

## CLINICAL INVESTIGATIONS

# Morphine consumption in patients receiving rectal paracetamol and diclofenac alone and in combination

J.E. MONTGOMERY, C.J. SUTHERLAND, I.G. KESTIN AND J.R. SNEYD

### Summary

Paracetamol and diclofenac have different mechanisms of action, and the combination may be more effective than each drug used alone in treating postoperative pain. In a double-blind, controlled design, we studied 60 patients undergoing elective abdominal gynaecological surgery, who received suppositories of paracetamol 1.5 g, diclofenac 100 mg or a combination of the two before the start of surgery. Patients received morphine in the intraoperative period, and cumulative morphine use from a patient-controlled analgesia system was recorded to measure the analgesic effect of the suppositories. Morphine consumption was greatest in the group that received paracetamol alone and lowest in the group given the combination ( $P < 0.01$ ). There was no difference in the incidence of morphine-related side effects between the groups. We conclude that a diclofenac-paracetamol combination reduced the amount of morphine used compared with paracetamol alone. (*Br. J. Anaesth.* 1996;77:445-447)

### Key words

Analgesics opioid, morphine. Analgesics non-opioid, diclofenac. Analgesics non-opioid, paracetamol. Pain, postoperative.

Non-steroidal anti-inflammatory drugs (NSAID), such as diclofenac, are effective in the treatment of postoperative pain. If given with opioids, the amount of opioid required is reduced with a consequent reduction in side effects<sup>1-3</sup>. In clinical studies, some patients with osteoarthritic pain found paracetamol to be as efficacious as NSAID, and it does not have the side effects of gastric irritation, altered platelet function or exacerbation of asthma<sup>4,5</sup>. Diclofenac and paracetamol have different mechanisms of action and the combination may be more effective than either drug used alone. We have undertaken a prospective, randomized, double-blind, comparative study to assess the analgesic efficacy of paracetamol alone and in combination with diclofenac.

### Patients and methods

With Ethics Committee approval and written informed patient consent, we studied 60 women, ASA I or II, aged 25-65 yr, undergoing elective abdominal gynaecological surgery. We excluded women weigh-

ing more than 100 kg, those unable to use a patient-controlled analgesia system (PCA) for postoperative pain control and those with a history of peptic ulceration, bleeding disorders, impaired renal or hepatic function, or sensitivity to NSAID or paracetamol. Patients received temazepam 20-30 mg, 1 h before operation and anaesthesia was induced with thiopentone 3-5 mg kg<sup>-1</sup>. Vecuronium 0.1 mg kg<sup>-1</sup> was given to facilitate orotracheal intubation. Morphine 0.1-0.15 mg kg<sup>-1</sup> was given as an i.v. bolus before the start of surgery; additional boluses were given during surgery if required up to a total of 0.2 mg kg<sup>-1</sup>. Anaesthesia was maintained with 0.5-2% enflurane and 60% nitrous oxide in oxygen.

Patients were allocated randomly to one of three groups by opening a sealed envelope, after induction of anaesthesia. Allocation was decided using random numbers generated by Claris Works software. Group P received a rectal suppository of paracetamol 1.5 g; group D received a rectal suppository of diclofenac 100 mg; and group PD received rectal suppositories of paracetamol 1.5 g and diclofenac 100 mg. The suppositories were given before the start of surgery.

At the end of surgery, residual neuromuscular block was antagonized with glycopyrronium 0.5 mg and neostigmine 2.5 mg. In the recovery area patients received morphine 2 mg i.v. at 5-min intervals until they described their pain as mild or absent. A PCA system (Graseby 3300, Graseby Medical Ltd, Watford, Herts) programmed to give a bolus of morphine 1 mg with droperidol 50 µg, with a 5-min lockout time and no background infusion, was connected to a dedicated i.v. cannula. Prochlorperazine 12.5 mg i.m. every 6 h if required and oxygen for the first 6 h were prescribed.

The amount of morphine given before connection to the PCA system and duration of anaesthesia and recovery were recorded. Hourly cumulative morphine requirements were recorded from the electronic memory of the PCA system. At 6 and 24 h after operation, patients were visited by an investigator who was unaware of the treatment group, and asked to complete two 10-cm visual analogue scales (VAS), one for pain and one for nausea. Both scales ranged from none to worst possible. The VAS for pain was recorded on deep breathing, as this has been shown to be more reproducible than a pain

J.E. MONTGOMERY, FRCA, C.J. SUTHERLAND, FRCA, I.G. KESTIN, FRCA, J.R. SNEYD, MD, FRCA, Department of Anaesthesia, Derriford Hospital, Derriford Road, Plymouth, Plymouth PL6 8DH. Accepted for publication: May 15, 1996.  
Correspondence to J. R. S.

score obtained at rest<sup>6</sup>. At these times the investigator also recorded a sedation score: 0 = fully awake; 1 = drowsy; 2 = sleeping but responds to gentle stimulus; 3 = sleeping no response to gentle stimulus. The nurses recorded routinely pain and sedation scores and ventilatory frequency every hour for 6 h, and every 2 h thereafter.

The sample size was chosen by *a priori* power calculation to provide 80% probability of demonstrating a reduction in the use of morphine by 30% when  $\alpha = 0.05$ . Results were analysed using repeated measures one-way analysis of variance for morphine consumption, one-way analysis of variance and Fisher's exact test; paired comparisons were made using Student's *t* test with Bonferroni correction for parametric data and Dunn's test for non-parametric data. The level of significance was 5%.

## Results

One woman, who received both paracetamol and diclofenac, was excluded from the analysis as she was unable to use the PCA because of severe vomiting and requested alternative analgesia 19 h after operation. Of the remaining 59 women, 20 received paracetamol, 20 received diclofenac and 19 received both.

There were small but statistically significant differences in age and body mass index between the three groups. Women who received both paracetamol and diclofenac were significantly older than those who received paracetamol (mean age 44.5 yr compared with 38.1 yr,  $P = 0.02$ ) (table 1). Body mass index for those given paracetamol was significantly less than for either of the other groups (22 compared with 26.1 and 24.4,  $P < 0.02$ ) (table 1). Duration of anaesthesia and amount of time spent in recovery were similar in all three groups (table 1).

The amount of morphine required before the start of the PCA was similar in each group (mean 12.5 mg, 14.8 mg and 13.4 mg) (table 2). Patients receiving paracetamol used significantly more morphine over the 24 h than those given paracetamol and diclofenac ( $P < 0.05$ ) (fig. 1, table 2). Women given diclofenac used an intermediate amount of morphine, although this was not significantly different from the two other groups (fig. 1). VAS pain scores were similar between groups (table 2).

There were no differences between the groups in any of the measures of nausea and vomiting (table 3), and sedation scores were similar between groups. No patient had a ventilatory frequency of less than 10

Table 1 Patient characteristics and recovery times (mean (SD or range)). \* $P < 0.05$  compared with combination group; † $P < 0.05$  compared with the two other groups

	Paracetamol (n=20)	Diclofenac (n=20)	Combination (n=19)
Age (yr)	38.1 (24–53)*	40.5 (26–60)	44.5 (33–59)
Body mass index	22 (17.5–30.8)†	26.1 (17.2–34.4)	24.4 (18.7–31.8)
Duration of anaesthesia (min)	94.4 (26.9)	94.7 (18.9)	97.3 (23.3)
Time in recovery (min)	71.1 (20.3)	72.5 (36.4)	68.9 (25.5)

Table 2 Pain scores and morphine use (mean (95% confidence intervals (CI))). \*\* $P < 0.01$  compared with paracetamol group (ANOVA)

	Paracetamol (n=20)	Diclofenac (n=20)	Combination (n=19)
Morphine during anaesthesia	11.1 (9.9–12.2)	11.7 (10.1–13.3)	11.9 (10.4–13.3)
Morphine in recovery area	1.5 (0.3–2.7)	3.1 (1.5–4.6)	1.5 (0–3.1)
Morphine from PCA, 0–6 h	16.4 (11.7–20.1)	14.1 (10.7–17.3)	9.4 (6.7–12.1)**
Morphine from PCA, 0–24 h	44.9 (36.1–53.6)	34.5 (27.4–41.6)	27.1 (18.5–35.8)**
Pain VAS, 6 h (median (range))	3.3 (0.0–7.1)	1.7 (0.3–5.1)	2.6 (0.0–7.9)
Pain VAS, 24 h (median (range))	3.4 (0.2–9.2)	1.9 (0.0–7.2)	2.1 (0.2–4.6)

Table 3 Sedation and nausea and vomiting scores (median (range))

	Paracetamol (n=20)	Diclofenac (n=20)	Combination (n=19)
Sedation score at 6 h	2 (0–2)	2 (0–2)	2 (2–0)
Sedation score at 24 h	0 (0–2)	0 (0–2)	0 (0–2)
Nausea VAS at 6 h	0.65 (0–6.7)	0.3 (0–4.4)	0.6 (0–5)
Nausea VAS at 24 h	2.6 (0–8.8)	2.3 (0–6)	1 (0–5.5)
Incidence of vomiting	8 (40%)	6 (30%)	5 (26%)

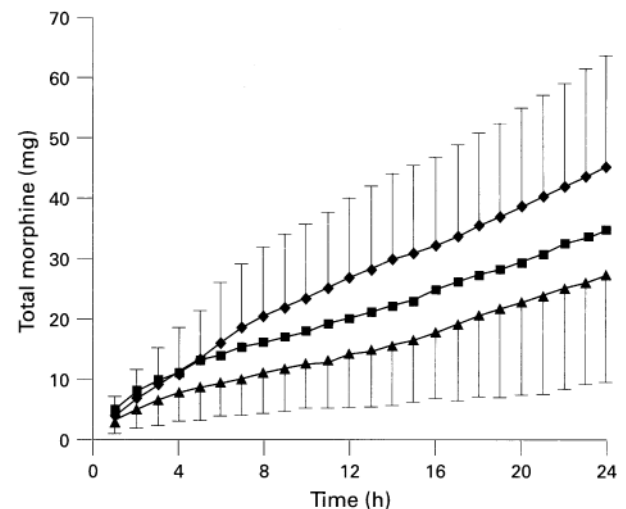


Figure 1 Cumulative morphine consumption (mean, SD) in the paracetamol (◆), diclofenac (■) and combination (▲) groups. For clarity error bars are omitted from the diclofenac group. At 6, 12, 18 and 24 h, the SD values of this group were 7.0, 9.0, 12.4 and 15.1 mg, respectively

bpm. One patient, who received both paracetamol and diclofenac, required transfusion because of excessive blood loss during difficult surgery. No other patient required blood transfusion.

## Discussion

The use of a combination of paracetamol with other NSAID has been shown to improve analgesia in dental and other pain models<sup>7–9</sup>. In our study, patients used a PCA system and therefore the effects of the drugs were measured by morphine consumption, not by differences in analgesia. Diclofenac and paracetamol have different mechanisms of action and their actions may therefore be additive or synergistic. The

use of the combination reduced the amount of morphine required during the first 24 h after operation compared with paracetamol alone. Patients who received both drugs used less morphine than those who received diclofenac alone, but this was not statistically significant. We would need to study approximately 100 patients per group for these differences to be statistically significant.

We did not include a placebo control group, who would have received morphine PCA alone, as a previous study has shown that diclofenac reduces morphine requirements, with reduced pain scores at 4 h after surgery<sup>3</sup>.

The dose of paracetamol used (1.5 g) was higher than the normal oral paracetamol dose, as the bioavailability of suppositories is lower than tablets<sup>10</sup> and only a single dose was given. Recent studies in children receiving rectal paracetamol have shown that doses as high as 35 mg kg<sup>-1</sup> may be needed to achieve plasma concentrations in the therapeutic range<sup>11</sup>. It may be that the initial dose of rectal paracetamol needs to be larger than currently recommended to provide better analgesia; further studies are needed to assess this.

Patients in the paracetamol group had a significantly lower body mass index than the two other groups, however, the effective dose of morphine is not necessarily dose related<sup>12</sup>. Women in the paracetamol group were also slightly younger than in the combination group, which would be likely to increase morphine consumption. However, morphine consumption is very variable between patients and the age difference was small, therefore we believe that this was unlikely to have had an important effect. The incidence and severity of nausea and vomiting were similar to those reported in other studies where droperidol was used in the PCA and were similar between groups<sup>13</sup>; if droperidol had not been included it may have been possible to show between-group differences.

In conclusion, the use of a diclofenac–paracetamol combination reduced the amount of morphine

required for adequate analgesia by about one-third compared with paracetamol alone.

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