CLINICAL TRIALS AND THERAPEUTICS

Effect of caffeine on ibuprofen analgesia in postoperative oral surgery pain

Recent studies have demonstrated that caffeine acts as an analgesic adjuvant when combined with acetaminophen, aspirin, or their mixture. Our objective was to determine whether similar enhancement of analgesia could be demonstrated when caffeine is combined with ibuprofen. On a double-blind basis, a single oral dose of ibuprofen (50, 100, or 200 mg), a combination of ibuprofen, 100 mg, with caffeine, 100 mg, a combination of ibuprofen, 200 mg, with caffeine, 100 mg, or placebo was randomly assigned to 298 outpatients with postoperative pain after the surgical removal of impacted third molars. With a self-rating record, subjects rated their pain and its relief hourly for 8 hours. All active treatments were significantly superior to placebo, and the caffeine effect was significant for every measure of analgesia. Relative potency estimates indicated that the combination was 2.4 to 2.8 times as potent as ibuprofen alone. The combination also had a more rapid onset and longer duration of analgesic action. The analgesic adjuvancy of caffeine clearly extends to combinations with nonsteroidal anti-inflammatory drugs other than acetaminophen or aspirin. (CLIN PHARMACOL THER 1991;49:674-84.)

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Caffeine has long been a constituent of both over-the-counter (OTC) and prescription analgesic combinations in conjunction with aspirin, acetaminophen, phenacetin, and salicylamide. Until recently, however, the evidence of caffeine's contribution to the efficacy of such combinations has been tenuous at best.[1-4] In the early 1970s the Food and Drug Administration sponsored a review of OTC drugs, and the panel responsible for internal analgesic, antipyretic, and antirheumatic products concluded that there was a lack of evidence for the efficacy of caffeine as a constituent of analgesic combinations.[5] This finding precipitated a flurry of controlled clinical trials sponsored by interested pharmaceutical manufacturers. Several individual studies succeeded in demonstrating the analgesic adjuvancy of caffeine.[6,7] In addition, Laska et al.[7] have assembled data from a large number of unpublished and previously published clinical trials that, taken together, also establish the efficacy of caffeine as an analgesic adjuvant in combination with acetaminophen or the combination of aspirin and acetaminophen. Using the classic analgesic relative potency assay technique developed by Houde et al.,[8] those investigators demonstrated that the addition of caffeine, 65 mg per dosage unit, to acetaminophen or an aspirin-acetaminophen mixture resulted in an analgesic combination approximately 1.4 times as potent as the analgesic administered alone.

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Table I. Demographic data, parameters related to surgical procedure, and baseline pain intensity

	Ibuprofen, 50 mg (n = 57)	*Ibuprofen, 100 mg (n = 49)*	*Ibuprofen, 200 mg (n = 48)*	*Ibuprofen, 100 mg, + caffeine, 100 mg (n = 49)*	*Ibuprofen, 200 mg, + caffeine, 100 mg (n = 44)*	*Placebo (n = 51)*
Age (yr)	22.28	22.67	22.29	22.47	22.36	20.69
Range	16-39	15-42	17-36	15-45	15-54	15-33
Sex (*n*/%)						
Male	17/30	22/45	20/42	21/43	23/52	18/35
Female	40/70	27/55	28/58	28/57	21/48	33/65
Race (*n*/%)						
White	55/96	49/100	48/100	49/100	42/95	50/98
Black	2/4	0/0	0/0	0/0	2/5	1/2
Height (inches)	66.88	66.82	66.35	67.00	67.82	66.90
Weight (pounds)	143.14	143.73	144.02	145.96	149.09	142.39
Length of surgical procedure (min)	30.72	28.51	29.38	27.88	31.41	28.51
No. impactions	2.77	2.67	2.65	2.73	2.59	2.84
Trauma rating	2.19	2.16	2.15	2.16	2.25	2.24
Mild (*n*/%)	7/12	7/14	10/21	8/16	6/14	6/12
Moderate (*n*/%)	32/56	27/55	21/44	25/51	21/48	27/53
Severe (*n*/%)	18/32	15/31	17/35	16/33	17/38	18/35
No. sutures	4.14	3.94	4.31	3.96	4.75	4.65
Time from procedure until taking study medication (hr)	2.56	2.55	2.37	2.92	3.22	2.37
Baseline pain intensity	2.46	2.51	2.50	2.49	2.48	2.53
Moderate (*n*/%)	31/54	24/49	24/50	25/51	23/52	24/47
Severe (*n*/%)	26/46	25/51	24/50	24/49	21/48	27/53

Mean values unless otherwise specified.

Table II. Measures of analgesic effect (summary scores)

	Ibuprofen, 50 mg (n = 57)	*Ibuprofen, 100 mg (n = 49)*	*Ibuprofen, 200 mg (n = 48)*	*Ibuprofen, 100 mg, + caffeine, 100 mg (n = 49)*	*Ibuprofen, 200 mg, + caffeine, 100 mg (n = 44)*	*Placebo (n = 51)*
Pain intensity differences						
Total score (SPID)	3.65*	3.91*	5.10*	5.92*	7.89*†‡§	0.22
Peak score	0.98*	1.04*	1.38*‖¶	1.45*†¶	1.68*†‡	0.35
Pain relief						
Total score	8.82*	8.46*	10.00*	11.29*	15.58*†‡#**	2.58
Peak score	1.95*	1.98*	2.38*	2.59*‖¶	2.95*†‡§	0.96
Hr of 50% relief	2.54*	2.96*	3.10*	3.57*	4.52*†§¶	0.53
Overall evaluation	1.14*	1.39*	1.77*‖	1.98*†¶	2.14*†‡	0.47
Hr until remedication	4.91*	4.84*	5.13*	5.37*	6.11*‖¶	3.00
Patients remedicating by hr 8 (*n*/%)	45/79††	38/78††	38/79	34/69*	25/57*§‖	48/94

Mean values unless otherwise specified.
SPID, Sum of the pain intensity difference scores.
Treatment effect significantly superior to placebo; †† $p < 0.05$, * $p < 0.01$.
Treatment effect significantly superior to ibuprofen, 50 mg; ‖$p < 0.05$, † $p < 0.01$.
Treatment effect significantly superior to ibuprofen, 100 mg; ¶ $p < 0.05$, ‡ $p < 0.01$.
Treatment effect significantly superior to ibuprofen, 200 mg; § $p < 0.05$, # $p < 0.01$.
Treatment effect significantly superior to ibuprofen, 100 mg, with caffeine, 100 mg; ** $p < 0.05$.

Table III. Measures of analgesic effect (hourly scores)

	½	1	2	3	4	5
PID						
Ibuprofen, 50 mg (n = 57)	0.28	0.60*	0.60*	0.58*	0.49*	0.44*
Ibuprofen, 100 mg (n = 49)	0.35	0.73*	0.82*	0.63*	0.59*	0.47*
Ibuprofen, 200 mg (n = 48)	0.31	0.90*	1.00*‡	0.98*‡§	0.85*‡	0.58*
Ibuprofen, 100 mg, + caffeine (n = 49)	0.43†	0.84*	1.22*§‖	1.06*§‖	0.86*‡	0.63*
Ibuprofen, 200 mg, + caffeine (n = 44)	0.59*	1.09*‖	1.25*§‖	1.36*‖¶#	1.20*‖¶	1.05*‖¶#**
Placebo (n = 51)	0.02	0.18	0.08	0.04	0.06	−0.02
Pain relief scores						
Ibuprofen, 50 mg	0.63	1.30†	1.44*	1.35*	1.12*	1.04*
Ibuprofen, 100 mg	0.69	1.24†	1.65*	1.27*	1.14*	1.04*
Ibuprofen, 200 mg	0.87	1.67*	1.92*	1.83*§	1.52*	1.23*
Ibuprofen, 100 mg, + caffeine	1.14*	1.59*	2.00*‡	1.98*‡¶	1.67*‡	1.20*
Ibuprofen, 200 mg, + caffeine	1.25*‡	2.14*‖¶	2.34*§‖	2.41*‖¶#	2.30*‖¶**††	2.05*‖¶††‡‡
Placebo	0.39	0.65	0.61	0.33	0.27	0.22
Patients with 50% relief (%)						
Ibuprofen, 50 mg	17.54	33.33*	38.60*	33.33*	35.09*	33.33*
Ibuprofen, 100 mg	12.24	40.82*	53.06*	42.86*	40.82*	36.73*
Ibuprofen, 200 mg	27.08†	52.08*‡	54.17*	52.08*‡	41.67*	37.50*
Ibuprofen, 100 mg, + caffeine	26.53†	51.02*	63.27*‖	63.27*§‖	42.86*	36.73*
Ibuprofen, 200 mg, + caffeine	25.00†	59.09*‖	61.36*‡	77.27*‖¶††	66.18*‖¶††‡‡	54.55*‡
Placebo	1.96	3.92	9.80	7.84	5.88	5.88

Mean values unless otherwise specified.
PID, Pain intensity difference.
Treatment effect significantly superior to placebo; † $p < 0.05$, * $p < 0.01$.
Treatment effect significantly superior to ibuprofen, 50 mg; ‡ $p < 0.05$, ‖ $p < 0.01$.
Treatment effect significantly superior to ibuprofen, 100 mg; § $p < 0.05$, ¶ $p < 0.01$.
Treatment effect significantly superior to ibuprofen, 200 mg; # $p < 0.05$, †† $p < 0.01$.
Treatment effect significantly superior to ibuprofen, 100 mg, with caffeine, 100 mg; ** $p < 0.05$, ‡‡ $p < 0.01$.

Although many of the effects of caffeine are apparently mediated through blockade of adenosine receptors, and caffeine potentiates the anti-inflammatory and antinociceptive activity of aspirin in the rat,[9] the mechanism of the analgesic adjuvant effect of caffeine is speculative. One cannot therefore predict with any certainty whether the adjuvant effect of caffeine demonstrated with acetaminophen and aspirin would also be manifest if caffeine were combined with other nonsteroidal anti-inflammatory drugs (NSAID).

Ibuprofen, 200 mg, is comparable in analgesic effect to the usual doses of aspirin or acetaminophen, and the 400 mg dose of ibuprofen is significantly more effective.[10-14] If caffeine were to function as an analgesic adjuvant when combined with ibuprofen, the resulting combination should be very effective indeed. This study is a relative potency assay designed to measure the adjuvant effect of 100 mg caffeine when combined with OTC dose levels of ibuprofen.

SUBJECTS AND METHODS

The method of evaluating analgesia has been reported by Forbes et al.[13,15,16] and is based on the method developed by Cooper and Beaver.[17] The subjects were private outpatients, at least 15 years of age, who had undergone surgical removal of one or more impacted third molars at one of two sites (site 1: W.K.S. or C.M.G.; site 2: J.R.Z. or J.W.S.). Anesthetic agents included methohexital sodium, lidocaine hydrochloride, mepivacaine hydrochloride, succinylcholine chloride, halothane, sodium pentothal, and nitrous oxide with oxygen. Preanesthetics included atropine sulfate and diazepam.

Potential subjects were interviewed before surgery by a nurse-observer (site 1: K.F.J.; site 2: C.J.K.). Patients were excluded if they were pregnant or lactating; had any history of hypersensitivity or serious adverse reaction to any agent similar to the study medications; had any clinically significant condition that would affect absorption, metabolism, or excretion of the study medications; or required concomitant medication that might confound quantitating analgesia. Long-term users of analgesics or tranquilizers were also excluded. On the basis of personal interviews, the nurse-observer selected patients who were able to communicate fluently and were willing to participate.

6	7	8
0.42*	0.39†	0.30
0.41†	0.24	0.20
0.46*	0.31	0.31
0.55*	0.49*	0.47*
0.82*‡§	0.73*§#	0.64*§
−0.02	0.00	−0.02
1.09*	0.96*	0.86†
0.96*	0.76†	0.67
0.92*	0.69	0.63
1.04*	0.98*	1.04*
1.77*‖¶††‡‡	1.59*‡¶††**	1.43*‡¶††
0.20	0.22	0.22
29.82*	26.32†	24.56†
34.69*	24.49	22.45
27.08†	22.92	22.92
34.69*	32.65*	32.65*
50.00*‖	43.18*#	38.64*
5.88	7.84	5.88

The purposes and procedures of the study were explained to participants in detail on the day of surgical consult and the day of surgery. Patients gave written informed consent. Participation of minors required the written informed consent of a parent or legal guardian.

On the day of surgery, after a briefing on the study procedures, each patient received a packet of materials containing a self-rating record, the study medication, a common kitchen timer and a supply of standard analgesics (site 1: Synalgos-DC [Wyeth-Ayest Laboratories, Philadelphia, Pa.], a combination of dihydrocodeine bitartrate, 16 mg, and aspirin, 356.4 mg, with caffeine, 30 mg; site 2: Phenaphen with codeine No. 3 [A.H. Robins Co., Inc., Richmond, Va.], a combination of codeine phosphate, 30 mg, with acetaminophen, 325 mg) to be used as a backup if additional pain relief was needed after taking the study medication. Patients were instructed to take the study medication when they had moderate or severe pain that required treatment and to record the time and intensity of the baseline pain. They were then required to complete the following statements at ½ hour and then at hourly intervals for up to 8 hours:

- My pain at this time is: none (0), slight (1), moderate (2), or severe (3)
- My relief from starting pain is: none (0), a little (1), some (2), a lot (3), or complete (4)
- My starting pain is at least one-half gone: no (0) or yes (1)

At the end of the 8-hour evaluation, or at the time the patient took the backup analgesic, he or she made an overall evaluation of the study medication as poor (0), fair (1), good (2), very good (3), or excellent (4), taking into consideration the onset, level, and duration of relief, as well as any other effects noted. Adverse effects were also noted on the self-rating record. Patients were asked to give the study medication at least 2 hours to manifest an effect before taking the first dose of backup medication and to complete the next hourly evaluation of the study medication before remedicating. Caffeine-containing foods and beverages were prohibited for 4 hours before taking the study medication and for the ensuing 8-hour observation period.

Patients returned to the oral surgeons' office approximately 5 days after surgery for a postoperative follow-up visit. The nurse-observer reviewed the self-rating records and conducted a debriefing at that time. Responses were clarified if necessary and patients were questioned concerning other effects noted while taking the study medication.

Patients who took the backup analgesic before completing the 8-hour evaluation were assigned a relief score of 0 (none) and a 50% relief score of 0 (no) for each hour after remedicating. The pain-intensity score after taking the backup analgesic was considered to be equal to the starting pain or the pain immediately before taking the backup analgesic, whichever was more severe. This convention for assigning scores makes the assumption, verified by our past experience, that almost all patients would continue to have pain and would not have had spontaneous relief during the remainder of the 8-hour study period if they had not remedicated.[18] The data for patients who remedicated with the backup analgesic before the hour-2 evaluation were excluded from the evaluation of efficacy. Patients who were asleep and did not complete a scheduled hourly evaluation were assigned a rating of pain intensity, pain relief, and 50% relief equal to the last evaluation before falling asleep.

The following measures of efficacy were derived from the patients' ratings: hourly pain intensity difference (PID) score, sum of the pain intensity difference (SPID) score, peak PID score, hourly pain relief score, total pain relief (TOTPAR) score, peak pain relief score, total hours of 50% relief, and overall evaluation. Hourly PID scores were derived by subtracting the hourly scores from the baseline score. Hourly scores were added to obtain the SPID and TOTPAR.

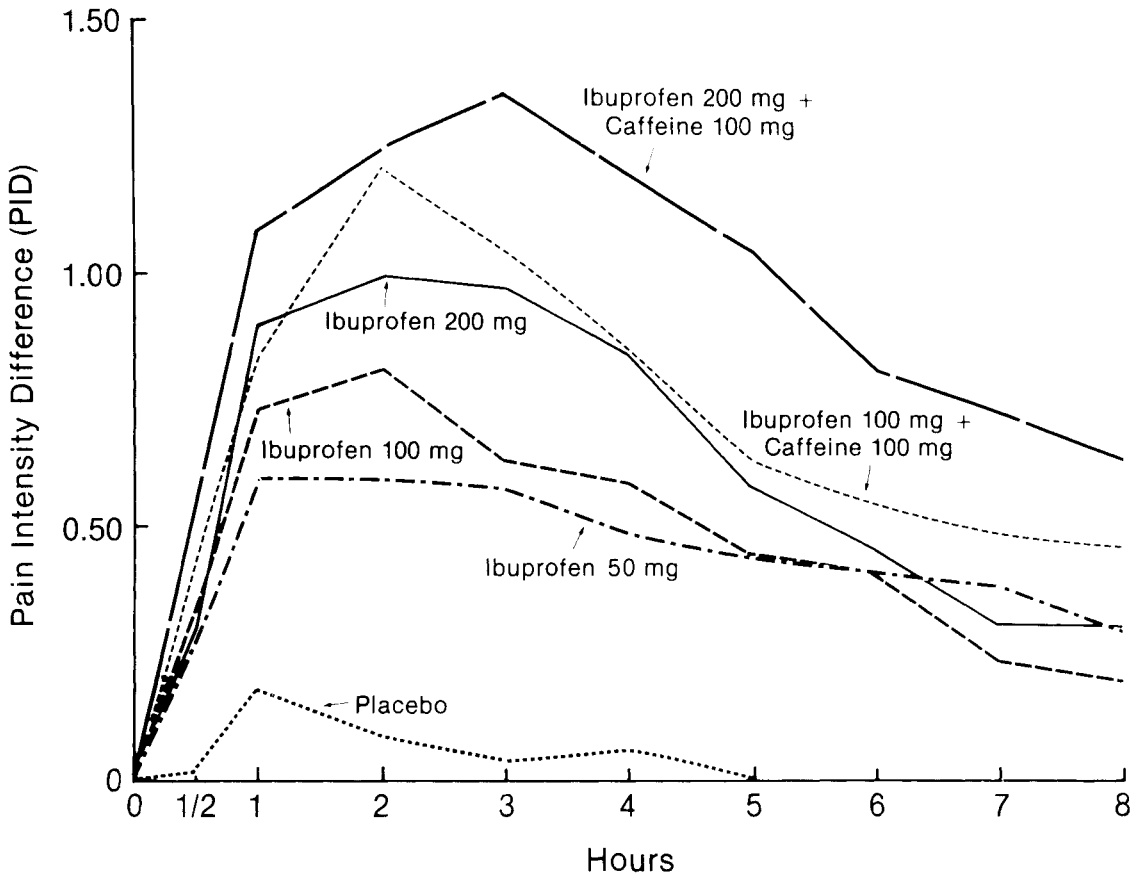

Fig. 1. Time-effect curves for ibuprofen, 50, 100, and 200 mg; the combination of 100 mg ibuprofen with 100 mg caffeine; the combination of 200 mg ibuprofen with 100 mg caffeine; and placebo. Mean pain intensity difference (PID) scores are plotted.

The peak score for these measures was the highest hourly score. Patients who did not remedicate, or who remedicated after the 8-hour evaluation period, were assigned a time until remedication score of 8 hours. This is a conservative procedure and would underestimate the mean time until remedication.

Subjects in this double-blind, parallel-group study were randomly assigned, in blocks of six patients, to treatment with a single dose consisting of two identically appearing capsules. The six treatments compared were 50 mg ibuprofen, 100 mg ibuprofen, 200 mg ibuprofen, a combination of 100 mg ibuprofen with 100 mg caffeine, a combination of 200 mg ibuprofen with 100 mg caffeine, or placebo.

RESULTS

Subject sample. Three-hundred ninety-five patients were selected for the study; all returned for the postoperative follow-up visit. Thirty-three patients did not need a postoperative analgesic. Sixty-four patients had invalid efficacy data; of these, nine patients remedicated despite having relief from the study medication, eight patients remedicated with slight pain, 14 patients remedicated before completing the evaluation at hour 2, one patient ingested food containing caffeine, two patients took the study medication for a headache instead of postoperative pain, one patient rated only one side of the mouth instead of the entire operative area, the ratings for one patient were completed by a relative, three patients had data that lacked internal consistency, the evaluations were too far off schedule for 22 patients, and three patients took the study medication but did not complete the patient self-rating record. Patients with invalid efficacy data were distributed relatively evenly across treatment groups. The evaluation of efficacy was based on the data for the remaining 298 patients. All 362 patients who took the study medication were included in the evaluation of adverse effect liability.

The demographic data, parameters related to the

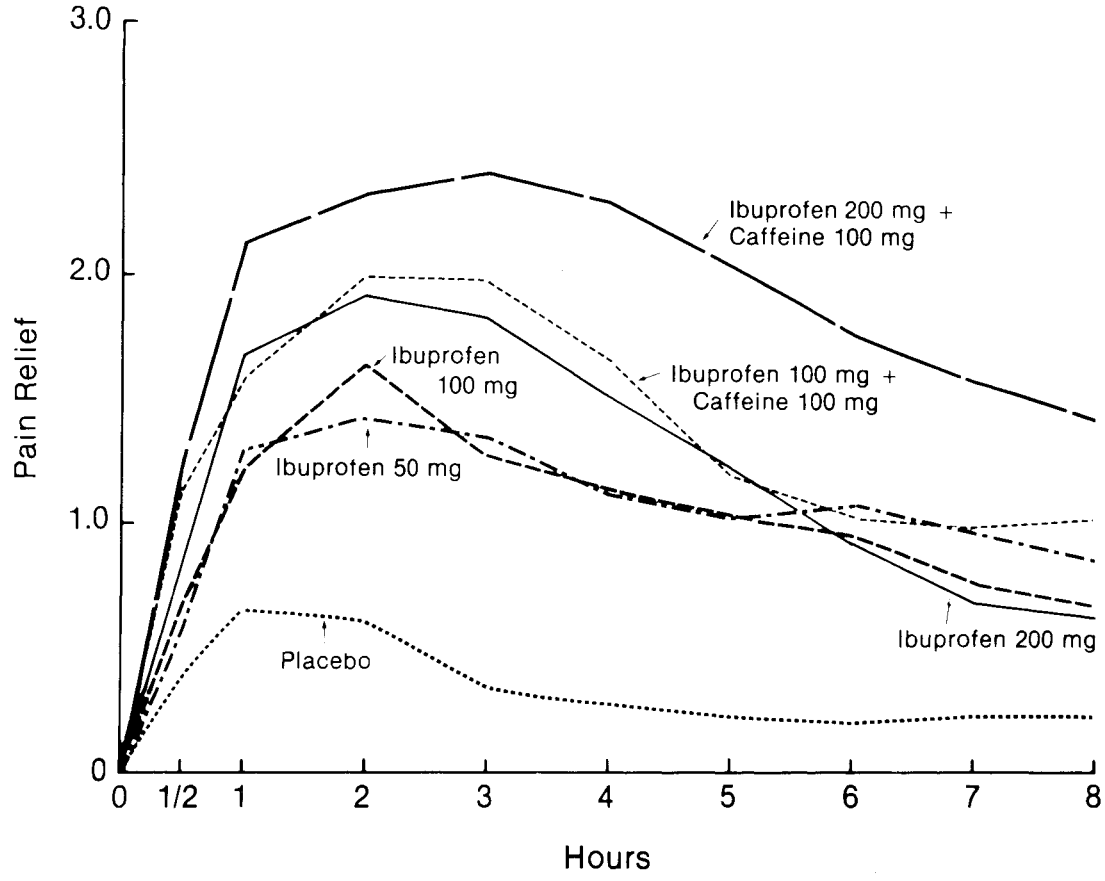

Fig. 2. Time-effect curves for ibuprofen, 50, 100, and 200 mg; the combination of 100 mg ibuprofen with 100 mg caffeine; the combination of 200 mg ibuprofen with 100 mg caffeine; and placebo. Mean pain relief scores are plotted.

surgical procedure, and baseline pain intensity are summarized in Table I. Differences among treatment groups were not statistically significant when evaluated by analysis of variance for parametric data[19] and χ^2 for discrete data.[20] The treatment groups were comparable with respect to the anesthetic and preanesthetic agents used, as well as the estimated usual daily caffeine consumption. Based on a two-way analysis of variance (ANOVA), the interaction between baseline pain intensity and treatment outcome was not statistically significant for any measure of efficacy; therefore the data for both groups (moderate and severe baseline pain) were combined. Because the treatment-by-site (nurse-observer) interactions were not statistically significant, the data from the two sites were pooled for analysis.

Pairwise comparisons. Summary measures of analgesic effect are presented in Table II. An ANOVA[19] was completed for each measure of total and peak analgesia, patient's overall evaluation, and the number of hours until taking the backup analgesic. Comparisons between treatments were made with Duncan's new multiple-range test.[21] Between-treatment comparisons in the percent of patients remedicating by hour 8 were made with χ^2.[20]

All active medications were significantly superior to placebo for every measure of total and peak analgesia (Table II). Although there was a general trend for a positive dose-response curve for ibuprofen, 50, 100, and 200 mg, this trend reached statistical significance for only a few measures of effect. The mean analgesic effects of the caffeine-containing treatments were uniformly greater than those of the respective doses of ibuprofen alone, and most of these differences were significant. In particular, measures of peak analgesia were usually significantly superior for the combination.

Time-effect curves. Hourly analgesic scores are presented in Table III. The time-effect curves for pain intensity difference and pain relief are presented in

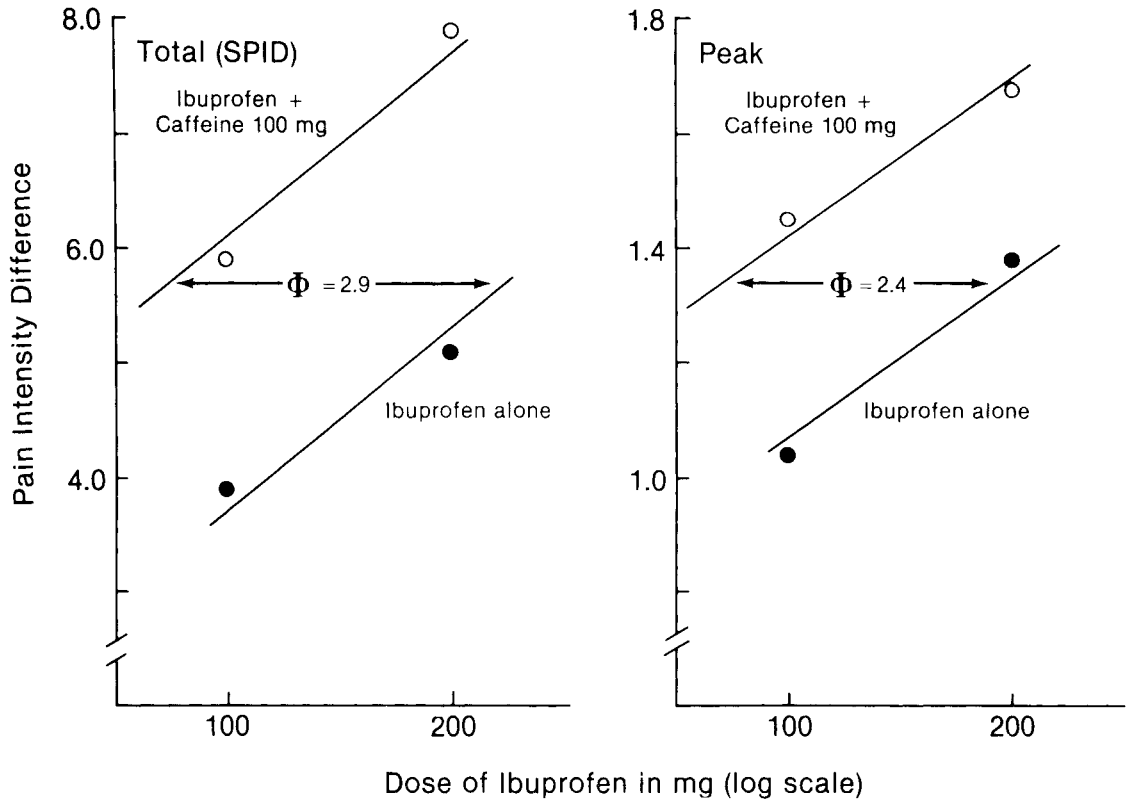

Fig. 3. Dose-response curves for ibuprofen (●) and the combination of ibuprofen with 100 mg caffeine (○). (SPID) The 8-hour sum of the pain intensity differences (SPID) **(left panel)** and peak pain intensity difference **(right panel)** are the response variables on the ordinate plotted against dose. Each point represents the mean effect of the 100 or 200 mg dose of ibuprofen alone or in combination with 100 mg caffeine. *Lines* represent the common slopes plotted through the mean effects for ibuprofen alone or the combination. *Arrows* indicate equieffective doses of ibuprofen and the combination, and Φ represents the relative potency of the two drugs.

Figs. 1 and 2, respectively; those for 50% relief were similar. Between-treatment comparisons in hourly scores were made with a repeated-measures analysis[22] and Duncan's new multiple-range test.[21]

Compared with placebo, the onset of analgesic effect for both caffeine combinations was always significant by the first observation point at ½ hour, whereas ibuprofen alone did not usually manifest significant analgesia until hour 1. Likewise, the duration of effect for both combinations was significant through 8 hours for every measure of analgesia and was frequently significantly greater than that for ibuprofen. The longer duration of analgesia provided by the combination of 200 mg ibuprofen with 100 mg caffeine is also reflected in significant differences in "hours until remedication" and "percent of patients remedicating by hour 8" (Table II). The time-effect curves for both combinations were consistently above the curves for the respective doses of ibuprofen, and at many hourly observations these differences were significant.

Relative potency assay. An ANOVA for a four-point relative potency assay[23-25] was performed on measures of total and peak analgesia for the ibuprofen, 100 and 200 mg, treatments with and without the addition of 100 mg caffeine. Because ibuprofen is usually administered on an every-4-hour or every-6-hour dosage regimen and, in this study, was usually not significantly superior to placebo after 6 hours, total scores were summed for 4 and 6 hours, as well as the full 8-hour observation period (Table IV). Significant common drug slopes were obtained for all measures of total and peak analgesia except for 8-hour SPID, but the common slopes for hours of 50% relief and overall evaluation were not significant. The differ-

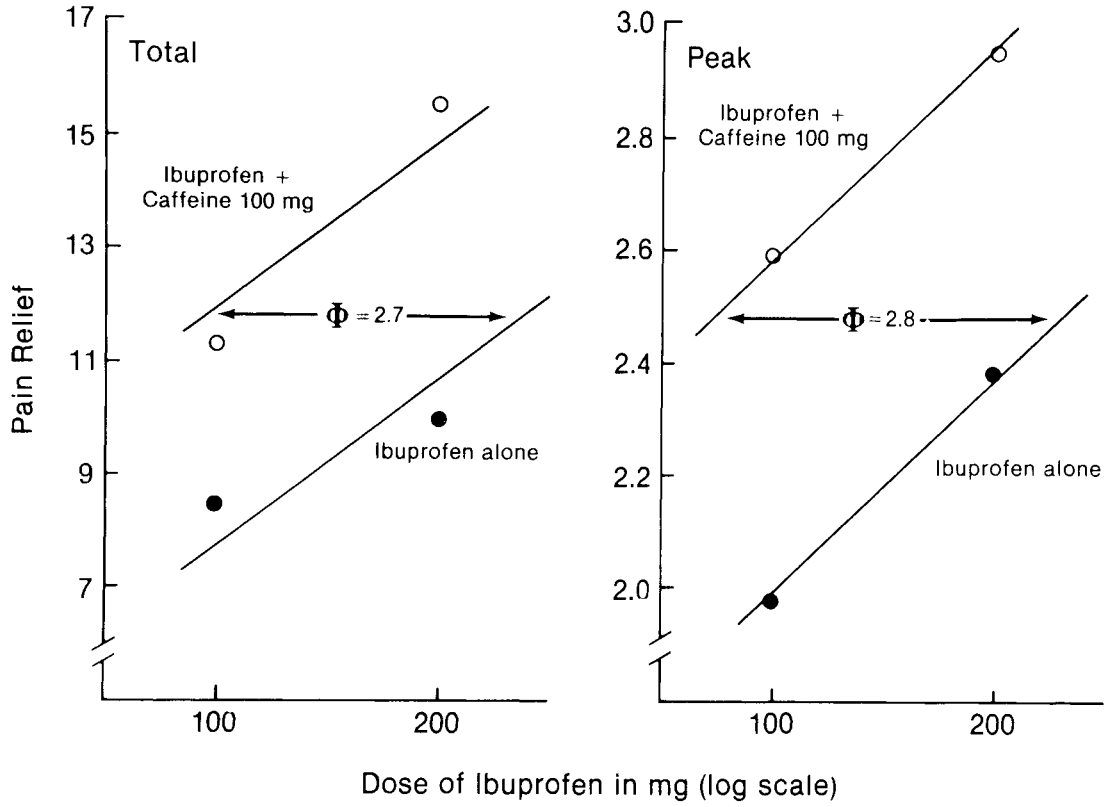

Fig. 4. Dose-response curves for ibuprofen (●) and the combination of ibuprofen with 100 mg caffeine (○). The 8-hour sum of the pain relief scores **(left panel)** and peak pain relief **(right panel)** are the response variables on the ordinate plotted against dose. Each *point* represents the mean effect of the 100 or 200 mg dose of ibuprofen alone or in combination with 100 mg caffeine. *Lines* represent the common slopes plotted through the mean effects for ibuprofen alone or the combination. *Arrows* indicate equieffective doses of ibuprofen and the combination, and Φ represents the relative potency of the two drugs.

ence in mean effect levels of standard and test drug (the "preparations" contrast or caffeine effect) was significant for every measure of analgesia, whereas the difference in slope of the standard and test drug (the "parallelism" contrast) was not significant for any measure of effect.

The relative potency estimates of the ibuprofen-caffeine combinations to ibuprofen alone ranged from 2.4 to 2.8 for those measures of effect with a significant common drug slope. The dose-response curves for PID and pain relief are presented in Figs. 3 and 4, respectively. Lambda, an index of the precision of a bioassay, is calculated by dividing the square root of the error mean square by the common slope.[24,25] Thus the lower the value for λ, the greater the sensitivity of the assay, and most values for λ reported in Table IV are in the range that reflects an adequately sensitive relative potency assay (i.e., 1 or less).[25] Greatest assay sensitivity for total effect was obtained with pain relief scores, whereas for peak effect PID proved the most sensitive index.

Adverse effects. Adverse effects reported by the patients are summarized in Table V. Because the patients were treated with a single dose of the study medication and then took a standard analgesic if additional relief was needed, adverse effects after taking the standard backup drug cannot be attributed clearly to either agent. The numbers in parentheses indicate the number of patients reporting adverse effects after taking the backup analgesic. The six treatment groups were comparable with respect to the number of patients reporting an adverse effect and the number of adverse effects reported. All adverse effects were transitory and none required treatment.

Table IV. Summary of relative potency analyses

	Relative potency	*95% Confidence interval*	λ	*Common slope*	*Preparations (caffeine effect)*	*Parallelism*
PID						
Total score, 8-hr sum	2.89	0.00,*	1.13	3.361	7.702†	0.129
Total score, 6-hr sum	2.60	1.27,‡	1.04	3.960§	7.369†	0.101
Total score, 4-hr sum	2.64	1.28‡	1.05	3.927§	7.549†	0.000
Peak score	2.41	1.32,123	0.86	5.845§	9.165†	0.472
Pain relief						
Total score, 8-hr sum	2.72	1.42,‡	0.90	5.284§	10.76†	1.071
Total score, 6-hr sum	2.35	1.35, 29	0.78	7.128†	10.51†	0.688
Total score, 4-hr sum	2.45	1.40, 35	0.78	7.106†	11.64†	0.031
Peak score	2.84	1.43,‡	0.94	4.932§	10.92†	0.001
Hours of 50% relief	3.31	0.00,*	1.43	2.123	6.21§	0.422
Overall evaluation	3.43	0.00,*	1.35	2.377	7.368†	0.000

F values are presented for common slope, preparations, and parallelism.
PID, Pain intensity difference.
*Estimate equals infinity.
†$p < 0.01$ ($F = 6.73$).
‡Estimate is greater than 1000.
§$p < 0.05$ ($F = 3.87$).

Table V. Adverse effects reported by patients

Adverse effects (n)	*Ibuprofen, 50 mg (n = 63)*	*Ibuprofen, 100 mg (n = 62)*	*Ibuprofen, 200 mg (n = 60)*	*Ibuprofen, 100 mg, + caffeine, 100 mg (n = 58)*	*Ibuprofen, 200 mg, + caffeine, 100 mg (n = 58)*	*Placebo (n = 61)*	*Total (N = 362)*
Chills	—	—	—	— (1)	—	—	— (1)
Depression	—	—	—	—	—(1)	—	— (1)
Dizziness	— (3)	1	—(1)	4 (3)	2 (1)	1 (5)	8 (13)
Earache	1	—	—	—	—	—	1
Fainting	1	—	—	—	—	—	1
Fever	— (1)	—	—	—	—	—	— (1)
Groggy	—	—	—	— (1)	—	—	— (1)
Headache	3	2 (1)	2	3 (1)	2	4	16 (2)
Heartburn	—	—	—	—	1	—	1
Insomnia	1	—	—(1)	1	—(1)	—	2 (2)
Itching	— (1)	—	—(1)	—	—(1)	—	— (3)
Nausea, queasy	1 (5)	— (4)	—(1)	1 (3)	2 (1)	2 (7)	6 (21)
Nervous, shaky	2	—	1 (1)	2 (1)	2 (1)	—	7 (3)
Restlessness	1	—	—	1	—	—	2
Ringing in ears	1	—	—	—	—	—	1
Sleepiness, drowsiness	3 (1)	2 (4)	1 (1)	1	—(1)	— (6)	7 (13)
Slurred speech	—	—	—	—	—	— (1)	— (1)
Sore throat	—	—	—	1	—	—	1
Stomach pain	—	—	—	—	—	1	1
Sweating	— (1)	—	—	—	—	—	— (1)
Tired	— (1)	1	—(1)	—	—	—	1 (2)
Vomiting	1 (2)	— (1)	2	— (3)	—	— (3)	3 (9)
Weakness in legs	—	—	—	1	—	—	1
No. pts. reporting adverse effects	10 (8)	5 (9)	6 (5)	12 (9)	8 (4)	8 (15)	49 (50)
No. adverse effects reported	15 (15)	6 (10)	6 (7)	15 (13)	9 (7)	8 (22)	59 (74)

Excludes adverse effects that occurred more than 12 hours after taking dose 1 of the study medication.
Numbers in parentheses indicate adverse effects reported after remedication with the backup analgesic.

DISCUSSION

This study was designed to examine several aspects of the potential adjuvant effect of caffeine on ibuprofen analgesia. Most pairwise comparisons that used the usual summary indexes of analgesic effect showed a significant superiority of the combination over the respective dose of ibuprofen alone (Table II). Likewise, pairwise comparisons of hourly analgesic scores demonstrate that the combination is significantly superior to ibuprofen in terms of onset and duration of action (Table III).

A relative potency assay was incorporated into the study design to provide a quantitative measure of the contribution of caffeine to the analgesia produced by ibuprofen. The criteria for validity in a relative potency assay are that the orthogonal contrast for common drug slope should be significant, and the contrast for deviation from parallelism of the dose-response curves should not be significant. In the conventional analgesic relative potency assay comparing two different single-entity drugs, it is also desirable that the "preparations" contrast (i.e., the difference in mean effect level of the test drug and the standard) should not be significant. When the relative potency assay is used to evaluate the analgesic adjuvancy of caffeine, however, this contrast takes on a different meaning. It is this contrast in the analysis that determines whether a significant adjuvant effect of caffeine has been demonstrated.

Another way of demonstrating a significant contribution of caffeine is to determine whether the 95% confidence interval of the relative potency estimate excludes 1.00. That is, if the lower 95% confidence interval falls above 1.00, the combination has been shown to be significantly more potent than ibuprofen alone, and the analgesic adjuvancy of caffeine has been demonstrated. Seven of the eight assays for pain intensity difference and pain relief in Table IV were valid in terms of the above criteria, and relative potency estimates for these ranged from 2.4 to 2.8. This means that approximately two and one half times the dose of ibuprofen alone must be administered to equal the analgesic effect of ibuprofen plus 100 mg caffeine.

We have demonstrated an unequivocal analgesic adjuvant effect for 100 mg caffeine in combination with ibuprofen in oral surgery pain. Laska et al.[6,7] have previously demonstrated an adjuvant effect of caffeine, 65 to 260 mg, combined with acetaminophen or an acetaminophen-aspirin mixture in postpartum pain, and Migliardi[26] has confirmed the adjuvancy of 130 mg caffeine in combination with an acetaminophen-aspirin mixture in tension headache and oral surgery pain and in combination with acetaminophen in tension headache. Schachtel[27] has recently demonstrated the adjuvancy of 65 mg caffeine in combination with aspirin in both tension headache and sore throat pain.

The analgesic adjuvancy of caffeine obviously extends across many pain models and to combinations with a variety of analgesics, but little information exists to explain the mechanism of this effect. The phenomenon is referred to as "adjuvancy" because efforts to demonstrate an analgesic effect for caffeine alone in controlled clinical analgesic studies have uniformly yielded negative results.[28] Antinociceptive and anti-inflammatory assays of caffeine administered alone to rodents have yielded conflicting results, although several of these studies have demonstrated enhancement of activity when caffeine was combined with NSAIDs.[9,29-31] Although many of the pharmacologic effects of caffeine are apparently mediated through the blockade of adenosine receptors,[32] in animal models adenosine and related agonists exert an antinociceptive effect and this effect is antagonized by caffeine.[33,34] Likewise, an enhancement of analgesic absorption from the gastrointestinal tract does not appear to be a plausable explanation for the adjuvant effect, because caffeine does not enhance the absorption of aspirin[9] or acetaminophen[30] in rats and has very little effect on the absorption of ibuprofen in humans (Sorrentino J. Personal communication, January 1990).

Whatever the mechanism of the analgesic adjuvancy of caffeine, this effect may have the potential for enhancing the efficacy of an NSAID above its usual analgesic ceiling. Ibuprofen exhibits an analgesic ceiling at a single dose of about 400 mg, but Bloomfield et al.[35] have demonstrated the significantly greater analgesic efficacy of a combination of 400 mg ibuprofen with 200 mg caffeine in oral surgery pain.

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