ORAL BROMFENAC 10 AND 25 MG COMPARED WITH SUBLINGUAL BUPRENORPHINE 0.2 AND 0.4 MG FOR POSTOPERATIVE PAIN RELIEF

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SUMMARY
The aim of this single-dose, randomized, positive control, double-dummy, double-blind, parallel group study was to compare oral bromfenac 10 and 25 mg with sublingual buprenorphine 0.2 and 0.4 mg for treatment of postoperative pain. We studied 91 patients with moderate or severe pain after general surgical or orthopaedic operations, using pain intensity, pain relief, adverse effect, mood and sedation outcomes. There was a significant analgesic dose-response for buprenorphine, showing study sensitivity, but not for bromfenac. The two bromfenac treatments were significantly superior to the two buprenorphine treatments. Significantly more patients reported nausea with buprenorphine. There was evidence of a ceiling effect for analgesia with bromfenac. (Br. J. Anaesth. 1993; 71: 814–817)

KEY WORDS

The precise roles of the two drug classes, opioids and non-steroidal anti-inflammatory drugs (NSAID), in the management of postoperative pain remain contentious. For many years opioids were the only injectable analgesics available, but the introduction of injectable NSAID has encouraged wider use of NSAID immediately after surgery. Oral opioids have a poor reputation for postoperative pain control [1], but there is strong evidence from randomized controlled trials for the effectiveness of oral NSAID in treating postoperative pain [2, 3].

The evidence from single-dose randomized controlled trials suggests that injectable NSAID can provide analgesia indistinguishable from that obtained with injected opioids [4], and that oral NSAID can also match the effect of an injected opioid [5]. However, a ceiling effect has been demonstrated for NSAID analgesic effect [5, 6] by both oral [6] and injected routes [7].

This study was designed to compare oral bromfenac, a new 2-amino-3-benzoylphenylacetic acid derivative NSAID, with an opioid, sublingual buprenorphine, for the treatment of postoperative pain.

Bromfenac has anti-inflammatory, antipyretic and analgesic properties. In a previous study of pain after dental extraction, bromfenac in doses of 5, 25 and 50 mg was significantly better than placebo and the 25- and 50-mg doses were also significantly superior to aspirin 650 mg [8]. Bromfenac 5, 10 and 25 mg was also compared with paracetamol 1 g and placebo for pain relief after orthopaedic surgery; the 5-mg dose of bromfenac was superior to placebo and the 10-mg dose was equivalent to paracetamol 1 g [2].

PATIENTS AND METHODS
This was a double-blind, double-dummy, parallel group, single-dose study, comparing oral bromfenac 10 or 25 mg with sublingual buprenorphine 0.2 or 0.4 mg. It was approved by the Central Oxford Research Ethics Committee. Men and women were eligible for the study if they were to undergo orthopaedic or general surgery. Patients were excluded if they had a history of peptic ulcer disease, hepatic or renal disease, intolerance to aspirin, buprenorphine or NSAID, respiratory disease sufficient to contraindicate the use of buprenorphine, or if they were taking coumarin-type anticoagulants or oral hypoglycaemic agents. Women were excluded if they were pregnant or breast feeding.

Patients experiencing moderate or severe pain (verbal rating scale) within 72 h of surgery were included if they had recovered sufficiently from surgery, were capable of taking oral medication, and if more than 3 h had elapsed since they had received any analgesic, tranquilizing or sedative drug. They were allocated to one of four groups: sublingual buprenorphine 0.2 mg (one buprenorphine 0.2 mg tablet, one placebo sublingual tablet and one placebo oral capsule); sublingual buprenorphine 0.4 mg (two buprenorphine 0.2 mg tablets and one placebo oral capsule); oral bromfenac 10 mg (two placebo sublingual tablets and one bromfenac 10 mg capsule); oral bromfenac 25 mg (two placebo sublingual tablets and one bromfenac 25 mg capsule).

Tablets and capsules were identifiable only by treatment number. Randomization was stratified at entry by initial pain intensity ("moderate" or
“severe”) and by type of surgery (general or orthopaedic). Randomization was in blocks of four, organized by random number generation.

A nurse observer administered all the study treatments. The oral capsule was given first and swallowed with water 100 ml, which was followed immediately by the two sublingual tablets, which were allowed to dissolve under the tongue. Patients were then assessed for up to 6 h after receiving the study treatment. If pain relief was inadequate after the first 1 h, patients were free to request further analgesia and standard postoperative analgesia was given.

Baseline assessments of patients were made for pain intensity, vital signs, mood and sedation. All assessments were made by one nurse observer (T.F.). Patients were reassessed at 0.5, 1, 1.5, 2, 3, 4, 5 and 6 h. Pain intensity, vital signs, mood and sedation assessments were repeated, together with assessments for pain relief and adverse effects. At the end of the 6-h study period, or at the time of remedication, an overall rating of the treatment was made by the nurse and by the patient.

Current pain intensity was measured by a categorical verbal rating scale (0 = none; 1 = mild; 2 = moderate; 3 = severe) using the question “how intense is the pain at the moment?”; by an eight-word scale (randomly placed words ranging from “no pain” to “excruciating”, scored 0-7) [9], by a visual analogue scale (100-mm line, left end labelled “no pain” and right end labelled “worst possible pain”) and by the McGill Pain Questionnaire using 78 descriptors in 20 groups. Pain relief was measured by a categorical verbal rating scale (0 = none; 1 = slight; 2 = moderate; 3 = good; 4 = complete) using the question “How much pain relief have you got at the present time?”; and by a visual analogue scale (100-mm line, left end labelled “no relief of pain” and right end labelled “complete relief of pain”).

Mood was measured with a visual analogue scale (100-mm line, left end labelled “worst I could feel” and right end labelled “best I could feel”). Sedation was measured by a categorical verbal rating scale (0 = alert; 1 = mildly drowsy; 2 = moderately drowsy; 3 = asleep). If patients were asleep, they were wakened for assessments. Systemic arterial pressure, heart rate and ventilatory frequency were measured by the nurse observer.

At the end of the 6-h study period, or at the time patients asked to withdraw from the study, both the nurse observer and the patient made a global rating of the study treatment (0 = poor; 1 = fair; 2 = good; 3 = very good; 4 = excellent). The nurse made her evaluation first, to avoid bias. Adverse effects, both volunteered and observed, were recorded, with scoring of intensity (0 = none; 1 = mild; 2 = moderate; 3 = severe).

Statistical analysis
It was estimated that 20 patients per group would be necessary to achieve power of 90% with an alpha level of 0.05 (one-tailed) to detect a difference between the four treatments of 1.5 on the categorical pain relief with SD of 0.3 [2].

Patients who were remedicated within the 6-h study period were given initial values of pain intensity and a pain relief score of zero for assessment times after remedication [10]. The McGill pain questionnaire was scored both for number of words chosen and for sum rank score. The sum of the pain intensity difference (four word SPID) and total pain relief (TOTPAR) scores were calculated [11], to produce an area under the curve of effect against time. The same calculation was used for the visual analogue equivalents (VASSPID for pain intensity and VASPR for pain relief), the eight-word verbal rating for pain intensity (WORDSPI) and the McGill word and total scores (McGill wordSPID and McGill scoreSPID, respectively). The overall sedation and mood scores (AUCSEDATION and AUCMOOD) were calculated by use of a trapezoidal formula.

Analysis of variance was used on the scores for the four treatments groups, and the Student’s t test was used for comparisons of pairs—one-tailed within drug between doses and two-tailed between drug. The incidence of adverse effects and time to remedication were compared using the chi-square test. All tests were performed using Statview 4 on a Macintosh IIci. Results are presented as mean (SEM).

RESULTS
We studied 91 patients between November 1989 and February 1991. Three patients did not fulfil the study design. Of these three, one was excluded from the final analysis, because she received additional analgesia at the 0.5-h assessment. Two were included: one developed a headache, thought to be caused by a dural tap, and was given paracetamol; the other inadvertently received an NSAID during the study. Their results to the time of remedication were included in the analysis (i.e. the same strategy as for other patients who were remedicated during the 6-h study period).

Details of the patients are shown in table 1; there were no significant differences between the four groups in age, sex, height, weight or duration of surgery (ANOVA).

Analgesic measures (table II)
There were statistically significant differences between the four groups for all analgesic outcome measures (ANOVA). Sublingual buprenorphine 0.4 mg gave significantly better analgesia than 0.2 mg on all analgesic outcome measures except for the patient and nurse global rating (one-tailed t test); there were no significant differences between the 10- and 25-mg doses of oral bromfenac (one-tailed t test).

Bromfenac 10 mg provided significantly better analgesia than both doses of buprenorphine on all analgesic measures (two-tailed t test). Bromfenac 25 mg provided significantly better analgesia than buprenorphine 0.2 mg on all measures, but was significantly better than buprenorphine 0.4 mg only for SPID, WORDSPI and patient global rating. The rank order was thus buprenorphine 0.2 mg < buprenorphine 0.4 mg < bromfenac 10 and 25 mg.
TABLE I. Patient characteristics, and duration and nature of surgical procedure (mean (range or SEM)). No significant difference between treatments overall (ANOVA)

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine 0.2 mg</th>
<th>Buprenorphine 0.4 mg</th>
<th>Bromfenac 10 mg</th>
<th>Bromfenac 25 mg</th>
</tr>
</thead>
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<td>24</td>
<td>23</td>
<td>21</td>
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<td>Age (yr)</td>
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<td>9:13</td>
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<td>170 (2)</td>
<td>168 (2)</td>
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<td>75 (3)</td>
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</table>

TABLE II. Analgesic outcome measures (mean (SEM)). Significant differences: *overall between the four treatment groups (ANOVA); ^between 0.2 and 0.4 mg buprenorphine (one-tailed t test); ¥between bromfenac 10 mg and buprenorphine 0.2 mg (two-tailed t test); ¥between bromfenac 10 mg and buprenorphine 0.4 mg (two-tailed t test); ¥between bromfenac 25 mg and buprenorphine 0.2 mg (two-tailed t test); ||between bromfenac 25 mg and buprenorphine 0.4 mg (two-tailed t test); **(chi-square)

Mean categorical verbal pain relief scores against time for the four groups reflect this rank order (fig. 1).

Non-analgesic outcome measures

There was a significant difference overall between the four treatment groups for AUCMOOD, with significantly greater mood scores with buprenorphine 0.4 mg than with 0.2 mg (one-tailed t test).

Bromfenac 10 mg provided significantly greater mood scores than either dose of buprenorphine (two-tailed t test) and AUCMOOD with bromfenac 25 mg was significantly greater than with buprenorphine 0.2 mg, but not buprenorphine 0.4 mg. There was no significant difference between the AUCMOOD scores for bromfenac 10 and 25 mg.

There was no significant difference overall between the four treatment groups for AUCSEDATION.

Adverse effects

More patients reported adverse effects after buprenorphine; twice as many patients (eight) had adverse effects with buprenorphine 0.2 mg compared with bromfenac 25 mg. The incidence of nausea was significantly greater with buprenorphine 0.4 mg, with five patients affected compared with none who received bromfenac (P < 0.02, chi-square).

Time to remedication

There was a statistically significant difference between the treatments for the number of patients who needed remedication before the end of the study (P < 0.02, chi-square). Only four patients who received the smaller dose of buprenorphine completed the 6-h study. In all but the two patients described above, this was because of inadequate pain relief and they were remedicated with standard analgesia.
DISCUSSION

The sensitivity of the study was demonstrated by the dose–response for sublingual buprenorphine—0.4 mg provided significantly better analgesia than 0.2 mg on all of the analgesic outcome measures (table II). Few other randomized, controlled trials have examined the dose–response for sublingual buprenorphine. In one such comparison of sublingual buprenorphine 0.2, 0.4 and 0.8 mg with i.m. morphine 4, 8 and 16 mg, a significant dose–response for sublingual buprenorphine was found, with a potency ratio to morphine of 1:15 [12].

Oral bromfenac provided better analgesia than sublingual buprenorphine (table II, fig. 1). Both 10- and 25-mg doses of bromfenac produced significantly better analgesia than the larger dose of buprenorphine (0.4 mg). Previous studies have suggested that oral NSAID provide better analgesia than i.m. opioids; oral ketoprofen 75 and 225 mg was equal to or more effective than i.m. morphine 5 and 10 mg [5]. It is perhaps less surprising, then, that oral bromfenac 10 mg was superior to sublingual buprenorphine 0.4 mg, and suggests that 0.8 mg would be necessary to provide equivalent analgesia, with an increased risk of unacceptable adverse effects.

There was no evidence of a dose–response for bromfenac; indeed, the analgesic scores for 10 mg were better than those for 25 mg on most outcomes. Such ceiling effects with NSAID have been reported previously in single-dose analgesic studies [5]; occasionally with NSAID, a dose–response is found for duration of analgesia, although not apparent on peak or total (TOTPAR) analgesia during the study period. The clinical conclusion is that in this setting there would be no advantage in giving bromfenac 25 mg rather than 10 mg. Bromfenac, in common with other oral NSAID, proved to be an effective analgesic for moderate or severe postoperative pain. The lesser incidence of adverse effects with NSAID compared with opioids at equivalent (or better) levels of pain relief suggests that oral NSAID should be used more in the management of postoperative pain.

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REFERENCES