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Combined acetaminophen and ibuprofen for pain relief after oral surgery in adults: a randomized controlled trial

A. F. Merry[1 2]*, R. D. Gibbs[3], J. Edwards[4], G. S. Ting[3], C. Frampton[5], E. Davies[1 2] and B. J. Anderson[1]

[1]Department of Anaesthesiology, University of Auckland, Private Bag 92019, Auckland, New Zealand. [2]Department of Anaesthesia, Auckland City Hospital, Auckland, New Zealand. [3]Oral Health Unit, Greenlane Clinical Centre, 214 Greenlane West, Epsom, Auckland, New Zealand. [4]Oral and Maxillofacial Service, Quay Park Medical Centre, 68 Beach Road, Auckland Central, Auckland, New Zealand. [5]Department of Medicine, Christchurch School of Medicine and Health Sciences, University of Otago, New Zealand

**Corresponding author. E-mail: a.merry@auckland.ac.nz*

Background. Acetaminophen is often used with a non-steriodal anti-inflammatory drug for acute pain. Hitherto, these drugs have had to be given separately, typically at different time intervals. Maxigesic® tablets combine acetaminophen and ibuprofen in clinically appropriate doses to simplify administration and dosage regimen. We compared this combination with each of the constituent drugs for the relief of pain after extraction of third molar teeth.

Methods. Adults (more than 16 yr) having one or more wisdom teeth removed under general or local anaesthesia were instructed to take two tablets before operation, then two tablets every 6 h for up to 48 h of: (i) a combination of acetaminophen 500 mg and ibuprofen 150 mg per tablet (Maxigesic®); (ii) acetaminophen 500 mg per tablet alone; or (iii) ibuprofen 150 mg per tablet alone. The primary outcome measure was the area under the curve (AUC) of the 100 mm visual analogue scale pain measurements taken for up to 48 h after surgery, divided by time, at rest and on activity. Pharmacokinetic data were collected in a subset of patients.

Results. The mean (SEM) time-corrected AUC on rest and activity, respectively, were: combination group 22.3 (3.2) and 28.4 (3.4); acetaminophen group 33.0 (3.1) and 40.4 (3.3); and ibuprofen group 34.8 (3.2) and 40.2 (3.4); $P<0.01$ for each of the four comparisons of combination *vs* constituent drug. There was no pharmacokinetic interaction between acetaminophen and ibuprofen administered together.

Conclusions. Maxigesic® tablets provide superior pain relief after oral surgery to acetaminophen or ibuprofen alone.

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The relief of pain has been described as a universal human right but is not always easily achieved.[1] Opioid analgesics are effective, but have troublesome and potentially dangerous side-effects, and their potential for abuse may lead to regulatory and logistical difficulties. Non-steroidal anti-inflammatory drugs (NSAIDs) have fewer regulatory restrictions, but they too have important adverse effects which are more likely at higher dose or with longer courses.[2] Acetaminophen is widely used and is very safe at the recommended dose of 4 g per day,[3] but does not always provide adequate pain relief on its own. Combining analgesics offers the possibility of increasing effectiveness without increasing dose (and therefore risk).[4 5] NSAIDs are often combined with acetaminophen, particularly for treating postoperative pain.[6–10]

Prescribing acetaminophen and ibuprofen together is common in clinical practice.[6 8 9 11–13] Ibuprofen has the advantage of a well-established safety record (particularly at doses below 1.5 g per day in adults),[14] and in many countries (including the UK), it is available without

prescription. Typically, acetaminophen is given in a dose regimen of 1 g 6 hourly whereas ibuprofen is given in a dose of 400 mg 8 hourly.[3] Compliance with the prescribed dosing regimen is important for achieving the desired result with any drug and is often poor with asynchronous dosing.[15] A single formulation with a simplified regimen would probably be appreciated by patients and might improve compliance.

Maxigesic® is a new formulation of acetaminophen 500 mg and ibuprofen 150 mg. Taking two tablets 6 hourly provides the appropriate daily dose of both drugs relatively simply. We have investigated the hypothesis that in adult patients undergoing a common surgical procedure (extraction of third molar teeth), this formulation provides superior analgesia to either of its components alone.

Methods

With ethics committee approval, we recruited and followed up patients between March 2005 and February 2008. Trial registration: ANZCTR.ORG.AU (identifier: ACTRN12606000291583).

Setting

This study was conducted at a publicly funded teaching hospital and a private day-surgical clinic in metropolitan New Zealand.

Participants

We included adults undergoing extraction of at least one lower wisdom tooth with or without one or more upper wisdom teeth by one of three participating surgeons. We excluded patients if they were under 16 yr old; weighed $<$50 kg; had taken any NSAID (other than aspirin in a dose of 150 mg daily or less) within 24 h of the operation; had taken acetaminophen or acetaminophen containing medicines within 12 h of the operation; were taking an angiotensin-converting enzyme inhibitor, warfarin, steroid (other than interoperative dexamethasone), or any immunosuppressive drug; were intolerant to any NSAID or acetaminophen; were suffering from a severe local infection; had a history of peptic ulceration, asthma, or severe haemopoetic, renal or hepatic disease; were participating in the investigation of another experimental agent; or if the clinician believed for any other reason that participation in the study might not be in their best interests.

Randomization and blinding

Tablets of identical appearance, packaging, and dosage instructions were provided in each of the following formulations: (i) acetaminophen 500 mg+ibuprofen 150 mg per tablet (Maxigesic®; Sigma Laboratories, Nashik, India which was MHRA approved for manufacturing pharmaceuticals under GMP); (ii) acetaminophen 500 mg per tablet; or (iii) ibuprofen 150 mg per tablet.

Patients were first approached by the surgeon and then by the study nurse. They were given written and verbal information about the study, and invited to participate. If they consented, patients were then randomized into one of the three study groups in a sequential order to receive one of these formulations, in blinded packs. The randomization sequence was computer generated by the study statistician as a 1:1:1 allocation ratio to the three treatments in a sequence of permuted blocks with stratification for anaesthetic type (local or general) and study centre. Stratification by anaesthetic type ensured a balance between treatments in terms of the number of teeth extracted, as most patients having more than two teeth extracted have a general anaesthetic. Only the statistician had access to the schedule of patient numbers by drug allocation. Participants and investigators were blinded and the randomization code was not broken until the final database had been checked and locked.

Intervention

Participants were asked to take two tablets of the study medication before operation (as close as possible to the start of surgery) and then 4 times a day (as close as possible to 6 hourly) for up to 48 h after surgery. All participants were given bupivacaine local anaesthetic blocks by the surgeons. For those participants undergoing general anaesthesia, this was induced with propofol and maintained with isoflurane and nitrous oxide in oxygen. Monitoring was in accordance with the guidelines of the Australian and New Zealand College of Anaesthetists.[16] All extractions were carried out by one of three surgeons, each using his normal technique.

If participants required additional postoperative pain relief while in hospital, a rescue dose of fentanyl 10 μg was given i.v., as required. After discharge to home, codeine was provided (again, as rescue medication) in 30 mg tablets, one to two to be taken as needed up to 4 hourly.

Outcomes

Participants were asked to rate their pain on 100 mm visual analogue scales (VAS), printed one per double page in a booklet that they took home. Ratings were requested at baseline (immediately before administration of the first dose of study medication); after operation (once the participants were sufficiently awake to respond); and 1–2 hourly thereafter, while awake, for 48 h. The study nurse maintained contact with participants by telephone to facilitate compliance with data collection and the return of diaries.

The primary outcome measure was the area under the curve (AUC) of these VAS ratings divided by time, at rest and on activity. The AUC was divided by the period of the completed assessments to adjust for the fact that some

patients recorded pain for shorter periods than others. This calculation in effect produces a measure of average pain intensity over the study period.

Secondary efficacy outcome measures were: a categorical global pain rating by the participants, taken at the end of the study period; rescue analgesia consumption over the study period; a categorical global rating of nausea by the participants, taken at the end of study period; the number of episodes of vomiting over the study period; and a rating of sleep disturbance on a 100 mm VAS assessed after each night during the study period. In addition, participants were asked to rate their experiences of participating in the study.

Sample size estimation

We obtained blood samples from the 38 participants undergoing general anaesthesia in order to have evaluable pharmacokinetic data for at least 30 patients. The first sample was obtained 30 min after the first dose of study medication, the second sample at the end of anaesthesia, and additional one or two samples after operation in hospital. The plasma concentration of acetaminophen and ibuprofen were measured by the sponsor and used to form individual time–concentration profiles. The analytical method used an HPLC-DAD (Diode Array Detector) assay for the simultaneous determination of acetaminophen and ibuprofen in plasma. Precision and accuracy for acetaminophen and ibuprofen assay were validated over the concentration range 0.5–50 $\mu g\ ml^{-1}$ for both drugs. The intra- and inter-batch precision of the assays at low, medium, and high concentrations of acetaminophen and ibuprofen varied from theoretical values by $<15\%$. The lower limit of quantification for each drug was 0.5 $\mu g\ ml^{-1}$. The sponsor monitored all data collected during the study and queries and corrections were made when any inaccuracies or inconsistencies were identified.

Sample size estimation

We estimated that 120 participants (40 per group) in the intention-to-treat (ITT) population would provide 80% power to detect differences between the groups of 9 (SD 14) mm in our primary endpoint for resting assessments and 13 (SD 21) for measures during activity,[10 17] with a one-sided type I error rate of 5%. These differences equate to $\sim$25%. Differences of this magnitude were considered clinically important and comparable with differences typical of previous published studies.[10]

Statistical methods

The data were analysed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Efficacy analyses were conducted on an ITT basis with the additional provision that there were at least three VAS measurements over at least 12 h available to calculate the primary endpoint. All participants who were randomized into the study were included in the safety evaluations. As the first dose of study medication was taken before operation while under the supervision of the surgeon, all randomized patients took at least a single dose of study medication. A last observation carried forward approach was used for those subjects who left the study prematurely for non-AUC based variables.

We compared the primary endpoint between the combination group and each of the acetaminophen and ibuprofen arms, at rest and on activity, using a general linear model (GLM) which included terms for treatment, the centre, and anaesthetic stratum. Additionally, to confirm the consistency of the treatment effects across strata, the stratum treatment interaction terms were tested and included in the final model. The analysis was also checked with number of teeth extracted as an additional factor. Continuous secondary efficacy endpoints were tested for significance using the same models as used for the primary endpoint.

A one-tailed $P \leq 0.05$ was pre-specified to indicate statistical significance. We required a statistically significant result favouring the combination from each of the two planned comparisons with the constituents to define superiority for either rest or on activity measures. We used one-tailed tests as there seemed no theoretical or empirical basis for expecting that combining these analgesics could result in a reduction in efficacy, and because the requirement for each of two comparisons to be significant at $P \leq 0.05$ is stringent. Secondary categorical efficacy endpoints were compared between the groups using χ^2 tests and Mann–Whitney *U*-tests as appropriate.

We used non-linear mixed effect models (NONMEM VI, Globomax LLC, Hanover, MD, USA) to estimate population pharmacokinetics, with a Compaq Digital Fortran Version 6.6A compiler on an Intel Celeron 333 MHz CPU (Intel Corp., Santa Clara, CA, USA) under MS Windows XP (Microsoft Corp., Seattle, WA, USA). This model allows assessment of inter-individual variability, covariance between pharmacokinetic parameters and residual error. We judged the quality of fit of the pharmacokinetic model to data using the NONMEM objective function examination of plots of observed *vs* predicted concentrations and visual predictive checks.

Results

After initial screening, 189 patients were approached; 135 agreed to participate. One to four teeth were extracted with local anaesthetic alone in 69 patients and with local anaesthetic in combination with general anaesthesia in 66. Thirteen patients did not return their patient diaries, so 122 patients were included in the evaluable ITT population for the analysis of the primary endpoints (Fig. 1). The treatment groups were adequately matched in baseline patient and clinical characteristics (Table 1). Of those in

the combination group, 60.0% had three or four teeth extracted compared with 43.6% for ibuprofen and 53.5% for acetaminophen.

Efficacy

The time-adjusted AUCs were substantially and significantly lower at rest and on activity in the combination group than in either of the other two treatment groups (Table 2, Figs 2 and 3), with all four $P<0.01$. The consistency of the treatment effects across strata was confirmed from the GLM with *P*-values for the treatment stratum interaction of 0.955 and 0.984 for time-adjusted AUCs at rest and on activity, respectively. The type of anaesthetic (local *vs* general) and number of teeth extracted did not change the outcome of either analysis.

Although all four secondary endpoints favour the combination treatment (Table 3), only the global pain rating reached statistical significance. More participants experienced 'nil' or 'mild' pain with the combination (68.4%) than with either other group; this difference was significant for acetaminophen (37.5%; $P=0.008$), but not for ibuprofen (54.3%; $P=0.263$). The use of any rescue medication also favoured the combination treatment (Table 4), but this did not reach statistical significance.

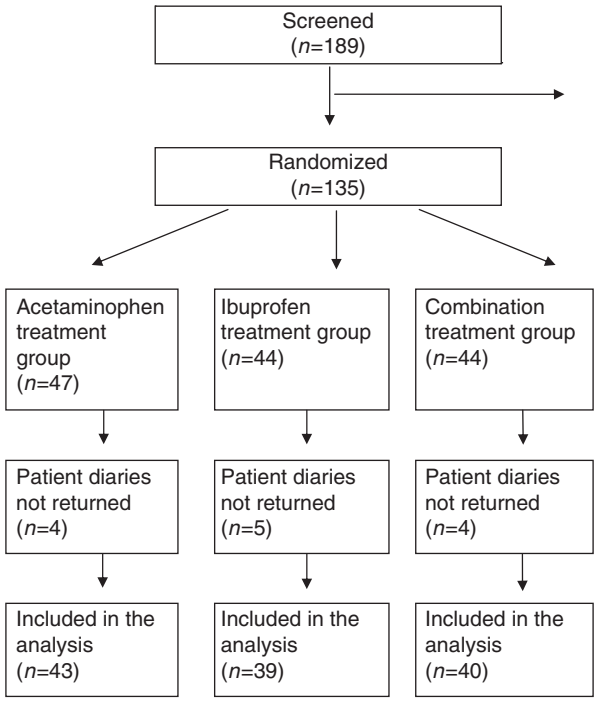

Fig 1 Flow of participants through trial. Not randomized ($n=54$): (i) declined to participate ($n=15$), (ii) did not meet inclusion criteria ($n=14$), (iii) other reasons ($n=25$); other reasons: the surgery was cancelled or rescheduled; patient could not be contacted; patient was given the wrong date of the surgery.

Pharmacokinetics

There were no significant differences between the combination group and either constituent group in any of the estimated pharmacokinetic parameters (Table 5). The visual predictive plots of individual concentration showed that ~90% of the observations were within the 90% prediction intervals.

Twelve participants were given both acetaminophen and ibuprofen. For calculation of the pharmacokinetic variables, a scaling factor was applied to clearance and volume of distribution in turn for those participants receiving the combination of acetaminophen and ibuprofen. This scaling factor had no impact on either acetaminophen or ibuprofen pharmacokinetic parameters, indicating that there was no pharmacokinetic interaction between acetaminophen and ibuprofen when administered together ($P>0.05$).

Clearance (CL/*F*) and volume of distribution (*V*/*F*) parameters observed in the study are consistent with those reported previously (acetaminophen: CL/F=12.6–21.0 litre h^{-1} 70 kg^{-1}, V/F=48.3–71.0 litre 70 kg^{-1}; ibuprofen: CL/F=2.9–5.9 litre h^{-1} 70 kg^{-1}, V/F=6.4–23.5 litre 70 kg^{-1}).[18–20]

Adverse effects

The frequency of adverse effects was consistent with the known effects of the constituent drugs, and there were no

Table 1 Patient characteristic and baseline information (SD)

	Acetaminophen ($n=47$)	Ibuprofen ($n=44$)	Combination ($n=44$)
Age [mean (range)] (yr)	23.5 (16.0–40.4)	23.7 (16.8–38.9)	25.0 (18.3–40.4)
Weight [mean (SD)] (kg)	71.3 (15.6)	80.8 (20.1)	71.1 (13.5)
Ethnicity [*n* (%)]			
Asian	4 (8.5)	1 (2.3)	2 (4.5)
Black	1 (2.1)	0 (0.0)	1 (2.3)
Caucasian	33 (70.2)	31 (70.5)	34 (77.3)
Maori	4 (8.5)	4 (9.1)	4 (9.1)
Pacific Islander	4 (8.5)	5 (11.4)	2 (4.5)
Other	1 (2.1)	3 (6.8)	1 (2.3)
Male [*n* (%)]	13 (27.7)	21 (47.7)	13 (29.5)
Shift workers [*n* (%)]	10 (21.3)	5 (11.4)	3 (6.8)
Preoperative pain scores at rest [mean (SD)] (mm)	1.9 (5.1)	2.1 (5.2)	2.6 (6.8)
Preoperative pain scores on activity [mean (SD)] (mm)	4.1 (13.3)	2.7 (8.3)	2.9 (6.6)
Sleep disturbance for night before surgery as VAS [mean (SD)] (mm)	64.7 (22.9)	69.1 (26.0)	71.5 (24.1)

Table 2 Mean (SEM, 95% CI) of time-adjusted AUC of visual analogue pain scores at rest and on activity by treatment group. The differences between combination and each constituent were significant at rest (*vs* acetaminophen $P=0.007$ and *vs* ibuprofen $P=0.003$) and on activity (*vs* acetaminophen $P=0.006$ and *vs* ibuprofen $P=0.007$)

	Acetaminophen ($n=43$)	Ibuprofen ($n=39$)	Combination ($n=40$)
At rest	33.0 (3.1, 27.9–38.1)	34.8 (3.2, 29.4–40.2)	22.3 (3.2, 17.0–27.7)
On activity	40.4 (3.3, 35.0–45.8)	40.2 (3.4, 34.6–45.9)	28.4 (3.4, 22.8–34.1)

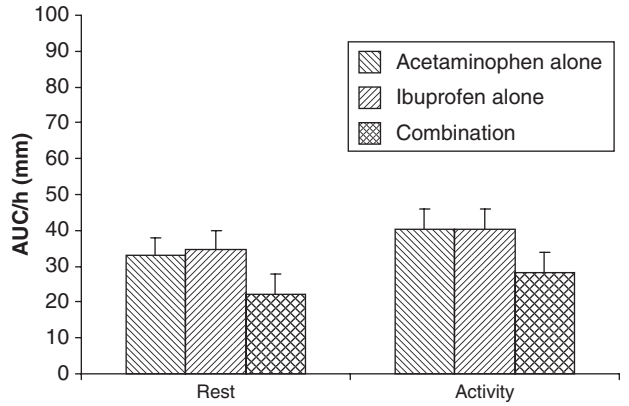

Fig 2 Mean (+95% CI) mm of time-adjusted AUC (AUC/time) for VAS at rest and on activity by treatment group.

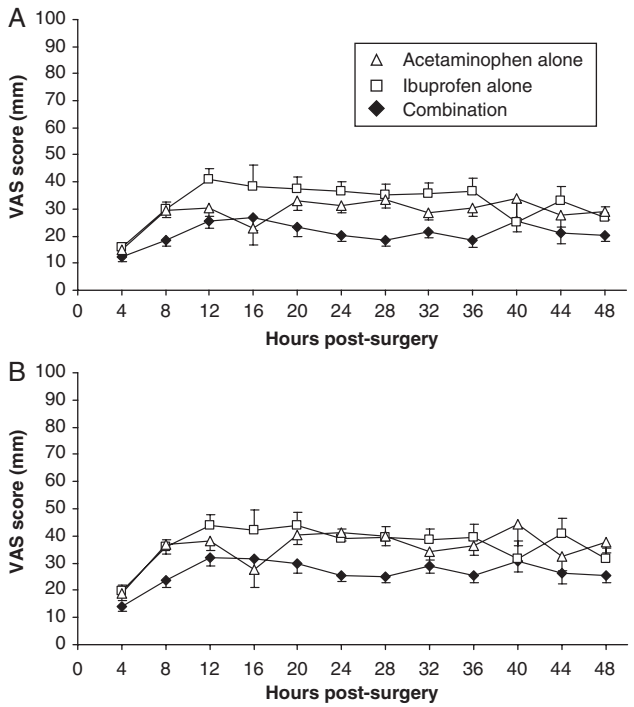

Fig 3 Mean (SE) mm VAS out of 100 at rest (A) and on activity (B).

definitive indications that the adverse event profile is changed when the two drugs are combined (Table 6); however, the numbers were too small to make meaningful

Table 3 Secondary efficacy endpoints by treatment group. The only significant difference was between the global pain ratings for combination and acetaminophen ($P=0.008$, Mann–Whitney *U*-test)

	Acetaminophen	Ibuprofen	Combination
Global pain rating [*n* (%)]			
Nil	3 (7.5)	4 (11.4)	4 (10.5)
Mild	12 (30.0)	15 (42.9)	22 (57.9)
Moderate	22 (55.0)	14 (40.0)	12 (31.6)
Severe	3 (7.5)	2 (5.7)	0 (0.0)
Global nausea rating [*n* (%)]			
Nil	26 (65.0)	25 (71.4)	30 (79.0)
Mild	10 (25.0)	8 (22.9)	7 (18.4)
Moderate	3 (7.5)	2 (5.7)	1 (2.6)
Severe	1 (2.5)	0 (0.0)	0 (0.0)
Vomiting episodes (*n*)	5 (in 3 subjects)	0	0
Sleep disturbance night 1 *vs* baseline VAS [mean (SD)] (mm)	−21.9 (29.2)	−17.4 (22.9)	−16.6 (24.7)
Sleep disturbance night 2 *vs* baseline VAS [mean (SD)] (mm)	−13.7 (32.9)	−9.6 (25.8)	−8.5 (20.1)

Table 4 Rescue analgesia by group, *n* (%); none of these differences were significant

Rescue analgesic	Acetaminophen	Ibuprofen	Combination
Fentanyl in hospital	5 (11.6%)	9 (23.7%)	6 (15.4%)
Codeine in the first 24 h	21 (47.70%)	16 (43.20%)	13 (32.50%)
Codeine in the second 24 h	22 (53.70%)	14 (42.40%)	16 (42.10%)
Any rescue medication over 48 h	25 (62.5%)	18 (58.10%)	21 (56.8%)

Table 5 Mean (SD) pharmacokinetic parameters (individual Bayesian estimates used for descriptive statistics) for a one-compartment, first-order absorption, first-order elimination model; none of the differences for combination formulations was significant. CL/*F*, clearance; *V*/*F*, volume of distribution; T_{abs}, absorption half-time; C_{max}, maximum concentration; T_{max}, time to achieve C_{max}

	Acetaminophen alone ($n=15$)	Acetaminophen in combination ($n=12$)	Ibuprofen alone ($n=11$)	Ibuprofen in combination ($n=12$)
CL/*F* (litre h^{-1})	14.1 (2.6)	14.2 (1.8)	3.9 (1.7)	3.8 (1.3)
V/*F* (litre)	55.7 (19.4)	48.2 (18.3)	10.6 (2.1)	9.8 (1.5)
T_{abs} (h)	0.42 (0.76)	0.16 (0.10)	0.58 (0.78)	0.85 (0.85)
T_{max} (h)	1.09 (1.12)	0.64 (0.31)	1.16 (0.90)	1.44 (0.93)
C_{max} (mg $litre^{-1}$)	15.8 (6.5)	19.2 (6.4)	20.8 (8.3)	19.1 (7.8)

comparisons between the groups. Two participants experienced postoperative bleeding (attributed to surgical causes), which resolved without readmission to hospital. No gastrointestinal bleeding was reported during the study. Most adverse events were evaluated as mild (57.4%) or moderate (35.2%) and on review were considered not related (17.5%) or unlikely to be related (66.7%) to study medication.

General

The majority of participants rated the experience of taking part in the study as very positive (31%) or positive (47%)

Table 6 Adverse events and their relationship with study medication as evaluated by the investigators. Postoperative pain was noted as a complication in 2, 0, and 1 patient in the acetaminophen, ibuprofen, and combination groups, respectively. Some individuals experienced more than one adverse event

Relationship	System organ class	Acetaminophen	Ibuprofen	Combination	Total
Not related	Gastrointestinal disorders (numbness of tongue)	1	0	0	1
	General disorders and administration site conditions (swollen arm, infusion site phlebitis)	0	0	2	2
	Infections and infestations (dry socket, alveolitis of jaw)	1	0	1	2
	Injury, poisoning, and procedural complications (bruising of arm, postoperative pain)	0	0	2	2
	Musculoskeletal and connective tissue disorders (jaw stiffness)	0	0	1	1
	Skin and s.c. tissue disorders (swelling face)	1	1	0	2
Subtotal		3	1	6	10
Unlikely related	Blood and lymphatic system disorders (swollen glands)	1	0	0	1
	Ear and labyrinth disorders (pain in ear, tinnitus)	2	0	0	2
	Gastrointestinal disorders (vomiting, nausea, stomach cramps, dry lips)	6	1	2	9
	Injury, poisoning, and procedural complications (postoperative bleeding)	0	0	1	1
	Musculoskeletal and connective tissue disorders (jaw stiffness, aches and pains in legs, jaw pain)	2	0	1	3
	Nervous system disorders (headache, felt faint, sleepy, balance difficulty, light headiness, dizziness, drowsiness, lethargic)	6	4	4	14
	Psychiatric disorders (disorientation)	0	1	0	1
	Respiratory, thoracic, and mediastinal disorders (sore throat, pharyngeal ulceration, hypoventilation, coughing)	1	1	2	4
	Investigations (body temperature increased)	0	0	1	1
	Skin and s.c. tissue disorders (rash, redness of external ear, swelling face)	0	1	1	2
Subtotal		18	8	12	38
Possibly related	Gastrointestinal disorders (stomach cramps, abdominal pain, constipation, stomach ache, vomiting)	3	0	2	5
	General disorders and administration site conditions (fever)	1	0	0	1
	Injury, poisoning, and procedural complications (postoperative bleeding)	0	0	1	1
	Nervous system disorders (sleepy, headache)	1	0	1	2
Subtotal		5	0	4	9
Total		26	9	22	57

and 19% rated the experience as neutral. Four participants (3%) found the experience negative, and none rated it as very negative. The ratings were not significantly different between the study groups.

Discussion

We found that patients using the combination of acetaminophen and ibuprofen experienced less pain during the first 48 h after oral surgery than those using the same daily dosage of either agent alone and we think the difference was clinically relevant. There was no evidence of any pharmacokinetic interaction between acetaminophen and ibuprofen. Patients receiving ibuprofen alone reported the lowest frequency of adverse events, but the numbers are too small for meaningful comparisons between the groups, and we saw no cause for concern in any group.

Our data are consistent with previous evidence showing that a combination of ibuprofen and acetaminophen provides better analgesia than acetaminophen alone.[8 9 13 21] Note, however, that two of these studies were in children,[9 13] so data in adults are relatively limited. On the other hand, there are many studies supporting the more general point that the addition of various NSAIDs improves the pain relief obtainable from acetaminophen alone. More importantly, our data add convincingly to the sparse evidence supporting the more controversial proposition that this combination is superior to ibuprofen alone.[12] In a smaller study in an orthopaedic pain model (which was positive for the combination in comparison with acetaminophen), Dahl and colleagues[8] showed no such benefit whereas Viitanen and colleagues[13] (in a paediatric tonsillectomy study) showed an advantage for the combination only in the period after discharge from hospital. The similarity in efficacy between ibuprofen and acetaminophen on their own seen in our study contrasts with the findings of superior pain relief from ibuprofen after dental surgery by Cooper and colleagues,[22] but theirs was a single-dose study.

Limitations and strengths of the study

Our results are limited to adults, and to the doses and model of pain studied. We think our conclusions are likely to apply to other age groups and other types of pain, but this will require confirmation. We have not explored the optimal dosage of the combination drug, but the dosage used is consistent with current clinical practice. The inclusion of patients who underwent both general and local anaesthesia implies that our findings are likely to apply in either case. It is not possible to draw firm conclusions on the safety of any drug from a study of only 40 participants per group, but acetaminophen and ibuprofen are well established, widely used, and considered very safe in appropriate doses.[3 23] There is no theoretical reason,

and no empirical suggestion from our data, to suggest that the combination would be any less safe than the constituent drugs on their own. Our safety data are observational rather than based on prospective laboratory investigations, but we followed up participants for adverse events for 3 weeks, and it seems unlikely that clinically important harm would have been missed.

Pain after oral surgery can persist for several days,[10] but we considered 48 h to be a clinically relevant period, and a longer period of study is likely to have resulted in poorer compliance with data collection.

It could be asked whether a more typical (albeit complex) regimen for ibuprofen alone might have provided better analgesia than seen with the 4 hourly approach used here, but this seems unlikely, particularly given that our clinical efficacy data were supported by estimates of population pharmacokinetics. We had planned to correlate drug plasma concentration with pain scores, but the drug plasma concentration results were too sparse and there were too many confounding variables (such as ethnicity, comparators, and rescue analgesia) for this to be undertaken. We did demonstrate a lack of interaction between the constituent drugs when used in combination and provided evidence that equivalent and predicted blood concentrations were achieved (the observations of time–concentration profile decreased within 90% of prediction limits for both acetaminophen and ibuprofen). Furthermore, pharmacokinetic parameter estimates observed in the current study are very similar to those previously reported.[18–20] The evaluations used in the efficacy analysis have established construct validity and are appropriate for parametric analysis.[24,25]

In designing analgesic studies, it is an advantage to minimize the exposure of participants to inadequate analgesia while controlling for various sources of bias. Some designs incorporate a placebo group, but the efficacy of both ibuprofen[26] and acetaminophen[27] in comparison with placebo are well established by previous research, and we would argue that the use of a placebo in this situation is unnecessary and perhaps even unethical.[28] There would be little value in another 'me too' analgesic unless it had clear advantages over established agents. Therefore, the question of interest lies in the comparisons between the new agent (Maxigesic®) and the reference standard of care, and in this case, we have actually shown superiority to both of two possible reference standards—acetaminophen alone and ibuprofen alone. One classic approach to analgesic studies involves treating established acute pain. This has the alleged advantage that pain relief can be assessed (e.g. by using AUC to estimate total pain relief, or TOTPAR,[29,30] or by calculating a pain reduction index per tablet).[31] Our design, in contrast, follows the widely accepted clinical practice of anticipating and treating pain before it occurs, which, in our unit at least, has long been considered best practice. Furthermore, rescue medication was readily available and those requiring it were evenly distributed between the groups. It is notable that most patients did require rescue medication, suggesting that pain after oral surgery can sometimes be severe enough that even the combination of ibuprofen and acetaminophen requires supplementation (and it might be asked whether it would be a good idea for codeine, for example, to be added to the combined formulation). Nevertheless, we think it important that the vast majority of the participants in all groups reported pain scores that were reasonably low, and that all received analgesic regimens accepted in contemporary practice. The predominantly positive evaluation by participants of their experience in taking part in the study provides empirical reassurance on this point (and also other aspects of the conduct of the study).

The treatment of pain is central to medical practice in hospitals and in primary care. If these results are confirmed in other settings, the already widely used combination of acetaminophen and ibuprofen may become the standard of care for the initial management of moderate acute pain, at least for those patients who do not have contra-indications to NSAIDs. Even using the drugs individually, the dosage regimen studied here is simpler than that currently recommended, and may well improve compliance with and therefore success with this combination. Providing both drugs in one tablet simplifies this regimen even further, and our data confirm that the specific formulation studied here is effective, and that there is no interaction between its constituent drugs.

Conclusions

Doctors treating pain after oral surgery, in hospital and at home, and probably pain in many other situations, should consider using acetaminophen and ibuprofen together four times a day, provided there are no contraindications to either drug, and taking into account the known risks of NSAIDs. The combination formulation studied here simplifies this regimen.

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Appendix

Declaration of interest

The Department of Anaesthesiology of the University of Auckland has received payment from AFT Pharmaceuticals for conducting this study, but none of the investigators has received payment in their personal capacity.

Contributors

A.F.M., B.J.A., C.F., and Hartley Atkinson* designed the study with input from R.D.G. and J.E. Hartley Atkinson* obtained funding. R.D.G., G.S.T., and J.E. performed the surgery, and contributed to patient recruitment and to the care of patients during their participation in the study. E.D. was the study coordinator, and was responsible for patient recruitment and follow-up, data collection, quality control, and many other logistic aspects of the study. The statistical analysis of clinical data was undertaken by C.F. and of the pharmacokinetic data by B.J.A. A.F.M. took primary responsibility for the manuscript, with assistance from Jennifer Zhang**. All authors edited and commented on the manuscript. A.F.M. is the guarantor.

*Chief Executive Officer, AFT Pharmaceuticals; **Clinical Trial/Regulatory Assistant, AFT Pharmaceuticals.

Ethics approval

This study was approved by the Northern X Regional Ethics Committee, 650 Great South Road, Penrose, Auckland, New Zealand.

Ethics Committee Approval Number: AKX/04/10/298.

Health Authorities (MEDSAFE) Approval Number: TT50-7316 (458).

Role of the sponsor

The sponsor (AFT Pharmaceuticals Ltd) participated in the study design and protocol development and provided logistical support during the trial. Monitoring of the study was performed by the sponsor, who also maintained the trial database. Statistical analyses were independently performed by the biostatistician and the results cross-checked by sponsors and investigators. The sponsor assisted with the preparation of the manuscript, and was permitted to review it and to make suggestions, but responsibility for the content of this paper lay with the academic authors, and the style and emphasis is that of the principle investigator. The academic authors had the explicit right to access all data and publish these results.

Provenance and peer review

This paper was not commissioned; informal external peer review has been obtained before submission to the Journal.

Additional contributions

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References

1 Cousins MJ, Brennan F, Carr DB. Pain relief: a universal human right. *Pain* 2004; **112**: 1–4

2 Merry A, Power I. Perioperative NSAIDs: towards greater safety. *Pain Rev* 1995; **2**: 268–91

3 *MARTINDALE: The Extra Pharmacopoeia.* London: The Royal Pharmaceutical Society of Great Britain, 1996

4 Mehlisch DR. The efficacy of combination analgesic therapy in relieving dental pain. *J Am Dent Assoc* 2002; **133**: 861–71

5 Desmeules J, Rollason V, Piguet V, Dayer P. Clinical pharmacology and rationale of analgesic combinations. *Eur J Anaesthesiol Suppl* 2003; **20**: 7–11

6 Altman RD. A rationale for combining acetaminophen and NSAIDs for mild-to-moderate pain. *Clin Exp Rheumatol* 2004; **22**: 110–7

7 Hyllested M, Jones S, Pedersen JL, Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. *Br J Anaesth* 2002; **88**: 199–214

8 Dahl V, Dybvik T, Steen T, Aune AK, Rosenlund EK, Ræder JC. Ibuprofen vs. acetaminophen vs. ibuprofen and acetaminophen after arthroscopically assisted anterior cruciate ligament reconstruction. *Eur J Anaesthesiol* 2004; **21**: 471–5

9 Gazal G, Mackie IC. A comparison of paracetamol, ibuprofen or their combination for pain relief following extractions in children under general anaesthesia: a randomized controlled trial. *Int J Paediatr Dent* 2007; **17**: 169–77

10 Merry AF, Swinburn PF, Middleton NG, Edwards JL, Calder MV. Tenoxicam and paracetamol–codeine combination after oral surgery: a prospective, randomized, double-blind, placebo-controlled study. *Br J Anaesth* 1998; **81**: 875–80

11 Mitchell A, van Zanten SV, Inglis K, Porter G. A randomized controlled trial comparing acetaminophen plus ibuprofen versus acetaminophen plus codeine plus caffeine after outpatient general surgery. *J Am Coll Surg* 2008; **206**: 472–9

12 Menhinick KA, Gutmann JL, Regan JD, Taylor SE, Buschang PH. The efficacy of pain control following nonsurgical root canal treatment using ibuprofen or a combination of ibuprofen and acetaminophen in a randomized, double-blind, placebo-controlled study. *Int Endod J* 2004; **37**: 531–41

13 Viitanen H, Tuominen N, Vääräniemi H, Nikanne E, Annila P. Analgesic efficacy of rectal acetaminophen and ibuprofen alone or in combination for paediatric day-case adenoidectomy. *Br J Anaesth* 2003; **91**: 363–7

14 Henry D, McGettigan P. Epidemiology overview of gastrointestinal and renal toxicity of NSAIDs. *Int J Clin Pract* 2003; Suppl. (**135**): 43–9

15 TGA Medicines Evaluation Committee, 2003. Review of non-prescription analgesics: Multiple Strength of Oral Liquids. Australia: Therapeutic Goods Administration, 2003

16 Australian and New Zealand College of Anaesthetists. *Monitoring during anaesthesia (Review P18)*. Melbourne: The College, 2008

17 Merry AF, Sidebotham DA, Middleton NG, Calder MV, Webster CS. Tenoxicam 20 mg or 40 mg after thoracotomy: a prospective, randomized, double-blind, placebo-controlled study. *Anaesth Intensive Care* 2002; **30**: 160–6

18 Davies NM. Clinical pharmacokinetics of ibuprofen. The first 30 years. *Clin Pharmacokinet* 1998; **34**: 101–54

19 Prescott LF. Pharmacokinetics of paracetamol. *Paracetamol (Acetaminophen): A Critical Bibliographic Review*. New York: Taylor & Francis Inc., 2001; 205–15

20 Rainsford KD. The pharmacokinetics of ibuprofen in humans and animals. *Ibuprofen: A Critical Bibliographic Review*. London: Taylor & Francis, 1999; 92–5

21 Ianiro S, Jeansonne B, McNeal S, Eleazer P. The effect of preoperative acetaminophen or a combination of acetaminophen and ibuprofen on the success of inferior alveolar nerve block for teeth with irreversible pulpitis. *J Endod* 2007; **33**: 11–4

22 Cooper SA, Schachtel BP, Goldman E, Gelb S, Cohn P. Ibuprofen and acetaminophen in the relief of acute pain: a randomized, double-blind, placebo-controlled study. *J Clin Pharmacol* 1989; **29**: 1026–30

23 *AHFS: Drug Information*. Bethesda, MD: American Society of Health-System Pharmacist, 2007

24 Coll AM, Ameen JRM, Mead D. Postoperative pain assessment tools in day surgery: literature review. *J Adv Nurs* 2004; **46**: 124–33

25 Philip BK. Parametric statistics for evaluation of the visual analogue scale. *Anesth Analg* 1990; **71**: 710

26 Schou S, Nielsen H, Nattestad A, *et al*. Analgesic dose–response relationship of ibuprofen 50, 100, 200, and 400 mg after surgical removal of third molars: a single-dose, randomized, placebo-controlled, and double-blind study of 304 patients. *J Clin Pharmacol* 1998; **38**: 447–54

27 Barden J, Edwards J, Moore A, McQuay H. Single dose oral paracetamol (acetaminophen) for postoperative pain. *Cochrane Database Syst Rev (Online)* 2004

28 Anderson B, Cranswick N. The placebo (I shall please)—is it so pleasing in children? *Paediatr Anaesth* 2005; **15**: 809–13

29 Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. *Acute Pain Management: Scientific Evidence*. Australian Government: National Health and Medical Research Council, 2005

30 Moore RA, Edwards JE, McQuay HJ. Acute pain: individual patient meta-analysis shows the impact of different ways of analysing and presenting results. *Pain* 2005; **116**: 322–31

31 Quiding H, Oksala E, Happonen RP, Lehtimaki K, Ojala T. The visual analog scale in multiple-dose evaluations of analgesics. *J Clin Pharmacol* 1981; **21**: 424–9