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METHODOLOGICAL CONSIDERATIONS IN THE EVALUATION OF ANALGESIC COMBINATIONS: ACETAMINOPHEN (PARACETAMOL) AND HYDROCODONE IN POSTPARTUM PAIN

WILLIAM T. BEAVER & DIANE McMILLAN

Departments of Pharmacology and Anaesthesia, Georgetown University Schools of Medicine and Dentistry, Washington DC 20007

1 In a double-blind study, 108 postpartum patients received single oral doses of either placebo, acetaminophen (paracetamol) 1000 mg, hydrocodone 10 mg, the combination of acetaminophen plus hydrocodone, or codeine 60 mg.

2 In the 2×2 factorial analysis, both the acetaminophen and hydrocodone effects were statistically significant, whereas the interaction contrast was not. This indicates that the analgesic effect of the combination represents the additive effect of its constituents and is consistent with the assumption that these constituents are producing analgesia by different mechanisms.

3 Although significantly superior to placebo, codeine seemed to be inferior to the other treatments.

4 Compared with placebo, both codeine and hydrocodone (centrally acting narcotics) seemed relatively more effective in uterine cramp than episiotomy pain; the reverse seemed true with acetaminophen (a peripherally acting analgesic).

5 Some methodological implications for the evaluation of analgesic combinations are discussed.

Introduction

ORALLY EFFECTIVE narcotics such as codeine, dihydrocodeine, oxycodone and propoxyphene are frequently prescribed in combination with antipyretic-analgesics such as aspirin, acetaminophen (paracetamol) or APC. The theoretical rationale behind such combinations is twofold. Efficacy might be enhanced by the additive effect of two analgesics that relieve pain by different mechanisms, and adverse effects might be reduced by prescribing reduced doses of two analgesics with different side-effects rather than an equieffective dose of a single agent (Beaver, 1966; 1975). Considering the diversity and huge sales volume of these combination products, however, there have been relatively few controlled clinical trials examining the contribution of each ingredient to the analgesic effect of their combination.

A classic factorial study of this sort was carried out by Houde, Wallenstein & Beaver (1965) in patients with cancer, comparing a placebo, aspirin 600 mg, codeine 32 mg, and the combination of aspirin 600 mg with codeine 32 mg (Figure 1). This study demonstrated a statistically significant effect for both the aspirin and codeine treatments. The interaction between the two drugs was not significant, which indicates that the analgesic effect of the combination represented the additive effect of its constituents. Although the mean effect of codeine 32 mg was slightly less than that of aspirin 600 mg, this difference was not statistically significant.

About seven years ago, Dr Stephen Cooper and I developed a method for evaluating mild oral analgesics in oral surgery outpatients. For a standardization study, we decided to try to replicate Houde's factorial study (1965) of codeine and aspirin. The results of our study in outpatients with extractions of impacted third molars were unanticipated (Figure 2) (Cooper & Beaver, 1976). Although the study model had sufficient sensitivity to demonstrate the analgesic efficacy of aspirin ($P<0.01$), the performance of codeine 30 mg was only slightly better than placebo, and this difference was not statistically significant for any measure of analgesic effect.

As the surgical procedure involved in the removal of an impacted third molar results in substantial tissue oedema and swelling of the jaw, we reasoned that an agent such as aspirin with associated anti-inflammatory activity might be expected to be a more effective analgesic in this model than a centrally acting narcotic analgesic. In addition, codeine 30 mg might constitute a marginally effective dose. As acetaminophen has often been said to be devoid of anti-inflammatory activity — a misconception that has subsequently been demonstrated to be erroneous

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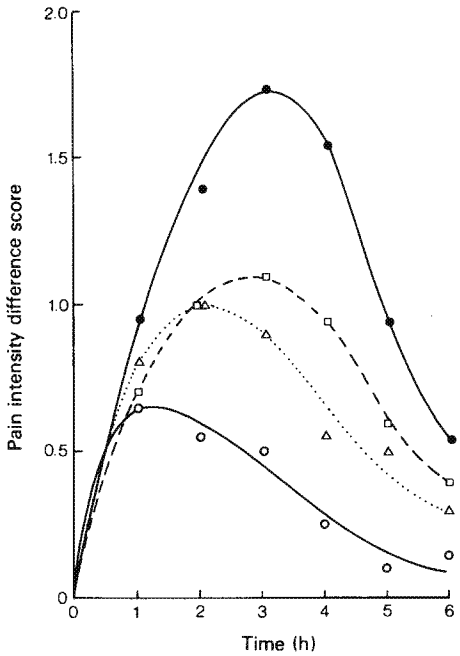

Figure 1 Time-effect curves for placebo (○), aspirin 600 mg (□), codeine 32 mg (△), and the combination of aspirin 600 mg plus codeine 32 mg (●). Pain intensity difference scores (ordinate) are plotted against time in hours (abscissa). Treatments were administered in randomized order using a complete cross-over design to 11 patients with cancer pain. Nine of these patients repeated the cross-over twice (Houde *et al.*, 1965).

(Skjelbred, Album & Lokken, 1977; Skjelbred & Løkken, 1979; Vinegar, Truax & Selph, 1976; Glenn, Bowman & Rohloff, 1977) — a second study was carried out replacing the aspirin with acetaminophen and increasing the codeine dose to 60 mg. The results of this study were consistent with those of the first (Figure 3) (Cooper & Beaver, 1976). The analgesic efficacy of acetaminophen 600 mg was easily demonstrated at the $P < 0.01$ level, but the performance of codeine 60 mg was very unimpressive and statistically significant for only one measure of analgesic effect at the first-hour observation point.

As there was no similar factorial study of acetaminophen and codeine in any other pain model available for comparative purposes, the same four treatments were compared in inpatients with general postoperative pain (Beaver & Feise, 1978). In this model, acetaminophen 600 mg and codeine 60 mg produced essentially identical pain relief, which was statistically superior ($P < 0.025$) to the effect of placebo. Analgesia produced by the combination of

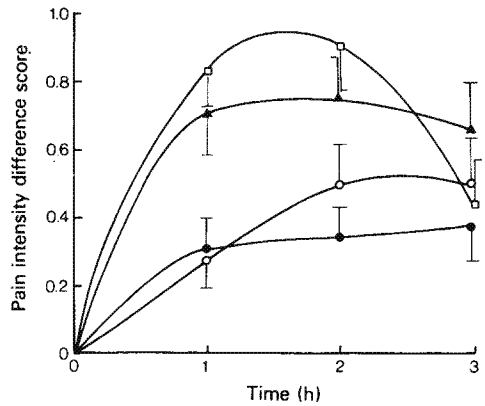

Figure 2 Time-effect curves for placebo (●), aspirin 650 mg (▲), codeine 30 mg (○), and the combination of aspirin 650 mg plus codeine 30 mg (□). Pain intensity difference scores (ordinate) are plotted against time in hours (abscissa). Treatments were allocated on a random, single-dose-only basis to outpatients with oral surgery pain (Cooper & Beaver, 1976).

aetaminophen 600 mg with codeine 60 mg was almost exactly equal to the additive effect of its two constituents.

Taken in conjunction, these studies indicate that the relative efficacy of analgesics with different mechanisms of action may differ in different pain models. Similarly, peripherally acting and centrally acting components of analgesic combinations are likely to vary in their relative contribution to the effect of the combination. Bloomfield, Barden & Mitchell (1976) have apparently observed a similar phenomenon in a series of their postpartum studies, from which they concluded that, "episiotomy pain seems sensitive to both aspirin and codeine, while uterine pain seems sensitive to aspirin but not to codeine."

Hydrocodone (Dicodid®) is a potent, orally effective narcotic which bears a structural relationship to codeine analogous to the relationship of hydromorphone (Dilaudid®) to morphine. Although, until recently, hydrocodone has not been the subject of controlled clinical analgesic studies (Hopkinson, 1978), structure-activity considerations suggest that oral hydrocodone should be about eight times as potent as codeine, and it has recently been marketed in a combination with acetaminophen (Vicodin®).

This study was done to compare the analgesic effect of acetaminophen and hydrocodone and to determine the contribution of each to the efficacy of their combination, to compare the analgesic effect of hydrocodone with codeine, and to explore further

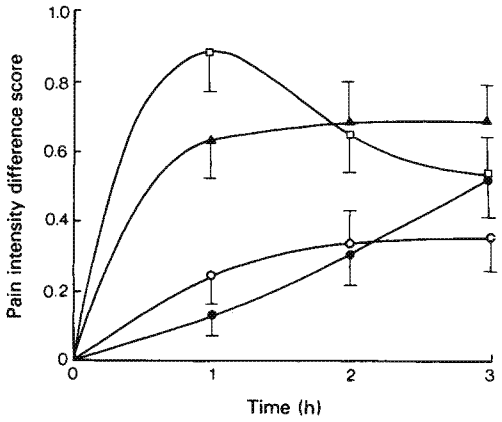

Figure 3 Time–effect curves for placebo (●; $n=40$) acetaminophen 600 mg (▲; $n=40$) codeine 60 mg (○; $n=37$), and the combination of acetaminophen 600 mg plus codeine 60 mg (□; $n=40$). Pain intensity difference scores (ordinate) are plotted against time in hours for 3 h (abscissa). Treatments were allocated on a random, single-dose-only basis to outpatients with oral surgery pain (157 patients) (Cooper & Beaver, 1976).

possible differential effects of narcotics and antipyretic-analgesics in pain of different etiologies.

Methods

Subjects

Subjects were postpartum patients with either episiotomy or uterine cramp pain within 48 h of vaginal delivery at Georgetown University Hospital. Shortly after delivery, they were visited by the nurse observer, who explained the details of the study and solicited the participation of those patients who were cooperative and seemed to be able to communicate information about their pain. Patients were excluded if there was a contra-indication to any of the study medications; if there was a history of eclampsia; or if there was any serious complicating psychiatric, neurological, cardiovascular, pulmonary, hepatic or renal disease or any recent history of drug dependence. Patients who volunteered for the study were instructed as to the system which they would use to describe the severity of their pain and the relief produced by analgesic medication. Psychoactive drugs, oxytocics and sitz baths were withheld during study hours.

Measuring analgesia

Our method of quantifying analgesia is a modification of that developed by Houde *et al.* (1960; 1965), and features peculiar to the evaluation of postpartum pain are patterned on methods described by Bloomfield *et al.* (1976) and Sunshine (1980).

Medications were administered by the nurse-observer only when the patient complained of moderate or severe pain and only if at least 3 h had elapsed since a routine analgesic. Neither the patient nor the observer was aware of the identity of the medications, which were physically indistinguishable and identified only by an individual numerical code (double-blind technique). Observations were made hourly for 6 h after administration of medication or until pain returned to the premedication level and another analgesic was administered (if at least 2 h had elapsed since administration of the study medication).

Awakening the patient if necessary, the observer asked her to classify the intensity of her pain as none (0), slight or a little (1), moderate or medium (2), or severe or a lot (3); to classify her estimate of relief obtained from the medication as none (0), slight (1), moderate (2), good (3), or complete (4); to state whether or not she felt her pain was at least "half-gone" (that is, 50% relief); and to rate the global acceptability of the medication in terms of over-all satisfaction on a five-point scale. Patients with episiotomy pain were questioned concerning their pain intensity and relief "right now", whereas questions concerning uterine cramps were directed to pain intensity and relief "during the last hour" or "since I saw you last". The observer also recorded apparent and volunteered side-effects and side-effects elicited by the question, "Is there anything else that bothers you?", on a 0–3+ scale. Leading questions on specific side-effects were avoided. Data from the administration of each medication were entered on a Sloan-Kettering Institute Analgesic Study Form (Wallenstein & Houde, 1975).

Various measures of analgesia were derived from these subjective reports. Changes in pain intensity (pain intensity differences) were derived from the patient's estimates of the intensity of her pain by subtracting the pain level at each hour after medication from the intensity at the time of administration. Total effect (an estimate of the area under the time–effect curve arrived at by totalling the hourly scores for 6 h) and peak effect (the highest effect obtained by a patient during the first 3 h after drug administration) were calculated for the patient's estimates of change in pain intensity (pain intensity difference), pain relief, and acceptability. A total 50% relief score was similarly calculated by summing the number of hours the pain was at least 50% relieved for 6 h after drug administration. Patients who were remedicated before 6 h had elapsed after administration of a study medication were assigned scores of zero (0) for change in pain intensity, pain relief, 50% relief, and acceptability for the remaining observation points of the 6 h observation period.

Table 1 Summary of mean analgesic scores for episiotomy and uterine cramp pain combined

Treatment	*Hour*						*Total*		*Peak*	
	1	*2*	*3*	*4*	*5*	*6*	*Raw score*	*Ridit**	*Raw score*	*Ridit**
Pain relief										
Placebo	1.9	1.8	1.3	0.9	1.0	0.5	7.36	0.32	2.45	0.30
Acetaminophen 1000 mg	1.9	2.7	2.7	2.0	1.5	0.9	11.77	0.52	3.18	0.53
Hydrocodone 10 mg	2.6	2.9	2.5	2.0	1.9	1.3	13.18	0.58	3.41	0.57
Acetaminophen 1000 mg + hydrocodone 10 mg	2.7	3.0	2.8	2.3	2.1	1.8	14.71	0.65	3.57	0.63
Codeine 60 mg	2.3	2.7	2.1	1.3	0.9	0.9	10.14	0.44	3.05	0.47
Change in pain intensity										
Placebo	0.8	0.9	0.6	0.5	0.6	0.4	3.77	0.36	1.32	0.39
Acetaminophen 1000 mg	0.8	1.3	1.5	0.9	0.8	0.5	5.68	0.51	1.64	0.50
Hydrocodone 10 mg	1.2	1.5	1.3	1.1	0.9	0.6	6.59	0.58	1.86	0.56
Acetaminophen 1000 mg + hydrocodone 10 mg	1.3	1.5	1.4	1.1	1.0	0.8	7.14	0.61	1.86	0.55
Codeine 60 mg	1.0	1.3	1.0	0.7	0.5	0.4	4.90	0.44	1.62	0.49
50% relief										
Placebo	0.73	0.55	0.36	0.27	0.32	0.18	2.41	0.35		
Acetaminophen 1000 mg	0.64	0.82	0.73	0.64	0.50	0.27	3.59	0.52		
Hydrocodone 10 mg	0.73	0.77	0.73	0.59	0.50	0.32	3.64	0.53		
Acetaminophen 1000 mg + hydrocodone 10 mg	0.95	1.00	0.86	0.76	0.62	0.43	4.62	0.67		
Codeine 60 mg	0.71	0.81	0.62	0.29	0.24	0.29	2.95	0.43		
Acceptability										
Placebo	2.0	1.6	1.4	1.2	1.0	0.7	7.91	0.29	2.50	0.32
Acetaminophen 1000 mg	2.3	2.5	2.6	2.5	2.2	1.6	13.73	0.54	3.14	0.52
Hydrocodone 10 mg	2.5	2.9	3.0	2.7	2.5	1.8	15.32	0.59	3.41	0.57
Acetaminophen 1000 mg + hydrocodone 10 mg	2.7	3.1	2.9	2.6	2.5	2.1	15.86	0.62	3.48	0.59
Codeine 60 mg	2.3	2.7	2.6	2.3	1.3	1.0	12.24	0.46	3.14	0.50

* Based on the distribution of response of all patients in the study.

Study design and medications

Patients were randomly allocated to treatments using a parallel or single-dose-only study design, and the allocation was stratified for moderate or severe initial pain intensity and also for episiotomy or uterine cramp pain.

The study was carried out using a classical 2×2 factorial design comparing placebo, acetaminophen 1000 mg, hydrocodone bitartrate 10 mg, and the combination of acetaminophen 1000 mg with hydrocodone 10 mg (equivalent to two tablets of Vicodin® (Knoll)). In addition, a codeine phosphate 60 mg treatment was included. Doses were prepared from appropriate combinations of acetaminophen 500 mg capsules (Tylenol®, McNeil), hydrocodone 5 mg tablets (Dicodid®, Knoll) and matching dummies of each. The codeine was prepared by inserting codeine phosphate 30 mg hypodermic tablets in dummy capsules containing a mixture of starch and lactose. Medications were administered with 240 ml of water at least 0.5 h before or at least 2 h after meals, and patients were instructed to sit up or remain on their right side for 1 h after medication to facilitate gastric emptying.

A total of 108 patients participated; there were no drop-outs. Patients were almost equally divided between episiotomy and uterine cramp pain. Initial pain intensity was severe in one-third of the patients and moderate in the other two-thirds. Fortuitously, the mean baseline pain severity was essentially identical for the episiotomy and uterine cramp subgroups.

Results

The mean analgesic scores for episiotomy and uterine cramp pain combined, as well as ridit transformed peak and total scores (Bross, 1958; Houde *et al.*, 1965; Wallenstein & Houde, 1975), are summarized in Table 1. The ridit is a non-parametric transformation developed by Bross (1958) especially for the analysis of data from subjective measurement scales

Table 2 Summary of statistical analyses (orthogonal contrasts) of analgesic scores for episiotomy and uterine cramp pain combined

	Pain relief		*Change in pain intensity*		*50% relief*		*Acceptability*	
	Raw score	*Ridit*	*Raw score*	*Ridit*	*Raw score*	*Ridit*	*Raw score*	*Ridit*
Total analgesia								
Acetaminophen effect	$P<0.05$	$P<0.05$	NS	NS	$P<0.01$	$P<0.01$	$P<0.05$	$P<0.05$
Hydrocodone effect	$P<0.001$	$P<0.001$	$P<0.05$	$P<0.01$	$P<0.01$	$P<0.01$	$P<0.001$	$P<0.001$
Interaction*	NS	NS	NS	NS	NS	NS	NS	NS
Codeine vs. placebo	NS	NS	NS	NS	NS	NS	$P<0.05$	$P<0.05$
Peak analgesia								
Acetaminophen effect	$P<0.05$	$P<0.01$	NS	NS			NS	$P<0.05$
Hydrocodone effect	$P<0.001$	$P<0.001$	$P<0.05$	NS			$P<0.01$	$P<0.01$
Interaction*	NS	NS	NS	NS			NS	NS
Codeine vs. placebo	$P<0.05$	$P<0.05$	NS	NS			$P<0.05$	$P<0.05$

* Interaction of acetaminophen effect with hydrocodone effect.

and compensates for non-normality in the distribution of such data.

An analysis of variance with orthogonal contrasts appropriate for a 2×2 factorial experiment (Houde *et al.*, 1965; Winer, 1962) was carried out on the various measures of total and peak analgesia and is summarized in Table 2. The hydrocodone effect was significant for all measures of total analgesia and for all measures of peak analgesia except one. This was also true for acetaminophen except for measures of analgesia based on change in pain intensity. The contrast for the interaction of acetaminophen with hydrocodone was not significant for any measure of analgesia, which indicates that the effect of the combination represented the additive effect of its two constituents.

In this study, 50% relief was the measure of analgesia that proved most sensitive in separating the various treatments; the time–effect curves for this measure of effect for the treatments constituting the 2×2 factorial comparison are illustrated in Figure 4. As would be expected, placebo was the least effective treatment. Acetaminophen 1000 mg and hydrocodone 10 mg produced comparable analgesia and their effects were significant ($P<0.01$). The orthogonal contrast for interaction approached 0; the analgesia produced by the combination was almost exactly equal to the sum of the effects of its two constituents.

Although the interaction term was not statistically significant for any measure of total or peak analgesia (Table 2), the mean scores for some measures of effect suggest that analgesia produced by the combination is somewhat less than the additive effect of its constituents (Table 1). For example, Figure 5 depicts the time–effect curves in terms of pain relief scores. The most likely explanation for this is that either acetaminophen 1000 mg or hydrocodone 10 mg alone is producing so much pain relief relative to the modest analgesic needs of these postpartum patients that there is only limited opportunity for the combination to demonstrate an analgesic effect that is substantially greater than that produced by either analgesic administered alone.

Figure 5 also compares the effect of codeine 60 mg with the other treatments in the study. Although codeine was significantly superior to placebo for peak pain relief and several other measures of total and peak analgesia (Table 2), it was consistently somewhat inferior in mean effect to either acetaminophen 1000 mg or hydrocodone 10 mg (Table 1).

A two-way analysis of variance utilizing treatment as one factor and type of pain as the other factor indicated that patients with episiotomy pain were responding differently to treatment than patients with uterine cramp pain. Patients with uterine cramp pain had higher mean analgesia scores than those with episiotomy pain for every measure of effect; and for most measures, this difference is statistically significant. Of more interest is the observation that the two-way analysis demonstrated a qualitative difference in the way patients with these two types of pain are responding to treatment, which is statistically significant for all measures of effect except one. The nature of this difference is apparent from Figure 6. Responses to placebo and the combination are similar for the two types of pain. Patients with uterine cramping, however, are experiencing much more pain relief from the narcotics, codeine and hydrocodone, than patients with episiotomy pain. On the other hand, patients with episiotomies seem to benefit somewhat more from acetaminophen than patients with uterine cramps.

Only a few minor subjective side-effects occurred,

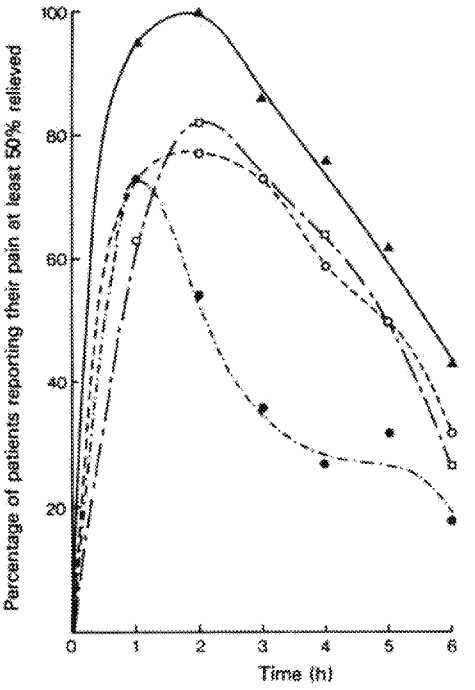

Figure 4 Time–effect curves for placebo (●; $n = 22$), acetaminophen 1000 mg (○; $n = 22$), hydrocodone 10 mg (□; $n = 22$), and the combination of acetaminophen 1000 mg plus hydrocodone 10 mg (▲; $n = 21$) (the treatments constituting the 2×2 factorial comparison). The percentage of patients reporting their pain at least 50% relieved at each hour is plotted on the ordinate against time in hours on the abscissa.

and the side-effect incidence for the combination was no greater than that for either acetaminophen or hydrocodone alone (Table 3).

Discussion

Hydrocodone and acetaminophen

Although it is obvious that a simple 2×2 factorial study design does not speak to all possible issues relevant to the rationale for an analgesic combination, this study does demonstrate the contribution of acetaminophen and hydrocodone to the effect of their combination. The absence of significant interaction indicates that the analgesic effect of the combination results from the additive effect of its two constituents, which is consistent with the well accepted theory that these two drugs produce analgesia by different mechanisms (Beaver, 1966; 1975).

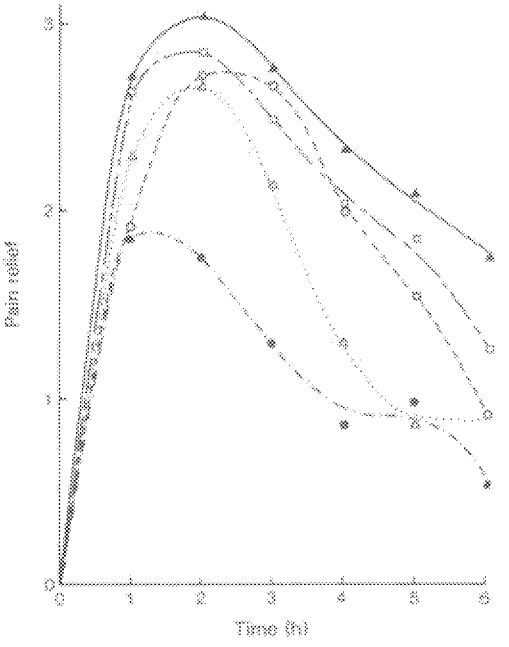

Figure 5 Time–effect curves for placebo (●; $n = 22$) acetaminophen 1000 mg (○; $n = 22$), hydrocodone 10 mg (□; $n = 22$), the combination of acetaminophen 1000 mg plus hydrocodone 10 mg (▲; $n = 21$), and codeine 60 mg (△; $n = 21$). Mean hourly pain relief scores on the ordinate are plotted against time in hours on the abscissa.

The slopes of the dose–response curves of orally administered narcotics are relatively flat, with the result that even successive doubling of the dose produces only modest increments of analgesic effect. Furthermore, aspirin and acetaminophen probably exhibit a ceiling of analgesic effect at doses of 650–1000 mg, and further increase in dose results in little increment in analgesia (Beaver, 1965). The simple additive effect of a narcotic, such as hydrocodone, and an antipyretic-analgesic, such as acetaminophen, given together, may therefore be significantly greater than the analgesia achieved by doubling the dose of either drug administered alone.

Considerations of side-effects are also germaine to the rationale for such combinations. Although a 1000 mg dose of acetaminophen has been found to provide significantly more analgesia than the usual 650 mg dose (Hopkinson *et al.*, 1975), and a single or a few 1000 mg doses are well tolerated, it is probably unwise to exceed a total daily dose of 4 g for either acetaminophen or aspirin.

On the other hand, the usual oral doses of narcotics have not been shown to be any more effective than aspirin 650 mg or acetaminophen 650

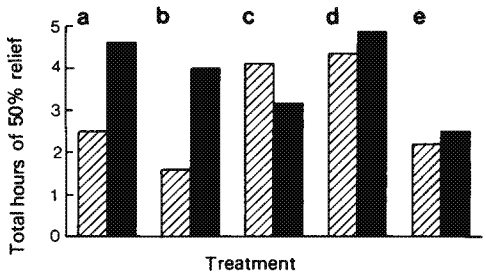

Figure 6 Analgesia (total hours of 50% relief) experienced by the sub groups of patients with episiotomy pain (hatched columns) and uterine cramp pain (solid columns) compared for each of the five treatments: *a*, hydrocodone 10 mg; *b*, codeine 60 mg; *c*, acetaminophen 1000 mg; *d*, acetaminophen 1000 mg plus hydrocodone 10 mg; *e*, placebo.

to 1000 mg (Beaver, 1980; Moertel, 1976). If the dose of narcotic is increased in an effort to enhance analgesia, there is a concomitant progressive increase in the incidence and severity of side-effects (Moertel, 1976) and, on chronic use, an increased risk of drug dependence.

The problem of providing adequate pain relief in the face of these limitations of single entity oral analgesics may be circumvented by combining an optimal dose of aspirin or acetaminophen with an orally effective narcotic in a modest dose that is reasonably safe and well tolerated. Indeed, in this study, the side-effect incidence for the combination of acetaminophen 1000 mg plus hydrocodone 10 mg was no greater than that for either constituent alone.

The performance of codeine 60 mg relative to acetaminophen 1000 mg is consistent with the results of the interaction study of these two drugs in postoperative pain (Beaver & Feise, 1978), and the efficacy of codeine 60 mg relative to hydrocodone 10 mg is consistent with our prediction of relative potency based on structure–activity considerations.

Methodological considerations

It has been recognized for some time that the relative efficacy of analgesics in patients with rheumatic disease can differ substantially from their efficacy in conventional general pain models such as postoperative and trauma pain, postpartum pain, cancer, non-rheumatic musculoskeletal pain and oral surgery. The results of this study, taken in conjunction with the other studies noted above (Beaver & Feise, 1978; Bloomfield *et al.*, 1976; Cooper & Beaver, 1976; Houde *et al.*, 1965) suggest that the problems of extrapolating relative analgesic efficacy across general pain models may be more pervasive than has been appreciated. This problem evidently emerges when comparing agents with different mechanisms of analgesic action and emphasizes the importance of careful consideration of the choice of pain model and positive control treatment in the evaluation of new analgesic drugs. As most analgesic combinations *ipso facto* contain drugs with different mechanisms of action, this caveat is particularly germaine to their evaluation.

The superior performance of the narcotics, hydrocodone and codeine, in uterine cramp as opposed to episiotomy pain is directly contrary to Bloomfield's (1976) findings, and we are at a loss to explain this discrepancy. The number of patients in our episiotomy and uterine cramp subgroups was relatively small, but the differential response was statistically significant for virtually every measure of effect, and this difference was consistent for both of

Table 3 Side effects reported by the 108 subjects

Side-effect	*Placebo (n = 22)*	*Acetaminophen 1000 mg (n = 22)*	*Hydrocodone 10 mg (n = 22)*	*Acetaminophen 1000 mg + hydrocodone 10 mg (n = 21)*	*Codeine 60 mg (n = 21)*
Patients without side-effects	15	11	11	11	13
Sleepy (groggy)	5	8	9	7	6
Tired	—	1	—	—	—
Lightheaded	1	—	3	2	1
Dizzy	1	—	1	2	—
High (euphoric)	—	—	1	—	1
Relaxed	1	2	2	—	1
Headache	—	—	1	—	—
Dryness of the mouth	—	—	—	1	—
Nausea	—	—	1	1	1
Warm feeling	—	—	1	—	—
Sweating	—	1	—	—	—
Marked increase in pain	—	1	—	—	—
Patients with side-effects	7	11	11	10	8
Number of side-effects	8	13	19	13	10

the narcotics in the study. Other investigators have demonstrated a significant effect for narcotics in either uterine cramp (Baptisti, Gruber & Santos, 1971; Bauer, Baptisti & Gruber, 1974) or episiotomy pain (Hopkinson, Bartlett, Steffens, McGlumpy, Macht & Smith, 1973; Hopkinson, 1978; Levin, Bare, Berry & Miller, 1974). It is therefore evident that both types of postpartum pain can respond to oral narcotics. However, none of these studies have included both an antipyretic-analgesic *and* a narcotic standard in a design stratified for episiotomy and uterine cramp pain, and this apparent discrepancy is only likely to be resolved by studies using that design.

This study also illustrates the problem of interpretation that may arise when an analgesic combination is evaluated in patients who achieve very high scores on an analgesic scaling system after receiving the individual constituents alone. The limited 'upside' assay sensitivity in such a pain model may prevent the full analgesic potential of the combination from being demonstrated. The same phenomenon may result in a factitious ceiling of effect when graded doses of an analgesic are administered and constitutes an important consideration when selecting a pain model and the doses of study medication for an analgesic clinical trial.

We are indebted to those postpartum patients at Georgetown University Hospital whose participation made this study possible. We also appreciate the cooperation of the nursing staff, house staff, and attending staff of the obstetrical service, and the editorial assistance of Ms Nancy Beaver. We particularly acknowledge the contribution of Mr James Forbes, Ms Alice Forbes and Mr James Williams in data processing, computer programming and statistical analysis. This study was supported in part by a grant from the Knoll Pharmaceutical Co. Presented in part at the Eightieth Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, Kansas City, Missouri, March 1979 (Beaver & McMillan, 1979). Reprint requests to Dr William T. Beaver, Department of Pharmacology, Georgetown University Schools of Medicine and Dentistry, 3900 Reservoir Road, NW, Washington DC 20007.

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DR WOERZ noted that in West Germany and Switzerland there were many fixed combinations on the market containing barbiturates, and that there was evidence that this was irrational as it has been shown that barbiturates have an anti-analgesic action. He also emphasized the marked differences between acute and chronic pain with regard to aetiology, pathogenesis, symptomatology and therapy. He asked whether Professor Beaver had studied the long-lasting effects of such combinations?

PROFESSOR BEAVER replied that in relation to the question about barbiturates, it all depended on the aetiology of the pain. He said recent unpublished work in the United States clearly demonstrated that small amounts of barbiturates enhanced the effect of APC-type combinations in the treatment of tension headache. But there were other studies that suggested barbiturates and minor tranquillizers, such as meprobamate, had no beneficial effect or were algesic — that is, enhanced pain perception — in the individual with acute postoperative pain. This illustrated one of the problems of analgesic combination evaluation: different models produced different results. He regarded Dr Woerz's second question as important. Most controlled clinical trials of analgesics and of analgesic combinations concerned single-dose studies. He quoted Dr Houde who was unable to show that chlorpromazine had any analgesic effect — or that it enhanced the analgesia produced by morphine — in patients with chronic pain due to cancer.

To his knowledge, there were no repeated-dose studies of combinations, say, of psychoactive drugs, and analgesics in chronic pain meeting modern criteria for well controlled clinical trials, although there were some anecdotal reports. He said it was a question which needed to be investigated.

DR DUGGAN asked whether caffeine had any role as an analgesic?

DR HOUDE replied that unfortunately he could not answer definitively. He had carried out a study in which caffeine was added in graded doses to combinations of acetaminophen and aspirin. With higher doses of caffeine he showed some effect, but not with lower doses. The study did not provide a conclusive answer.

PROFESSOR BEAVER said that existing data on caffeine were equivocal.

DR HOUDE observed that many of the studies reported concerned single dose levels of drugs, from which conclusions were being drawn whether the drugs were analgesic, antanalgesic or had no effect at all. If they were animal studies, graded doses would be used. He asked whether some of the problems would be resolved if graded doses of both the test drug and of the standard were used in man.

PROFESSOR BEAVER agreed but said that practically there was a limitation to the number of different treatments that could be included in a study. Although it would be desirable to have graded doses of each constituent and different ratios in combinations, in addition to placebo, very few such studies had been carried out. Those that had been carried out almost invariably failed to produce clear results.