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AN ORAL BUPRENORPHINE AND PARACETAMOL COMBINATION COMPARED WITH PARACETAMOL ALONE: A SINGLE DOSE DOUBLE-BLIND POSTOPERATIVE STUDY

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1 An oral combination of buprenorphine and paracetamol was compared with paracetamol alone in a single dose, double-blind postoperative study. One hundred and twenty patients undergoing elective minor orthopaedic operations were allocated to four groups of 30 patients. The four treatments were 1, 1.5 or 2 mg of buprenorphine with paracetamol 1000 mg or paracetamol 1000 mg alone.

2 There were no significant differences between the groups in analgesia measured by the observer over the 6 h period of direct observations. The oral opiate produced a significant increase in duration of analgesia beyond the 6 h study period. A significant increase in side-effects was seen only at the highest buprenorphine dose compared with paracetamol.

3 The problems of trial design for analgesic combinations are considered. Drug mixtures create additional complexities which decrease the certainty of the conclusion that no real benefits result from such mixtures.

Introduction

The oral use of narcotic drugs in the acute treatment of postoperative pain is unsatisfactory. Interindividual variation in the large first pass effect of this class of drug leads to unpredictable activity. Only when titration is possible, as in the chronic situation, can good results be obtained (Twycross, 1974).

The mixed agonist-antagonist opiate buprenorphine is, however, potentially useful by the oral route. Its advantages include low addiction potential (Jasinski, Pevnick & Griffith, 1978), non-controlled drug status, long duration of action (McQuay *et al.*, 1980), and limited respiratory depressant effect (Watson *et al.*, 1981), even in overdose (Banks, 1979).

A relatively slow onset of effect with oral buprenorphine would have been predicted from sublingual use (Bullingham *et al.*, 1981) where the mean peak plasma level was not achieved until 2 h after administration. This problem of slow onset of action may be overcome by covering the initial period with a non-opiate drug. The choice of paracetamol for the combination in this trial was based on animal studies which showed synergistic analgesic activity using a paracetamol buprenorphine combination (Reckitt and Colman, on-file data). The choice of the appropriate oral dose of buprenorphine was based on an extraction ratio of about 85% (Bullingham *et al.*, 1980) and an effective parenteral or sublingual dose of between 0.3 and 0.6 mg, giving an oral dose estimation of around 2 mg.

This trial was designed to establish the efficacy and safety of three doses of buprenorphine, when administered simultaneously with paracetamol by the oral route to patients suffering from moderate to severe pain. A postoperative pain model was used which involved minor hand surgery. This allowed the study of male and female patients undergoing the same operations after the use of standardised non-analgesic premedication and anaesthesia.

Methods

The trial was designed as double blind, single dose and noncrossover. Ethical Committee approval was obtained to study patients undergoing elective hand surgery at the Nuffield Orthopaedic Centre, Oxford.

Patients were included in the trial if aged 18 years or older and if their weight was between 45 and 90 kg. They were excluded if suffering from severe renal or hepatic damage, marked ventilatory impairment due to underlying respiratory disease, if taking regular narcotics or if they were pregnant.

All patients received the same premedication and anaesthetic. Premedication was with 0.6 mg of atropine intramuscularly 1 h prior to operation, as

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prophylaxis for intraoperative bradycardia. Intravenous induction of anaesthesia with thiopentone 5 mg/kg was followed with spontaneous ventilation on the Bain circuit. The patients breathed 33% oxygen in nitrous oxide with halothane 1–3%. Venous blood (10 ml) was taken prior to induction and on the morning after surgery for haematological and biochemical studies.

Postoperatively all patients were transferred to a recovery ward where they remained until the following morning. They were looked after solely by the trained, full-time nurse observer (L.W.). Pain was assessed on a four point scale (none = 0, mild = 1, moderate = 2 and severe = 3). Pain of moderate or severe intensity occurring within 2 h of entering the recovery room was treated with the test medication. The test medications consisted of three tablets. The four treatment groups received either paracetamol (2 × 500 mg) + buprenorphine placebo, paracetamol (2 × 500 mg) + buprenorphine 1 mg, paracetamol (2 × 500 mg) + buprenorphine 1.5 mg or paracetamol (2 × 500 mg) + buprenorphine 2 mg.

Before receiving the test medication, measurements of pain intensity, sedation (0 = alert, 1 = mildly drowsy, 2 = moderately drowsy and 3 = asleep), pulse rate, blood pressure and respiratory rate were made. These were repeated with measurements of pain relief (0 = none, 1 = slight, 2 = moderate, 3 = good and 4 = complete) at 0.5, 0.75, 1, 1.5, 2, 3, 4 and 6 h. In addition, visual analogue scale measurements of pain intensity, pain relief and mood were made, using 10 cm lines, at 0, 1, 2, 3, 4 and 6 h, together with an assessment of the pain intensity on a 7 word verbal rating scale (no pain, just noticeable, mild, weak, moderate, strong, severe and excruciating; same random word display to each patient, scored 0 to 7 in this order). Volunteered side-effects and their severity were noted. Any medication required before the patients left the recovery room the following morning was recorded. If no pain relief was obtained from the test medications after one hour or if the pain intensity reverted to initial values, papaveretum was administered intramuscularly.

The sum of pain intensity difference (SPID) and total pain relief (TOTPAR), peak pain intensity difference (PEAK PID) and peak pain relief (PEAK REL) were calculated by standard procedures (Wallenstein & Houde, 1975) with and without stratification of the initial pain intensity values. The visual analogue equivalents, VAS-SPID for pain intensity, VAS-TOTPAR for pain relief, and the verbal rating scale equivalent for pain intensity, VRS-SPID were derived in the same way as for SPID and TOTPAR. Patients who required remedication before the end of the 6 h study period were ascribed initial values of pain intensity and a pain relief score of zero (Lasagna, 1980).

The overall sedation and mood measures, AUC sedation and AUC mood were calculated as the area under the curves of the effect v time data by a trapezoidal formula.

Statistical analysis for the analgesic measures and demographic data was by the Kruskal-Wallis one way analysis of variance. Side effect incidence and time to next analgesic were analysed by the chi-square test.

Results

One patient out of the 120 studied was omitted from all analyses, because he regurgitated the test medica-

Table 1 Patient data (mean ± s.e. mean)

Buprenorphine (mg)	0	1.0	1.5	2.0
Paracetamol (mg)	1000	1000	1000	1000
Number	30	30	29	30
Age (years)	40.0 ± 2.5	48.1 ± 3.0	46.2 ± 2.5	45.8 ± 2.8
Weight (kg)	64.6 ± 2.0	66.0 ± 2.3	66.9 ± 2.2	66.2 ± 2.6
Height (cm)	166.0 ± 1.5	165.0 ± 1.7	163.0 ± 1.7	166.0 ± 1.8
Sex ratio (M:F)	10:20	10:20	8:21	10:20
Initial pain intensity:				
Number of patients				
Moderate	20	21	16	15
Severe	10	9	13	15
Operative procedure:				
Carpal tunnel release	11	12	15	9
Ganglion removal	8	4	5	6
Dupuytren's contracture	2	3	3	5
Trigger finger release	1	3	2	5
Other	8	8	4	5

Other includes synovectomy, amputation of phalanx, arthroplasty, trapeziumectomy and osteotomy.

Table 2 Total and stratified SPID and TOTPAR scores (mean ± s.e. mean)

Buprenorphine (mg)	0	1.0	1.5	2
Paracetamol (mg)	1000	1000	1000	1000
SPID				
Overall	6.72 ± 0.87 (n = 30)	6.18 ± 0.90 (n = 30)	8.86 ± 0.92 (n = 29)	7.49 ± 0.89 (n = 30)
Severe	11.00 ± 1.42 (n = 10)	6.03 ± 2.40 (n = 9)	12.27 ± 1.24 (n = 13)	8.93 ± 1.49 (n = 15)
Moderate	4.58 ± 0.74 (n = 20)	6.24 ± 0.83 (n = 21)	6.09 ± 0.84 (n = 16)	6.05 ± 0.85 (n = 15)
TOTPAR				
Overall	13.78 ± 1.22 (n = 30)	13.23 ± 1.55 (n = 30)	16.10 ± 1.08 (n = 29)	14.70 ± 1.21 (n = 30)
Severe	15.88 ± 1.85 (n = 10)	8.36 ± 3.32 (n = 9)	17.10 ± 1.53 (n = 13)	13.73 ± 2.00 (n = 15)
Moderate	12.74 ± 1.56 (n = 20)	15.32 ± 1.53 (n = 21)	15.30 ± 1.53 (n = 16)	15.67 ± 1.39 (n = 15)

tion 2 min after it was given. Demographic details of the remaining patients in the four groups are given in Table 1. There were no statistically significant differences between the groups (Kruskal-Wallis). Comparison of pre- and postoperative biochemical and haemotological results showed the only significant differences to be rises in white blood cell count and blood urea, but there was no difference between the groups.

Mean values for SPID and TOTPAR are shown in Table 2. There was a tendency to higher values of SPID and TOTPAR in the group which received paracetamol plus 1.5 mg of buprenorphine, but this did not achieve statistical distinction from paracetamol alone. These results were supported by data obtained from visual analogue scales, VAS-SPID & VAS-TOTPAR, and from verbal rating scales, VRS-SPID (Table 3). Paracetamol (1000 mg) alone provided 48% of theoretically maximal SPID and 57% of theoretically maximal TOTPAR; the addition of 1.5 mg of buprenorphine produced increases of 12% and 10% respectively over these figures during the six hour study period.

Duration of analgesia as measured by time to next analgesic, however, showed a significant difference between those groups which received the oral opiate and that which did not (Table 4). The differences between the groups receiving different opiate doses were not significant and so they are combined in this table.

Clinically important changes in vital signs, defined as a respiratory rate of less than 10, a fall in systolic blood pressure to less than 80 mm Hg and a fall in pulse rate of more than 20 beats/min are shown in Table 5. The only significant change found was a decrease in respiratory rate with increasing buprenorphine dose.

Recorded side effects are shown in Table 6. There was an increased incidence of dizziness, nausea and sweating at the highest dose of buprenorphine. One patient who had received the highest dose of buprenorphine became confused. There were no significant differences in either mood or sedation detected between the four groups (Table 3).

Table 3 Visual analogue and peak intensity and relief scores (mean ± s.e. mean)

Buprenorphine (mg)	0	1.0	1.5	2
Paracetamol (mg)	1000	1000	1000	1000
Number	30	30	29	30
Peak PID	1.77 ± 0.16	1.47 ± 0.18	2.03 ± 0.15	1.90 ± 0.15
Peak REL	3.23 ± 0.21	2.73 ± 0.31	3.55 ± 0.12	3.37 ± 0.19
VAS-SPID	257 ± 38	257 ± 43	324 ±42	363 ± 49
VRS-SPID	16.2 ± 1.8	18.6 ± 3.6	29.8 ± 3.3	27.2 ± 3.5
VAS-TOTPAR	424 ± 30	390 ± 41	458 ± 24	411 ± 32
AUC Mood	492 ± 15	457 ± 31	493 ± 15	466 ± 15
AUC Sedation	4.66 ± 0.73	4.99 ± 0.97	7.03 ± 1.12	5.72 ± 0.91

Table 4 Measures of duration of analgesia

Percentage of patients remedicated	Paracetamol (1000 mg)	Buprenorphine (+ paracetamol 1000 mg) (All doses)
Total number of patients	30	89
by 6 h	30	25
12 h	80	63*
15 h	90	66****
20 h	93	75***
24 h	93	79**

Chi-square: * = $P < 0.01$, ** = $P < 0.05$, *** = $P < 0.02$, **** = $P < 0.01$.

Discussion

Analgesic preparations which contain two or more components in a fixed ratio may be criticised on several counts. Individual requirements may vary for the different drugs used. The drugs may have distinct pharmacokinetics and multiple dosing may then disrupt their intended proportions. Further, the patient is exposed to the potentially toxic effects of all the compounds used.

The compensation sought from combination preparations usually centres around differences in mechanisms of action of the drugs which can produce potentiation or increased duration of effect. The popularity of combination preparations with the public and medical profession (Shenfield, Jones & Paterson, 1980) indicates the power of this argument. However, the real disadvantages of mixtures make it especially necessary to show by careful controlled trials that the balance of evidence favours co-administration of drugs. The present study illustrates some of the particular difficulties of trial design which can arise with analgesic combinations.

Over the 6 h study period no statistically significant increase in analgesic effect was shown between paracetamol alone and paracetamol in combination with buprenorphine. This was true even at the highest content of buprenorphine (2 mg), although this dose was exerting some effects during this period as shown by the significant increase in side effects of an opiate nature (Table 6). The trial was properly conducted: double-blind, randomised, controlled and with all analgesic measurements made by a single trained observer. The conclusion must be that the addition of buprenorphine to a dose of paracetamol is of no benefit. Three further considerations, however, should be taken into account. One is general and the other two are specific to combination preparations.

Firstly, the conclusion may be statistically erroneous. The certainty of a negative result is determined by the power of the statistical test used against the null hypothesis (Siegel, 1956). Nonparametric methods, such as the Kruskal-Wallis analysis of variance seem more appropriate for data of the nature of pain assessments. Unfortunately, the power of such tests for a particular number of points is not known.

Secondly, a comparatively large dose of paracetamol (1 g) was chosen to provide quick onset of effective analgesia in the early period from a single dose. This paracetamol dose alone proved to be very effective, with SPID and TOTPAR scores of about 50% of theoretically maximal values. In contrast placebo or codeine (60 mg) in a similar orthopaedic model produced only very slight effects (less than 10% maximum SPID, Bullingham *et al.*, unpublished observations). There were increases in SPID and TOTPAR values when buprenorphine was added to paracetamol but the extra effects were not statistically significant. If one component of the combination

Table 5 Vital signs (after treatment)

Buprenorphine (mg)	0	1.0	1.5	2
Paracetamol (mg)	1000	1000	1000	1000
Number of patients	30	30	29	30
Respiration < 10 breaths/min	2	6	6	8****
Blood pressure < 80 mmHg	7	2	3	7
Pulse fall of > 20 beats/min	11	12	13	10

**** = chi-square $P < 0.01$, buprenorphine 2 mg + paracetamol *v* paracetamol alone.

Table 6 Side-effects

Buprenorphine (mg)	0	1.0	1.5	2.0
Paracetamol (mg)	1000	1000	1000	1000
Number of patients	30	30	29	30
Dizziness	5	4	4	9**
Euphoria	1	1	1	2
Depression	1	2	3	2
Nausea	5	5	4	10**
Vomiting	1	1	4	2
Sweating	1	2	1	5****
Headache	13	10	13	11
Thirst	3	3	9	3

Chi-square, buprenorphine 2 mg + paracetamol *v* paracetamol alone, ** = $P < 0.05$, **** = $P < 0.01$.

contributes a substantial analgesic effect, as with paracetamol in this trial, then this is equivalent to a marked decrease in the sensitivity of the model for the measurement of analgesic effects from any other component.

Lastly, buprenorphine did result in statistically significant differences in analgesia beyond the 6 h period of direct observations. This suggests that the analgesic action of the buprenorphine component did not become evident until well into the study period and long outlasted that period.

It is the drug mixture that creates these additional complexities. The large dose of paracetamol and the short observation period relative to the duration of action of oral buprenorphine made the design of this trial inadequate to be certain that there is no real benefit from the addition of the opiate. Certainty is achieved only through an unimpeachable trial design, which becomes much more critical than in the usual single dose study. Both existing and novel analgesic combinations require examination with these principles in mind.

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