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Onset of analgesia with sodium ibuprofen, ibuprofen acid incorporating poloxamer and acetaminophen—a single-dose, double-blind, placebo-controlled study in patients with post-operative dental pain

Stephen Daniels · Sandie Reader · Phillip Berry · Michael Goulder

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Abstract

Objective To compare the onset of action and efficacy of sodium ibuprofen (ibuprofen sodium dihydrate) and ibuprofen acid incorporating poloxamer (ibuprofen/poloxamer) with that of acetaminophen and placebo in patients with post-operative dental pain.

Methods A double-blind, randomised, placebo-controlled, active comparator, two-centre study assessing the analgesic efficacy of sodium ibuprofen (512 mg, equivalent to 400 mg ibuprofen acid), ibuprofen/poloxamer (containing 400 mg ibuprofen acid and 120 mg poloxamer 407), acetaminophen (1000 mg) and placebo in patients with moderate-to-severe pain after third molar extraction ($n=322$). Onset of action was assessed using the two-stopwatch technique, and pain intensity and relief were measured using validated traditional descriptor scales.

Results Significantly more patients achieved confirmed perceptible pain relief and meaningful pain relief with sodium ibuprofen (96.3%, $P<0.0001$) and ibuprofen/poloxamer (90.0%, $P=0.0005$) than with acetaminophen (67.5%). The onset of action of both ibuprofen formulations was comparable with that of acetaminophen up to 45 min post-dose; a marked divergence in onset times in favour of the ibuprofen formulations occurred from 45 min onward. Mean values for the area under the pain relief and pain intensity differences curve (0–6 h) were significantly greater for sodium ibuprofen (3.46) and ibuprofen acid (3.49) than for acetaminophen (2.25) ($P<0.001$). Other pain relief and pain intensity endpoints favoured both ibuprofen formulations over acetaminophen. Distractibility from pain (6 h) was significantly greater with the ibuprofen formulations than with acetaminophen ($P=0.008$ for sodium ibuprofen; $P=0.03$ for ibuprofen/poloxamer). In patients receiving ibuprofen, pain interfered less with daily activities (at 1 and 6 h) than in those receiving acetaminophen ($P\leq 0.015$). Both ibuprofen formulations had significantly better mean global assessment scores than acetaminophen ($P<0.001$). Tolerability profiles of the ibuprofen formulations were comparable with that of acetaminophen.

Conclusions Compared with acetaminophen, sodium ibuprofen was associated with significantly greater analgesic efficacy, pain relief in a greater proportion of patients and greater patient satisfaction.

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Introduction

Ibuprofen [2-(4-isobutylphenyl) propionic acid] is a widely used non-steroidal anti-inflammatory drug (NSAID) currently licensed and marketed worldwide. It exhibits anti-inflammatory, analgesic and antipyretic effects in humans by working as a potent inhibitor of the cyclooxygenase enzyme system and is used to treat pain resulting from a wide variety of ailments. There is an extensive amount of published literature describing the efficacy of ibuprofen [1–7].

Patients with acute pain require rapid relief from over-the-counter (OTC) analgesics. Rapidly absorbed ibuprofen formulations have been developed [8], and it was anticipated that this rapid absorption would result in early onset of analgesia. This placebo-controlled, double-blind, randomised, single-dose study was conducted to measure the time to onset and degree of analgesia from two investigational ibuprofen formulations. The first investigational ibuprofen formulation contains the sodium salt of the drug, ibuprofen sodium dihydrate (sodium ibuprofen). The formulation used in this study contains 256 mg of the ibuprofen sodium salt, equivalent to 200 mg ibuprofen acid. It is well documented that ibuprofen salts, such as ibuprofen sodium, lysine and arginate, are more rapidly absorbed than formulations of free ibuprofen acid [9], and several studies have shown that faster absorbed formulations lead to faster onset of analgesia [10–12]. The salt dissolves rapidly in the gastrointestinal tract, leading to faster absorption. Pharmacokinetic analyses show that the time to peak plasma concentration (T_{max}) with ibuprofen sodium dihydrate is achieved in approximately 30–40 min [8], in contrast to the 1–2 h reported for standard ibuprofen tablets [13, 14]. The second investigational ibuprofen formulation contains ibuprofen acid plus the surfactant poloxamer 407 [from the poloxamer family of polymeric non-ionic surface active agents (ibuprofen/poloxamer)]—to increase the rate of dissolution of the tablet and enable more rapid absorption relative to standard ibuprofen formulations. Acetaminophen, another widely used OTC analgesic and antipyretic indicated for the same mild-to-moderate pain conditions as ibuprofen, was included in the study as a reference.

The dental pain model was used because it is the most appropriate model to investigate onset of analgesic action. It is an established post-surgical pain model that involves extraction of impacted third molars (wisdom teeth), a relatively consistent surgical technique that predictably produces moderate-to-severe pain. The model is widely accepted and has a proven record of assay sensitivity (i.e. separating active drugs from each other as well as from placebo) [11, 12, 15–18]. The model is sensitive enough to demonstrate a correlation between plasma levels of ibupro-

fen and onset of analgesia, with faster absorbed formulations, such as ibuprofen arginate, having a faster clinical response time than standard ibuprofen [11, 12, 19]. The results from dental pain studies have been widely extrapolated to other general pain conditions, including most common OTC conditions.

Onset of analgesic action was assessed using the two-stopwatch technique [11, 12, 19], and pain intensity and pain relief at each of the assessment timepoints were assessed using traditional descriptor scales. Exploratory analyses were conducted to give additional information about the rate of onset of action of the medications and to compare the extent of relief provided by each of the active formulations.

Both ibuprofen formulations were given at a dose equivalent to 400 mg ibuprofen acid. The acetaminophen product included in the study was Tylenol Extra Strength (1000 mg), a commercially available product. The branded printing was removed from the Tylenol caplets, to enable a matched placebo to be produced. The doses of both drugs are the maximum licensed OTC doses in the USA and most other countries, and they have well-established safety and efficacy profiles.

The primary objective of the study was to determine the time to onset of analgesia following dosing with sodium ibuprofen tablets (2×256 mg ibuprofen sodium dihydrate) and ibuprofen acid tablets incorporating poloxamer (2×200 mg ibuprofen plus 60 mg poloxamer 407), hereafter referred to as ibuprofen/poloxamer, in patients with post-operative dental pain. The secondary objective was to compare the efficacy of the two ibuprofen formulations with that of 1000 mg acetaminophen and placebo in terms of onset, peak and duration of analgesic action.

The study was conducted in accordance with the Declaration of Helsinki [20] as referenced in EU Directive 2001/20/EC [21] and complies with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

Methods

Study design

This study was a randomised, double-blind, placebo-controlled, single-dose, parallel-group study using the dental pain model. It was conducted in two clinical research centres (Austin, Texas and San Marcos, Texas).

Patients and/or their legal guardians provided informed consent before the conduct of study-related procedures. Patients were screened within the 28 days before surgery. On the day of surgery, patients underwent surgical removal of one partially or full bone impacted mandibular third

molar, or two ipsilateral third molars, with a total impaction score of 4, 5 or 6.

Degree of impaction	Points
Erupted	0
Soft tissue	1
Partial bone	2
Complete (full) bone	3
Unusual impaction (horizontal/inverted or posterior-anterior)	4

Surgery was performed under local anaesthetic (approximately 100 mg lidocaine 2% with 1:10000 epinephrine) with conscious sedation (3.5 l/min 50% nitrous oxide for 15 min) using standard surgical techniques. Following surgery, patients who fulfilled the inclusion criteria regarding baseline pain intensity were randomly allocated to one of four treatment groups (sodium ibuprofen, ibuprofen/poloxamer, acetaminophen or placebo) in a 1:1:1:1 ratio according to a computer-generated randomisation schedule that stratified patients by sex and baseline pain intensity. After dosing, patients remained in the centre for 8–15 h. Onset of action and efficacy assessments were recorded at pre-determined intervals during the 6 h post-dose. A post-operative follow-up was conducted 5–12 days after surgery.

The study protocol and its amendments, together with the patient information and consent documents, were reviewed and approved by Quorum Review Inc. (Seattle, WA).

Patients

Patients were recruited from the Premier Research Group Clinical Research Centers database via advertising and practitioner referral. Eligible patients were males and females 16–40 years of age with a primary diagnosis of:

- at least one mandibular third molar (with full bony impaction and an impaction score of ≥ 4 on a 5-point scale) indicated for removal;
- two ipsilateral third molars with a combined total impaction score no greater than 6.

In either case, patients were required to have moderate or severe baseline pain intensity as assessed using a 4-point categorical pain intensity scale and confirmed with a visual analogue scale (VAS) score of ≥ 50 mm but ≤ 85 mm (where 0=no pain and 100 mm=worst pain).

The main exclusion criteria were history of significant disease that rendered the patient unsuitable for inclusion; significant ongoing painful conditions other than that associated with third molar surgery; any ongoing condition that may have interfered with the absorption, distribution, metabolism or excretion of study medications; history of allergy, gastrointestinal complaints (including ulcers, heartburn, dyspepsia and indigestion); migraine headaches

within the last year; psychotic illness or drug abuse; use of concomitant medication that may have confounded assessments of pain relief (e.g. psychotropic drugs, antidepressants or sedative-hypnotics); pregnancy/lactation; ingestion of any analgesic or anti-inflammatory drug from midnight of the night before surgery.

Sample size determination

For the primary endpoint, data were available for the time to perceptible relief from three studies using ibuprofen arginate [11, 12, 19]. These data suggested that the time to perceptible relief would be 9 to 14 min for the two test formulations, assuming a similar onset of action to that of ibuprofen arginate. Since it was assumed that the majority of placebo patients would not achieve meaningful relief, it was planned that the time to confirmed perceptible relief for these patients would be censored at 4 h. Although the spread of observations was not provided for the arginate formulation, it was assumed conservatively that the standard deviation (SD) for time to confirmed perceptible relief would be 1 h (based on the possible range being 0–4 h and covering ± 2 SD). Hence this study was highly powered ($>99\%$) to detect such a large difference for the time to confirmed perceptible relief using the Wilcoxon test.

For the area under the curve (AUC) (pain relief intensity difference [PRID] from 0 to 6 h), data were available from two previous studies which compared ibuprofen lysine [22] and liquigel [23] ibuprofen with acetaminophen. In the former study, PRID to 6 h was not provided, but the sum of pain intensity differences (SPID) to 6 h was given. This gave a difference of 2.51 between ibuprofen lysine and acetaminophen. The within-group SD for acetaminophen was 4.47. Using these data, it was calculated that with 80 patients per group, this study would have a 90% power to detect a difference between the ibuprofen formulations and acetaminophen at a significance level of 0.025. If the data from the liquigel paper were used for sum of the measures of pain relief and pain intensity difference (SPRID) to 6 h, a slightly higher power would be achieved. It was not possible to perform formal power calculations for the second endpoint in the closed test procedure, namely time to meaningful relief.

Study and concomitant treatments

Following surgery, eligible patients received a single oral dose (four tablets and two caplets) of one of the following four study treatments:

- sodium ibuprofen: 2 \times 256 mg ibuprofen sodium dihydrate tablets (each tablet equivalent to 200 mg ibuprofen acid) plus two matched placebo for ibuprofen/poloxamer tablets plus two matched placebo for 500 mg acetaminophen caplets;

- ibuprofen/poloxamer: 2×200 mg ibuprofen acid tablets, each tablet incorporating 60 mg of the surfactant poloxamer 407, plus two matched placebo for sodium ibuprofen tablets plus two matched placebo for 500 mg acetaminophen caplets;
- acetaminophen: 2×500 mg acetaminophen (Tylenol Extra Strength) caplets plus two matched placebo for sodium ibuprofen tablets plus two matched placebo for ibuprofen/poloxamer tablets;
- placebo: two matched placebo for sodium ibuprofen tablets plus two matched placebo for ibuprofen/poloxamer tablets plus two matched placebo for 500 mg acetaminophen caplets.

Patients were encouraged to wait at least 90 min after receiving the study treatment before consuming rescue medication, although rescue medication was available at any time after dosing. If rescue medication was needed within the first 4 h of dosing, an intra-muscular injection of ketorolac tromethamine (60 mg) was administered. If rescue medication was needed later than 4 h after study drug administration, acetaminophen 500 mg/hydrocodone 5 mg or ketorolac tromethamine was given. A prescription for acetaminophen 500 mg/hydrocodone 5 mg was provided to patients for home use at the time of discharge.

The use of intravenous, oral or inhaled (nitrous) sedation during surgery was prohibited. Analgesic and anti-inflammatory drugs (except for the permitted rescue medications, antibiotics and anaesthetics) were not permitted during the 6-h post-dose assessment period. Penicillins, macrolide antibiotics, clindamycin and topical tetracycline gel foam were permitted; the use of selective serotonin-reuptake inhibitors (SSRIs) and selective norepinephrine-reuptake inhibitors (SNRIs) was also acceptable in patients who had maintained a stable dose for at least 4 weeks prior to the first visit. Caffeine-containing foods and drinks were to be discontinued from midnight prior to surgery until the end of the 6-h post-dose assessment period. Ice packs were not allowed for the first 3 h after dosing.

Efficacy endpoints

Patients were queried at pre-determined intervals by the study staff, and all pain assessments were recorded by the patient in their diary.

Pain intensity (categorical and VAS)

Pain intensity (PI) was assessed at the following times: baseline (0 h) and at 5, 10, 15, 20, 25, 30, 35, 40, 45, 60, 90, 120, 180, 240, 300 and 360 min after dosing. The PI was measured on a categorical scale in response to the question

“What is your pain level at this time?”, with patient response choices of none=0, mild=1, moderate=2, and severe=3. In addition, patients were also asked to draw a single vertical line to indicate their current level of PI on the 100-mm VAS. Patients were randomised to treatment when they rated their baseline PI as moderate or severe, and the score on the VAS was ≥ 50 mm but ≤ 85 mm.

Pain relief and pain half-gone

Pain relief (PR) was assessed at the same times as PI (with the exception of 0 h) in response to the question “How much relief have you had from your starting pain?”, with patient response choices of none=0, a little=1, some=2, a lot=3 and complete=4. In addition, patients were also asked: “Is your starting pain at least half gone?”, with patient responses as no=0 or yes=1.

Perceptible and meaningful PR

Two stopwatches were started at the time of dosing. Each patient was instructed, “Stop the first stopwatch when you first feel any pain relief whatsoever. This does not mean you feel completely better, although you might, but when you first feel any relief in the pain you have now.” The patient was instructed, “Stop the second stopwatch when the pain relief is meaningful to you.” If the patient did not press the stopwatches within the first 4 h of the treatment period or if rescue medication was required, the patients were no longer required to use the stopwatches.

Distractibility from pain

Distractibility from pain was assessed at baseline and at 60 and 360 min after dosing in response to the question “How easy is it for you to distract yourself from your pain?” Patients responded using a 100-mm VAS scale where 0 = very easy and 100 = impossible.

Rainier scale

Patients completed the Rainier scale at baseline and at 60 and 360 min after dosing. This assessed perceived functional impairment of activities of daily living (i.e. eating, driving, sleeping, reading, working and speaking). Patients rated the perceived pain interference with each activity on a scale of 1 to 10, where 1 = would not interfere at all and 10 = would completely interfere.

Rescue medication

The time of rescue medication was recorded. Patients taking rescue medication completed all pain intensity and

pain relief assessments immediately before rescue medication and continued to record their pain assessments throughout the 6-h assessment period.

Global evaluation

At the end of 6 h or at the time of rescue medication, patients were asked, “How effective do you think the study medication is as a treatment for pain?” Response choices were 1 = excellent, 2 = very good, 3 = good, 4 = fair or 5 = poor.

The primary efficacy endpoint was the time to first confirmed perceptible pain relief. There were two key secondary endpoints: (1) the AUC for SPRID from 0 to 6 h, and (2) the time to meaningful pain relief.

Other secondary endpoints included: (1) total pain relief (TOTPAR), SPID (categorical and VAS), SPRID from 0 to 4 h; (2) TOTPAR, SPID (categorical and VAS) from 0 to 6 h; (3) individual pain relief and pain intensity (categorical and VAS) readings at each timepoint from 5 min to 6 h; (4) peak pain relief and pain intensity difference (PID) (categorical and VAS) throughout the 6-h evaluation period; (5) first time at which PID was ≥ 1 ; (6) time to first use of rescue medication; (7) time to and proportion of patients with pain half-gone; (8) distractibility from pain at baseline and at 1 and 6 h post-dose and perceived pain interference with daily activities (Rainier scale) at 1 and 6 h post-dose; (9) patient’s overall assessment of the medication.

Safety assessments

Adverse events (AEs) were assessed by non-directed questioning, recorded in the source documentation, and then assessed by the Investigator with respect to severity and relationship to study medication. Vital signs (blood pressure, heart rate and oral temperature) were assessed at screening, baseline (pre-dose), at 6 h post-dose and at the follow-up visit. A physical examination was also conducted at screening and at the follow-up visit 5–12 days after surgery.

Statistical analyses

All calculations and figures were produced using SAS ver. 9.1 or S-PLUS 6.2 (SAS Institute, Cary, NC). The analysis of the primary endpoints was performed via a closed test procedure. The actual protocol-defined primary endpoint was the time to first confirmed perceptible pain relief. Pairwise differences between the two ibuprofen formulations and placebo were assessed at a significance level of 2.5% so the overall alpha-level of 5% was maintained. For the primary endpoint, pairwise differences between the two ibuprofen formulations and placebo were assessed using the Wilcoxon rank-sum test. A sensitivity analysis was also

performed, where differences between the ibuprofen formulations and placebo were assessed using a Cox regression analysis with treatment group, study site, gender and baseline pain intensity (categorical) included in the model. The hazard ratio and associated 97.5% confidence intervals (CIs) were calculated for the pairwise comparisons.

It was planned that if either of the primary pairwise comparisons were significant at the 2.5% level, the key secondary endpoints (SPRID 0–6 h and time to meaningful pain relief) were to be assessed for that formulation under a closed-test procedure. Each endpoint was assessed in the order specified and only if the previous assessments for that formulation were significant, were the subsequent endpoints assessed in a confirmatory sense. Once the endpoint was not significant, then all subsequent assessments were considered exploratory.

Endpoints aggregated over several time points were calculated using AUC as per the secondary endpoint. Differences between the treatments were assessed at a two-sided alpha of 0.05. A 95% CI for the pairwise differences between the treatments was calculated from the parameter estimates of the fitted model. The pairwise comparisons of interest were between each of the ibuprofen formulations and placebo, and between each of the ibuprofen formulations and acetaminophen. For the time-to-event parameters, such as time to first (unconfirmed) perceptible pain relief, differences between the treatment groups were assessed as per the primary endpoint.

Differences between each of the two ibuprofen formulations and acetaminophen in the key secondary endpoints and in the majority of the other secondary endpoints were analysed by analysis of covariance (ANCOVA), including treatment group, study site, gender and baseline pain intensity (categorical scale) as factors.

All assessments completed after the patient had taken rescue medication were considered to be missing. For both pain relief and pain intensity differences, missing values between two available assessments were linearly interpolated. Missing readings that could not be interpolated were replaced with the baseline pain intensity or zero relief.

All enrolled patients who received a dose of study medication were included in the safety population. All AEs were listed and tabulated by treatment, severity, relationship to therapy and body system according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 8.1.

Results

Between June and October 2005, a total of 322 patients (mean age 21.3 years) were randomised to receive study treatment. Of the 322 randomised patients, 318 (98.8%)

completed the study. The trial profile, including the total number of patients withdrawn and analysed, is illustrated in Fig. 1. A total of 321 patients, all of whom were balanced across treatment groups with respect to baseline demographics, pain intensity and clinical characteristics (Table 1) were included in the intent-to-treat (ITT) population.

Primary efficacy endpoint

Significantly more patients reported confirmed perceptible pain relief with sodium ibuprofen (96.3%) and ibuprofen/poloxamer (90.0%) than with acetaminophen (67.5%) ($P < 0.0001$ and $P = 0.0005$, respectively). In the placebo group, only 25.9% patients reported confirmed perceptible pain relief. Kaplan–Meier median times to confirmed perceptible pain relief were 17.0 min for sodium ibuprofen, 18.5 min for ibuprofen/poloxamer and 20.1 min for acetaminophen (Fig. 2). Median time could not be estimated for placebo, as fewer than 50% of patients assigned to this group experienced confirmed perceptible pain relief. Comparisons of pairwise differences between the two ibuprofen formulations and placebo using Wilcoxon rank-sum tests and Cox regression analysis were highly significant ($P < 0.001$ for both analyses).

Key secondary efficacy endpoints

Mean SPRID (0–6 h) values were 3.46, 3.49, 2.25 and 0.73 for the sodium ibuprofen, ibuprofen/poloxamer,

acetaminophen and placebo groups, respectively. Pairwise comparisons of ibuprofen and acetaminophen were highly significant in favour of both ibuprofen formulations ($P < 0.001$).

Significantly more patients reported meaningful pain relief with sodium ibuprofen (96.3%) or ibuprofen/poloxamer (90.0%) than with acetaminophen (67.5%) ($P < 0.0001$ and $P = 0.0005$, respectively) (Fig. 3). Of the patients receiving placebo, 25.9% reported meaningful pain relief. The Kaplan–Meier median times to meaningful relief were 45.1 min (sodium ibuprofen), 44.7 min (ibuprofen/poloxamer) and 54.1 min (acetaminophen). Neither of the two Wilcoxon rank-sum comparisons between the ibuprofen formulations and acetaminophen were statistically significant, whereas pairwise comparisons obtained via Cox regression analysis were statistically significantly different ($P \leq 0.002$). The Kaplan–Meier survival curves were similar for the ibuprofen and acetaminophen groups up to 45 min, but the degree of separation from 45 min onward was marked, with more patients achieving meaningful pain relief with ibuprofen.

Site–treatment interactions

In general, site was a statistically significant factor; subjects from the San Marcos site had less favourable outcomes. For the primary efficacy endpoint and for the key secondary efficacy endpoints of SPRID (0–6 h) and time to meaningful pain relief, site was statistically significantly. For all three measures, the

Fig. 1 Flow diagram illustrating patient inclusion and exclusion throughout the study. *ITT* Intent to treat ^aThe ITT population consisted of all patients who were randomised, who completed the baseline efficacy assessments, and who had at least one post-baseline assessment (primary efficacy set)

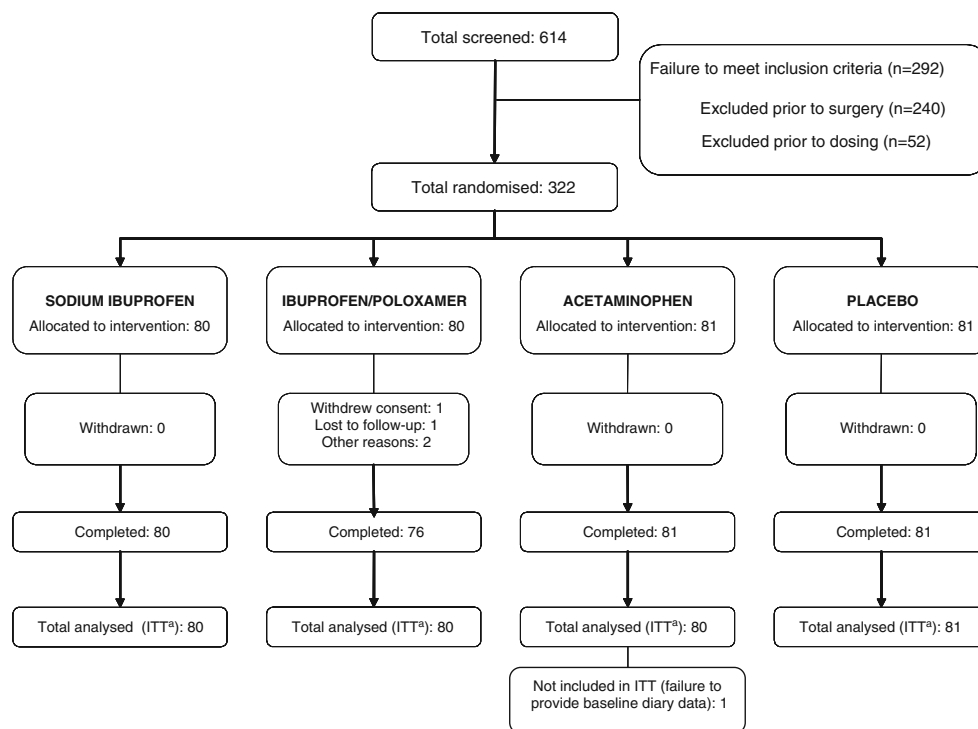


Table 1 Patient demographics and clinical characteristics at baseline (ITT population)

Baseline patient characteristics	Treatment group				
	Sodium ibuprofen (n=80)	Ibuprofen/poloxamer (n=80)	Acetaminophen (n=80)	Placebo (n=81)	Total (n=321)
Age (years), mean (SD)	21.4 (3.88)	21.4 (3.60)	21.2 (4.43)	21.1 (4.08)	21.3 (3.99)
Sex, n (%)					
Male	31 (38.8)	31 (38.8)	30 (37.5)	31 (38.3)	123 (38.3)
Female	49 (61.3)	49 (61.3)	50 (62.5)	50 (61.7)	198 (61.7)
Baseline pain intensity (categorical), n (%)					
Moderate	61 (76.3)	60 (75.0)	60 (75.0)	62 (76.5)	243 (75.7)
Severe	19 (23.8)	20 (25.0)	20 (25.0)	19 (23.5)	78 (24.3)
Baseline pain intensity (VAS), mean (SD)					
Mean (SD)	68.16 (8.74)	68.81 (9.49)	67.03 (9.32)	67.37 (10.03)	67.84 (9.39)
Range	51–85	50–89	52–84	50–85	50–89

ITT, intent-to-treat; SD, standard deviation; VAS, visual analogue scale
 Treatment definitions: sodium ibuprofen=2×256 mg ibuprofen sodium dihydrate tablets (each tablet equivalent to 200 mg ibuprofen acid);
 ibuprofen/poloxamer=2×200 mg ibuprofen acid tablets; acetaminophen=2×500 mg acetaminophen caplets

interaction between site and treatment was formally investigated. In all cases, the interaction term was not statistically significant, implying that treatment group responses were consistent between the sites.

Exploratory secondary efficacy endpoints

Pain relief and/or reduction in pain intensity

All summary endpoints related to pain relief and/or PID were significantly more favourable for the two ibuprofen formulations than for acetaminophen or placebo ($P < 0.001$ for both ibuprofen formulations vs. acetaminophen or placebo in all comparisons).

A summary of pain relief scores at specified time points from 5 min to 6 h is displayed in Fig. 4. The superiority of

the two ibuprofen formulations over acetaminophen can clearly be seen from 45 min post-dose onward. A summary of PID (categorical) scores at specified time points from 5 min to 6 h is displayed in Fig. 5. The superiority of the two ibuprofen formulations over acetaminophen can be clearly seen from 60 min post-dose onward.

Individual PR and PID

The pain relief and PID (categorical and VAS) scores show that sodium ibuprofen provided more effective pain relief than placebo at 15 min [$P = 0.021$ (PR), $P = 0.04$ (PID categorical), $P = 0.036$ (PID VAS)]. Similarly, ibuprofen/poloxamer provided more effective relief than placebo at 25 min [$P = 0.002$ (PR), $P = 0.002$ (PID categorical)] and at 20 min [$P = 0.008$ (PID VAS)].

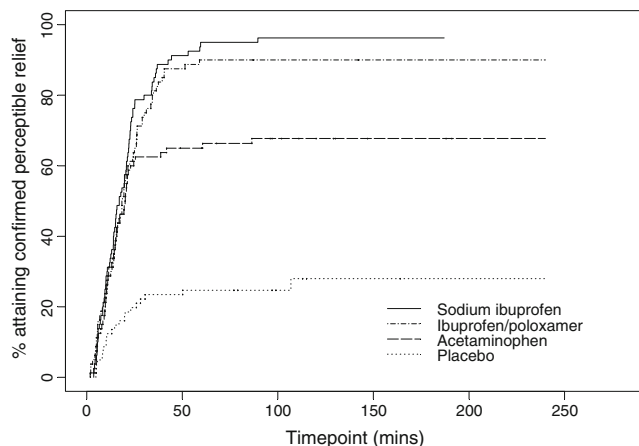


Fig. 2 Kaplan–Meier curves for time to first confirmed perceptible pain relief

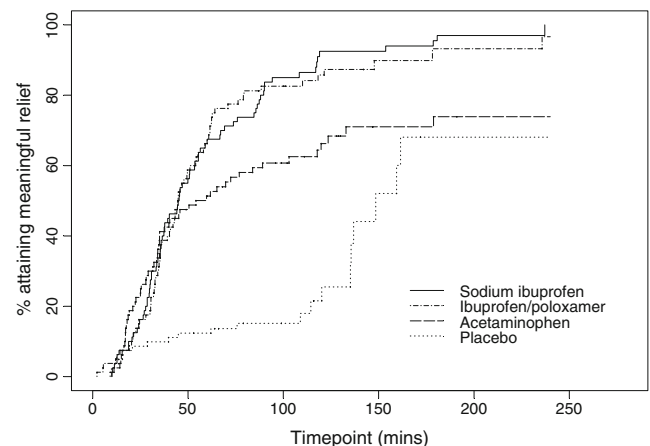


Fig. 3 Kaplan–Meier curves for time to meaningful pain relief

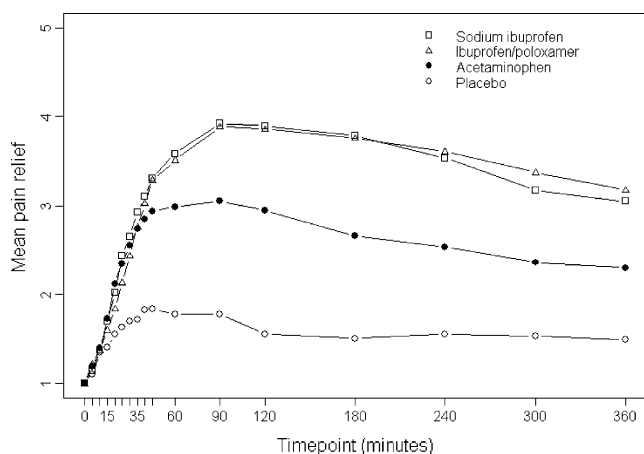


Fig. 4 Mean pain relief at each timepoint

First time to PID ≥ 1

There were no significant differences between the active treatment groups in the proportion of the time to reporting of PID ≥ 1 .

Time to first use of rescue medication

Rescue medication was required by significantly fewer patients in the sodium ibuprofen group (32.5%) and the ibuprofen/poloxamer group (22.5%) than in the acetaminophen (43.8%) group. Owing to the relatively small proportion of patients reporting the use of rescue medication, Kaplan–Meier median times to first use of rescue medication could not be calculated. The pairwise comparisons between the two ibuprofen formulations and acetaminophen were both statistically significant using the Wilcoxon rank-sum test, with $P=0.019$ and $P=0.001$ for sodium ibuprofen and the ibuprofen/poloxamer formulation, respectively (Fig. 6). The vast majority of patients randomised to placebo took rescue medication (82.7%).

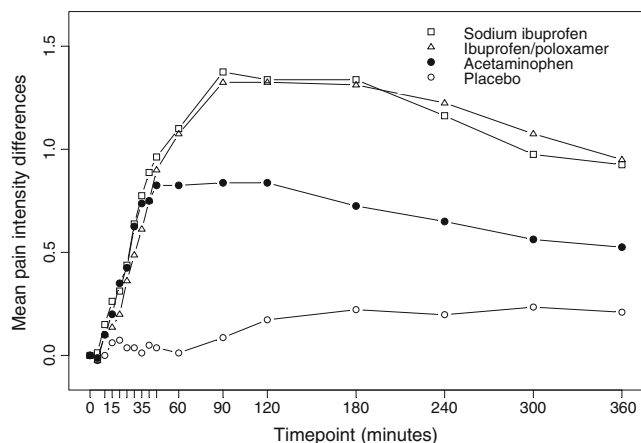


Fig. 5 Mean pain intensity difference (categorical) at each timepoint

Time to and proportion of patients with pain half-gone

The proportion of patients reporting pain half-gone were 93.8, 88.8, 75 and 37.0% for sodium ibuprofen, ibuprofen/poloxamer, acetaminophen and placebo, respectively. The median time to pain half-gone was similar for all three active treatment groups—35.0 min (sodium ibuprofen), 37.5 min (ibuprofen/poloxamer) and 45.0 min (acetaminophen). The Wilcoxon rank-sum comparisons between the ibuprofen formulations and acetaminophen were not statistically significant ($P=0.07$ and $P=0.18$ for sodium ibuprofen and ibuprofen/poloxamer, respectively), but the two equivalent comparisons were statistically significant when the Cox regression was used ($P=0.013$ and $P=0.02$ for sodium ibuprofen and ibuprofen/poloxamer, respectively). This may be explained in terms of a greater proportion of patients randomised to either of the ibuprofen formulations reporting the endpoints compared with acetaminophen. However, as for time to meaningful relief, the separation in onset times in favour of ibuprofen was only apparent from 45 min post-dose onward.

Distractibility from pain (VAS)

At 1-h post-dose, the mean values for the "distractibility from pain" (VAS) scores were 29.0, 32.1, 38.1 and 65.7 mm for sodium ibuprofen, ibuprofen/poloxamer, acetaminophen and placebo, respectively. Both ibuprofen formulations had lower (more favourable) scores than placebo ($P<0.001$), and sodium ibuprofen versus acetaminophen was statistically significant ($P=0.010$), whereas the ibuprofen/poloxamer versus acetaminophen comparisons were non-significant ($P=0.083$).

At 6 h post-dose, both ibuprofen formulations had more favourable "distractibility from pain" scores than acetaminophen ($P=0.008$ and $P=0.03$ sodium ibuprofen

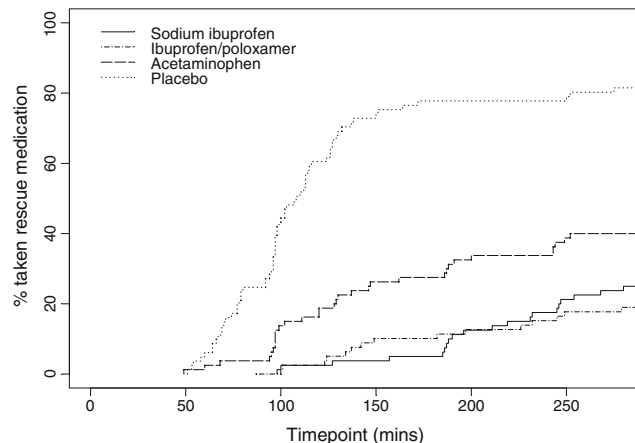


Fig. 6 Kaplan–Meier curves for time to first use of rescue medication

and ibuprofen/poloxamer, respectively). The vast majority of patients randomised to placebo took rescue medication, so only 14 patients provided valid data within this group; hence, this analysis was not performed for the placebo group.

Pain interference with daily activities (Rainier scale)

At 1-h post-dose, the mean values on the Rainier scale were 18.8, 22.3, 26.8 and 43.2 for the sodium ibuprofen, ibuprofen/poloxamer, acetaminophen and placebo groups, respectively. The scores were statistically significantly lower for both ibuprofen formulations than for placebo ($P<0.001$) and acetaminophen [$P=0.001$ (sodium ibuprofen) and $P=0.015$ (ibuprofen/poloxamer)]. At 6-h post-dose, the mean values were 15.1, 17.1, 22.4 and 16.3 for the sodium ibuprofen, ibuprofen/poloxamer, acetaminophen and placebo groups, respectively. Both ibuprofen formulations maintained significantly lower (more favourable) values on the Rainier scale than acetaminophen ($P=0.004$ and $P=0.011$ for sodium ibuprofen and ibuprofen/poloxamer). Placebo treatment was not analysed for this comparison, as only 14 patients in this group provided valid data.

Patient's overall assessment of medication as a treatment for pain

Significantly more patients in the sodium ibuprofen (81.3%) and ibuprofen/poloxamer (84.8%) groups rated the study medication as good, very good or excellent than in the groups that received acetaminophen (53.8%) or placebo (17.3%). Furthermore, the mean global assessment scores were significantly lower (more favourable) for both ibuprofen formulations—2.40 (sodium ibuprofen) and 2.44 (ibuprofen/poloxamer)—than for acetaminophen or for placebo (3.41 and 4.46, respectively; $P<0.001$).

Safety findings

A total of 11.8% of all patients had AEs that were considered by the investigators to be possibly related to study medication; no events were classified as definitely or probably related to study treatment. Adverse events were experienced by 30.0, 23.8, 30.9 and 29.6% of patients receiving sodium ibuprofen, ibuprofen/poloxamer, acetaminophen and placebo, respectively. The majority of AEs (73%) were mild-to-moderate in severity, and the most frequently reported AEs included nausea, headache, vomiting and dizziness. Adverse events occurring in at least 5% of all patients in any treatment group are summarised in Table 2. Severe AEs (including vomiting, nausea, dizziness, abdominal pain and headache) occurred at rates of 6.3% (sodium ibuprofen), 2.5% (ibuprofen/poloxamer), 12.3% (acetaminophen) and 9.9% (placebo); there were no deaths or withdrawals attributable to AEs during the study period. There were no significant differences between study medications in terms of tolerability.

Discussion

This placebo-controlled study demonstrated excellent assay sensitivity for every measure of efficacy, with both ibuprofen formulations and acetaminophen showing clinically and statistically significant analgesia that was superior to placebo. Furthermore, the overall analgesic efficacy (duration and total effect) of both ibuprofen formulations was shown to be superior to acetaminophen.

Data from this study showed statistically significant differences between both the ibuprofen test formulations and placebo for the primary endpoint, i.e. the time to first confirmed perceptible pain relief. In addition, a significantly greater proportion of patients receiving ibuprofen experienced confirmed perceptible pain relief than those receiving acet-

Table 2 Adverse events occurring in >5% of patients in any treatment group

	Sodium ibuprofen ($n=80$)		Ibuprofen/poloxamer ($n=80$)		Acetaminophen ($n=81$)		Placebo ($n=81$)	
	Number of events	Number of patients n (%) ^a	Number of events	Number of patients n (%) ^a	Number of events	Number of patients n (%) ^a	Number of events	Number of patients n (%) ^a
Any AE	43	24 (30.0)	27	19 (23.8)	41	25 (30.9)	39	24 (29.6)
Gastrointestinal								
Nausea	10	9 (11.3)	5	5 (6.3)	8	8 (9.9)	14	14 (17.3)
Vomiting	2	2 (2.5)	1	1 (1.3)	6	6 (7.4)	8	8 (9.9)
Nervous system								
Dizziness	4	4 (5.0)	0	0 (0.0)	6	5 (6.2)	5	5 (6.2)
Headache	11	11 (13.8)	5	4 (5.0)	4	4 (4.9)	3	3 (3.7)

AE, Adverse event

Treatment definitions: sodium ibuprofen=2×256 mg ibuprofen sodium dihydrate tablets (each tablet equivalent to 200 mg ibuprofen acid); ibuprofen/poloxamer=2×200 mg ibuprofen/poloxamer tablets; acetaminophen=2×500 mg acetaminophen caplets

^a Percentages based on total number of patients per treatment group

aminophen. The median time to meaningful pain relief was 45 min for both ibuprofen formulations and 54 min for acetaminophen. Although a much greater proportion of patients reported relief on the two ibuprofen formulations, the divergence in onset times was only apparent from 45 min post-dose onward, i.e. there was a much higher proportion of responders from 45 min onward for the ibuprofen treatments than for acetaminophen. Because of this late divergence, the Wilcoxon rank-sum test was not sensitive enough to detect significant differences whereas the Cox proportional hazards regression analysis showed significant differences in favour of ibuprofen over acetaminophen. In terms of SPRID over 6 h, both ibuprofen test formulations were significantly more efficacious than acetaminophen.

Previous studies using the post-operative dental pain model have demonstrated that treatment with a different ibuprofen salt formulation, ibuprofen arginate (l-arginine salt of ibuprofen), resulted in faster onset times to analgesia and greater overall efficacy than treatment with conventional (standard) ibuprofen [11, 12, 19]. The pharmacokinetic profile of the ibuprofen sodium formulation used in this study has been shown to be similar to that of ibuprofen arginate with peak plasma concentrations achieved at approximately 30–40 min, compared with 1–2 h for standard ibuprofen [8, 13, 14]. Therefore, it was anticipated that the rapid absorption associated with sodium ibuprofen would result in early onset of analgesia similar to that observed for ibuprofen arginate. This study was not intended nor was it sufficiently powered to compare the two ibuprofen formulations.

When comparing the median time to meaningful pain relief data from this study with previous studies, both ibuprofen test formulations in this study were found to be at the upper end of the range for ibuprofen arginate and ibuprofen lysine data (range 24–42 min) [11, 12, 19, 22], i.e. 45.1 min (sodium ibuprofen) and 44.7 min (ibuprofen/poloxamer). In the earlier studies where ibuprofen arginate was compared with conventional ibuprofen, the median time to meaningful pain relief obtained for ibuprofen arginate was approximately half that of the conventional ibuprofen [11, 12, 19]. A recent bioavailability study has also shown that the T_{max} for sodium ibuprofen was less than half that of standard ibuprofen (i.e. 35 min vs. 90 min, respectively) [8]. Therefore, it was not unexpected that sodium ibuprofen had a fast onset of analgesic effect in this study that was in a similar order of magnitude as those previously reported for faster absorbed formulations.

The analyses of secondary endpoints related to degree of pain relief and/or reduction in pain intensity (TOTPAR, SPRID, SPID, peak PID and peak PR) consistently favoured both ibuprofen formulations over acetaminophen. Only in terms of time to PID of at least 1 were there no statistically significant differences observed

compared with acetaminophen. Measures of analgesic duration—the proportion of patients taking rescue medication and the time to rescue medication—showed that those in the acetaminophen group received rescue medication sooner than those in either of the two ibuprofen groups. This suggests that both ibuprofen formulations had a longer duration of action than acetaminophen, which is in keeping with that previously reported for ibuprofen lysine [22] and ibuprofen liqigel [23]. In terms of pain relief and PID, the timepoint at which a significant difference was first observed between either of the ibuprofen formulations and placebo was 15 min (sodium ibuprofen); a significant difference between either of the ibuprofen formulations and acetaminophen was first observed at 45 min (sodium ibuprofen). In comparison with previously published data, studies with ibuprofen arginate and ibuprofen lysine demonstrated significant differences in pain relief and PID between ibuprofen and placebo at 10–15 min [11, 12, 19, 23]. Furthermore, significant differences between ibuprofen lysine and acetaminophen were observed at 15 min, much sooner than the 45 min observed in our study [22]. These differences could be explained by the different formulations of ibuprofen, the fact that a different brand of acetaminophen was used in each of the respective studies or the inherent variability associated with a small sample size.

Patients in both ibuprofen groups were able to distract themselves from their pain at 1 and 6 h after dosing significantly more easily than those in the placebo and acetaminophen groups (6 h only). Patients in both ibuprofen groups also reported that pain would interfere with their daily activities significantly less than patients in the acetaminophen group. Patients in the two ibuprofen groups rated the study medication as good, very good, or excellent more frequently than those in the acetaminophen and placebo groups.

Ibuprofen is a well-tolerated NSAID at low doses [24]. However, even at prescribed doses, ibuprofen is associated with the least risk of gastrointestinal complications compared with other NSAIDs [25–27]. No new safety concerns were raised by the current study; treatment with single doses of sodium ibuprofen and ibuprofen/poloxamer were well tolerated, with AE profiles comparable to that of acetaminophen. The most frequently reported AEs considered to be related to study treatment (i.e. nausea, headache, vomiting and dizziness) are not unexpected in patients recovering from dental surgery.

In conclusion, these results suggest that compared with acetaminophen, both the sodium ibuprofen and ibuprofen acid incorporating poloxamer formulations are more efficacious in providing rapid and sustained analgesia, and are associated with pain relief in a greater proportion of patients undergoing surgical removal of impacted third

molars. Together with the favourable safety profile of ibuprofen, these findings support a recommendation for this agent as an analgesic of choice for the treatment of post-operative dental pain.

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