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NEW PERIPHERALLY-ACTING ORAL ANALGESIC AGENTS

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INTRODUCTION

Aspirin was recognized as an analgesic and anti-inflammatory agent even before the advent of modern medicine. It still remains the standard agent in this class; however, many new drugs are seriously challenging its position for both analgesia and anti-inflammatory indications. This review surveys the recent work on the analgesic efficacy and side effects of several new peripherally-acting, orally administered analgesic agents. It focuses on single-dose clinical assays using a variety of pain models as this type of study has proven most useful for relative efficacy comparisons.

Mechanism of Action

The mechanism of action for peripherally-acting analgesics is elucidated in reviews by Ferreira & Vane (1, 2). The primary action of these drugs appears to be in inhibiting the cyclo-oxygenase enzyme system that metabolizes arachidonic acid to its endoperoxide intermediates. If uninhibited, the endoperoxides, in turn, are biosynthesized to thromboxanes, prostacyclins, and prostaglandins. Various intermediates and endproducts of this arachidonic acid cascade interrelate with other local mediators such as bradykinin, histamine, and 5-hydroxytryptamine to promote erythema, edema, and pain. Some evidence suggests that the recently introduced agents may owe their exceptional efficacy not only to more specific inhibition of the enzymes within the cyclo-oxygenase system at the site of insult, but also to secondary effects of cyclo-oxygenase inhibition within the central nervous sytem (3). Of course, unknown peripheral and central mechanisms also may contribute to their efficacy.

In addition to differential effects on the cyclo-oxygenase isoenzyme system, differences in pharmacokinetic parameters including lipid solubility, protein binding, penetration of the blood-brain-barrier, and liver metabolism also may affect the clinical efficacy and side effect profiles of the new peripherally-acting analgesics. These differences are highlighted as the particular drugs are discussed.

REVIEW OF ANALGESIC THERAPY

Since 1893 aspirin has been the standard of the peripherally-acting (NSAIDs) analgesics. Its analgesic and anti-inflammatory properties result primarily from the inhibition of cyclo-oxygenase enzymes at the site of tissue insult. However, aspirin also has potent antipyretic properties, thus demonstrating its centrally mediated activity at least in the areas of the brain related to temperature control. Until recently, no peripherally-acting analgesic could claim superiority to aspirin as an analgesic.

Acetaminophen also is widely used as an analgesic and is approximately equianalgesic and equipotent to aspirin (Figures 1 and 2) (4, 5), but it lacks aspirin's potency for anti-inflammatory effects (4, 6). The therapeutic differences between these two drugs probably result from differential effects on the cyclo-oxygenase system both peripherally and centrally. This differential effect could also explain their different side effect profiles. While aspirin inhibits platelet aggregation and causes irritation to the gastrointestinal tract, acetaminophen is relatively free of these side effects. Unlike opioid analgesics both aspirin and acetaminophen are free of mood altering effects such as euphoria, dizziness, and lightheadedness.

Clinically, aspirin and acetaminophen have limited analgesic efficacy due to a plateauing of the dose-effect curves between 650 mg to 1300 mg (4). In addition, taking multiple dosages in excess of 1300 mg per dose could result in unwanted toxicities. In spite of this limitation, they remain extremely useful for a large variety of painful conditions.

In pain situations requiring mood altering drugs or enhanced analgesia above the plateau effects of aspirin or acetaminophen, codeine or other similar centrally-acting opioid drugs are combined with a peripherally-acting component. Generally the opioid components are used at marginally effective dosages and with current methodology their contribution to the combination is sometimes difficult to ascertain when statistics are applied (Figures 3 and 4) (7). Considering the substantial first-pass metabolism of opioid drugs, it is understandable that small dosages administered orally provide inconsistent and, at best, marginal analgesia (8, 9). Increasing the dosage of the opioid component results in greater analgesia but invariably increases the incidence and severity of centrally-mediated side effects such

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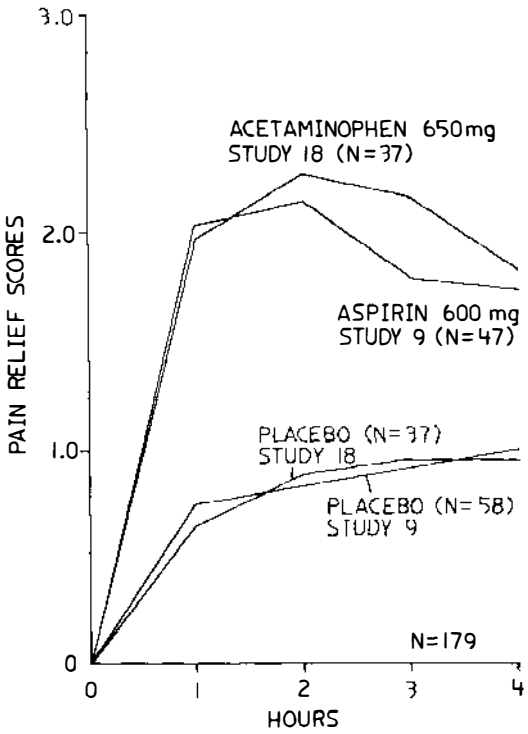

Figure 1 Composite time-effect curves from two dental impaction pain studies comparing aspirin 600 mg and acetaminophen 650 mg. Time in hours is plotted against pain relief scores. Adapted from Cooper (43, 45).

as drowsiness, dizziness, nausea, and vomiting. In a study by Cooper et al (10) comparing acetaminophen and oxycodone, this was apparent even after a single dose administration (Table 1). Other combinations using phenyltoloxamine, promethazine, phenobarbital, or meprobamate have never been demonstrated to be more effective than the traditionally used opioid combinations. In fact, Kantor et al (11) reported that meprobamate appeared to have a paradoxical algesic effect.

As in many areas of medicine, the clinicians often find themselves in a quandary. In an extremely painful situation, injectable narcotics, such as morphine, are most efficacious with side effects being tolerated; and in mild to moderate episodic pain, peripherally-acting OTC preparations or combinations with minimal dosages of the opioid component are effective. However, in a large number of clinical situations, the patient's pain may require more effective analgesics than aspirin alone or aspirin combined with codeine 30 mg; yet injectable narcotics clearly are not indicated. Until re-

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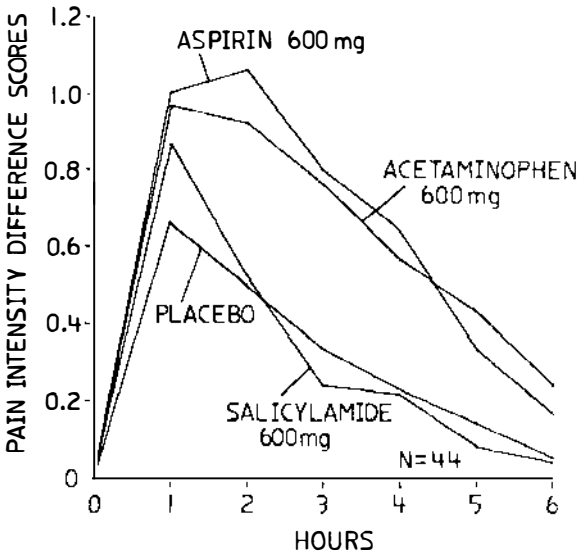

Figure 2 Time-effect curves from a cancer pain study comparing aspirin 600 mg, acetaminophen 600 mg, salicylamide 600 mg, and placebo. Time in hours is plotted against pain intensity difference scores. Adapted from Wallenstein and Houde (5).

cently, the only solution was to increase the dosage of the opioid component in the combinations and accept the inconsistency of the opioid analgesic effect as well as the dose-related side effects. The new generation of nonsteroidal antiinflammatory drugs (NSAIDs) appear to fill a void between the older nonnarcotic, mild analgesics and potent injectable narcotic analgesics. In order to place these new analgesic agents in proper perspective, it is first necessary to appreciate the utility and limitations of current analgesic methodology.

REVIEW OF METHODOLOGY

The principles governing a clinical study intended to evaluate the relative efficacy of different drugs are not essentially different from the ground rules for a foot race. The contestants (drugs) must begin at comparable starting points and follow a similar course if the race is to be a meaningful comparison of their abilities. The job of the clinical investigator, therefore, is to assemble as fair and uniform a "race course" as possible within the framework of a realistic clinical environment.

The race course in a study of analgesic drugs is called the "pain model." It is a collection of patients experiencing pain symptoms who will be asked to evaluate test drugs under controlled clinical conditions. As in the foot

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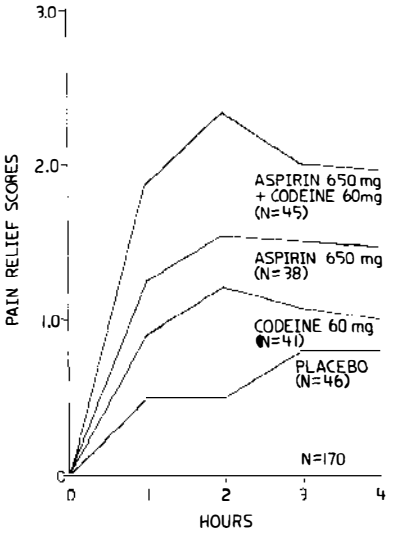

Figure 3 Time-effect curves from a dental impaction pain study comparing aspirin 650 mg with codeine 60 mg, aspirin 650 mg, codeine 60 mg, and placebo. Time in hours is plotted against pain relief scores. Adapted from Cooper et al (15).

race, if the pain model is to provide a meaningful basis for comparing drug performance, each test drug must be evaluated under equivalent circumstances. The inherent complexity of pain, however, makes the designing of such a model difficult.

There are many different types of pain. Some types, such as the pain caused by surgical trauma, are fairly consistent and predictable. Others, e.g. headache pain, are far less susceptible to quantitative measurement. Moreover, the interpretation of comparable pain experiences can differ not only from one individual to the next but also within the same individual at different time periods. When the investigator sets out to design a serviceable pain model, he attempts to control or limit pain variables such as the source, consistency, intensity, and psychological component. A reliable test model, therefore, is one that minimizes the extraneous variables affecting pain.

Three relatively constant types of pain that are frequently utilized for analgesic testing are postsurgical pain (dental, orthopedic, general), postpartum/episiotomy pain, and chronic pain such as cancer pain. Generally speaking, these models involve fairly intense, constant, and quantifiable pain. The testing is generally conducted in a hospital setting but, in some instances, can be performed with outpatients. Equally as important to the type of etiology of the pain is adequate evidence that the particular site performing the study has demonstrated clearly that it has assay sensitivity. This can only be demonstrated by repeated studies that include placebo

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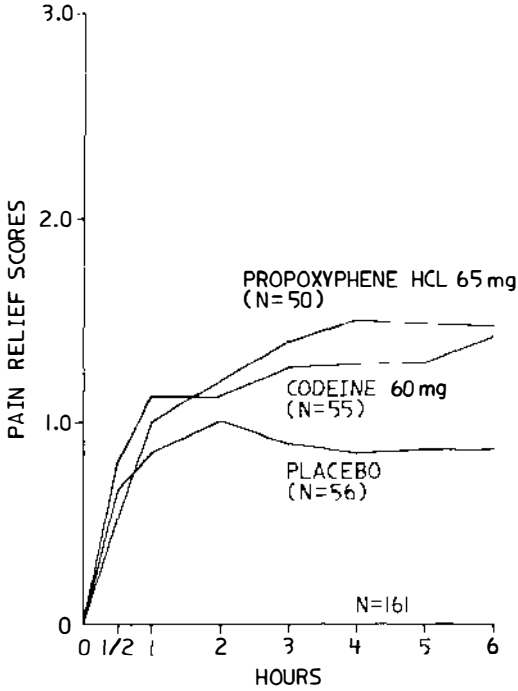

Figure 4 Time-effect curves from a periodontal pain study comparing propoxyphene HCL 65 mg, codeine 60 mg, and placebo. Time in hours is plotted against pain relief scores. (Adapted from Cooper et al, unpublished data.)

controls and graded dosages of standard and test drugs. Because of high levels of pain intensity and unique clinical settings, some models may be more appropriate for evaluating potent injectable analgesics, while other models may be useful only for evaluating more mild analgesics such as aspirin and acetaminophen. Sometimes within the same general category of pain etiology, a population can be subdivided into various levels of pain intensities. For example, postsurgical dental pain can be subdivided into at least two populations. The complicated extraction population is most suitable for evaluating mild analgesics, and the third molar impaction population is more appropriate for evaluating stronger analgesics such as opioid combinations.

The ability to regulate the underlying intensity of pain is most critical in clinical testing. The pain must be intense enough that medication is truly necessary, otherwise active drug and placebo may score equally high; but not so intense that the test drug is incapable of producing any perceptible reduction in pain, otherwise active drug and placebo may score equally low. In short, if the pain is either too mild or too severe, the study may fail to

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Table 1 Side effect and efficacy data from a single-dose dental impaction pain study

	Placebo	Aceta-minophen 500 mg	Oxy-codone 5 mg	APAP[a] 500 mg + OXYCOD 5 mg	APAP 1000 mg + OXYCOD 5 mg	APAP 1000 mg + OXYCOD 10 mg
Nausea	2	3	3	7	4	10
Drowsy	3	1	3	12	13	14
Dizzy	0	1	4	4	5	15
Lightheaded	0	0	1	4	1	6
Headache	2	1	0	2	1	2
Total number of subjects reporting side effects	6/38	3/37	8/42	21/45	19/40	29/45
SPID	0.87	1.49	1.38	3.00	3.55	4.49
TOTPAR	4.76	5.08	4.79	7.49	8.05	9.44
GLOBAL	0.89	0.89	0.88	1.76	1.95	1.96

[a] APAP = Acetaminophen.

detect any drug efficacy whatsoever, even though the drug is, in fact, efficacious.

The pain intensity factor becomes even more important where the objective of a study is to demonstrate differences between two active drugs, as opposed to merely showing differences between active drug and placebo. In a multicell study of this type, the degree of pain selected for the model should be intense enough to test the full analgesic capacity of both active medications. Where the pain is too mild, the drugs may appear equipotent when, in fact, under more intense pain conditions one drug would outperform the other. Thus the more control there is in regulating pain intensity, the greater the likelihood of having a sensitive test model.

Aside from these considerations about the various pain models utilized in analgesic research, certain methodological procedures are essential to a well-controlled clinical study. One fundamental requirement is that an analgesic study be conducted on a "double-blind" basis. This means that all medication should be given in identically appearing formulations so that neither the investigator nor the patients know which drug is being evaluated. Another basic requirement is that a placebo and an active drug be included as controls to gauge the sensitivity of the model. For more precise studies, the investigator may include more than one standard to explore the sensitivity at both the low and high ends of the analgesic scales. As previously noted, a finding of no difference between active drug and placebo does not necessarily indicate that the drug has no efficacy. It could mean that the model is not working because the pain is too mild, too severe, or too variable.

Unfortunately, many analgesic assays are conducted under less than ideal conditions. Because of the great number of agents under investigation, the demand is high for studies while the supply is sparse for experienced investi-

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gators and established pain models. This situation has resulted in some analgesic agents being evaluated in models with insufficient assay sensitivity. One has to be very careful to discern whether the results of a study reflect the pharmacological activity of the study medications or the limitations of the pain model.

With these basic principles in mind, I turn to the review of the new nonsteroidal anti-inflammatory agents that are marketed or being developed for use as peripherally-acting analgesics. Table 2 broadly categorizes these analgesic agents according to chemical class. Several of the older compounds, such as phenylbutazone and mefanamic acid, are not discussed as they are not indicated for general analgesic purposes and there are few new derivatives of these compounds that appear to be near marketing.

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NEW PERIPHERALLY-ACTING ORAL ANALGESIC AGENTS

Ibuprofen

Ibuprofen was the first phenylalkanoic acid approved by the FDA for general analgesic use. Its chemical name is 2(p-isobutylphenyl) propionic acid. There now are several others marketed in the USA and several more are near approval (Table 2). Ibuprofen has a serum half-life of approximately two hours and is almost entirely eliminated by 24 hours after the last dose. The suggested dosage is 400 mg every 4–6 hours for mild to moderate pain. Davies & Avery (12) and Adams and associates (13) have published comprehensive reviews of ibuprofen's pharmacological properties.

Table 2 Summary of peripherally-acting analgesic agents that are either marketed or near final approval in the United States[a]

Salicylates	Phenylalkanoic (propionic acids)	Indol-pyrrol acetic acids	P-Amino phenols
Aspirin	Carprofen	Indomethacin	Acetaminophen
Diflunisal	Fenoprofen	Tolmetin	
	Flurbiprofen	Zomepirac	
	Ibuprofen		
	Indoprofen		
	Ketoprofen		
	Naproxen		
	Suprofen		

[a] Many NSAIDs are not included because of the lack of published analgesic data.

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The analgesic efficacy of ibuprofen is best represented in postsurgical dental pain. Cooper and associates (14) found a positive dose-effect for ibuprofen 200 mg and 400 mg, with the 400 mg dosage having a greater peak effect and longer duration of action than aspirin 650 mg. In a follow-up study (15) ibuprofen 400 mg was found to be more effective than both codeine 60 mg and aspirin 650 mg alone and when combined (Figures 5 and 6). In other dental studies, Winter et al (16) also found ibuprofen 400 mg more effective than both aspirin 650 mg and d-propoxyphene HCL 65 mg, and Rondeau et al (17) concluded that ibuprofen 400 mg was more effective than codeine 60 mg. In two pretreatment studies (18, 19) using dental pain, ibuprofen 400 mg administered 30 minutes prior to surgery significantly delayed the onset and intensity of postoperative dental pain (Figure 7) (Table 3).

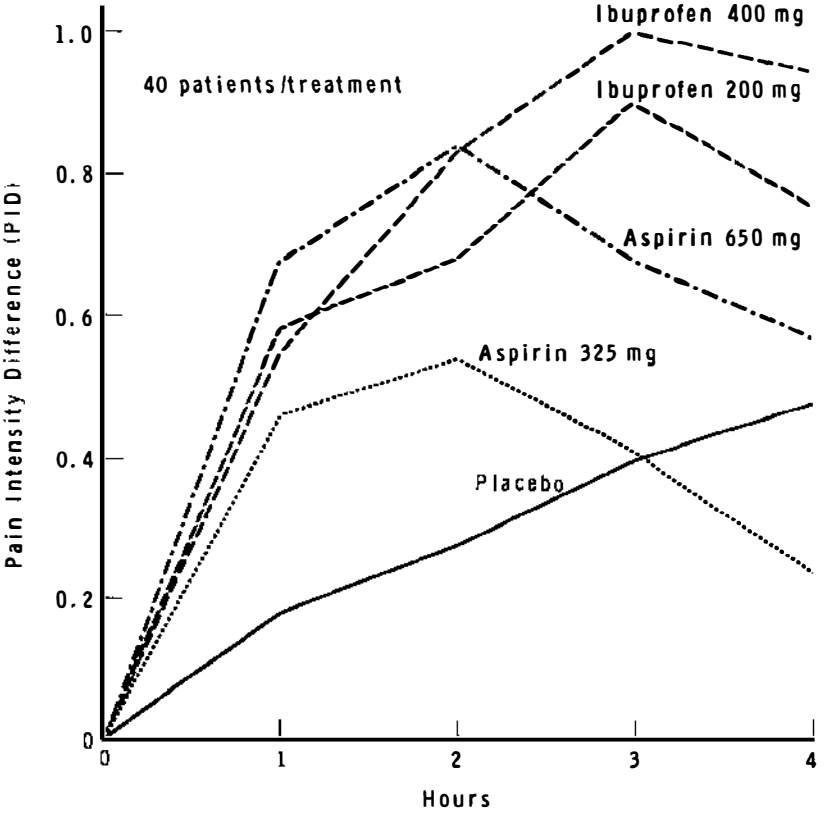

Figure 5 Time-effect curves from a dental impaction pain study comparing ibuprofen 200 mg and 400 mg, aspirin 325 mg and 650 mg, and placebo. Time in hours is plotted against pain intensity difference scores. Adapted from Cooper et al (14).

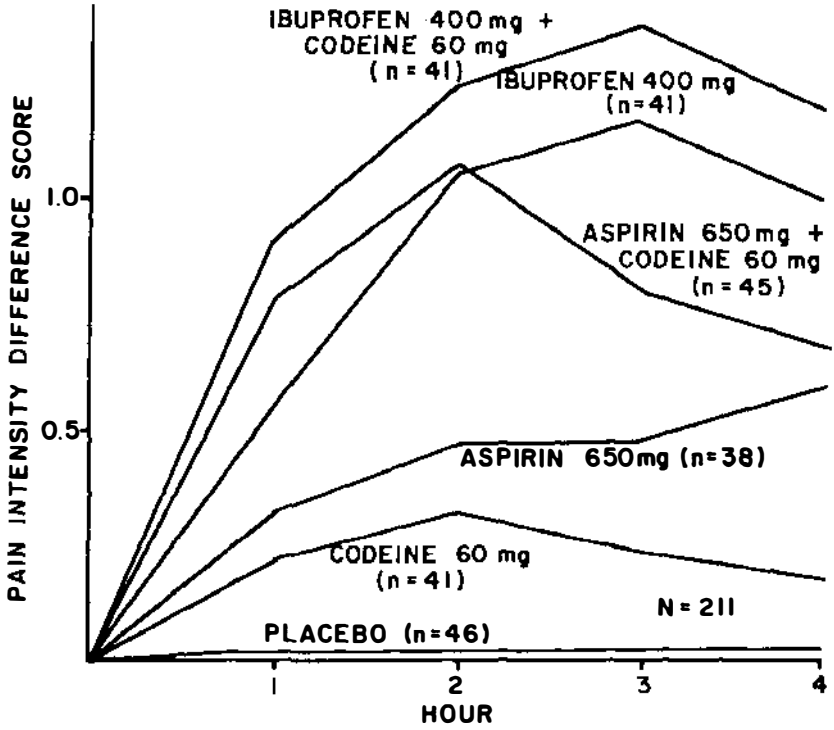

Figure 6 Time-effect curves from a dental impaction pain study comparing ibuprofen 400 mg with codeine 60 mg, ibuprofen 400 mg, aspirin 650 mg with codeine 60 mg, aspirin 650 mg, codeine 60 mg, and placebo. Time in hours is plotted against pain intensity difference scores. Adapted from Cooper et al (15).

In other types of pain, the results are not quite as clear-cut; but to some extent the fault may reside in the study design. Bloomfield (20) used episiotomy pain to compare ibuprofen 300 mg and 900 mg to aspirin 900 mg. Although all the treatments were more efficacious than placebo, there were no differences among the three active agents. Since no measure of "upside" assay sensitivity was included in this particular study, there is no way to ascertain if the drugs or the model reached a ceiling effect. Hopkinson (21) also used episiotomy pain and found that ibuprofen 400 mg was significantly more effective than d-propoxyphene HCL 65 mg and placebo; however, no other standard agents were included. Other pain models that demonstrated ibuprofen's efficacy included post-herniorrhaphy (22) and pain due to soft-tissue injuries (23).

The studies that evaluated dosages of ibuprofen above 400 mg (16, 20, 21) did not demonstrate any dose-related enhancement of analgesic efficacy either in terms of peak effect or duration of effect.

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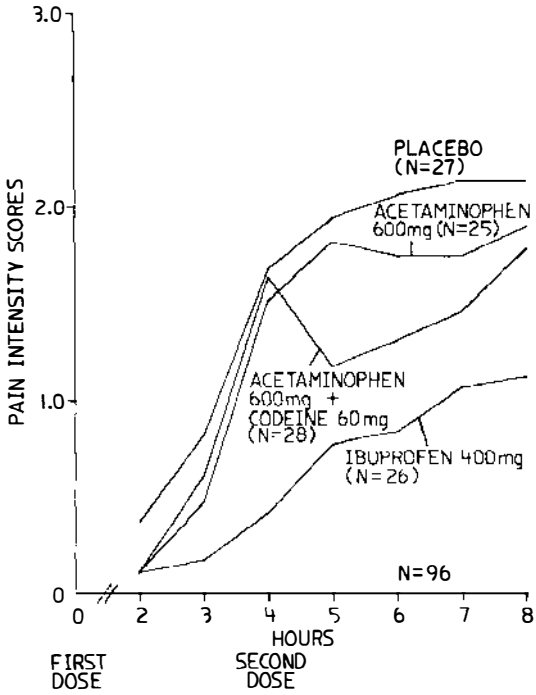

Figure 7 Time-effect curves from a dental impaction pretreatment study comparing ibuprofen 400 mg, acetaminophen 600 mg with codeine 60 mg, acetaminophen 600 mg, and placebo. Time in hours is plotted against pain intensity scores for the pretreatment and first posttreatment doses. Adapted from Dionne et al (19).

The side effect profile of ibuprofen appears very similar in spectrum, but more favorable than that of aspirin. Although ibuprofen inhibits platelet aggregation, this effect quickly reverses once the drug is cleared from the body (24). The clinical significance of this platelet inhibition is overemphasized and with the exception of very rare individuals presents no clinical problems. The gastric irritation also appears to be less intense than with aspirin, but neither drug should be used in patients with a history of ulcers (12, 13).

Ibuprofen is highly bound to plasma albumin, but there is minimal drug interaction with warfarin or oral hypoglycemics. Nevertheless, ibuprofen should be used cautiously in such situations.

Naproxen and Naproxen Sodium

Naproxen is available both as the free chemical and as the sodium salt. In biologic fluid an identical material is formed that is determined by the pKa of naproxen acid and the pH of the biologic fluid in which it is dissolved.

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Table 3 Summary of analgesic efficacy data from a pretreatment dental impaction pain study evaluating ibuprofen

Treatment	Time to postoperative medication (minutes)	Baseline pain (no. of subjects)		
		Severe	Moderate	None
Pre-placebo Post-aspirin, 650 mg	133.0 ± 11.8[a]	6	15	0
Pre-placebo Post-ibuprofen, 400 mg	140.6 ± 11.1	10	14	0
Pre-ibuprofen, 400 mg Post-aspirin, 650 mg	236.3 ± 30.8	5	17	1
Pre-ibuprofen, 400 mg Post-ibuprofen, 400 mg	241.2 ± 24.9	3	17	2
All placebo pretreated	137.1 ± 8.0	16	29	0
All ibuprofen pretreated	238.5 ± 19.9	8	34	3

[a] Standard error of mean.

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Administration of naproxen sodium simply permits more rapid absorption from the gastrointestinal tract. Naproxen sodium is the form marketed as an analgesic agent.

Naproxen sodium is one of a series of substituted acetic acids (propionic acids) with the chemical name of (+)6-methoxy-2-methyl-2-naphthalene acetic acid. It has a metabolic half-life of approximately 13 hours and is highly bound to plasma albumin. The protein binding does not appear to affect the therapeutic effect of warfarin or tolbutamide. Excretion is almost entirely through the kidney as either the parent compound, 6-desmethyl naproxen or glucuronic acid conjugates. On an empty stomach, peak blood levels are reached in one hour, but this time can double if naproxen sodium is taken with a meal. The pharmacological properties of naproxen and naproxen sodium are discussed in reviews by Segre (25) and Brogden et al (26).

Naproxen has been studied in a variety of pain states against several analgesic agents including aspirin, propoxyphene HCL, codeine, and indoprofen. The single-dose, double-blind efficacy studies are summarized below.

In postoperative surgical pain, Mahler and associates (27) compared naproxen 200 mg and 400 mg, aspirin 600 mg and 1200 mg, and placebo. Although the study was conducted at two hospitals, only one site demonstrated usable assay sensitivity. At this site, naproxen 400 mg appeared to be only slightly more effective than aspirin 600 mg with peak and total effects and duration of action similar to aspirin's. The incidence of side effects was high for all treatment groups including placebo.

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Ruedy & McCullough (28) compared naproxen 400 mg and 600 mg to propoxyphene HCL 65 mg in patients suffering pain from orthopedic surgery. No placebo treatment was included and traditional efficacy measures such as TOTPAR and SPID were not utilized.[1] Patients were categorized as either a success or a failure depending on whether they achieved a two-category change in reduction of relief sometime during the four-hour evaluation. Based on this criterion, naproxen 600 mg was the most effective treatment, followed by naproxen 400 mg and propoxyphene HCL 65 mg. There were no noteworthy side effects in this study.

Bloomfield et al (29) studied the efficacy of both naproxen and naproxen sodium in postpartum uterine pain. In the first study, naproxen 300 mg and 600 mg were superior to placebo and codeine 60 mg; but the codeine and placebo were clinically and statistically inseparable. The two dosages of naproxen appeared to have a seven-hour duration of action but there was no dose-response evident between the two dosages. In the second part of the study, naproxen sodium 275 mg was compared to aspirin 650 mg and placebo (Figure 8). Both active treatments were significantly better than placebo, and naproxen sodium appeared only marginally better than aspirin. In this two-part study, the advantage of naproxen was most pronounced at hours 6 and 7; however, its onset of activity did not equal aspirin's until the third hour. There was no indication in either study of any dose-dependent side effects with naproxen.

In postsurgical dental pain, Reudy (30) performed a crossover study comparing naproxen 400 mg to aspirin 325 mg with codeine 30 mg. Naproxen provided successful analgesia, measured as achieving moderate relief at some point during the six-hour evaluation, in a far greater percentage of patients for both the first and second dose when compared to the aspirin-codeine combination. Because of its design, this study only permits one to conclude that naproxen is more efficacious than a suboptimal dosage of aspirin with codeine.

A more recent study by Forbes and associates (31)[2] compared naproxen sodium 550 mg alone and in combination with codeine 60 mg to aspirin 650 mg and placebo. In this postsurgical dental study, naproxen sodium combined with codeine 60 mg was significantly more effective than all other treatments, and naproxen sodium alone was better than aspirin. The duration of action for the naproxen sodium combination was at least eight hours (personal communication).

The overall analgesic efficacy of naproxen and naproxen sodium is difficult to ascertain. The drug certainly has peak effects comparable to those

[1]SPID = Subjective pain intensity difference scores summed over the hourly observation. TOTPAR = Subjective pain relief scores summed over the hourly observations.

[2]Partial data reported.

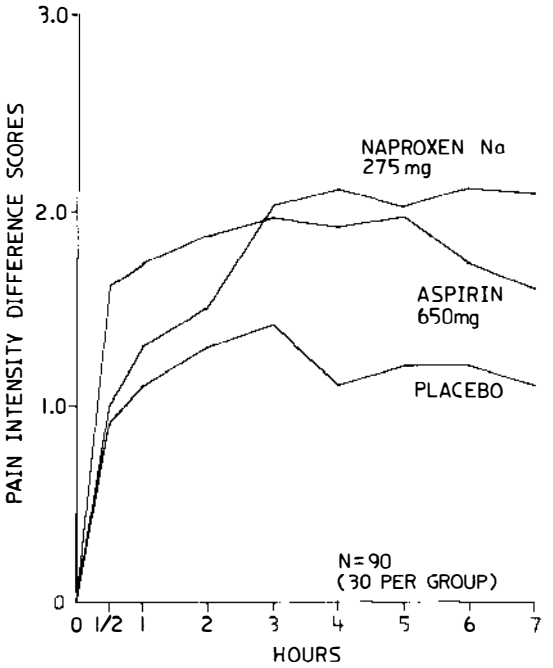

Figure 8 Time-effect curves from a postpartum uterine cramp study comparing naproxen sodium 275 mg, aspirin 650 mg, and placebo. Time in hours is plotted against pain intensity difference scores. Adapted from Bloomfield et al (29).

of aspirin or acetaminophen and its duration of action appears more prolonged. However, the drug has not been systematically compared to optimal dosages of opioid combinations; thus the consistent data necessary to conclude whether it is actually superior to aspirin or acetaminophen is lacking. This situation is unlike that of most of the other new peripherally-acting analgesics, whose superiority to aspirin is unquestioned.

At the recommended dosage range of 275–550 mg, naproxen sodium's side effect profile appears similar to that of aspirin's. One recent study indicated that naproxen sodium may cause less gastric pathology than aspirin (32).

Indoprofen

Indoprofen is an iso-indoline propionic acid defined as dL–α[4-(1-oxo-2-isoindolinyl)-phenyl]-propionic acid. It is a weak acid with relatively low pKa. The drug remains predominantly in the ionized form in blood and diffuses poorly through the blood-brain-barrier, which explains its weak antipyretic activity.

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After oral administration, indoprofen is rapidly absorbed and reaches peak plasma levels within 2 hours. Although the drug is approximately 99% protein bound, the half-life is estimated to be only approximately 2 hours. Within 24 hours 80% of the drug is excreted in the urine primarily as the glucuronide metabolite (33, 34).

Indoprofen appears similar to other propionic acids in relation to drug interactions. A reversible inhibition of platelet aggregation occurs which peaks in 4–8 hours and may last up to 24 hours (35). On chronic administration, prothrombin time can increase significantly, but this effect should not be a factor in short-term therapy. As with aspirin, indoprofen should be used cautiously with asthma patients, and patients taking anticoagulants or hypoglycemic agents.

Indoprofen has been studied in a variety of painful conditions including cancer, postpartum, postsurgical, and dental surgery. Oral indoprofen was administered to 329 cancer patients in 10 studies. In one well-controlled single-dose study, Ventafridda et al (36) reported dose-related analgesic effects for indoprofen 100 mg and 200 mg with the indoprofen found to be slightly more efficacious than aspirin 1000 mg (Figure 9). Fucella et al (37)

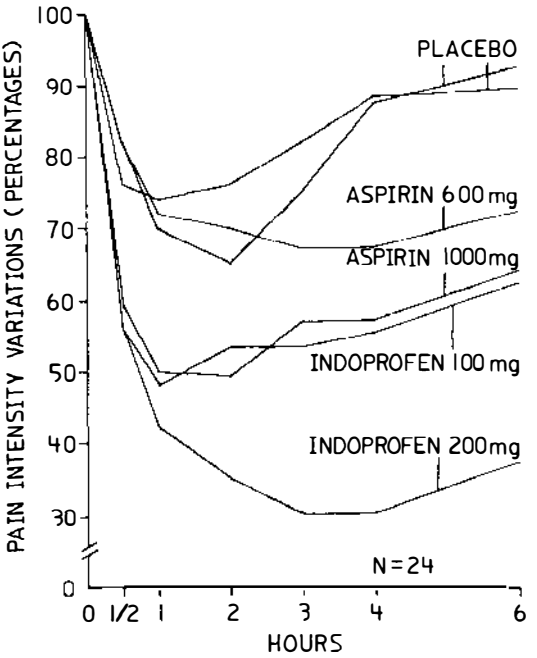

Figure 9 Time-effect curves from a cancer pain study comparing indoprofen 100 mg and 200 mg, aspirin 600 mg and 1000 mg, and placebo. Time in hours is plotted against pain intensity variation percentages. Adapted from Ventafridda et al (36).

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also found a dose-related analgesic effect for indoprofen 100 mg and 200 mg with both dosages being superior to placebo. Unfortunately, this study had no standard agent for comparison. In both of these studies indoprofen appeared to have an analgesic effect for six hours. Other cancer studies have supported these results (38, 39).

Postpartum pain resulting from episiotomy is one of the most commonly used models. Indoprofen was evaluated in three separate well-controlled studies using postpartum episiotomy pain. Wideman (40) compared the single dose efficacy of indoprofen 200 mg and 100 mg, aspirin 600 mg, and placebo in 95 postpartum patients. The indoprofen treatments did not differ from each other, but both were statistically more effective than placebo and aspirin. However, the comparison to aspirin is not completely valid in this study owing to a discovery of a delayed dissolution of the aspirin.

Sunshine (41) performed a six-cell postpartum study with 210 patients in which each patient received a single dose of either placebo, aspirin 300 mg, aspirin 600 mg, indoprofen 50 mg, 100 mg, or 200 mg. Patients were interviewed hourly for six hours and standard statistical methods were applied to the derived efficacy measures SPID and TOTPAR. All active treatments were more effective than placebo, with indoprofen 100 mg and 200 mg being the most effective treatments. A dose-response was evident only between indoprofen 50 mg and 100 mg (Figure 10). This is one of many studies that indicated 100 mg is the optimal analgesic dosage of indoprofen.

McMahon (42) compared single doses of 50 mg and 100 mg of indoprofen, 600 mg aspirin, and placebo in 120 postpartum patients with similar results to the two previously cited postpartum studies. Overall, in the postpartum studies, indoprofen 100 mg appeared to have a higher peak effect and longer duration of action than aspirin 600 mg.

The most definitive studies were performed using pain resulting from dental surgery. Cooper et al first compared indoprofen 100 mg and 200 mg to aspirin 600 mg and placebo in 201 subjects (43). Although there was no significant difference between the two dosages of indoprofen, both were clearly superior to aspirin. Using the same study design McMahon produced very similar results (44). In a follow-up study by Cooper et al including 200 subjects, indoprofen 200 mg was significantly more effective than acetaminophen 650 mg alone and in combination with either codeine 60 mg or propoxyphene napsylate 100 mg (Figure 11) (45).

In postsurgical orthopedic and abdominal pain, Okun (46) compared single doses of indoprofen 100 mg and 200 mg, aspirin 600 mg, and placebo. All active treatments were statistically better than placebo and indoprofen was the most effective treatment.

Many other studies in a variety of painful conditions were performed using open designs or protocols not including a placebo control. Although

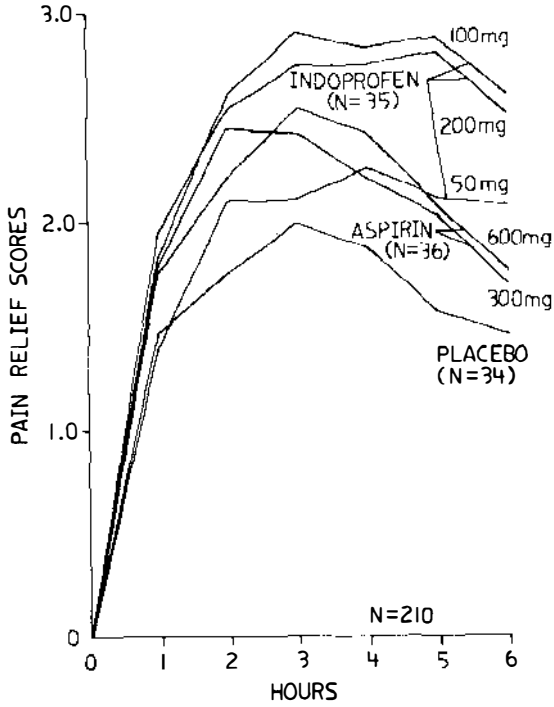

Figure 10 Time-effect curves from a postepisiotomy pain study comparing indoprofen 50 mg, 100 mg and 200 mg, aspirin 300 mg and 600 mg, and placebo. Time in hours is plotted against pain relief scores. Adapted from Sunshine (41).

these studies are of limited use, they also supported the conclusions that indoprofen 50 mg to 200 mg is an effective analgesic in a variety of painful conditions.

The side effect profile of indoprofen appears similar to that of aspirin, and ibuprofen. Several large multicenter trials account for the most accurate delineation of the side effect profile for indoprofen (33, 34). A review of these longer term studies did not reveal any unusual toxicities. In addition, in the variety of laboratory tests performed during the course of the clinical studies, there was no consistent alteration in any particular test. Occult blood loss occurred but was consistently less than that found with aspirin. There also was some prolongation of prothrombin time on chronic administration and a self-limiting inhibition of platelet inhibition. As previously stated, the clinical relevance of these findings is not substantiated.

Overall indoprofen appears to be a safe and effective analgesic in the dosage range of 50 mg to 200 mg every 4–6 hours. Both its peak effect and duration of activity appear significantly better than usual dosages of aspirin

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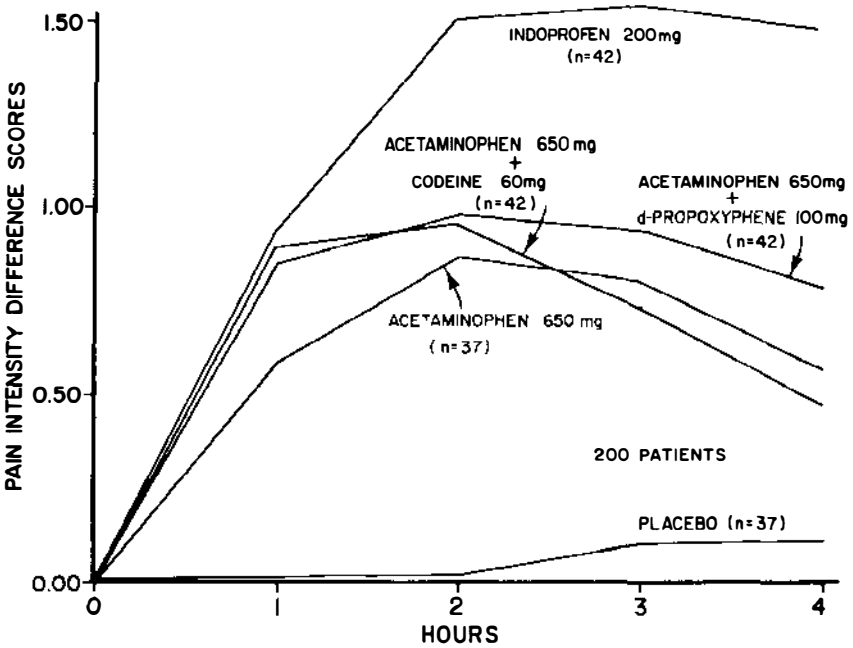

Figure 11 Time-effect curves from a dental impaction pain study comparing indoprofen 200 mg, acetaminophen 650 mg with codeine 60 mg, acetaminophen 650 mg with propoxyphene napsylate 100 mg, acetaminophen 650 mg, and placebo. Time in hours is plotted against pain intensity difference scores. Adapted from Cooper et al (45).

or acetaminophen. The drug may offer an additional advantage by having only weak antipyretic activity in that fever resulting from postsurgical infections would not be masked.

Zomepirac Sodium

Zomepirac sodium is one of the most interesting new peripherally-acting analgesics. Structurally, it most closely resembles indomethacin but substitutes a pyrrole nucleus in place of an indole nucleus (Figure 12). Indomethacin is one of the most potent inhibitors of prostaglandin biosynthesis, and clinically it has both analgesic and anti-inflammatory properties. Although indomethacin is widely used for treating rheumatoid arthritis, it was never promoted for analgesic indications. The few studies that evaluated indomethacin's analgesic properties demonstrated efficacy in the range of aspirin 650 mg (47, 48). Probably because of centrally-mediated side effects, its analgesic potential was never fully explored.

The zomepirac sodium and tolmetin sodium molecules were formulated in the hopes of retaining the anti-inflammatory and analgesic properties of the indole-type structure without the side effect liabilities. Based on the

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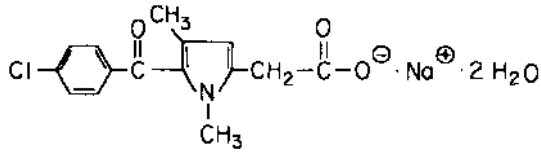

zomepirac sodium

Figure 12 Structure of zomepirac sodium -5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrole-2-acetate dihydrate.

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single-dose efficacy studies and multiple dose safety studies, the structural manipulation was quite successful. Tolmetin sodium now is marketed as an anti-inflammatory agent and zomepirac sodium as an analgesic.

The initial study performed by Cooper et al in 128 postsurgical dental impaction patients clearly demonstrated that the linear part of the dose-effect curve for zomepirac was between 25 and 100 mg and that both 50 and 100 mg were significantly more efficacious than aspirin 650 mg (Figure 13) (49). In two subsequent studies by Cooper and associates, zomepirac

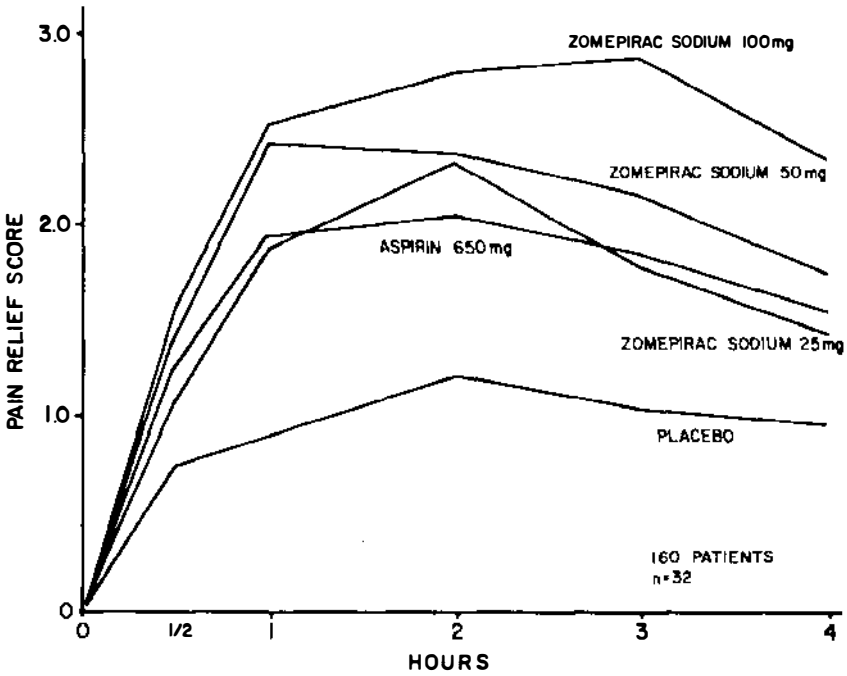

Figure 13 Time-effect curves from a dental impaction pain study comparing zomepirac sodium 25 mg, 50 mg and 100 mg, aspirin 650 mg, and placebo. Time in hours is plotted against pain relief scores. Adapted from Cooper et al (50).

sodium 100 mg was comparable to codeine 60 mg combined with APC 720 mg and to propoxyphene napsylate 100 mg combined with acetaminophen 650 mg (50, 51). In additional dental pain studies, Forbes et al found zomepirac sodium 50 mg and 100 mg statistically superior to orally administered codeine 60 mg, pentazocine 50 mg and propoxyphene napsylate 100 mg with acetaminophen 650 mg (52).

In a six-hour postoperative inpatient study, Baird et al repeated the APC-codeine comparison done by Cooper et al and obtained very similar results (Figure 14) (53).

The next series of studies were unique in that they were designed to find the dose of intramuscular morphine equivalent to zomepirac sodium 100 mg and 200 mg. Generally NSAIDs are not compared to intramuscularly administered narcotics. The studies utilized a "double-dummy" (oral lactose or i.m. saline) technique to maintain double-blind conditions. In the first postoperative study conducted by Wallenstein et al (54), zomepirac sodium 100 mg was consistently more effective than morphine 8 mg. In the second study (55), Forrest found zomepirac sodium 100 mg and 200 mg more effective than morphine 8 mg (Figure 15). These results are impressive in that both these investigators have much experience in evaluating centrally-acting injectable analgesics.

In several repeated-dose studies, zomepirac sodium proved equieffective, and in some cases more effective, than the codeine-containing combination products (56–58). These studies also indicated that zomepirac sodium is generally better tolerated with a lower incidence of gastrointestinal and central-nervous system effects than combinations containing optimal amounts of opioid agents.

At the indicated dosage of 100 mg, zomepirac sodium is clearly superior to aspirin 650 mg. It has a fast onset and approximately a six-hour duration of effect. The most common side effects include gastrointestinal reactions similar to those caused by aspirin. Other side effects include drowsiness, dizziness, sweating, and fluid retention.

Zomepirac sodium is excreted mainly in the urine as the glucuronide metabolite (59). Patients with impaired renal function should be closely monitored and whenever aspirin therapy is contraindicated, zomepirac sodium should not be used.

Beaver edited a comprehensive review of original research on zomepirac sodium, and Lewis published a more general review (60, 61).

Diflunisal

Diflunisal, 5-(2',4'-difluorophenly)-salicylic acid, is a derivative of salicylic acid (Figure 16). However, it is not metabolized to salicylic acid. Peak plasma concentrations are attained within approximately two hours, and

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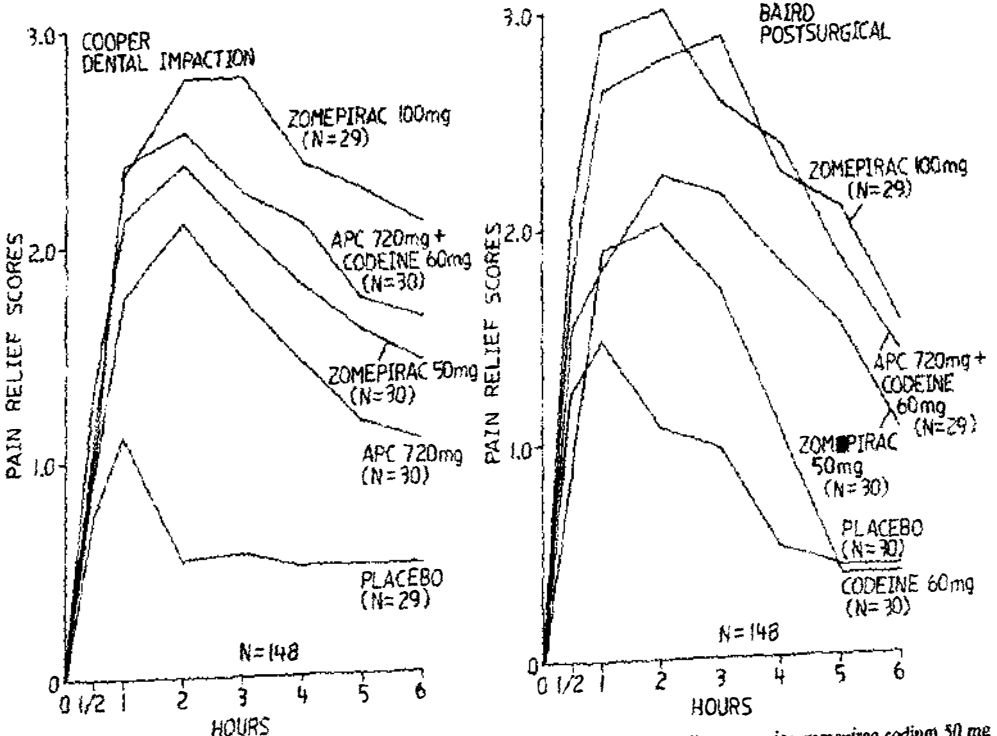

Figure 14 Time-effect curves from both general postsurgical and dental impaction pain studies comparing zomepirac sodium 50 mg and 100 mg, APC 720 mg with codeine 60 mg, codeine 60 mg, and placebo. Time in hours is plotted against pain relief scores. Adapted from Cooper (50) and Baird et al (53).

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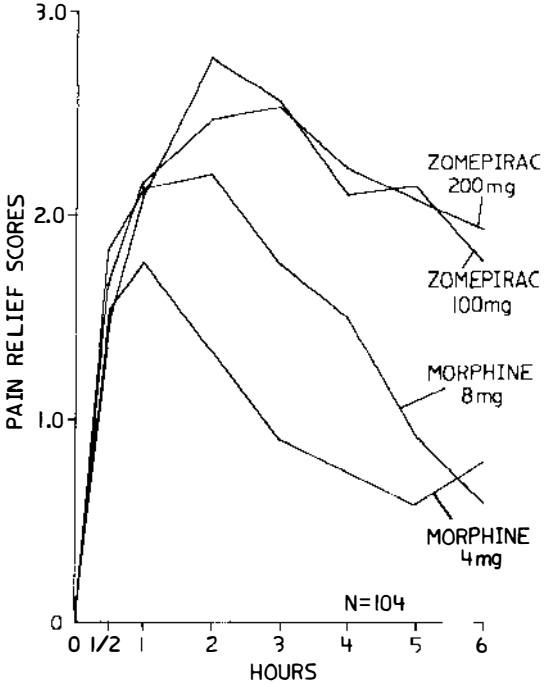

Figure 15 Time-effect curves from a postsurgical study comparing oral zomepirac sodium 100 mg and 200 mg to intramuscular morphine 4 mg and 8 mg. Time in hours is plotted against pain relief scores. Adapted from Forrest (55).

with twice a day dosages of 500 mg, steady-state concentrations are reached in 7–9 days. The drug is highly protein bound and is excreted in urine as unchanged or conjugated drug. Diflunisal has a half-life of approximately eight hours. In patients with renal insufficiency, this figure can change markedly. In contrast to aspirin, diflunisal reversibly inhibits platelet aggregation, and it also appears to be less irritating to the gastrointestinal tract (62). The general spectrum of side effects is similar to aspirin's. Brogden et

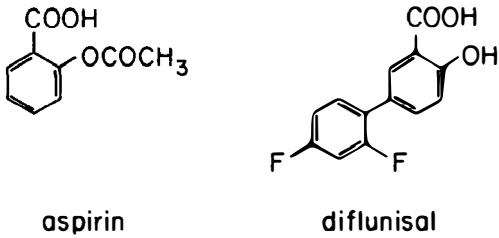

Figure 16 Structure of diflunisal -5-(2',4'-difluorophenyl)-salicylic acid.

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al (63) and Tempero et al (64) have published comprehensive reviews on diflunisal's pharmacokinetic and pharmacodynamic properties.

The recommended dosage of diflunisal is 500 mg twice a day. The primary studies to support this indication were performed in postoperative dental pain. Forbes et al have done four separate twelve-hour dental studies recording data hourly under double-blind conditions. In one study, diflunisal 500 mg and 1000 mg appeared to have a substantially longer duration of action and a higher peak effect than aspirin 650 mg (65). A second study demonstrated that diflunisal 1000 mg was superior to propoxyphene napsylate 100 mg -acetaminophen 650 mg combination in terms of peak and total effects and percentage of patients achieving 50 percent relief (Figure 17) (66). In a third study (67), diflunisal 500 mg and 1000 mg was compared to an acetaminophen 600 mg with codeine 60 mg combination. Both dosages of diflunisal were similar, with peak effects slightly greater than the combination drug. Diflunisal had a much longer duration of action than any of the other treatments. In the fourth dental study, diflunisal 1000 mg was compared to zomepirac sodium 100 mg. Diflunisal appeared to have a slightly slower onset of activity, an equivalent peak effect, and a longer duration of action (68).

In postoperative pain following general and orthopedic surgery, Forbes and associates did a 12-hour evaluation comparing diflunisal 500 and 1000

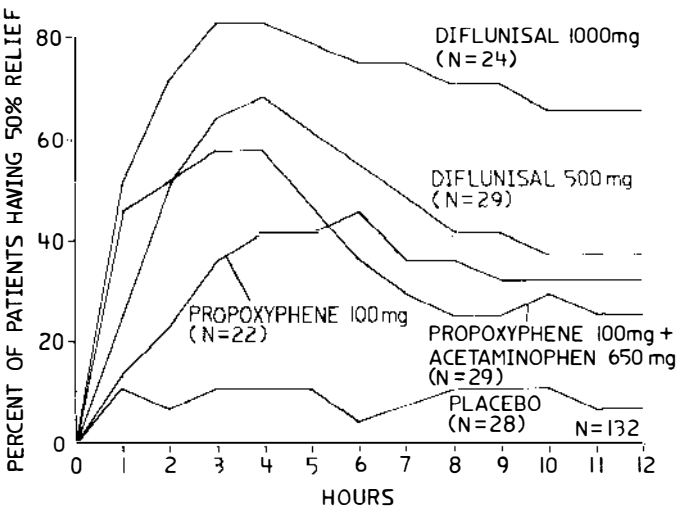

Figure 17 Time-effect curves from a dental impaction pain study comparing diflunisal 500 mg and 1000 mg, propoxyphene napsylate 100 mg, propoxyphene napsylate 100 mg with acetaminophen 650 mg, and placebo. Time in hours is plotted against percent of patients having 50 percent relief. Adapted from Forbes et al (66).

mg to an acetaminophen 600 mg -codeine 60 mg combination (69)[3]. Diflunisal 1000 mg appeared equal in peak analgesia to the combination with a significantly longer duration of effect.

In other studies using postepisiotomy (70) and postsurgical meniscectomy (71) pain, diflunisal's 500 mg peak effect was quite similar to aspirin's, whereas its duration of effect appeared more prolonged. Unfortunately no investigator has reported studies comparing diflunisal 1000 mg to equivalently large dosages of aspirin or acetaminophen. This would give a better approximation of diflunisal's peak and total effects compared to the maximum allowable over-the-counter NSAIDs. Aside from the work of Forbes and associates, there is little published to substantiate a greater peak effect for diflunisal compared to aspirin. However, there is substantial data demonstrating an 8–12 hour duration of effect for diflunisal 500–1000 mg. In addition to its greater duration of effect, diflunisal appears to have a more favorable side effect profile than aspirin.

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Other Peripherally-Acting Analgesics

There are many other agents in various stages of development that may eventually be approved for analgesic indications. Space constraints permit only brief mention of a few of these agents that are near NDA submission. The majority of these drugs are propionic acid derivatives.

Our group has evaluated suprofen, carprofen, flurbiprofen, and ketoprofen using the dental pain model. A summary of results from these studies is presented in Figures 18–20 (72–75). Again, all four of these propionic acid drugs appear substantially more effective than aspirin 650 mg both in terms of peak and total effects. Their side effect profiles appear similar to the other marketed propionic acid derivatives. Flurbiprofen is quite potent and possibly can be formulated for a time-released effect while maintaining a small tablet size.

Fenoprofen is a marketed propionic acid derivative that has both anti-inflammatory and analgesic indications. There is little published data on its analgesic efficacy, but the available data indicates that the drug is quite similar to ibuprofen (76, 77, 77a).

Aside from some variation in potency and some small differences in duration of action, there does not appear to be very much difference among the propionic acid derivatives.

Piroxicam, 4-hydroxy-2-methyl-N-(2 pyridyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide, was recently approved by the FDA as a once per day anti-inflammatory agent (78). The drug also may have prolonged analgesic activity, but more definitive studies are necessary (personal communication, Pfizer laboratories).

[3]Partial data reported.

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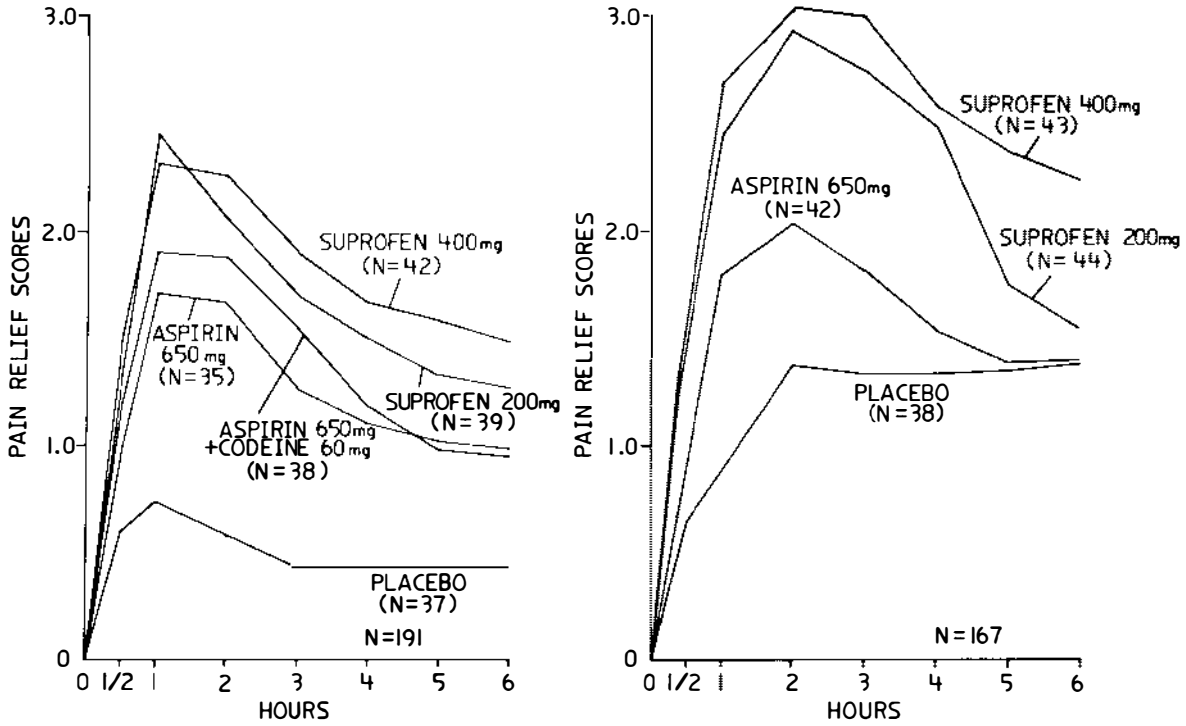

Figure 18 **Time-effect curves from dental impaction and periodontal pain studies comparing suprofen 200 mg and 400 mg, aspirin 650 mg with codeine 60 mg, aspirin 650 mg, and placebo. Time in hours is plotted against pain relief scores. Adapted from Desjardins et al (72).**

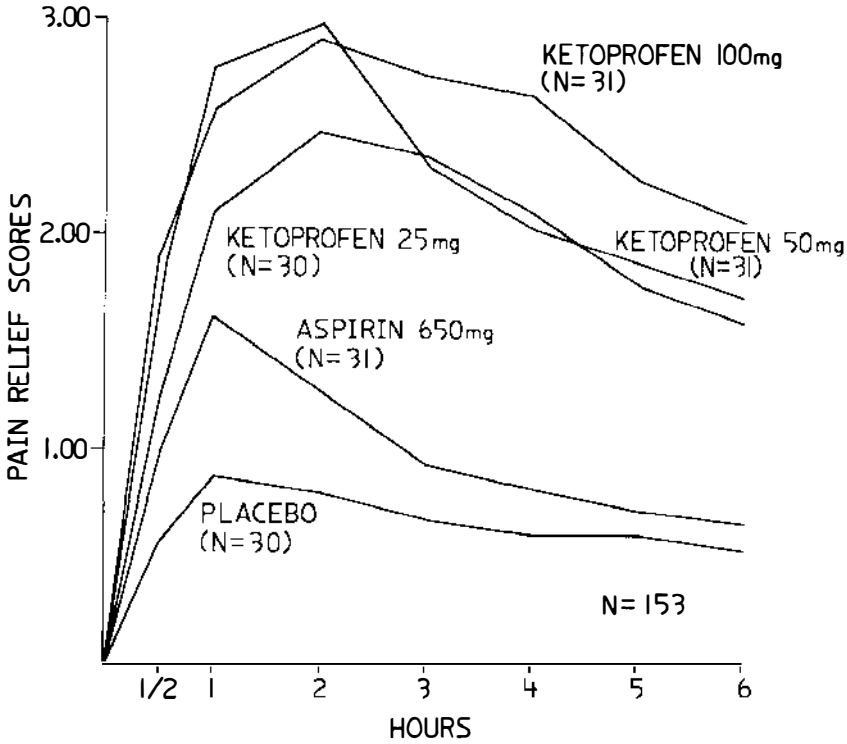

Figure 19 Time-effect curves from a dental impaction pain study comparing ketoprofen 25 mg, 50 mg and 100 mg, aspirin 650 mg, and placebo. Time in hours is plotted against pain relief scores. Adapted from Cooper et al (74).

Fendosal, a salicylic acid derivative, also appears to have a similar peak effect to aspirin with a prolonged duration of action (79). This drug also may eventually be approved for both anti-inflammatory and analgesic indications.

CONCLUSIONS

It is obvious from the available data that the new peripherally-acting analgesics provide greater analgesia than aspirin and acetaminophen. The propionic acid derivatives and zomepirac sodium appear to have a fast onset and greater peak activity than aspirin. For several, the duration of action also appears to be moderately improved over aspirin and acetaminophen. A few of the new agents have exceptionally prolonged duration of activity. Diflunisal appears to be at least as effective as aspirin with a much longer duration of effect. Piroxicam possibly may be a once per day analgesic.

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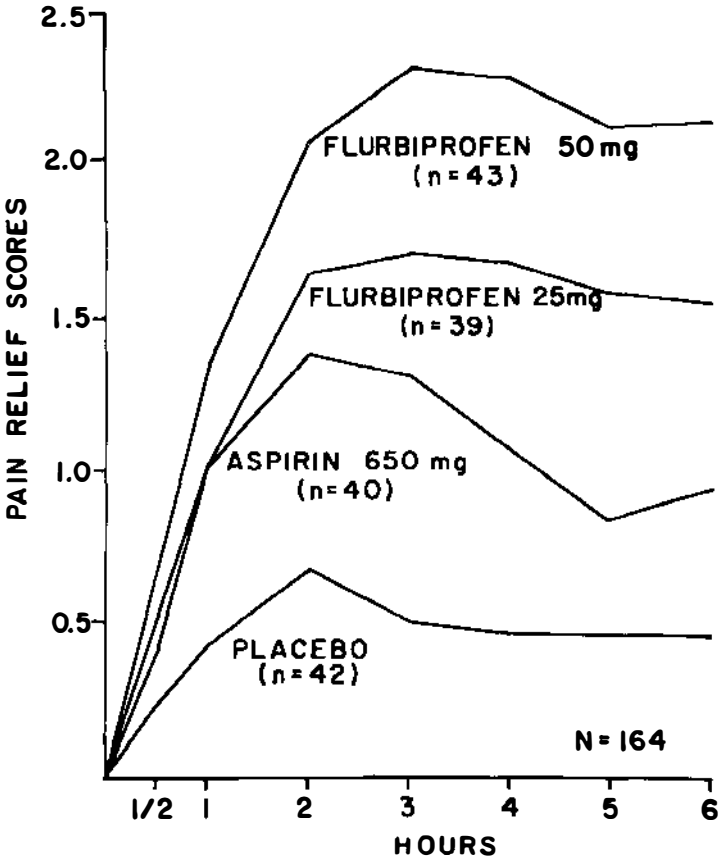

Figure 20 Time-effect curves from a dental impaction pain study comparing flurbiprofen 25 mg and 50 mg, aspirin 650 mg, and placebo. Time in hours is plotted against pain relief scores. Adapted from Cooper et al (75).

However, the drugs with unusually long activity do not appear to have as consistently high peak effect as zomepirac sodium or many of the propionic acid agents.

Almost without exception the new peripherally-acting analgesic agents have a more favorable side effect profile than aspirin. However, when aspirin is contraindicated, all of these new agents are either contraindicated or must be used with extreme caution. Acetaminophen still remains the safest agent when used in therapeutic dosages.

The new peripherally-acting analgesics have a totally different mechanism of action than the centrally-acting analgesics, and this is reflected in the qualitatively different results when used clinically. Several of the new

peripherally-acting agents are currently being studied in combination with codeine or other similar opioid derivatives (15, 31). The increased efficacy of the peripheral component should permit using minimal dosages of the central component to obtain the desired centrally-mediated effects. Certainly in many instances where previously an opioid combination was necessary, the new peripherally acting agents now can be substituted without compromising analgesic efficacy.

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