Efficacy of Low Dose Combination Analgesics: Acetaminophen/Codeine, Aspirin/Butalbital/Caffeine/ Codeine, and Placebo in Oral Surgery Pain

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Summary

A double-blind, randomized, single-dose study was performed to compare the efficacy and safety of two commonly prescribed combination analgesic products to placebo. The combinations were acetaminophen 300 mg/codeine 30 mg†, and aspirin 325 mg/butalbital 50 mg/caffeine 40 mg/codeine 30 mg††. One hundred twenty-three (123) oral surgery outpatients took study medications when their pain became moderate to severe and recorded the levels of pain intensity, pain relief, anxiety and relaxation at 30 minutes and hourly for 6 hours after dosing. Remedication was permitted if study medications did not provide adequate pain relief. Time to remedication, and the number of observations with 50% or better relief, were noted as were any side effects. An overall evaluation was obtained from each patient. Results of the study showed that the aspirin/butalbital/caffeine/codeine combination was significantly more effective than placebo for total pain relief, peak relief and global evaluation. While the acetaminophen/codeine combination was numerically superior to placebo, it achieved statistical significance only for global evaluation. The aspirin/butalbital/caffeine/codeine combination was numerically superior to acetaminophen/codeine for every measure of analgesic efficacy but the differences did not achieve statistical significance. Both active treatment groups experienced significantly less total anxiety than did the placebo group. Only 11 patients reported mild, transient adverse effects; the most common was drowsiness. The adverse effects occurred equally among the three treatment groups. In this study, the aspirin/butalbital/caffeine/codeine combination was significantly superior to placebo and somewhat better than acetaminophen/codeine.

Introduction

Controlled trials in several different pain models have concluded that aspirin and acetaminophen are equipotent analgesic agents.[1-2] Numerous clinical trials have shown that the ideal analgesic dose range for these two agents is between 600 to 1000 mg. In spite of these findings, fixed dose combinations containing aspirin or acetaminophen are commonly prescribed as one to two tablets which usually provides 300-650 mg.

Aspirin and acetaminophen are peripherally-acting analgesics which presumably act by blocking the cyclooxygenase enzyme system preventing the formation of prostaglandins and similar compounds at the site of injury. Codeine, a centrally-acting opioid, can have additive analgesic effects when combined with peripherally-acting agents.[3]

Butalbital (allyl isobutyl barbituric acid) is a sedative with a duration of action of approximately 6 hours. In tension headache and postoperative pain, butalbital has been shown to provide some improvement in analgesia.[4] Caffeine has been added to analgesic combinations for many years and is reported to enhance analgesia of acetaminophen and aspirin combinations.[5,6]

The purpose of this study was to compare the relative efficacy and safety of two popular combination analgesics at the low dose (one tablet) level versus placebo. The doses of active drugs used were aspirin 325 mg/butalbital 50 mg/caffeine 40 mg/ codeine 30 mg and acetaminophen 300 mg/codeine 30 mg.

Patients and Methods

This double-blind, parallel group, single-dose study was designed to include three treatment groups with a minimum of 40 patients per group. All

Supported by a grant from Sandoz Pharmaceuticals Corp.

Accepted for publication January 21, 1986.

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†Tylenol® with Codeine No. 3 (McNeilab, Inc.)
††Fiorinal® with Codeine No. 3 provided by Sandoz Pharmaceuticals

patients were at least 18 years of age and provided informed consent in writing prior to participation in the study. Nursing mothers and women who were pregnant or of child-bearing potential were excluded from the study, as were patients with a known hypersensitivity to any of the study medications. No concomitant analgesics or other agents which could confound the quantification of analgesia were permitted during the study or within 4 hours preceding the study. All surgery was performed under local anesthesia and sedation with diazepam (Valium®) and/or methohexital (Brevital®). No narcotics were permitted.

Of the 137 patients who entered the study, 123 were acceptable for the efficacy analysis. Fourteen patients either did not medicate, were lost to follow-up or provided uninterpretable results. Demographic characteristics and baseline pain intensities of the study groups are shown in Table 1. Data on the surgical characteristics and the time elapsed before study medications were taken are shown in Table 2. The treatment groups differed significantly in only one of the demographic and surgical characteristics — duration of surgery. However, the numerical differences were small and, in all likelihood, did not bias the efficacy data.

Patients who qualified for the study were assigned randomly to a treatment group to receive a single dose of either placebo, acetaminophen 300 mg plus codeine 30 mg* or aspirin 325 mg/butalbital 50 mg/caffeine 40 mg plus codeine 30 mg**. The study medications were contained in identically appearing capsules.

TABLE 1. Patient Demographic Characteristics and Baseline Pain Intensity

Variable	Placebo	Acetaminophen + Codeine	ASA/Butal/ Caffeine + Codeine
No. of patients	41	39	43
Gender - M/F	16/25	13/26	17/26
Race - W/B/other	40/1/0	35/4/0	38/4/1
Mean age (yrs.)	23.0	24.1	24.4
Mean weight (lbs.)	143.0	142.0	146.2
Mean baseline Pain intensity[a]	2.0	2.0	2.0

[a]Severe = 3, moderate = 2, slight = 1, none = 0

TABLE 2. Patients' Surgical Characteristics

Variable	Placebo (n=41)	Acetaminophen + Codeine (n=39)	ASA/Butal/ Caffeine + Codeine (n=43)
No. of extractions	3.1	3.5	3.3
Duration of surgery (min.)	39.9	45.0*	45.1*
Time to medication after procedure (min.)	109.2	108.4	112.5

Mean values
*p <.05 significantly greater than placebo.

Each patient was instructed by a trained research assistant who explained the study design and the evaluation procedures. Before patients left the office they were instructed in the use of the take-home questionnaire and were told to take the study medication when their pain intensity was enough to require an analgesic. The questionnaire provided space for recording the severity of the initial pain and the time the medication was taken. At 30 minutes, and hourly for 6 hours post-administration, the patient recorded pain intensity as severe (3), moderate (2), mild (1) or none (0); pain relief as complete (4), a lot (3), some (2), a little (1) or none (0); whether the starting pain was half gone, yes or no; anxiety level as very high (3), moderate (2), mild (1) or none (0); relaxation as none (0), some (1), a lot (2), or complete (3); and what, if any, side effects occurred.

Patients were permitted to terminate their participation in the study and remedicate with a standard analgesic of the surgeon's choice if the study drug did not provide adequate relief. Patients were encouraged to wait at least 60 minutes before remedicating with the rescue analgesic. For patients remedicating prior to the final evaluation, pain intensity, pain relief, anxiety and relaxation scores at the time of remedication were carried through for the remaining observations. At the conclusion of the 6 hour evaluation period, or at the time of remedication, the patient recorded an overall evaluation of the study medication as excellent (4), very good (3), good (2), fair (1) or poor (0).

Statistical Analysis

The analysis was designed to delineate any statistically significant differences among the treatment groups in terms of the primary indices of analgesic efficacy and safety. All efficacy scores were derived from the patients' responses recorded on the diary form. Hourly PID values were calculated by subtracting the pain intensity scores at each observation from the baseline pain score. SPID was calculated by summing the hourly PID scores.

The One-Way Analysis of Variance[7] was used to analyze Sum of Pain Intensity Difference (SPID), Peak Pain Intensity Difference, Total Pain Relief (TOTPAR), Peak Pain Relief, Sum of Observations with Pain Half Gone, Total Anxiety, Peak Anxiety, Total Relaxation, Peak Relaxation, Overall Evaluation and Time to Remedication with an Alternate Analgesic.

*Prepared from the product Tylenol® with Codeine No. 3 (McNeilab, Inc.), obtained from commercial sources.

**Prepared from the product Fiorinal® with Codeine No. 3, obtained from Sandoz Pharmaceuticals.

For each efficacy measure, an overall F-test was performed. If the F-test was significant ($p<.10$), then pairwise contrasts were performed using both the two-sided least square difference with 1 degree of freedom and the Duncan's New Multiple Range Test[8]. All possible pairs of treatments were compared.

Safety data and nominal patient characteristics were analyzed using the Chi Square Test.[7]

Results

The analysis of variance was significant ($p<0.1$) for Total Pain Relief (TOTPAR), Peak Relief, Overall Evaluation and Total Anxiety (Tables 3 and 4). For all of these efficacy measures, the aspirin/butalbital/caffeine plus codeine combination was significantly more effective than placebo ($p<.05$). Acetaminophen plus codeine was significantly more effective than placebo only for Overall Evaluation and Total Anxiety ($p<.05$). There were no statistically significant differences between the two active treatments.

TABLE 3. Mean Measures of Analgesic Efficacy

Variable	Placebo (n=41)	Acetaminophen + Codeine (n=39)	ASA/Butal/ Caffeine + Codeine (n=43)
SPID	−0.90±0.63	0.33±0.75	1.21±0.74
Peak PID	0.44±0.12	0.64±0.12	0.77±0.13
TOTPAR	5.10±0.90	7.82±1.08	8.37+1.08*
Peak relief	1.32±0.20	1.72±0.21	2.02±0.23*
No. observ. with pain 1/2 gone	1.05±0.27	1.95±0.39	1.88±0.33
Time to remedicate (min)	179.7±16.2	204.9±16.6	214.5±15.2
Global	0.71±0.16	1.33±0.22*	1.47±0.20*

Mean values ± S.E.
*p <.05, superior to placebo, Duncan's Multiple Range Test.

TABLE 4. Mean Measures of Anxiety and Relaxation

Variable	PI Codeine (n=41)	Acetaminophen + Codeine (n=39)	ASA/Butal/ Caffeine + Codeine (n=43)
Total anxiety	10.5±1.0	7.4±1.1*	7.5±1.0*
Total relaxation	7.3±1.0	9.5±0.9	9.1±0.8

Mean ± S.E.
*p <.05, superior to placebo, Duncan's Multiple Range Test.

Figures 1 and 2 present the time action curves for hourly pain intensity difference and pain relief scores. These curves illustrate that the low doses, while being somewhat more effective than placebo, are not in the optimal dose range for this type of pain. By the third and fourth hour, mean pain intensity had returned to or exceeded baseline pain.

The mean anxiety scores reported by patients over the 6-hour study period are presented in Figure 3.

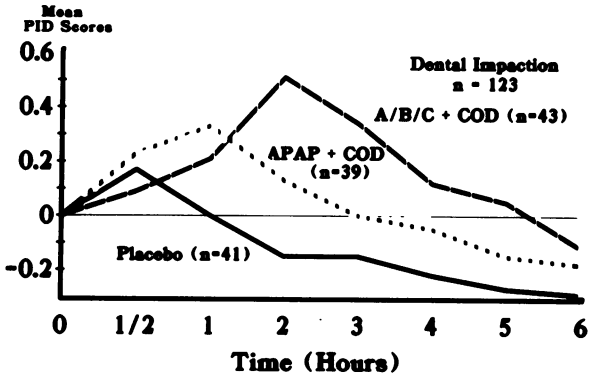

Fig. 1—Time-action curves for mean hourly Pain Intensity Differences. A/B/C + COD = Aspirin 325 mg, Butalbital 50 mg, Caffeine 40 mg plus codeine 30 mg (Fiorinal #3); APAP + COD = acetaminophen 300 mg plus codeine 30 mg (Tylenol #3).

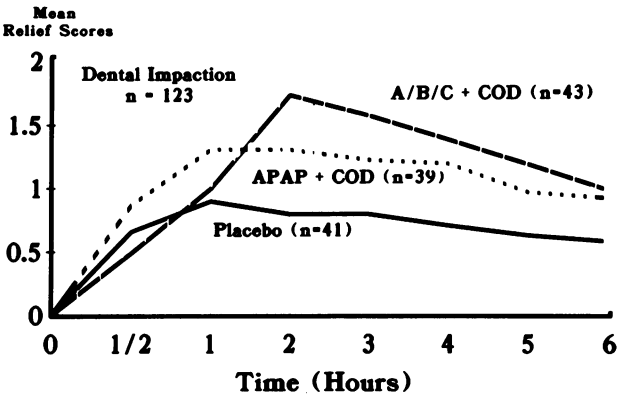

Fig. 2—Time-action curves for mean hourly pain relief scores. A/B/C + COD = Aspirin 325 mg, Butalbital 50 mg, Caffeine 40 mg plus codeine 30 mg (Fiorinal #3); APAP + COD = acetaminophen 300 mg plus codeine 30 mg (Tylenol #3).

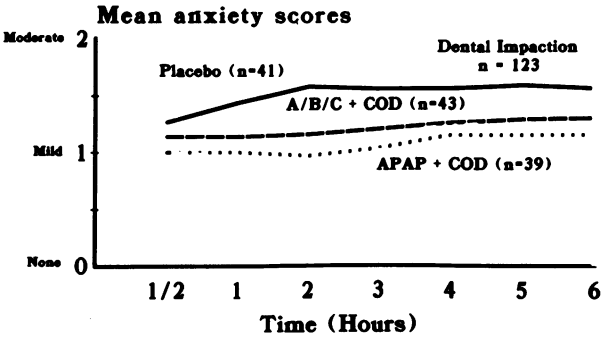

Fig. 3—Time-action curves for mean hourly anxiety scores. A/B/C + COD = Aspirin 325 mg, Butalbital 50 mg, Caffeine 40 mg plus codeine 30 mg (Fiorinal #3); APAP + COD = acetaminophen 300 mg plus codeine 30 mg (Tylenol #3).

Anxiety worsened over time only in the placebo group. This probably was related to the worsening pain experienced by this group. Even in this relatively low-anxiety study sample, the anxiety measure separated active treatments from placebo.

A total of 11 patients reported 12 mild, transient adverse effects (Table 5). Drowsiness was the most common adverse effect (6 reports) followed by nausea (3). None of these required additional treatment and no patients withdrew from the study because of adverse effects.

TABLE 5. Adverse Effects

	Placebo (n=41)	Acetaminophen + Codeine (n=39)	ASA/Butal/Caffeine/ + Codeine (n=43)	Total
Sleepy (drowsy)	2	1	3	6
Nausea	1	1	1	3
Dizzy	0	0	1	1
Lightheaded	0	1	0	1
Headache (neckache)	1	0	0	1
Total incidence	4	3	5	12
Total patients	4	2	5	11

Discussion

The present study did demonstrate modest assay sensitivity. Pain relief scores tended to provide more sensitive measures of analgesic efficacy than did pain intensity differences. Figure 4 illustrates the relationship between the derived measures for Peak PID and Peak Relief. While the trends were similar for both measures, only the relief measure achieved the traditional $p<.05$ level of significance. This is consistent with prior studies reported by our group[9,10] and is probably related to the 5 point scale for relief as compared to the 4 point scale for pain intensity.

It is striking that in the present outpatient study where patients returned home soon after surgery, the state anxiety remained relatively low in spite of having significant pain. Only the placebo group's anxiety score worsened somewhat over time. This contrasts dramatically with postoperative dental patients we have studied in an inpatient clinic setting.[11] In that study, postoperative state anxiety worsened considerably if not treated. These results suggest that postoperative anxiety is largely affected by setting as well as pharmacologic and non-pharmacologic treatment regimens.

Both low-dose combinations provided marginally effective analgesia at this dose level. Both active treatments were, however, more effective than placebo. For most efficacy parameters, the aspirin/butalbital/caffeine plus codeine combination appeared somewhat more effective than the acetaminophen-codeine combination. Whether the slight improvement in analgesia is therapeutically exploitable or whether it can be attributed to a caffeine or butalbital effect cannot be answered by the present study design.

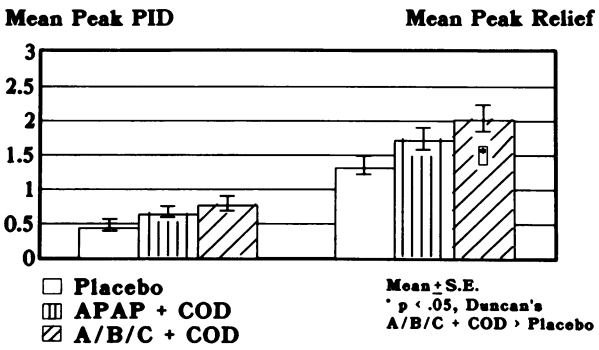

Fig. 4—Relationship between peak pain intensity differences and peak pain relief scores. A/B/C + COD = Aspirin 325 mg, Butalbital 50 mg, Caffeine 40 mg plus codeine 30 mg (Fiorinal #3); APAP + COD = acetaminophen 300 mg plus codeine 30 mg (Tylenol #3).

It is feasible that the low dose (single tablet or capsule) of fixed combination analgesics would be more efficacious in patients undergoing less extensive surgery. However, after bony impaction surgery, higher doses of these analgesics are required to produce optimal pain relief.

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