Br. J. clin. Pharmac. (1982), **14**, 539–543

CODEINE ADDED TO PARACETAMOL INDUCED ADVERSE EFFECTS BUT DID NOT INCREASE ANALGESIA

P. SKJELBRED
Department of Oral Surgery and Oral Medicine, and Institute of Pharmacology, University of Oslo, Norway
P. LØKKEN
Institute of Pharmacology, University of Oslo, Norway

1 In a double-blind crossover study identical oral surgical procedures were performed on two separate occasions in 24 outpatients.

2 At one operation they were given tablets containing paracetamol + codeine phosphate (400 mg + 30 mg), and at the other plain paracetamol (400 mg). The day of operation 2 tablets were taken 3, 6 and 9 h after surgery, the following two days 1 tablet four times daily.

3 Several measurements/assessments were recorded for a paired comparison of the postoperative courses.

4 No increase in the analgesic effect could be demonstrated by addition of codeine to paracetamol.

5 On the day of operation 18 patients reported adverse effects like nausea, dizziness and drowsiness with paracetamol + codeine, while only 3 patients experienced side effects with paracetamol alone ($P < 0.001$).

6 Measurements revealed almost identical swelling after the two operations.

7 Compared with results obtained in previous studies, the present findings indicate that paracetamol may exert anti-inflammatory activity and reduce postoperative swelling, even when given 3 h after surgery.

8 On the day of operation and the following two days 20 patients preferred the treatment with plain paracetamol, while only 4 favoured paracetamol + codeine ($P < 0.001$).

Introduction

Opioids such as codeine and dextropropoxyphene are frequently combined with non-opioids like acetylsalicylic acid or paracetamol. The theoretical rationale is that efficacy might be enhanced by the additive effect of two analgesics which act by different mechanisms, and adverse effects avoided by giving reduced doses of two analgesics with different side effects rather than a larger equieffective dose of a single agent (Beaver, 1966, 1975).

In two recent studies, we used codeine as a supplementary analgesic, but many patients reported poor pain relief. Codeine seemed, however, to result in adverse effects (Skjelbred & Løkken, 1982a, b). Previously, we have demonstrated reduced postoperative swelling and adequate pain relief with paracetamol (Løkken & Skjelbred, 1980). Combination products with paracetamol and codeine are frequently used in oral surgery. In spite of the huge sales volume of these and related products, there have been relatively few controlled trials examining the analgesic contribution of each ingredient (Beaver & McMillan, 1980).

The present study aimed at investigating the merits and adverse efffects of paracetamol + codeine as compared to plain paracetamol. A model for clinical evaluation of postoperative drug effects has been established in our department. It is based upon young, healthy outpatients who at two separate occasions undergo identical oral surgical procedures. Various assessments are recorded for a paired comparison of the postoperative courses (Løkken *et al.*, 1975).

Methods

Patients

Healthy, young outpatients were asked to volunteer. They were all in need of prophylactic surgical removal

0306–5251/82/100539–05 $01.00

of bilateral, asymptomatic, impacted third molar teeth of similar shape and position, as evaluated clinically and by means of orthopantomograms. Twenty-four patients completed the trial, 14 females and 10 males (mean age 24 years, range 16–31 years). Two other patients entered the trial but had to be excluded as they were unable to continue medication at the second operation.

Drugs

Tablets containing 400 mg paracetamol and 30 mg codeine phosphate (Paralgin forte®, Weiders Farmasøytiske A/S, Oslo, Norway) were given at one operation, and matching tablets containing 400 mg paracetamol at the other. On the day of operation a total of 6 tablets were taken (2 tablets 3, 6 and 9 h after surgery). The following two days a total of 4 tablets were taken daily (1 tablet 08.00, 12.00, 16.00 and 20.00 h). The trial was on a double-blind cross-over basis, and treatments were allocated according to a randomization list, so that half of the patients received the combination (paracetamol + codeine) at the first operation. No other drugs were permitted during the observation period and 10 days prior to surgery.

Operations

All the patients had an interval of 14 days between the two operations. Eleven patients had both upper and lower third molars removed, the remaining only the lower ones. The mean amount of local anaesthetic (Xylocain® Adrenaline, Astra, Sweden) used was the same in both operations (4.95 ml, range 3.6–7.2 ml). The mean duration from injection to incision was 3.4 min (range 2–6 min), and from incision to the last suture 8.9 min (range 3–15 min) in the operation when paracetamol + codeine was given. The corresponding durations were 3.7 min (range 2–7 min) and 9.3 min (range 3–20 min) when paracetamol was administered.

Assessments/statistical analyses

Pain was rated on a visual analogue scale with lines that ran from 'no pain' (0 mm) to 'pain cannot be worse' (100 mm). On the day of operation assessments were made each hour in a 9 h period, starting 1 h after completion of surgery, and with an extra assessment at 3.5 h. The first postoperative day pain was assessed in the morning just before taking one tablet, and then each hour for the next two hours. Pain was further assessed at bedtime the day of operation and the following 5 days. The patients were allowed to compare with previous marks.

Adverse effects On the printed sheets the patients answered the question 'Have you experienced any discomfort that could possibly be related to the medication?' at bedtime 6 evenings in each observation period. If any discomfort was registered the nature of this was specified.

Preference After the second operation the patients gave an overall assessment of the course after this operation compared to the previous one by means of a visual analogue scale with vertical lines that ran from 0 mm (no difference) upwards to 100 mm (maximal preference for the last course) and downwards to 100 mm (maximal preference for the previous course). Three separate preference assessments were made (the day of operation, day 1 and 2 after operation, and day 3, 4 and 5 after operation).

Swelling in the jaw region was measured with a mechanical device designed in our department. For each patient a bite-block was made at the preoperative sitting by taking a thermoplastic impression. The individual bite-block was then locked to a facial bow with bilateral vertical plates, each perforated by 8 adjustable plastic screw pins. When the screws were brought in touch with the skin, measurements of the remaining length of the screws outside the plate gave exact values, which could be related to the degree of facial swelling by simple subtraction of post- and preoperative measurements (Løkken *et al.*, 1975).

The *mouth-opening* ability was measured between the central incisors with a vernier gauge (Løkken *et al.*, 1975). The probe of an electronic thermometer (Omron MC-320®, Japan) registered the *local oral temperature* distobuccal to the 2nd lower molars (Skjelbred *et al.*, 1977). The patients assessed *bleeding* on a 4 graded scale (Hepsø *et al.*, 1976). At the visits on the third and sixth postoperative day, the patients were examined for *haematoma/ecchymosis* (Hepsø *et al.*, 1976). *Wound-healing* was assessed by the surgeon the sixth postoperative day.

Statistical analyses were performed with a two-sided Wilcoxon signed rank test with corrections for ties (Lehmann & d'Abrera, 1975). A significance level of 5% was used.

Results

Pain

There was no significant difference in pain relief comparing the two treatments (Figure 1). The mean differences in pain between paracetamol + codeine and paracetamol alone were after 4h: 4 mm (95% confidence limits −4 to 12 mm), 5 h: 7 mm (−3 to 10 mm), 6 h: 2 mm (−6 to 12 mm), 7 h: 5 mm (−6 to 16 mm), and 8 h: 1 mm (−7 to 9 mm). The results

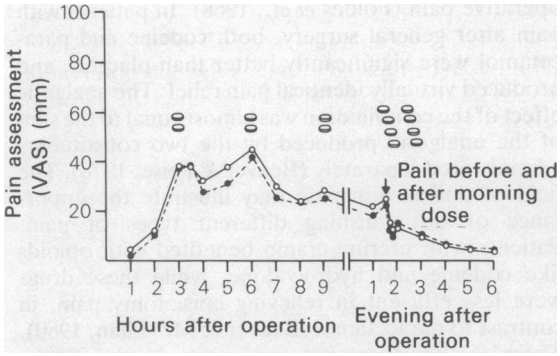

Figure 1 The effect of the two treatments (● paracetamol, ○ paracetamol + codeine) on pain relief as assessed on a visual analogue scale.

therefore strongly indicate that after this kind of surgery and at the dosages used, addition of codeine to paracetamol does not increase the analgesic effect.

Adverse effects

Drug-induced adverse effects were significantly increased when taking the combination (Table 1). On the day of operation 18 patients reported complaints after paracetamol + codeine and only 3 after paracetamol ($P < 0.001$). On the forms which the patients filled in each evening in the two observation periods, 6 patients reported nausea, dizziness or drowsiness under general comments. They did not relate these symptoms to the medication, but probably considered them to be a normal reaction after surgery. These reports were included in Table 1. There was a striking lack of complaints when medication stopped (day 3, 4, 5 and 6 after operation).

Table 1 Side effects in 24 patients treated with paracetamol and paracetamol + codeine at two separate oral surgical procedures. Medication lasted for 3 days.

	Paracetamol	*Paracetamol + codeine*
Day of operation	1 nausea 1 drowsiness 1 sleepless	8 nausea 6 nausea and dizziness 2 nausea and drowsiness 1 nausea and urticaria 1 drowsiness
Day 1 after operation	None	10 nausea 4 nausea 1 nausea and urticaria 1 drowsiness
Day 2 after operation	None	8 nausea 1 nausea and dizziness 1 nausea and urticaria 1 drowsiness
Day 3, 4, 5 and 6 after operation	None	None

Swelling

The mean measurement of swelling on the third postoperative day was 29 mm after the operation when paracetamol was given and 31 mm after the other operation when paracetamol + codeine was administered ($P > 0.10$). The corresponding measurements on the sixth post-opeative day were 8 and 9 mm ($P > 0.10$).

Mouth-opening

On the third postoperative day the mean reduction in mouth-opening in percentage of the preoperative values was 30% after both operations. On the sixth postoperative day the reduction averaged 16% after paracetamol and 21% after paracetamol + codeine ($P > 0.10$).

Local oral temperature

On the third day the differences between the operated and non-operated side averaged 0.5°C after paracetamol + codeine and 0.4°C after paracetamol ($P > 0.10$). On the sixth day the respective temperature differences were 0.4°C and 0.3°C ($P > 0.10$).

Bleeding

Bleeding episodes were not reported after any of the operations, and the bleeding scores did not reveal any noticeable differences between the two postoperative courses.

Haematoma/ecchymosis

On the third postoperative day 5 patients had visible haematomas/ecchymoses after both operations. There were no noticeable differences in extent of the discolorations when given paracetamol + codeine or paracetamol. On the sixth postoperative day haematomas/ecchymoses, of almost equal extent after both operations, were still observed in 4 patients.

Wound-healing

This was without complication in all the patients.

Preference

The preference scores were significantly in favour of the postoperative course when given paracetamol (the day of operation: $P < 0.001$, day 1 and 2 after operation: $P < 0.001$, day 3, 4 and 5 after operation: $P = 0.02$ (Figure 2).

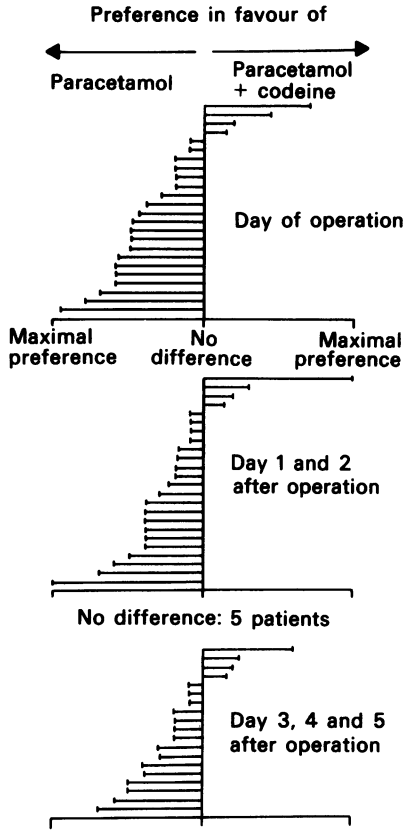

Figure 2 Preference scores for the two treatments.

Discussion

In the present study codeine failed to increase the analgesic effect when added to paracetamol. It is possible that an additive analgesic effect of codeine might have been demonstrated at a lower dosage of paracetamol. In another oral surgical trial, paracetamol showed marked analgesic superiority compared to placebo, while codeine was just slightly better than placebo. Although the combination of paracetamol and codeine demonstrated the greatest efficacy, it was not significantly better than plain paracetamol (Cooper & Beaver, 1976). No noticeable difference between placebo and codeine in relieving postoperative dental pain was observed by Petersen (1978). Compared with placebo, dihydrocodeine actually increased pain after bilateral oral surgery (Seymour & Rawlins, 1980).

There may be differences in relative efficacy when different classes of analgesics are compared in models using pain of different aetiologies (Beaver & McMillan, 1980). The site of surgical incision and the type of operation are the main determinants of postoperative pain (Foldes *et al.*, 1968). In patients with pain after general surgery, both codeine and paracetamol were significantly better than placebo, and produced virtually identical pain relief. The analgesic effect of the combination was almost equal to the sum of the analgesia produced by the two constituents administered separately (Beaver & Feise, 1978). The field of postpartum pain may illustrate the importance of distinguishing different types of pain. Patients with uterine cramp benefited with opioids like codeine and hydrocodone, while these drugs were less efficient in relieving episiotomy pain, in contrast to paracetamol (Beaver & McMillan, 1980). There is, however, not conformity in the results obtained in studies on postpartum pain (e.g. Bloomfield *et al.*, 1976; Sunshine, 1980). In patients undergoing minor orthopaedic operations addition of 1, 1.5 or 2 mg buprenorphine to a 1 g dose of paracetamol, did not significantly increase the analgesic effect of paracetamol over a 6 h period. The authors concluded that addition of buprenorphine to a dose of paracetamol is of no benefit (Bullingham *et al.*, 1981). This paracetamol dose alone proved to be very effective, with SPID and TOTPAR scores of about 50% of the theoretically maximal values. In contrast placebo or codeine (60 mg) in a similar orthopaedic model produced only slight effects, less than 10% of the maximal relief. Their demonstration that a 1 g dose of paracetamol alone was very effective, agrees well with our results in oral surgical patients. At least in these two fields the oral use of opioid drugs in the treatment of postoperative pain seems to be unsatisfactory and to offer no advantage compared to an adequate dose of plain paracetamol.

It is well known that codeine may cause side effects like nausea, dizziness and drowsiness, which may be dose dependent. We were surprised, however, by the large number of complaints reported with paracetamol + codeine, since this combination has been the routine analgesic in our department and apparently well tolerated. One possible explanation is that ambulatory patients may be more attentive to the effects of opioids on the vestibular apparatus than patients confined to bed. There was a marked tendency towards more pronounced adverse effects in females, particularly the younger ones.

One reason for including an opioid in our series of trials was the recent evidence of an involvement of the opioid peptidergic system in the reaction to stressful conditions, as stressed rats with the opiate receptors blocked by naloxone showed an increased intensity of the inflammatory reaction (Arrigo-Reina & Ferri, 1980). According to this observation, codeine might possibly reduce postoperative swelling. The present study, however, failed to support this finding in humans, since almost identical swelling was measured after both treatments.

In a previous study with medication starting before

surgery, paracetamol reduced swelling on the third postoperative day by 29% compared to placebo (Løkken & Skjelbred, 1980). The present results give some indirect evidence that even delayed administration of paracetamol may reduce postoperative swelling, since the mean measured swelling after the two operations was 30 mm, which is about 30% less than the mean measurement in the 132 patients who received placebo (44 mm) in the 6 previous trials (Løkken *et al.*, 1975; Album *et al.*, 1977; Skjelbred & Løkken, 1980; Løkken & Skjelbred, 1980; Skjelbred & Løkken, 1982a, b). It should be emphasized that comparison of results obtained in different studies is to be interpreted with caution. However, if paracetamol actually did reduce the swelling when given 3 h after surgery, this is an important property with regard to the use of the drug in traumatology, which deserves further investigations.

The authors are indebted to Leiv Sandvik, M.Sc. (Ciba-Geigy Pharma A/S, Norway) for performing the statistical analyses. We are further grateful to Weider Farmasøytiske A/S, Oslo, Norway, for supply of drugs.

References

ALBUM, B., OLSEN, I. & LØKKEN, P. (1977). Bilateral surgical removal of impacted mandibular third molar teeth as a model for drug evaluation: a test with oxyphenbutazone (Tanderil®). *Int. J. oral Surg.*, **6**, 177–189.

ARRIGO-REINA, R. & FERRI, S. (1980). Evidence of an involvement of the opioid peptidergic system in the reaction to stressful conditions. *Eur. J. Pharmac.*, **64**, 85–88.

BEAVER, W.T. (1966). Mild analgesics: a review of their clinical pharmacology. (Part II). *Am. J. med. Sci.*, **251**, 576–599.

BEAVER, W.T. (1975). Analgesic combinations. In *Combination Drugs: Their Use and Regulation*, ed. Lasagna, L., pp. 52–72. New York: Stratton.

BEAVER, W.T. & FEISE, G. (1978). Comparison of the analgesic effect of acetaminophen and codeine and their combination in patients with postoperative pain. *Clin. Pharmac. Ther.*, **23**, 108.

BEAVER, W.T. & McMILLAN, D. (1980). Methodological considerations in the evaluation of analgesic combinations: Acetaminophen (paracetamol) and hydrocodone in postpartum pain. *Br. J. clin. Phamac.*, **10**, 215S–223S.

BLOOMFIELD, S.S., BARDEN, T.P. & MITCHELL, J. (1976). Aspirin and codeine in two postpartum pain models. *Clin. Pharmac. Ther.*, **20**, 499–503.

BULLINGHAM, R.E.S., McQUAY, H.J., MOOR, R.A. & LESLEY WEIR (1981). An oral buprenorphine and paracetamol combination compared with paracetamol alone: a single dose double-blind postoperative study. *Br. J. clin. Pharmac.*, **12**, 863–867.

COOPER, S.A. & BEAVER, W.T. (1976). A model to evaluate mild analgesics in oral surgery outpatients. *Clin. Pharmac. Ther.*, **20**, 241–250.

FOLDES, F.F., SWERDLOW, M. & SIKER, E.S. (1968). Postoperative Schmerzstillung. In *Morphinartige Analgetika und ihre Antagonisten*, Kapitel IX: *Anaesthesiologie und Wiederbelebung*. Pp. 155–173. Berlin: Springer-Verlag.

HEPSØ, H.U., LØKKEN, P., BJØRNSON, J. & GODAL, H.C. (1976). Double-blind crossover study of the effect of acetylsalicylic acid on bleeding and post-operative course after bilateral oral surgery. *Eur. J. clin. Pharmac.*, **10**, 217–225.

LEHMANN, E.L. & D'ABRERA, H.J.M. (1975). Nonparametrics: *Statistical methods based on ranks*. Pp. 129–131. San Francisco: Holden-Day Inc.

LØKKEN, P., OLSEN, I., BRUASET, I. & NORMAN-PEDERSEN, K. (1975). Bilateral surgical removal of impacted lower third molar teeth as a model for drug evaluation: A test with ibuprofen. *Eur. J. clin. Pharmac.*, **8**, 209–216.

LØKKEN, P. & SKJELBRED, P. (1980). Analgesic and anti-inflammatory effects of paracetamol evaluation by bilateral oral surgery. *Br. J. clin. Pharmac.*, **10**, 253S–260S.

PETERSEN, J.K. (1978). The analgesic and anti-inflammatory efficacy of diflunisal and codeine after removal of impacted third molars. *Curr. med. Res. Opin.*, **5**, 525–535.

SEYMOUR, R.A. & RAWLINS, M.D. (1981). Paracetamol (acetaminophen), aspirin, dihydrocodeine tartrate and post-operative dental pain. *Pain, Suppl.* 1, p. S248.

SKJELBRED, P., ALBUM, B. & LØKKEN, P. (1977). Acetylsalicylic acid vs paracetamol: effects on post-operative course. *Eur. J. clin. Pharmac.*, **12**, 257–264.

SKJELBRED, P. & LØKKEN, P. (1980). Phenazone versus placebo: effects on post-operative course. *Eur. J. clin. Pharmac.*, **18**, 327–331.

SKJELBRED, P. & LØKKEN, P. (1982a). Post-operative pain and inflammatory reaction reduced by injection of a corticosteroid. A controlled trial with bilateral oral surgery. *Eur. J. clin. Pharmac.*, **21**, 391–396.

SKJELBRED, P. & LØKKEN, P. (1982b). Reduction of pain and swelling by a corticosteroid injected 3 hours after surgery. *Eur. J. clin. Pharmac.* (in press).

SUNSHINE, A. (1980). Clinical evaluation of mild analgesics in post partum pain. *Br. J. clin. Pharmac*, **10**, 335S–337S.

(Received February 4, 1982, accepted May 14, 1982)