Double-Blind Comparison of an Acetaminophen-Codeine-Caffeine Combination in Oral Surgery Pain

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Summary

The purpose of this paper was to evaluate the contribution of low dosages of codeine and caffeine when added to acetaminophen. Subjects were dental outpatients undergoing oral surgery involving bone removal. This was a single-dose, parallel group, double-blind assay evaluting 99 subjects. The treatment groups were acetaminophen 1000 mg, acetaminophen 1000 mg + codeine 16 mg + caffeine 30 mg and placebo. The results demonstrated that both active treatments were superior to placebo. Overall, the combination was slightly better than acetaminophen alone. The advantage of the combination appeared more evident in the "severe" baseline pain group.

Introduction

Combinations containing acetaminophen and codeine are among the most widely prescribed of all pain relieving drugs.[1] This study was designed to determine the relative efficacy of an acetaminophen-codeine-caffeine combination compared to acetaminophen alone and placebo.

The oral surgery pain model was chosen because of its proven assay sensitivity in evaluating these types of drugs.[2,3]

Methods

This was a double-blind, single-dose parallel group study with patients randomly allocated to the possible treatment groups. The three treatment groups were placebo, acetaminophen 1000 mg, and the combination of acetaminophen 1000 mg, codeine 16 mg and caffeine 30 mg. The randomization procedure was weighted so that approximately one-half the number of patients would receive placebo as would receive the other two treatments. In order to qualify, patients had to be at least 16 years of age, be in good general health, have no contraindications to any study medication and sign an informed consent. The surgery consisted of an oral surgical procedure involving bone removal that, in the opinion of the surgeon, could have resulted in moderate to severe post-surgical pain. Both simple extractions and major dental impaction surgery cases were excluded. The study was conducted at a single site by one surgeon.

Before surgery and again before leaving the office, patients were instructed by the research assistant on the procedures of the study. A single-dose of study medication was taken for moderate to severe post-surgical pain and the baseline pain intensity was recorded on a diary form. After medicating, patients recorded responses hourly for six hours on their pain intensity, pain relief, and side effects. After the last observation (either at hour 6 or before if the patient remedicated), a global evaluation was recorded. Figure 1 shows the diary form.

Patients were permitted to terminate their participation in the study and remedicate with a standard analgesic if the study drug did not provide adequate relief. Patients had to fill in at least the first hourly observation to be included in the efficacy analysis. For patients remedicating prior to the final hour, the scores at the time of remedication were carried through for the remaining observations.

The primary measures of efficacy were total pain relief (TOTPAR), sum of pain intensity differences (SPID), sum of observations with pain half relieved, overall evaluation and time to remedication. These data were analyzed using one-way ANOVA in conjunction with least square difference pairwise contrasts.

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A more detailed explanation of the study design and statistical analysis has been presented elsewhere.[4]

Results

Of the 112 patients entered into the study, 99 were included in the efficacy analysis. Of the 13 not included, 6 were in the combination group, 6 in the acetaminophen group and 1 in the placebo group. Of the 13, 6 patients never required analgesic medication, 3 fell asleep and the other 4 were various protocol violations.

The mean ages for the treatment groups ranged between 24 and 26, there was a slight majority of females and all except one patient was Caucasian. There were no significant differences among the treatment groups for height, weight, number of extractions, surgeon's trauma rating, length of the surgical procedure or time to medication after surgery. The mean length of surgery ranged from 14 to 19 minutes for the treatment groups and the mean time to medication was approximately 3 hours (Table 1).

The majority of patients chose to medicate with moderate baseline pain. Only 26 patients reported severe baseline pain. Due to this small number, the statistical analysis was not blocked for baseline pain.

For every measure of analgesic efficacy both active study medications were substantially better than placebo ($p<0.05$). There were no significant differences between acetaminophen alone and the combination (Table 2, Figure 2).

However, the tabulated data looked much different when blocked for baseline pain. Although the group sizes were relatively small, the patients with severe

COMPLETE THIS WHEN YOU TAKE THE STUDY MEDICATION

My starting pain is: ☐ **MODERATE** ☐ **SEVERE (Check one)**

I took drug at: TIME: ______ ☐ **A.M.** ☐ **P.M. DATE** __/__/__

PLEASE ANSWER THE FOLLOWING QUESTIONS HOURLY AFTER TAKING THE STUDY MEDICATION ↓	1 HOUR AFTER MEDICATING TIME: ☐ AM ___:___ ☐ PM	2 HOURS AFTER MEDICATING TIME: ☐ AM ___:___ ☐ PM	3 HOURS AFTER MEDICATING TIME: ☐ AM ___:___ ☐ PM	4 HOURS AFTER MEDICATING TIME: ☐ AM ___:___ ☐ PM	6 HOURS AFTER MEDICATING TIME: ☐ AM ___:___ ☐ PM	8 HOURS AFTER MEDICATING TIME: ☐ AM ___:___ ☐ PM
HOW MUCH PAIN DO YOU HAVE AT THIS TIME? ➡	☐ SEVERE ☐ MODERATE ☐ SLIGHT ☐ NONE	☐ SEVERE ☐ MODERATE ☐ SLIGHT ☐ NONE	☐ SEVERE ☐ MODERATE ☐ SLIGHT ☐ NONE	☐ SEVERE ☐ MODERATE ☐ SLIGHT ☐ NONE	☐ SEVERE ☐ MODERATE ☐ SLIGHT ☐ NONE	☐ SEVERE ☐ MODERATE ☐ SLIGHT ☐ NONE
HOW MUCH RELIEF DO YOU HAVE FROM THE STARTING PAIN AT THIS TIME? ➡	☐ COMPLETE ☐ A LOT ☐ SOME ☐ A LITTLE ☐ NONE	☐ COMPLETE ☐ A LOT ☐ SOME ☐ A LITTLE ☐ NONE	☐ COMPLETE ☐ A LOT ☐ SOME ☐ A LITTLE ☐ NONE	☐ COMPLETE ☐ A LOT ☐ SOME ☐ A LITTLE ☐ NONE	☐ COMPLETE ☐ A LOT ☐ SOME ☐ A LITTLE ☐ NONE	☐ COMPLETE ☐ A LOT ☐ SOME ☐ A LITTLE ☐ NONE
IS YOUR STARTING PAIN AT LEAST HALF GONE AT THIS TIME? ➡	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
WERE THERE ANY SIDE EFFECTS FROM THE STUDY MEDICATION? ➡	☐ NO ☐ YES IF YES, WHAT?	☐ NO ☐ YES IF YES, WHAT?	☐ NO ☐ YES IF YES, WHAT?	☐ NO ☐ YES IF YES, WHAT?	☐ NO ☐ YES IF YES, WHAT?	☐ NO ☐ YES IF YES, WHAT?

OVERALL IMPRESSION

Answer after the last hourly observation

How would you rate this medication? Time: ______ ☐ AM ☐ PM

EXCELLENT ☐ VERY GOOD ☐ GOOD ☐ FAIR ☐ POOR ☐

FOR EXTRA PAIN MEDICATION ONLY

1. DID YOU TAKE ANY OF THE EXTRA PAIN MEDICATION PROVIDED? ☐ NO ☐ YES
2. WHEN DID YOU TAKE THE FIRST DOSE OF THE EXTRA PAIN MEDICATION? TIME: ______ ☐ AM ☐ PM DATE______
3. WAS THE EXTRA PAIN MEDICATION ☐ SATISFACTORY ☐ UNSATISFACTORY
4. TOTAL NUMBER OF TABLETS TAKEN OF EXTRA PAIN MEDICATION. ______

TABLE 1. Summary of Demographic Data

	Placebo	Acetaminophen 1000 mg	Acetaminophen 1000 mg-codeine 16 mg-& caffeine 30 mg
Age	24.3	26.6	26.6
Height (inches)	67.5	66.0	65.8
Weight (pounds)	155.6	139.9	142.7
# Extractions	2.3	2.4	2.0
Trauma rating	2.5	2.3	2.3
Length Procedure (min.)	18.9	16.5	14.4
Time to medication	175.6	173.1	173.9
Baseline Pain			
Mean	2.1	2.2	2.4
Moderate	19	30	24
Severe	3	8	15
Sample size	22	38	39

TABLE 2. Summary of Analgesic Efficacy Data

	Placebo	Acetaminophen 1000 mg	Acetaminophen 1000 mg-codeine 16 mg & caffeine 30 mg
SPID	—0.64	3.89	4.26
TOTPAR	4.27	11.55	10.95
Sum pain half gone	0.82	2.97	2.82
Overall impression	0.77	1.87	2.03
Time to remedication (minutes)	212.6	281.8	277.3
Sample size	22	38	39

baseline pain demonstrated much greater assay sensitivity. For these data, the combination of acetaminophen-codeine-caffeine was substantially more effective than acetaminophen alone which, in turn, was more effective than placebo. For SPID and TOTPAR, the scores for the combination were approximately double those for acetaminophen; for sum of observations with pain half gone, there was over a three fold difference and the mean time to remedication for the combination was over two hours longer than for acetaminophen alone (Table 3, Figure 3).

A total of 15 patients reported 16 side effects. Of these 16 side effects, 12 occurred in the acetaminophen group and 4 in the combination group. Over half of the reported side effects were "drowsiness" and there were 2 reports of nausea. No other side effects occurred more than once and no side effect was considered serious.

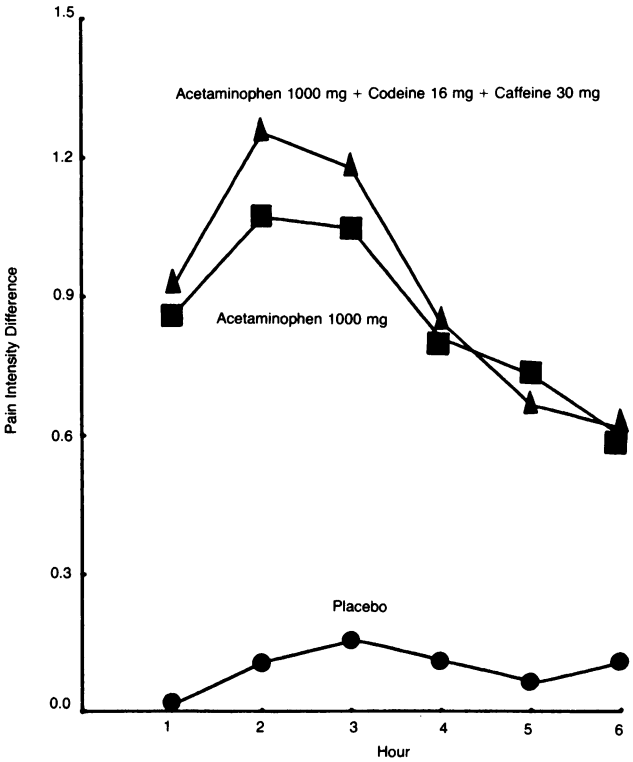

Fig. 2 — Pain Intensity Difference scores are plotted against time in hours for placebo (n=22), acetaminophen 1000 mg (n=38) and acetaminophen 1000 mg + codeine 16 mg + caffeine 30 mg (n=39).

TABLE 3. Summary of Data For Severe Baseline Pain Subgroup

	Placebo	Acetaminophen 1000 mg	Acetaminophen 1000 mg-codeine 16 mg-& caffeine 30 mg
SPID	0.33	3.38	6.26
TOTPAR	0.33	4.25	9.73
Sum pain half gone	0.00	0.75	2.53
Overall impression	0.00	0.88	1.53
Time to remedication (minutes)	135.0	108.0	230.0
Sample size	3	8	15

Discussion

Combination analgesics are a popular and useful part of pain control therapy. It is well established that centrally and peripherally acting analgesics have additive effects.[4-6] The purpose of this study was to determine the relative efficacy of an acetaminophen-codeine-caffeine combination compared to acetaminophen alone.

The overall results indicated that both active treatments were superior to placebo but not different from

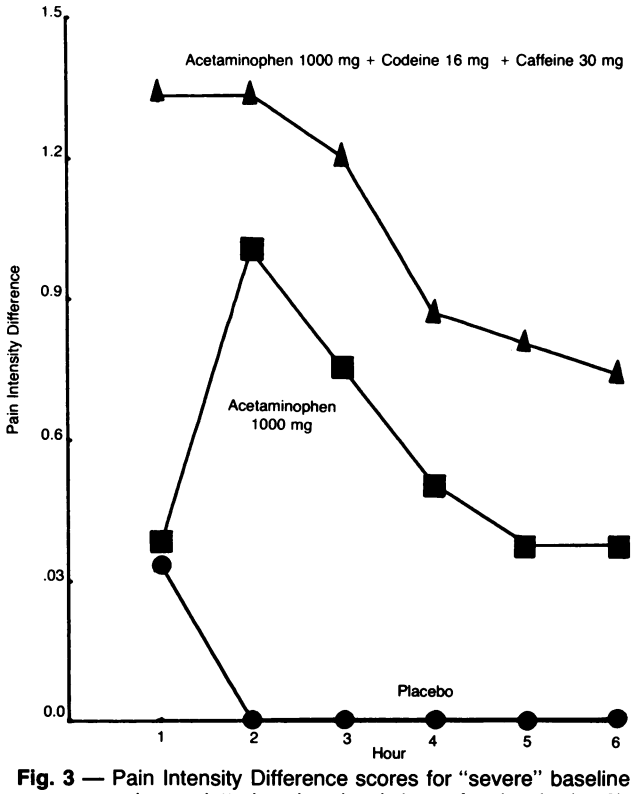

Fig. 3 — Pain Intensity Difference scores for "severe" baseline pain are plotted against time in hours for placebo (n=3), acetaminophen 1000 mg (n=8) and acetaminophen 1000 mg + codeine 16 mg + caffeine 30 mg (n=15).

each other. The question then became whether the drugs were pharmacologically similar or whether the model lacked assay sensitivity. To answer this question, the data were blocked for initial baseline pain. When only the more severe group was tabulated, it appeared that there was much greater assay sensitivity and that the combination was substantially more effective than acetaminophen alone. Unfortunately, the sample size was not very large and no statistical analysis was performed on this subgroup. However, it was obvious that by increasing the post-surgical pain, the assay sensitivity was enhanced. In retrospect, the surgery should have been restricted to more extensive surgical procedures rather than general oral surgery involving bone removal.

The results indicate that for mild to moderate pain, acetaminophen 1000 mg is a very effective analgesic; for more severe pain, the acetaminophen 1000 mg-codeine 16 mg-caffeine 30 mg combination is the more effective analgesic agent.

Further studies using more painful surgical procedures should be performed to reinforce this conclusion.

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