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# DOUBLE-BLIND COMPARISON OF THE MORPHINE SPARING EFFECT OF CONTINUOUS AND INTERMITTENT I.M. ADMINISTRATION OF KETOROLAC

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## SUMMARY

*The morphine sparing effect of ketorolac 10 mg administered 4-hourly by intermittent i.m. injection was compared with a continuous i.m. infusion in a double-blind, placebo-controlled trial in patients undergoing upper abdominal surgery. During the 48-h postoperative period, each patient was provided with a patient-controlled analgesia (PCA) system which delivered bolus doses of morphine and administered the intermittent i.m. doses automatically via a computer controlled pump. In the first 24 h after surgery, there was a significant reduction in morphine demanded by both groups receiving ketorolac compared with placebo. Patients who received a continuous infusion of ketorolac after abdominal surgery required a median dose of morphine by PCA which was 49% less than controls. In the second 24 h and over the entire 48 h of the study, patients in the continuous group required significantly less morphine than those in the placebo group. The intermittent group used less than the placebo group, but this was not significant.*



**KEY WORDS**

*Analgesia: postoperative, PCAS. Analgesics: ketorolac, morphine.*


Patient controlled analgesia (PCA) provides better postoperative analgesia, as each patient determines the appropriate dose of analgesic necessary to produce acceptable pain relief [1]. If the patient is provided with morphine on demand from a PCA system, the analgesic efficacy of supplementary non-opioid analgesics and of techniques such as suggestion during anaesthesia may be determined objectively by measuring the reduction in morphine requirements compared with patients receiving placebo [2–4].

Ketorolac is a new non-opioid analgesic which has been shown in some studies to have analgesic activity which was not significantly different from that of morphine and pethidine [5, 6]. It has been used successfully in the treatment of postoperative orthopaedic pain [7, 8], and other types of acute pain. A previous placebo controlled study [9] using PCA has confirmed the analgesic potency of ketorolac following upper abdominal surgery. The present study was designed to compare the efficacy of intermittent with continuous administration of ketorolac during the first 48 h after upper abdominal surgery.

## PATIENTS AND METHODS

We studied patients aged 18–75 yr, weighing 40–95 kg, undergoing elective upper abdominal surgery. Patients with respiratory insufficiency, hepatic or renal impairment, or those known to abuse alcohol or drugs were excluded. The study was approved by the hospital Ethics Committee and conducted under a clinical trials exemption certificate. All patients were visited before surgery, the nature of the study explained, and written informed consent obtained.

All patients were premedicated with temazepam 20–40 mg orally; anaesthesia was induced with

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TABLE I. *Administration of drugs. All patients received a continuous i.m. infusion together with computer controlled i.m. injections every 4 h in the sequence shown*

| Patient group | Intermittent injection | Continuous infusion |
|---|---|---|
| Continuous | Placebo | Ketorolac |
| Intermittent | Ketorolac | Placebo |
| Placebo | Placebo | Placebo |

thiopentone 3–6 mg $kg^{-1}$ and maintained with nitrous oxide and enflurane in oxygen, with supplements of alfentanil as required.

At the end of surgery, patients were allocated randomly to receive one of three regimens (table I): a continuous i.m. infusion of ketorolac with intermittent injections of placebo (continuous group), intermittent i.m. injections of ketorolac with continuous infusion of placebo (intermittent group) or continuous and intermittent administration of placebo (placebo group). The continuous infusion was delivered by a Graseby Dynamics battery-powered syringe driver and the intermittent bolus doses by a computer controlled Braun Perfusor Secura syringe driver. Both were administered i.m. via a non-return valve into the deltoid through a 22-gauge Teflon cannula inserted in one site. Medications were identical in appearance and thus the study was conducted double-blind.

*Continuous ketorolac group*

Patients received a continuous i.m. infusion of ketorolac at a loading dose of 12.5 mg $h^{-1}$ for 30 min and at 2.5 mg $h^{-1}$ for the remainder of the study. The initial faster rate was designed to achieve a steady state concentration more rapidly. In addition, they received also intermittent i.m. injections of saline every 4 h under automatic computer control.

*Intermittent ketorolac group*

Patients received computer controlled intermittent i.m. injections of ketorolac 10 mg 4-hourly, together with a continuous i.m. infusion of saline administered as for the continuous group.

*Placebo group*

The placebo group received intermittent injections and continuous infusions of saline.

Immediately after the end of surgery, all three groups of patients were connected to the i.m. ketorolac delivery systems and to a PCA apparatus from which they were able to obtain i.v. bolus doses of morphine. The PCA system consisted of a standard Apple IIe microcomputer which was linked to an Imed 929 computer controlled infusion pump [10]. Data were stored automatically on magnetic disc for analysis later. This PCA system permitted the patient to signal to the machine when analgesia was required, by pressing a hand-held button twice within 1 s. A bolus dose of morphine 0.02 mg $kg^{-1}$ was delivered i.v. by the Imed pump with a "lock-out" time of 2 min. The Apple IIe computer also controlled a Braun Perfusor Secura syringe pump. This injected automatically every 4 h the intermittent i.m. dose of either ketorolac or saline.

Pain was measured using 100-mm visual analogue scores at 2–6 h after the start of the study (day 0), and on the morning and afternoon of postoperative day 1 and day 2.

Patient data were analysed using Student's *t* test or chi-square test as appropriate. Morphine consumption and visual analogue pain scores were analysed using repeated measures analysis of variance.

## RESULTS

Sixty-seven patients entered the study; 63 completed 24 h of the study satisfactorily and 61 completed the entire study. The magnetic disc used to store data from one patient in the continuous group was damaged and the data lost. Two patients were withdrawn from the continuous and one from the intermittent group during the first 24 h of the study because of machine failure. One patient was withdrawn from the intermittent group on request at 36 h and one from the continuous group at 34 h because the i.v. cannula was removed inadvertently. All patients who were withdrawn from the study received

TABLE II. *Patient data (mean (range or SD)).* * $P < 0.05$

| | Continuous | Intermittent | Placebo |
|---|---|---|---|
| Sex (M/F) | 9/10 | 10/13 | 10/11 |
| Age (yr) | 47.2* (27–71) | 48.6* (23–68) | 56.1 (42–68) |
| Weight (kg) | 63.5 (9.6) | 62.7 (12.1) | 68.3 (12.0) |
| Surgical procedure | | | |
| Cholecystectomy | 11 | 13 | 12 |
| Gastric surgery | 6 | 5 | 4 |
| Miscellaneous | 2 | 5 | 5 |

TABLE III. *Consumption of morphine (median and range).* ** $P < 0.01$; *** $P < 0.001$ *compared with placebo*

| | Morphine consumption (mg) | | |
|---|---|---|---|
| | Continuous group | Intermittent group | Placebo group |
| First 24 h | 48 (25–137)*** ($n = 19$) | 74 (22–130)** ($n = 23$) | 95 (22–198) ($n = 21$) |
| Second 24 h | 26 (1–74)*** ($n = 18$) | 32 (2–102) ($n = 22$) | 44 (2–113) ($n = 21$) |
| Total over 48 h | 80 (31–211)*** ($n = 18$) | 111 (31–221) ($n = 22$) | 139 (43–258) ($n = 21$) |

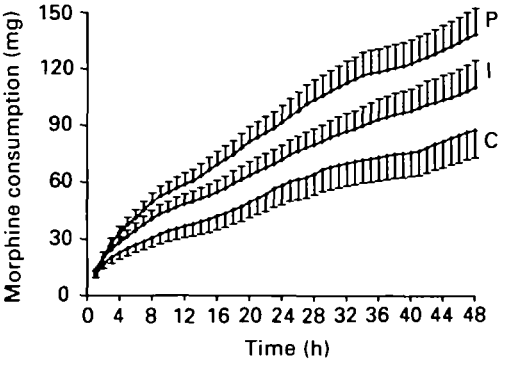


FIG. 1. Cumulative morphine consumption of patients receiving placebo (P), intermittent (I) or continuous (C) ketorolac for 48 h after upper abdominal surgery (mean, SEM).

TABLE IV. *Visual analogue pain scores (median and range) (no significant differences between groups)*

| | Pain score (mm) | | |
|---|---|---|---|
| | Continuous group | Intermittent group | Placebo group |
| 2–6 h | 39.5 (3–88) | 31.0 (5–83) | 48.5 (7–82) |
| 09:00 day 1 | 24.0 (6–98) | 16.5 (1–99) | 32.0 (4–93) |
| Afternoon day 1 | 26.5 (0–79) | 21.0 (2–61) | 24.0 (5–82) |
| 09:00 day 2 | 13.0 (0–40) | 12.5 (0–61) | 25.0 (1–68) |
| Afternoon day 2 | 14.0 (0–36) | 18.0 (0–54) | 23.0 (0–67) |

TABLE V. *Distribution of the most frequent side effects*

| | Continuous group | Intermittent group | Placebo group |
|---|---|---|---|
| Nausea/vomiting | 3 | 5 | 4 |
| Urinary retention | 3 | 1 | 2 |
| Injection site pain | 2 | 3 | 0 |

intermittent i.m. morphine administered as required. There were no withdrawals from the study because of adverse events. Patients who received ketorolac were significantly younger than those who received placebo ($P < 0.05$), but there were no differences in sex or weight between the groups (table II).

The morphine requirements of patients in the continuous ($P < 0.001$) and intermittent ($P < 0.01$) groups were significantly less during the first 24 h after operation compared with the placebo group (table III, fig. 1). The continuous group used significantly less morphine during the second 24 h and also during the entire 48-h study period compared with placebo ($P < 0.001$). While the intermittent group required less morphine than the placebo group during the second 24-h period and over the total 48 h of the study, this difference was not significant.

Median visual analogue pain scores of patients who received ketorolac were less than those receiving placebo (ns) (table IV).

The most common side effects were nausea or vomiting and urinary retention (table V), but there were no differences between the groups. Five of the 46 patients who received ketorolac complained of pain at the injection site, but this was mild in nature and no patient requested to be withdrawn because of this discomfort.

## DISCUSSION

Ketorolac does not alter the ventilatory response to increasing concentrations of inspired carbon dioxide [11]. The results of a study of patients undergoing minor surgical procedures demonstrated lack of cardiorespiratory effects after administration of ketorolac 30 mg, but the expected depression of respiration occurred after a bolus dose of alfentanil 0.5 mg [12]. Ketorolac

may, therefore, provide useful analgesia, either alone or as a supplement to an opioid, with minimal depressant effects.

The younger mean age of patients who received ketorolac in the present study would be expected to increase their morphine demands [1], but both ketorolac groups required less morphine compared with the placebo group. However, in the first 24 h the morphine sparing effect was greater for those patients given the continuous infusion. During the second 24 h of the study, patients in the intermittent group required less morphine compared with the placebo group, but this difference was not significant. Patients who received the same rate of dosing of ketorolac, but administered by a continuous infusion instead of intermittent doses, did show a significant morphine sparing effect during the second 24-h period compared with placebo. Over the entire 48-h duration of the study, the intermittent group used less morphine than the placebo group (ns). However, there was a significant reduction in morphine requirements in the group which received a continuous infusion of ketorolac.

The improvement in morphine sparing effect with the continuous mode of infusion occurred possibly because, during the periods of low plasma concentrations inherent in an intermittent dosing regimen, there was a decrease in analgesic efficacy for which extra morphine was required in compensation. The use of a larger intermittent dose or more frequent administrations may have resulted in improved efficacy. However, more frequent i.m. injections would not be favoured by the patient or the nursing staff, and the use of larger doses would cause greater peak concentrations of the drug, which may increase the incidence of any adverse effects such as gastric irritation. Therefore, a method of providing continuous delivery of the drug would seem to be useful in this situation.

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