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An evaluation of different ibuprofen preparations in the control of postoperative pain after third molar surgery

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1 Two separate placebo-controlled studies of parallel design were carried out to evaluate the efficacy of single doses (400 mg) of soluble ibuprofen, ibuprofen liquid in a gelatin capsule and ibuprofen tablets (Nurofen®), in patients with postoperative pain after third molar surgery.
2 All ibuprofen preparations provided significant pain relief ($P < 0.05$) over a 6 h investigation period.
3 Mean pain scores after ibuprofen tablets and ibuprofen liquid in a gelatin capsule were similar.
4 Soluble ibuprofen 400 mg provided an earlier onset of pain relief (20 min) than ibuprofen tablets (30 min).
5 No unwanted effects were reported in the various ibuprofen treatment groups.
6 The ibuprofen preparations evaluated in this study are effective up to 4 h for controlling postoperative pain after third molar surgery. The soluble form is more efficacious with regard to onset of action.

Keywords ibuprofen soluble ibuprofen postoperative pain third molar surgery

Introduction

Postoperative pain after removal of impacted third molars is widely used as a model for evaluating analgesic efficacy. Findings from many studies suggest that analgesics with an anti-inflammatory action are effective for controlling postoperative dental pain (Seymour & Walton, 1984). Ibuprofen is a peripherally acting analgesic with a potent anti-inflammatory action. The drug has been evaluated extensively in postoperative dental pain and several studies support its efficacy (Cooper, 1984; Frame *et al.*, 1989; Giles, 1981; Hill *et al.*, 1987; Jain *et al.*, 1987; Rondeau *et al.*, 1980; Winter *et al.*, 1978). In these efficacy studies ibuprofen has been given as a tablet. In a previous study, we showed that the formulation of aspirin was an important determinant of efficacy in the treatment of postoperative dental pain (Holland *et al.*, 1988). Soluble aspirin provided an earlier and more prolonged period of pain control than aspirin tablets when used in the immediate period after third molar surgery. We suggested that the differences in efficacy between the two aspirin products was related to the higher plasma concentrations of acetylsalicylate obtained from the soluble preparation.

Although ibuprofen is currently available in a tablet formulation, new soluble preparations have become available which include a tablet that dissolves in 100 ml of water and ibuprofen liquid which is encased in a gelatin capsule. A soluble preparation has been shown to produce earlier and higher peak plasma concentrations of ibuprofen than ibuprofen tablets (Nurofen® registered trademark of The Boots Company PLC) (Unpublished data, Reckitt & Colman).

The aim of the present study was to compare the efficacy of single doses (400 mg) of soluble ibuprofen, ibuprofen liquid in a gelatin capsule and ibuprofen tablets (Nurofen) in patients with postoperative pain after removal of their impacted third molars.

Methods

One hundred and eighty patients (120 females) who required the removal of their impacted third molars agreed to participate in the study, which had received prior ethical approval from the joint Health Authority and the University Ethics Committee. Informed written consent was obtained from all patients in accordance with the Declaration of Helsinki, 1975. The patients

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were recruited from the waiting list of the Department of Oral Surgery and had been admitted for routine removal of their impacted third molars.

Third molar surgery was carried out under general anaesthesia after administration of atropine 0.6 mg intramuscularly as a premedication. Anaesthesia was induced with 4–6 ml of thiopentone 2.5% w/v and muscle relaxation was achieved with intravenous suxamethonium 75–100 mg. A mixture of nitrous oxide, oxygen and enflurane was used to maintain anaesthesia. The third molars were removed by a standard technique and, where necessary, bone removal was carried out with a drill under saline spray. Operating time was recorded from first incision to completion of last suture.

On completion of surgery, patients were returned to the ward and time was allowed for them to recover from the effects of the general anaesthetic. In this early post-operative period, patients recorded their pain intensity on 100 mm visual analogue scales (VAS). The boundaries of the scale were marked 'no pain' and 'unbearable pain'. When pain was recorded at a level greater than 30 mm on the VAS, and/or when it reached an intensity such that an analgesic was requested, the patients were entered into the study. The first 90 patients participated in the soft gelatin capsule study (Study 1), the remaining 90 took part in the soluble ibuprofen study (Study 2).

In Study 1, patients received either a single dose (400 mg) of ibuprofen tablets (Nurofen), liquid ibuprofen in a soft gelatin capsule or matched placebo. In Study 2, again patients received either single doses (400 mg) of ibuprofen tablets (Nurofen), soluble ibuprofen tablets dissolved in 100 ml of water, or matched placebo. Allocation of patients to each trreatment group was randomised and double-blind. To achieve double-blind conditions in both studies, the double-dummy technique was used. Thus, in Study 1 each patient received 2 tablets and 2 gelatin capsules. In Study 2, each patient received 2 oral tablets and two soluble tablets dissolved in 100 ml of water to make an effervescent solution. Approximately 30 patients were allocated to each treatment group. Randomisation ensured that in each treatment group, there was the same proportion of males to females.

Patients continued to register their pain experience on serial, plain vertical VAS at 0, 10, 20, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min after dosage. Drug administration and the explanation of the VAS was by the same nurse/observer on all occasions. The area under the pain score (mm) against time (h) was calculated by the linear trapezoidal method to provide an integrated measure of pain (AUEC(360)—area under effect-time curve) experienced in units of mm pain h throughout the 6 h investigation period. The incidence and severity of adverse effects during the investigation period were recorded separately.

During the study, patients were permitted escape analgesics (Co-codamol, 1 g) and were withdrawn in the event of poor pain control by the test medication. For those patients who took escape analgesics, the time of dosage was recorded, and their previous VAS recording extrapolated at this level for all subsequent time points (Lasagna, 1980).

At the end of the 6 h investigation period, patients were asked to complete a 5-point global scale which evaluated their overall impression of the test medication. The categories of the scale were very good, good, satisfactory, poor and very poor.

Statistical analysis

An analysis of covariance with correction for baseline score was used to assess differences in pain scores at each time and throughout the 6 h investigation period (AUEC(360)). The Kruskal-Wallis test was used to assess differences between treatment groups in patients' overall impression of the test medication. The chi-squared test and analysis of variance was used to assess differences in the number of patients taking escape analgesia and the time to dosing between treatment groups.

Results

Patient and operative variables for the various treatment groups are shown in Table 1. All groups proved to be matched for numbers, age, weight, operating time and baseline pain scores. The proportion of males to females was different between Study 1 and 2. However, within each treatment group in these studies the proportions were approximately the same.

Mean pain scores in mm (± s.e. mean) for each time point for the various treatments are illustrated in Figures 1a and 1b. In Study 1 (Figure 1a), treatment with ibuprofen soft gel 400 mg and ibuprofen tablets 400 mg was associated with significantly less pain ($P < 0.05$) than treatment with placebo at all times between 30 and 240 min after dosage. At no time point during the investigation period was there a statistically significant difference between the two ibuprofen treatments. Overall pain scores assessed by AUEC(360) values are reported in Table 1. Again, both ibuprofen treatments resulted in significantly less pain ($P < 0.01$) than treatment with placebo.

In Study 2 (Figure 1b), patients in both ibuprofen treatment groups reported significantly less pain ($P < 0.05$) than those treated with placebo. Patients treated with soluble ibuprofen 400 mg reported significantly less pain ($P < 0.05$) than placebo from 20–360 min after dosage, whereas in those treated with ibuprofen tablets, a significant difference from placebo was observed from 30–360 min. Overall pain scores (AUEC(360)) after both ibuprofen treatments were significantly less ($P < 0.01$) than after placebo (Table 1).

The number of patients who required escape analgesics during the 6 h investigation period is reported in Table 1. In both studies, there were significantly more patients in the placebo group taking escape analgesic ($P < 0.05$) than those receiving active treatment. Mean time to escape analgesic is also reported in Table 1. Patients in both placebo groups required their escape analgesic at an earlier time ($P < 0.05$) than those who received the various ibuprofen preparations.

Patients' overall assessment of their various medications is reported in Table 2. A significant difference ($P < 0.05$) in favour of the ibuprofen preparations was found when compared with placebo.

Table 1 Patient and operative variables for each treatment group

	Study 1			*Study 2*		
	Soft gelatin ibuprofen (400 mg)	*Ibuprofen tablets (400 mg)*	*Placebo*	*Soluble ibuprofen (400 mg)*	*Ibuprofen tablets (400 mg)*	*Placebo*
Number of patients	32	31	32	32	30	30
Males to females	13:19	13:18	14:18	7:25	6:24	7:23
Median age (years)	26	24	25	26	27	24
Range	19–50	18–49	20–40	18–42	18–24	19–40
Median weight (kg)	66.7	60.8	66.3	63.6	63.6	60.8
Range	44.1–101.7	51.3–89	50.8–89	50.9–95	40–100	45.4–92.2
Median operating time (min)	17	17	18	20	13	16
Range	5–53	4–43	6–40	3–31	5–50	6–39
Median baseline pain score (mm)	66	72	70	62	61	65
Range	35–100	37–98	32–99	33–91	40–88	37–93
Median AUEC(360) (mm pain h)	158.0**	138.5**	306.6	121.9**	165.9**	298.6
Range	5.1–447	11.7–561.5	5–586.2	4.6–397.4	4.6–301.3	31–516.3
Number of patients taking escape analgesic	14	12	22	23	18	28
Mean time (h) to escape analgesic dosage	3.47*	3.56*	2.13	3.15**	3.24**	1.4
± s.e. mean	± 0.4	± 0.5	± 0.34	± 0.3	± 0.36	± 0.27

* Significant difference from placebo $P < 0.05$
** Significant difference from placebo $P < 0.01$

Table 2 Distribution of overall assessment scores for the various analgesic treatments as evaluated on a 5-point global scale

Study 1

	Very poor	*Poor*	*Satisfactory*	*Good*	*Very Good*	*N.R.*
Soft gelatin ibuprofen*	1	5	7	8	6	5
Ibuprofen tablets*	3	2	9	12	3	2
Placebo	9	11	6	3	1	2

Study 2

	Very poor	*Poor*	*Satisfactory*	*Good*	*Very Good*	*N.R.*
Soluble ibuprofen*	3	4	8	12	4	1
Ibuprofen tablets*	4	0	7	11	4	4
Placebo	13	11	2	3	1	0

* Significant difference from placebo ($P < 0.05$)
N.R. = assessment not recorded

None of the patients in the ibuprofen treatment groups recorded any adverse effect from their medication. One patient from the placebo group from Study 1 reported a headache and nausea during the investigation period.

Discussion

Using a variety of pain assessments, we have demonstrated that single doses of various ibuprofen preparations are effective analgesics for the management of pain in the immediate postoperative period after third molar surgery. Furthermore, none of the patients in the various ibuprofen treatment groups experienced any unwanted effects during the investigation period.

Although ibuprofen has been evaluated extensively in postoperative dental pain, most of the studies have been of a comparative nature, whereby ibuprofen has been evaluated against placebo and other analgesics. Ibuprofen has been shown to be more effective than aspirin 650 mg, paracetamol 600 mg, the compound analgesic of aspirin, paracetamol and codeine phosphate 60 mg (Cooper, 1984), codeine phosphate 15, 30 and 60 mg (Rondeau *et al.*, 1980), and propoxyphene hydrochloride 65 mg (Winter *et al.*, 1978). Most of these studies have assessed efficacy of the various drugs at hourly intervals over a 4–6 h period. Thus, there is little information on

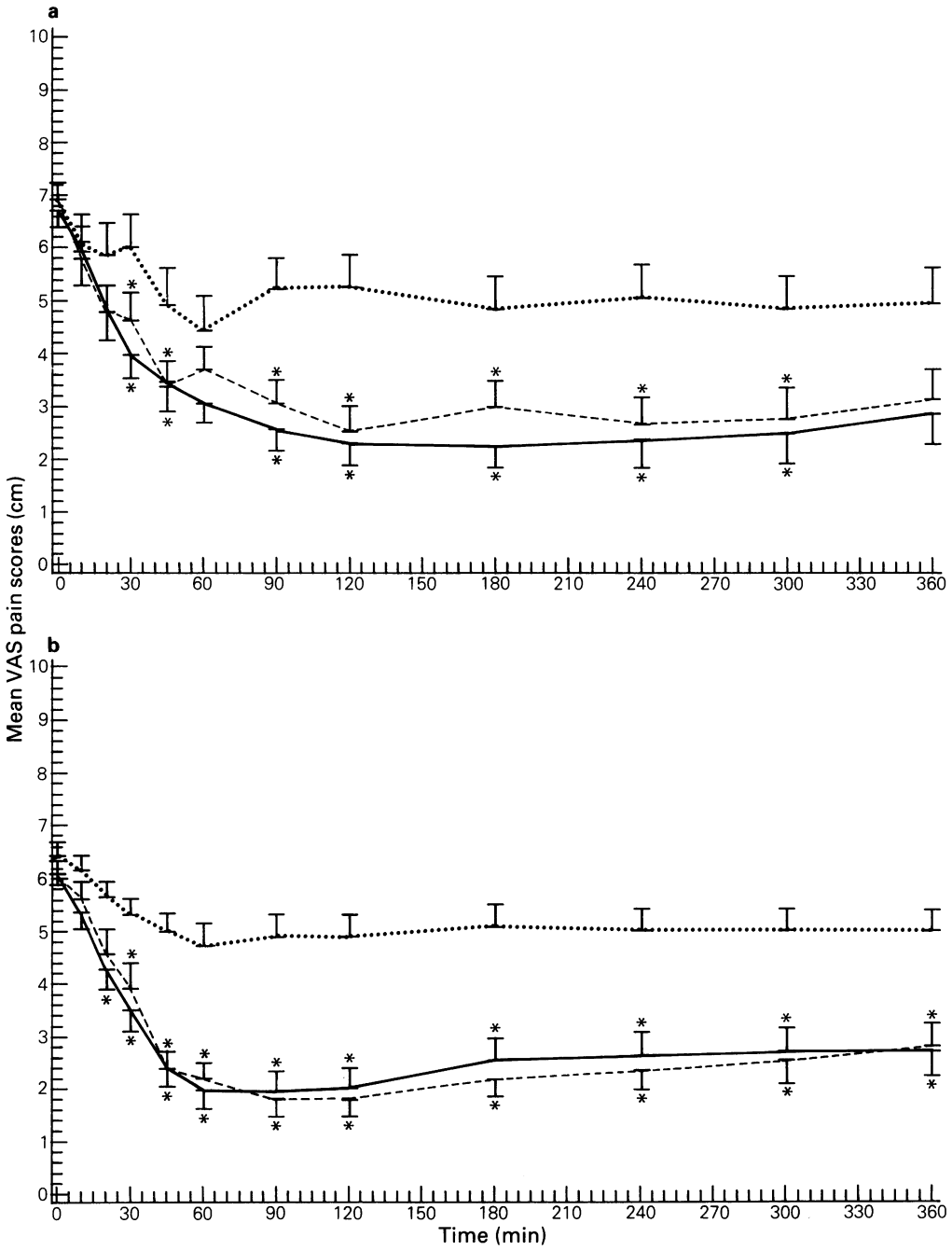

Figure 1 a) Mean pain scores (mm) ± s.e. mean compared with placebo after treatment with placebo (·····) and after treatment with liquid ibuprofen 400 mg in a soft gelatin capsule (soft gel, ——) and an ibuprofen tablet 400 mg (Nurofen, ---.) b) Mean pain scores (mm) ± s.e. mean compared with placebo after treatment with placebo (····) and after treatment with ibuprofen tablets 400 mg (Nurofen, ---) and soluble ibuprofen 400 mg (——). * Significantly different from placebo ($P < 0.05$).

the onset of pain relief from ibuprofen. Study 1 has shown that ibuprofen tablets start to provide significant pain relief (when compared with placebo) some 30 min after dosage and then provide satisfactory analgesia for up to 4 h (Figures 1a and 1b). However, many patients towards the end of the study were taking escape analgesics. Thus beyond 4 h, efficacy is uncertain.

No difference was shown in the efficacy of the two ibuprofen preparations used in Study 1. In Study 2, soluble ibuprofen 400 mg provided an earlier onset of pain relief (20 min) than ibuprofen tablets (30 min). The earlier onset of action may be clinically important, since it is during this time that patients usually experience their highest level of postoperative pain (Seymour *et al.*, 1985).

The earlier onset of pain relief attributable to soluble ibuprofen may be related to differences in the pharmacokinetic profiles of the soluble and tablet formulation of the drug. Soluble ibuprofen produces an earlier and greater peak plasma concentration of ibuprofen than the tablet (Reckitt & Colman, unpublished data). This would suggest that the rate of absorption of ibuprofen is an important determinant of the drug's efficacy. Further studies are planned to evaluate the efficacy of different ibuprofen preparations in patients who have undergone removal of their bi-

laterally similar impacted lower third molars under local anaesthesia. Such patients can act as their own placebo controls and provide an opportunity to investigate the relationship between plasma concentrations of ibuprofen and efficacy. Such a view has been substantiated in a dose-rising study which evaluated single doses of ibuprofen 400, 600, and 800 mg in patients with post-operative dental pain (Laska *et al.*, 1986). Thus serum concentrations of ibuprofen at 1, 2 and 3 h after dosage correlated with the global analgesic response.

Other ibuprofen preparations are available but there is little information on their comparative efficacy. Ibuprofen syrup has been shown to be efficacious in controlling pain after tonsillectomy (Parker *et al.*, 1986). Post-tonsillectomy pain may well be a useful indication for soluble ibuprofen since these patients may have difficulty in swallowing tablets.

We conclude that single doses of the three ibuprofen preparations evaluated were efficacious in controlling postoperative pain in the immediate period after third molar surgery. Soluble ibuprofen provides a slightly earlier onset of action, but the number of patients taking escape analgesics suggests that they should be remedicated 3–4 h after the initial dose.

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