesic, followed by tramadol (n = 5), with or without metoclopramide. Paracetamol (n = 2) and other NSAIDs, and dipyrone or thiocolchicoside were also used. One patient in the etofenamate group who had reported significant improvement at the 30-min evaluation unexpectedly left the emergency care unit before the 60-min evaluation.

Efficacy

A total of 119 patients were enrolled in the study and were randomly assigned to treatment with either etofenamate (n = 59) or diclofenac (n = 60). Groups were similar with regard to baseline characteristics (table I). Most of the patients were diagnosed by means of abdominal x-ray (82.4%) and/or ultrasonography (69%). Fourteen (11.8%) patients spontaneously voided a calculus and four (3.4%) were submitted to urography.

No significant difference was found between the treatments with regard to the primary efficacy parameter: at 60 min, the VRS showed that 84.5% of patients treated with etofenamate and 83.3% treated with diclofenac had improved (figure 1) [p = 0.73; χ² test]. At the other timepoints (30, 120 and 240 min), the proportions of patients improved were, respectively, 69.5%, 82.6% and 79.3% in the etofenamate group and 75.0%, 81.7% and 80.0% in the diclofenac group (figure 1).

The VAS score showed a statistically significant improvement in both groups (figure 2). At 30 and 60 min, the average VAS scores were, respectively, 40.7 ± 27.8 and 33.2 ± 25.3 (95% CI 33.6–47.8; 26.7–39.7; not significant) and 23.1 ± 26.5 and 18.3 ± 24.9 (95% CI 16.1–30.1; 11.7–24.9; not significant) in the etofenamate and diclofenac groups, respectively. VAS scores remained not significantly different at 120 and 240 min.

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Tolerability

In the etofenamate group, a total of two adverse events (somnolence and pain at the injection site) were reported by two (3.4%) patients. In the diclofenac group, three (5.0%) patients reported a total of five adverse events (upper abdominal pain [n = 2], nausea, vomiting and somnolence). All adverse
events were mild to moderate in intensity and no withdrawal due to adverse events was reported.

Discussion

The efficacy of intramuscular etofenamate in several painful conditions has been confirmed in a number of controlled studies, including those comparing intramuscular indomethacin in the treatment of postoperative pain and swelling,[11] and those comparing intramuscular diclofenac in the treatment of fresh blunt injuries[12] and the acute lumbar syndrome.[13] To date, only one exploratory open-label study with etofenamate in renal colic has been reported.[14] Our study aimed to obtain additional evidence about the potential usefulness of etofenamate in this indication, comparing it with a standard NSAID. In spite of some concerns about the use of intramuscular diclofenac, such as delay in renal transit time[15] or exacerbation of pain as a result of the injection,[16] it was chosen as the comparator because it is widely used and is considered a treatment of choice in acute renal colic by some investigators.[6,17]

A single-blind design was used because the distinct product visual characteristics (volume, colour and viscosity) made blinding of the healthcare personnel unfeasible. A double-blind design would have been preferable, but was not possible to implement because of logistic constraints. However, the efficacy variables of this study were dependent on self-assessment scales (VRS and VAS) and, therefore, the chance of bias was minimised. These scales have been frequently used in similar studies and are generally considered to be reliable tools in the assessment of subjective symptoms such as pain.[10]

After intramuscular injection of diclofenac, an aqueous solution, maximum plasma concentrations occur at 20–30 min post-administration and decline rapidly, with an elimination half-life of 1.15h.[18] This pharmacokinetic profile is consistent with a rapid onset of action, but no sustained effects are guaranteed because the active moiety is rapidly cleared. In contrast, plasma concentrations of etofenamate, an oily solution, increase less rapidly, reaching a plateau 2h post-administration. Relatively high plasma levels persist for up to 10h, probably because of a ‘depot-like’ phenomenon resulting from the oily nature of the solution.[19] Theoretically, this profile would allow a more prolonged action when compared with diclofenac.

Both etofenamate and diclofenac markedly improved pain in all efficacy variables. Pain relief obtained with diclofenac in this study was consistent with that reported in the literature.[7,8,20] No statistically significant differences were found between the groups in any of the efficacy variables.

Diclofenac and etofenamate were well tolerated; only a few mild to moderate side effects were reported, consistent with the known adverse event profile of the drugs.

Conclusion

In conclusion, the results of this single-blind, randomised, controlled study confirm previous preliminary evidence that intramuscular etofenamate is a useful option in the treatment of patients with acute renal colic.

Acknowledgements

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References

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