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A multiple dose comparison of combinations of ibuprofen and codeine and paracetamol, codeine and caffeine after third molar surgery

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Summary

In a randomised, double-blind, double-dummy, multiple dose, crossover study in 30 patients we compared an ibuprofen/codeine combination (400 mg ibuprofen/25.6 mg codeine phosphate) with a paracetamol/codeine/caffeine combination (1 g paracetamol/16 mg codeine phosphate/60 mg caffeine) for pain relief over 6 days after two-stage bilateral lower third molar removal. The ibuprofen combination produced significantly greater analgesia than the paracetamol combination, both on single-dose analysis of the first and second days and on multiple-dose measures for days 1, 2, 3 and 4. The mean incidence of adverse effects over the 6 days was 20% for both combinations. This trial design (crossover with multiple dosing in outpatients) is a sensitive way of testing for analgesia, and is potentially more predictive of adverse effect problems than single-dose studies. It confirms that mutliple dosing may show increased efficacy.

Key words

Analgesics; codeine, ibuprofen, paracetamol.
Pain; postoperative.
Surgery; dental.

Single dose analgesic studies can be sensitive and precise. However, extending these methods to the context of multiple dosing may provide more clinically relevant data [1]. Additional information about the optimal dosing schedule may be gleaned from multiple dosing studies because some analgesics show increased effect on multiple dosing [2] and multiple dosing studies may provide a better evaluation of adverse effects than single doses [3].

Our current postoperative oral surgery model [2, 4] has been shown to be appropriate for testing analgesics in multiple dosing studies. The fact that the patient has the same operation twice (the extraction of a molar tooth on each side), provides ideal circumstances for a crossover design. This design was sufficiently sensitive to show the additional analgesic effect of adding 20 mg of codeine base to 400 mg of ibuprofen compared with 400 mg of ibuprofen alone on both single and multiple dosing [2], although half that dose of codeine did not produce measurable additional benefit [4].

In the present study we compared an ibuprofen–codeine combination with a commercially available paracetamol–codeine–caffeine combination, developing the multiple dosing aspect by asking patients to record pain measurements throughout the day of surgery and the following days. In addition to standard efficacy measures, a pain intensity and pain relief index per dose was derived over the study period.

Methods

Trial design

Ethics committee approval was obtained for the study, which was of randomised, double-blind, double-dummy, multiple-dose, crossover design (Fig. 1). Informed consent was obtained from 30 patients undergoing elective outpatient surgery for surgical removal of bilateral lower (or lower plus upper) third molars, at the Oral Surgery Department, John Radcliffe Hospital, Oxford. Removing upper third molars, either because they have erupted or are just beneath the mucosa, produces minor and insignificant discomfort when the local anaesthetic wears off compared

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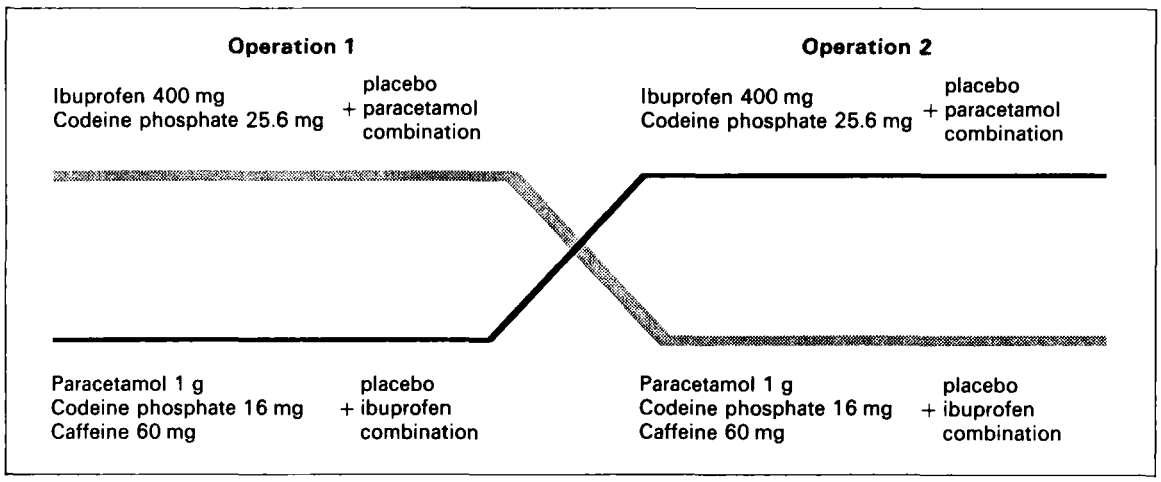

Fig. 1. Study design (10 mg of codeine base is equivalent to 12.8 mg of codeine phosphate).

with removal of lower third molars. After the first operation (removal of the lower third molar on one side), if the patients had pain of moderate or severe intensity they took the first test analgesic and continued to use it for up to 6 days if necessary, at a rate of up to four times a day if required. Diary measurements of pain and pain relief were made on the day of surgery (day 1) and over the next 5 days. The patients were seen 7 days after operation. After a minimum period of 3 weeks they had the second operation and took the second treatment in the same way as on the first occasion.

Test analgesics

The dose of the ibuprofen combination was two tablets, each containing 200 mg of ibuprofen with 12.8 mg of codeine phosphate. The dose of the paracetamol combination was two effervescent tablets, each containing 500 mg of paracetamol with 8 mg of codeine phosphate and 30 mg of caffeine. The trial design was double-dummy with appropriate placebos (Fig. 1). The effervescent placebo tablets were formulated so that there was minimal effect on ibuprofen dissolution. For each dose patients were told to swallow the tablets (envelope 'a') with the dissolved contents of the sachet (envelope 'b'). Envelope 'a' therefore contained two oblong white tablets, either placebo or ibuprofen combination, and envelope 'b' either placebo or paracetamol combination. The fourth dose of the ibuprofen combination for each day was a placebo; this was necessary because of safe prescribing recommendations for the maximum daily ibuprofen dose in this context. The tablet schedules were presented in the diaries (each day's four doses on a separate page). Tablets were identifiable only by patient and treatment numbers. The drugs were supplied by Beecham Products, Weybridge, England.

Patients and operations

We studied men or women aged between 18 and 40 years who were undergoing surgical removal of bilateral symmetrical impacted lower third molars with or without removal of upper third molars. Patients were not studied if they were taking concurrent analgesics, had previously reacted to, or were hypersensitive to, any of the test drugs, or had any gastrointestinal disturbance. Psychiatric disorders which required medical treatment or any existing illness were grounds for exclusion as were pregnancy or breast-feeding.

Patients were operated on before midday, in order to allow sufficient time for multiple dosing on the day of surgery. Each surgical procedure was carried out under identical conditions, with the same oral surgeon and nursing assistant. The same local anaesthetic (lignocaine 2% with adrenaline 1 : 80 000) was given before surgery. For each procedure the volume of the local anaesthetic and the time at which it was given were recorded. The type, time and duration of each surgical procedure were recorded. Patients were discharged when the oral surgeon judged that they had recovered fully. Routine postoperative mouth care instructions were given before discharge. Patients were given a prophylactic antibiotic (metronidazole 400 mg) to be taken twice daily for 3 days postoperatively.

Analgesic measurements and adverse effects

Self-report information was obtained in diaries using the following scales: pain intensity, 4-point categorical verbal rating scale (0 = none, 1 = slight, 2 = moderate, 3 = severe); pain relief, a 5-point categorical verbal rating scale (0 = none, 1 = a little, 2 = some, 3 = a lot, 4 = complete); preference, at the postoperative visit 1 week after the second operation the patients were asked to record which of the two treatments they preferred; pain-free hours, the numbers of hours on the day of surgery for which verbal categorical pain intensity scores of zero were noted and were compared for the two treatments, as were the numbers of hours for which maximal verbal categorical pain relief scores were recorded; daily global rating scores, daily global rating scores for the 6 days of each treatment were recorded (0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent).

Adverse effects

Adverse effects were recorded by the patient daily, in answer to the diary question 'Did the tablets upset you in any way?' If the answer was 'yes' the patients were asked to provide details. Any comments made by the patient were discussed at the next clinic visit.

Timing of recordings

The first 2 days. Pain intensity and the time were noted immediately before taking the first dose. The patients then recorded pain intensity and pain relief half an hour after the dose and then hourly until going to sleep.

Days 3, 4, 5 and 6. Daily global rating and timed tablet consumption on days 3, 4, 5 and 6 were noted, together with adverse effects. Patients were seen in the Oral Surgery department 7 days after each extraction, to check that there were no postoperative complications. The diaries and any remaining tablets were then collected, a tablet count was made, and after the second operation the patient's preference was recorded.

Analysis and statistics

Only patients with initial (pre-dose) pain intensity values of moderate or severe on the categorical verbal scale were included in the analgesic measures analysis for the relevant day. This judgment was made separately for day 1 and day 2.

Single dose analysis: Spid and Totpar. Summed pain intensity difference (Spid) and total pain relief (Totpar) [5] were calculated for the 6-h period after the first dose on both the day of surgery and the following day, using the verbal categorical pain intensity and relief scores, respectively. If the patients took another dose before the end of the 6-h study period, then for each reading between the time of remedication and 6 h from the dose, the initial pain intensity reading and a pain relief score of zero were used for the analysis [6].

Repeat dose analysis: PRIX, PRIX/dose, TOTPRIX and TOTPRIX/dose. The pain intensity reduction index (PRIX) [7] was calculated from the categorical verbal pain intensity scale recordings for the first and second days, respectively, using the formula:

$$\text{PRIX} = \frac{\text{initial pain intensity} - \text{mean hourly pain intensity}}{\text{initial pain intensity}} \times \text{no. of hours} \times 100$$

where initial pain intensity was the pain intensity (4-point verbal categorical scale) recorded before the analgesic was taken, and no. of hours was the time from the first dose to the last recorded pain measurement on that day. PRIX/dose was calculated by dividing the PRIX score by the total number of doses of active drug taken on that day. TOTPRIX was calculated from the categorical verbal pain relief scale recordings for the first and second days, respectively, using the formula:

$$\text{TOTPRIX} = \text{mean pain relief} \times \text{no. of hours} \times 100$$

where the no. of hours was the time from the first dose to the last recorded pain measurement on that day. TOTPRIX/dose was calculated by dividing the TOTPRIX by the total of active doses taken on that day.

Statistics

The Wilcoxon signed-ranks matched pairs test was used for a within-patient comparison of analgesic effect scores after the two treatments. Patient preference and adverse effect incidence were compared using the Chi-squared test. The data are presented as mean (SEM). Significance was assumed at the $p < 0.05$ level.

Table 1. Patient details. Values are expressed as mean (SEM).

Number	30	
Age; years	24 (1)	
Sex; M : F	11 : 19	
Weight; kg	66 (2)	
Height; cm	169 (2)	
	Ibuprofen combination	Paracetamol combination
Duration of surgery; min	10 (1.0)	10 (0.8)
Volume of local anaesthetic; ml	6.4 (0.3)	6.5 (0.3)
Time from local anaesthetic to operation start; min	13 (0.7)	14 (0.7)
Operation type: (lower + upper) vs lower alone	16 : 14	14 : 16
Drill used during surgery	22	22

Results

Details of the patients and of the surgical procedures are shown in Table 1. There were no significant differences between the treatments for the type of operation (lower versus lower and upper third molars), volume of local anaesthetic, duration of surgery or the interval between the local anaesthetic and the start of surgery. More women than men took part in the study. There were no withdrawals from the study because of adverse effects.

Analgesia

Single dose: first day. The ibuprofen combination produced significantly greater Spid ($p = 0.022$) and Totpar ($p < 0.001$) values than the paracetamol combination (Table 2).

Repeated doses: first day. The ibuprofen combination had a significantly greater effect on PRIX ($p < 0.014$), PRIX/dose ($p < 0.01$), TOTPRIX ($p < 0.001$), and TOTPRIX/dose ($p < 0.002$) (Table 2). The mean pain relief scores derived from the verbal pain relief scores at each time point are shown in Figure 2. On day 1 the ibuprofen combination produced a mean TOTPRIX/dose 50% greater than the paracetamol combination.

Single dose: second day. There was no significant difference on either Spid or Totpar (Table 2).

Repeated doses: second day. The ibuprofen combination had significantly greater efficacy only on TOTPRIX/dose ($p = 0.013$; Table 2). The mean pain relief scores derived from the verbal pain relief scores at each time point are shown in Figure 2. On day 2 the mean TOTPRIX/dose was 72% more with the ibuprofen combination than with the paracetamol combination.

Doses taken on days 1 and 2 and dose intervals. The interval between first and second doses on the first day was significantly longer for the ibuprofen combination ($p = 0.001$, Table 2). Over half the patients in each group needed a third dose on that day, with a significantly longer interval between the second and third doses with the ibuprofen combination ($p = 0.023$, Table 2). Five patients took a fourth dose of the ibuprofen combination compared with 12 on the paracetamol combination, and overall for the first day significantly fewer doses were taken with the ibuprofen combination ($p = 0.013$, Table 2). On the second

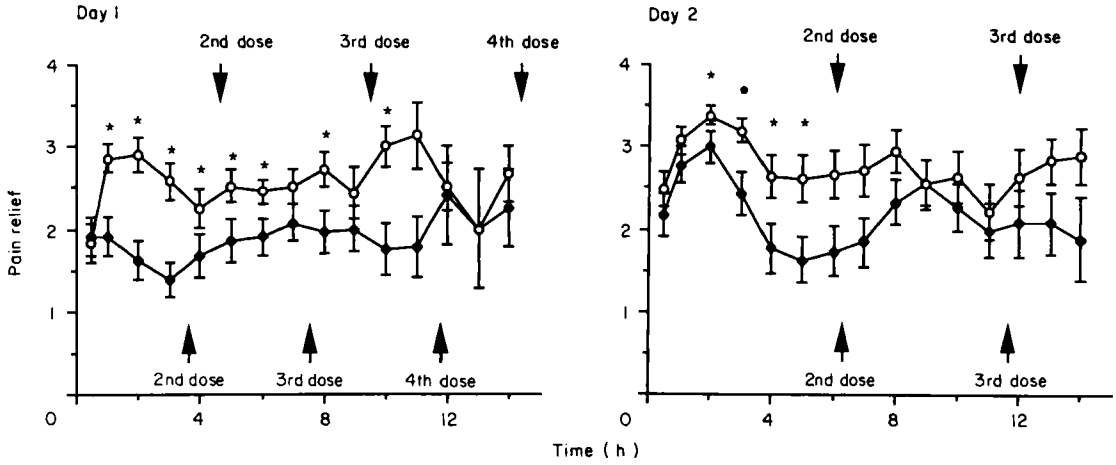

Fig. 2. Mean (SEM) pain relief scores against time for days 1 and 2. —○— Ibuprofen combination, —◆— paracetamol combination. * Significant difference on Wilcoxon matched-pairs signed-ranks test ($p < 0.05$).

day there were no significant differences in the intervals between doses or in total doses taken.

Patient preference. Twenty-nine preferences were obtained: 21 patients preferred the ibuprofen combination, 8 preferred the paracetamol combination, and 1 expressed no preference ($p = 0.01$, Chi-squared).

Pain-free hours. The ibuprofen combination gave significantly more hours of maximal pain relief and hours of zero pain intensity on the day of surgery than the paracetamol combination (0.5(0.1) vs 0.2(0.1) h, $p < 0.01$ and 0.4(0.1) vs 0.2(0.1) h, $p < 0.1$, respectively). There were no significant differences on the second day.

Daily global rating. There was no significant difference between the global rating for the two combinations on day 1, but on day 2 the ibuprofen combination gave a significantly higher rating (Table 2).

Efficacy on days 3, 4, 5 and 6. Daily global rating scores and mean doses taken for days 3, 4, 5 and 6 are shown in Table 3. The ibuprofen combination produced significantly better global scores on days 3 and 4.

Adverse effects

The incidence of adverse effects for the two test drugs is shown in Table 4. The incidence of nausea was significantly

Table 2. Analgesic measures days 1 and 2. Values are expressed as mean (SEM).

	Ibuprofen combination	(*n*)	Paracetamol combination	(*n*)	Statistical significance
Day 1					
Pain intensity before first dose	2.2 (0.1)	29	2.2 (0.1)	27	
SPID	3.9 (0.6)	29	2.0 (0.5)	27	0.022
PRIX	406 (56)	29	185 (67)	27	0.014
PRIX per dose	173 (26)	29	93 (33)	27	0.01
Global	2.3 (0.2)	29	1.7 (0.2)	27	
Time to 2nd dose; min	292 (20)	29	217 (15)	26	< 0.001
Time to 3rd dose; min	285 (14)	17	237 (14)	21	0.023
Time to 4th dose; min	287 (93)	5	261 (17)	12	
Time to last reading; min	612 (23)	29	616 (29)	27	
Total doses taken	2.8 (0.1)	29	3.2 (0.2)	27	0.013
TOTPAR	10 (1)	29	5.2 (0.8)	27	0.001
TOTPRIX	222 (13)	29	159 (16)	27	0.001
TOTPRIX per dose	92 (8)	29	62 (11)	27	0.002
Day 2					
Pain intensity before first dose	2.1 (0.1)	24	2.2 (0.2)	21	
SPID	5.9 (0.6)	24	4.9 (0.6)	21	
PRIX	359 (116)	24	478 (66)	21	
PRIX per dose	195 (54)	24	177 (23)	21	
Global	2.7 (0.2)	24	1.9 (0.3)	21	< 0.01
Time to 2nd dose; min	377 (32)	19	376 (26)	19	
Time to 3rd dose; min	310 (21)	13	322 (23)	14	
Time to 4th dose; min	286 (35)	7	259 (41)	7	
Time to last reading; min	707 (46)	24	670 (43)	21	
Total doses taken	2.6 (0.2)	24	3.0 (0.2)	21	
TOTPAR	11 (1)	24	8.1 (1.2)	21	
TOTPRIX	235 (17)	24	167 (18)	21	
TOTPRIX per dose	120 (16)	24	70 (13)	21	0.013

Only patients with moderate or severe pain before taking first dose included in analysis (see text).

Table 3. Analgesic measures and number of doses. Values are expressed as mean (SEM).

	Ibuprofen combination	(n)	Paracetamol combination	(n)	Statistical significance
Daily global rating					
Day 3	2.6 (0.2)	23	1.9 (0.2)	21	$p < 0.003$
Day 4	2.8 (0.3)	20	1.7 (0.4)	10	$p < 0.05$
Day 5	2.8 (0.3)	16	1.8 (0.4)	10	
Day 6	2.4 (0.4)	9	1.6 (0.5)	8	
Total doses					
Day 3	2.5 (0.2)	23	2.6 (0.2)	21	
Day 4	2.1 (0.2)	20	2.1 (0.4)	11	
Day 5	2.1 (0.3)	17	2.5 (0.3)	10	
Day 6	2.1 (0.2)	9	1.9 (0.4)	8	

Statistical significance from Wilcoxon's test.

higher with the paracetamol combination ($p < 0.05$, Chi-squared). The incidence of adverse effects tended to increase with duration of exposure, but few patients were still taking medication by the last day. The mean percentage incidence (across days) was 21.5% for the ibuprofen combination and 20.9% for the paracetamol combination, higher than for day 1 alone.

Discussion

These results provide further evidence that the effects of postoperative multiple doses of analgesics can be studied and that differences between medications can be detected with this model.

On both single and multiple dosing the ibuprofen combination produced a statistically significant increase in efficacy over the paracetamol combination. This was apparent on both simple measures, such as hours of maximal pain relief, and on the derived indices. Of the derived indices, those calculated from pain relief measures proved more sensitive than those calculated from the pain intensity measures. The ibuprofen combination gave 50% greater TOTPRIX/dose than the paracetamol combination on day 1 and 70% on day 2. This refutes the idea that pain relief measures are unlikely to work well in multiple dosing [8] because the 'anchor point', against which the patient makes the judgment of relief, is long past.

One argument for multiple dosing studies is that they could detect evidence of increased efficacy on multiple dosing. Codeine particularly has a reputation for such an effect [2]. There was some evidence for an increase in this study; the mean TOTPRIX/dose within medication was 36% higher for the ibuprofen combination on day 2 compared with day 1, and 18% higher for the paracetamol combination. Postoperative pain usually decreases with time, so that this judgment of increased effect should be treated cautiously.

The argument that multiple dosing studies can also provide evidence for deciding on optimal dosing strategies is also supported by these results. With patients deciding when to self-medicate within safe prescribing limits, the results showed a significantly greater duration of the effect of the ibuprofen combination compared with the paracetamol combination, in addition to a greater degree of efficacy.

Table 4. Adverse effects (for all patients).

	Ibuprofen combination	Paracetamol combination
Number of patients	30	30
Postoperative secondary infection	2	1
Number of patients reporting adverse effects	9	15
Number of patients reporting more than one adverse effect	4	5
Nausea	3	10*
Drowsy	2	2
Headache	2	0
Dizziness	1	1
Constipation	1	1
Vomiting	0	4
Abdominal pain	1	1
Faint feeling	1	1
Increased bleeding	1	0
Light-headed	1	0
Number of reports of adverse effects	13	20

* Significant difference (Chi-squared).

This multiple dosing model is very sensitive. We asked patients to take the first dose of analgesic when they had moderate or severe pain, rather than to take the drugs prophylactically. The analysis of days 1 and 2 excluded those patients who did not fulfil this criterion; sensitivity might have been lost if this had not been done. An example of this problem is a recent oral surgery comparison of ibuprofen Continus (2×300 mg, $n = 49$) with ibuprofen Continus plus codeine ($2 \times 300 + 20$ mg, $n = 48$) [9]. Prophylactic dosing was used in that study, which may explain the poor sensitivity.

A second general methodological point is the ability to distinguish between true-negative and false-negative results in clinical trials which compare only two treatments and show no difference between them. This particular multiple dosing model can only compare two medications within patients (since lower third molars only occur on two sides). While the present study did show a significant difference between the two treatments, circumstances may arise when this is not the case [9]. More sophisticated design measures may be necessary to guard against this problem.

The clinical relevance of this study is that it showed that an ibuprofen–codeine combination produced better analgesia than a paracetamol–codeine–caffeine combination. Used without an opiate, ibuprofen may be a better choice on its own for postoperative pain relief than opiates such as dihydrocodeine [10]. A nonsteroidal anti-inflammatory drug combined with an opiate may do even better [10–13]. This idea of additive analgesia has been questioned recently [9], but historically such additivity has been well shown. Recent postoperative work [14] has indicated that both components are necessary to achieve maximal pain relief. The disadvantage of such combinations is the potential for an increased incidence of adverse effects, particularly from the opiate component [15]; for example, a higher (60 mg) dose of codeine produced significant adverse effects in older patients. This balance of increased efficacy versus increased adverse effects is unresolved; the present and previous [2] studies in this patient group show that an increase in efficacy can be obtained with little increase in the risk of adverse effects.

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