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Evaluation of different doses of soluble ibuprofen and ibuprofen tablets in postoperative dental pain

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SUMMARY. **The object of the study was to assess the comparative efficacy of three single doses (200, 400, 600 mg) of soluble ibuprofen and ibuprofen tablets after third molar surgery in 148 patients aged 18–40 years.**

Outcome was measured by overall assessment of pain (AUC_{360}) assessed from serial visual analogue scales, the number of patients taking additional analgesic and by overall assessment of medication evaluated on a five-point categorical scale.

Over the 6-hour investigation period all the ibuprofen treatments with the exception of ibuprofen tablets 200 mg resulted in significantly less pain ($p < 0.05$) than placebo treatment. A large number of patients required additional analgesia during the investigation period, but the time to taking it was significantly earlier in the placebo group. No significant dose response ($p > 0.05$) was observed for either ibuprofen preparations assessed by the outcome variable of overall pain experience (AUC_{360}) or time to additional analgesia. There was no significant difference in pain scores or time to taking additional analgesics between the respective doses of soluble and tablet formulations of ibuprofen.

Both soluble and tablet formulations of ibuprofen provide effective pain control in the early postoperative period after removal of impacted third molars. There is little analgesic advantage in increasing the dose to 600 mg and only minimal benefit from using a soluble formulation of the drug.

INTRODUCTION

Ibuprofen is both efficacious and used extensively in the management of postoperative pain after dental surgical procedures.[1–6] It has been reported that a soluble formulation of the drug provided a more rapid onset of analgesia than ibuprofen tablets in patients with early postoperative pain after third molar sugery.[7] Differences in efficacy were attributable to earlier and greater peak concentrations of ibuprofen after taking the soluble formulation compared with the tablets, but ibuprofen tablets give a poor dose response in this model of acute pain. There were no significant differences in efficacy after single doses of ibuprofen 100, 200, and 400 mg[8] or between 400, 600, and 800 mg.[9] It was suggested that this shallow dose response resulted from a 'ceiling effect' or individual patient variation in pharmacokinetic variables.[9]

The aim of the present study was to investigate the dose-response relationships of soluble and tablet formulations of ibuprofen in patients with postoperative pain after removal of impacted third molars.

METHOD

148 adult patients (78 women) who required the removal of at least two lower impacted third molars participated in the study, which had received prior ethical approval from the local Health Authority Ethics Committee. Written informed consent was obtained from all patients in accordance with the Declaration of Helsinki, 1975. Patients who participated in the study were taken from the waiting list of the Department of Oral and Maxillofacial Surgery, and had been admitted for routine third molar surgery. Patients with serious renal, hepatic, respiratory, cardiac, endocrine, or metabolic impairment, persistent mental confusion, active gastrointestinal symptoms; and women who were pregnant or lactating, were excluded from the study. In addition, patients with a history of asthma, drug or alcohol misuse, or those who required antibiotic or corticosteroid prophylaxis were also excluded.

Impacted third molars were removed under general anaesthesia. Oral temazepan 20–30 mg was given to all patients 2 h before operation as premedication. Anaesthesia was induced with intravenous propofol 2.5 mg/kg body weight, and muscle relaxation achieved with intravenous suxamethonium chloride 100 mg. A mixture of nitrous oxide, oxygen, and isoflurane was used to maintain anaesthesia.

The third molars were removed by a standard technique and bone removal was carried out with a drill under saline spray. Operating time was recorded from first incision to completion of last suture. At the end of the operation, patients returned to the ward and time was allowed for them to recover from the effects of the general anaesthetic. In this early

postoperative period, patients recorded their pain intensity on 100 mm visual analogue scales (VAS). The boundaries of the scale were marked 'no pain' and 'as severe as it could be'. When patients' pain reached a level greater than 30 mm on the VAS, or when their pain reached an intensity at which they requested an analgesic, they were entered into the study. Most patients entered the study within an hour of returning to the ward. If after 2 h their pain sensation still remained below 30 mm, they were withdrawn from the study. Those in the study then received in random, double-blind order either a single dose of soluble ibuprofen tablets (200, 400, or 600 mg), dissolved in 150 ml of water, or ibuprofen tablet (Nurofen) (200, 400, or 600 mg) or placebo. To ensure double-blind conditions, the double-dummy technique was used. Each patient received three soluble tablets dissolved in water to make a tasteless effervescent solution, and three tablets to swallow without chewing. About 20 patients were allocated to each treatment group. Randomisation ensured that in each group there was about the same proportion of men to women.

Patients continued to register their pain experience on serial, plain vertical VAS at 0, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, and 360 min after dosage. The drugs were given and the VAS explained by the same nurse or observer on all occasions. The area under the graph of pain (mm) against time (hours) was calculated by the trapezoidal method to provide an integrated measure of pain experienced throughout the 6-h investigation period (AUC_{360}). In addition, the incidence and severity of adverse effects during the study period was recorded separately.

During the study period, patients were permitted to take additional analgesics (paracetamol 1 g), and withdraw in the event of poor pain control by the test medication. For those patients who took additional analgesics, the time was recorded, and their previous VAS recording was projected on at the same level for all subsequent time points.[10]

At the end of the 6-h investigation period, patients were asked to complete a five-point global scale that evaluated their overall impression of the test medication. The categories of the scale were very good, good, satisfactory, poor and very poor.

STATISTICAL ANALYSIS

One-way analysis of variance was used to establish that the placebo control group had a poorer response (in terms of a significantly higher mean AUC) than the active treatment groups. The active treatment groups were analysed and compared using two outcome variables, AUC as described earlier, and the time taken to take the additional analgesia (t = 360 min if not taken). The unadjusted and adjusted analyses of these outcome variables were done using analysis of variance and covariance, respectively, and were calculated with the Genstat statistical package. The dose/response effect was examined by the use of contrasts between doses for each method of drug delivery, and were based on the appropriate standard errors of the differences between doses within methods calculated from the ANOVA table. The Kruskal-Wallis test was used to assess differences in the time to additional analgesic between treatment groups, and the chi-square test to compare patients' overall assessment of their medication.

RESULTS

Of the 148 patients who were enrolled in the study, only 119 completed the evaluation. Four were excluded because of unwanted effects and the remaining 25 patients failed to reach a level of pain of sufficient magnitude for entry into the study.

Patients and operative variables for the various treatment groups are shown in Table 1. The variable of age, weight, operating time, and initial pain scores were similar for all treatment groups, as were the sex distributions. Mean pain scores (mm) for each time point after the various doses of ibuprofen and soluble ibuprofen are shown in Figures 1, 2 and 3.

Overall pain scores as assessed by the AUC_{360} values are shown in Table 1. All the ibuprofen treatments with the exception of ibuprofen tablets 200 mg resulted in significantly less pain ($p<0.05$) than placebo treatment.

The number of patients who took additional analgesic during the 6-h investigation period is shown in Table 1. The numbers were high in all treatment groups, but the time to additional analgesia was significantly earlier in the placebo group ($p<0.05$) when compared with all the treatment groups.

Patients' overall assessment of their medication is shown in Table 2. There was significant difference ($p<0.05$) in favour of the ibuprofen preparations compared with placebo.

Dose response

The dose response analysis for both soluble and tablet formulations with respect to AUC_{360} and time to additional analgesia is shown in Tables 3 and 4. There is no evidence of a significant dose response for either of these outcome variables as indicated by the lack of significant differences between AUC's$_{360}$ for ibuprofen tablets 400 and 600 mg, and the apparent increase in AUC_{360} from soluble ibuprofen 400 to 600 mg (Table 3). Furthermore, there were no significant differences between soluble and tablet preparations of ibuprofen at any of the doses for either of the unadjusted or adjusted outcome variables.

Unwanted effects

Three patients treated with ibuprofen tablets and one patient in the placebo group vomited their medication soon after dosage. These patients were excluded from the analysis.

Table 1 – Clinical variables for each treatment group

	Placebo	Ibuprofen tablets			Soluble ibuprofen		
		200 mg	400 mg	600 mg	200 mg	400 mg	600 mg
No. of patients	19	18	15	17	17	16	17
Male : female ratio	7:12	5:13	5:10	6:11	5:12	7:9	6:11
Median weight (kg)	69.5	64.4	67.4	60.6	65.7	66.2	64.2
(range)	(50.8–95)	(50.4–90.2)	(52.1–85)	(50.5–79)	(51–86.4)	(49.9–89.2)	(50.4–85)
Median operating time (min)	20	25	25	25	25	20	27
(range)	(5–50)	(15–60)	(10–45)	(5–60)	(10–55)	(5–65)	(10–60)
Mean (SD) initial pain scores on	66	67	69	68	68	65	61
100 mm VAS	1.5	1.7	1.2	2.2	2.1	1.7	1.8
(range)	(39–94)	(33–98)	(38–86)	(36–99)	(33–95)	(39–92)	(36–100)
Mean $AUC_{360}(mm^2.h^{-1})$	2116	1619	933*	1082*	1379*	874*	1338*
(SEM)	(175)	(199)	(166)	(187)	(217)	(156)	(201)
No. of patients taking additional analgesics	19	18	10	15	15	13	15
Median time to escape (min)	50	117.5*	167.5*	180*	90*	125*	95*
(range)	(30–195)	(30–357)	(35–305)	(35–370)	(29–350)	(45–360)	(35–365)

*Significant difference from placebo ($p<0.05$).

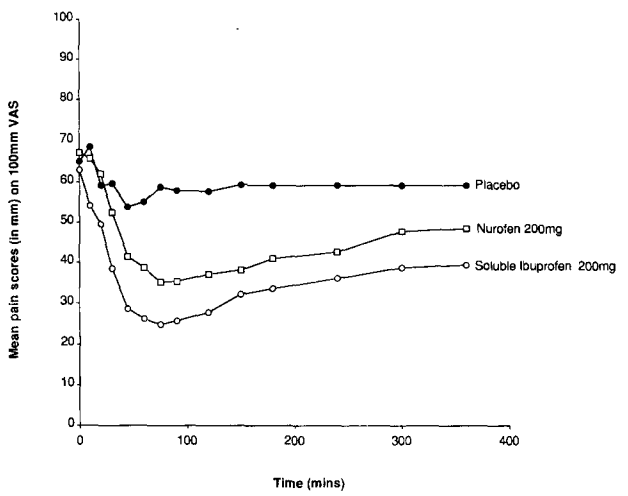

Fig. 1 – Mean pain scores (mm) compared with time (minutes) for placebo, soluble ibuprofen 200 mg and ibuprofen tablets 200 mg.

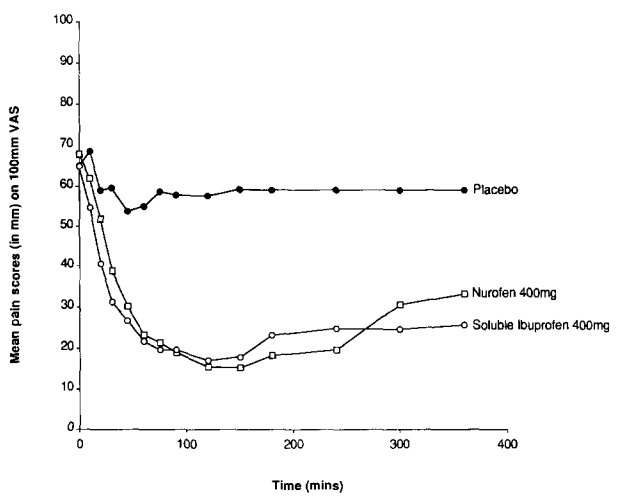

Fig. 2 – Mean pain scores (mm) compared with time for placebo, soluble ibuprofen 400 mg and ibuprofen tablets 400 mg.

DISCUSSION

Ibuprofen is an effective analgesic for controlling postoperative pain after third molar surgery, and the

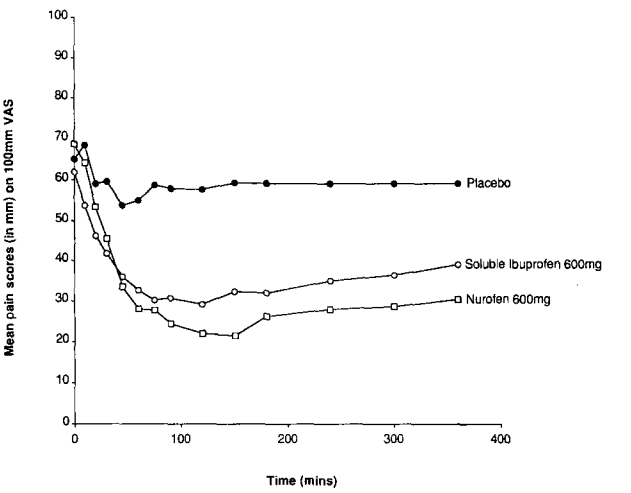

Fig. 3 – Mean pain scores (mm) compared with time for placebo, soluble ibuprofen 600 mg and ibuprofen tablets 600 mg.

results from the present study support this finding. Although the drug is widely used, there is little information about the factors which influence its efficacy. In a previous study, using a similar protocol, we showed that a single dose of soluble ibuprofen 400 mg provided quicker analgesia than ibuprofen tablets 400 mg.[7] The differences in efficacy were attributed to the soluble preparation providing an earlier and greater peak plasma concentration of the drug compared with the tablet. This suggests that plasma concentrations are important determinants for the drug's efficacy. In a further crossover study, however, we failed to find any relationship between measures of efficacy and pharmacokinetic variables of ibuprofen in patients with postoperative pain after bilateral third molar surgery treated with a single dose of soluble ibuprofen 400 mg.[11] When these results are taken in conjunction with the poor dose response elicited in the present study, it seems that plasma concentrations of ibuprofen are not important determinants of the drug's efficacy.

The poor dose response to ibuprofen has also been confirmed in postoperative dental pain, using single dose of 100, 200, and 400 mg,[8] 400, 600, and 800 mg[9]

Table 2 – Distribution of the overall assessment scores for the various doses of ibuprofen and placebo as evaluated on a five-point global scale

	Very poor	Poor	Satisfactory	Good	Very good	Not recorded
Placebo	2	5	10	3	0	1
Ibuprofen tablets 200 mg.*	0	6	6	5	3	2
Ibuprofen tablets 400 mg.*	0	6	6	5	3	2
Ibuprofen tablets 600 mg.*	0	0	4	9	7	1
Soluble ibuprofen 200 mg.*	0	4	6	6	5	0
Soluble ibuprofen 400 mg.*	0	1	3	8	6	3
Soluble ibuprofen 600 mg.*	0	2	6	8	5	9

*Significant differences ($p < 0.05$) in the distribution of scores from placebo treatment.

Table 3 – Dose response analysis for overall pain scores (AUC_{360}) expressed in $mm^2.h$ after the different ibuprofen treatments. AUCs adjusted for sex, baseline pain scores, and time to additional analgesia

Preparation	Dose 200 mg	400 mg	600 mg	SE of difference between doses within preparation
Tablets	1428	1197	1192	131
Soluble	1191	955	1300	131
SE of difference between preparations for each dose	184.1	184.1	184.1	

Table 4 – Dose response analysis for time to additional analgesia (minutes) after the different ibuprofen treatments. Times adjusted for sex and baseline pain scores

Preparation	Dose 200 mg	400 mg	600 mg	SE of difference between doses within preparation
Tablet	140	242	205	28.2
Soluble	143	192	153	28.2
SE of difference between preparation for each dose	39.9	39.9	39.9	

and 400, and 800 mg.[1] Similar poor dose responses to the drug have been reported in rheumatoid arthritis[12] using divided doses of 1600 mg and 2400 mg/day, and in pain after episiotomy[13,14] using single dose of 300 or 900 mg or 400 and 800 mg, respectively.

It has been suggested that the shallow dose response to ibuprofen is caused by a 'ceiling effect' arising from variations in pharmacokinetic variables.[9] One such variable may be the stereospecific inversion of the racemic mixture of ibuprofen to the S(+) enantiomer. The anti-inflammatory and perhaps analgesic activity of ibuprofen may reside with the S(+) enantiomer,[15,16] which is an effective analgesic for patients with rheumatoid arthritis,[17] but this compound has not been evaluated in postoperative dental pain, or subjected to an increasing dose study. If plasma concentrations of S(+) ibuprofen are important determinants of the drug's efficacy, then the poor dose response may be caused by a dose-related inhibition on the rate of stereospecific conversion of the racemic mixture.

A large number of patients in this study required additional analgesia (Table 1), and so many failed to complete the 6-h investigation period. All patients were given their respective medication within 1–2 h after operation. Intensity of pain after removal of impacted third molars reaches its maximum about 3–5 h after the end of the operation.[18,19] Though these findings relate to third molar removal under local anaesthesia, there is likely to be a similar development of symptoms when general anaesthetic agents are used to complete the operation, so the widespread need for additional analgesia found in this study may be a reflection of the increasing pain. All the ibuprofen treatments provided significant pain relief during the first two to three hours after dosage. Our findings suggest that further medication is desirable at the end of this period. None of the patients experienced any unwanted effects that could be attributed to their medication, which supports the safety of ibuprofen in the management of postoperative dental pain.

We conclude that both soluble and tablet preparations of ibuprofen provided effective pain control in the early postoperative period after removal of impacted third molars, but further medication after 3 h (when pain intensity is likely to increase) is recommended. Ibuprofen 400 mg seems to be satisfactory for the management of postoperative pain after third molar surgery. There seems to be no advantage in increasing the dose to 600 mg.

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