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Analgesic Activity of Floctafenine in Post-Cholecystectomy Patients

by

Marilyn Emily Brown

Thesis presented to the School of Graduate Studies in partial fulfillment of the requirements for the degree of Master of Science in Pharmacology

UNIVERSITY OF OTTAWA
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I LITERATURE REVIEW

A. INTRODUCTION

Pain is a major human concern influencing every aspect of life; in disease it is the most frequent symptom which compels patients to seek medical counsel. Whereas acute symptomatic pain serves the useful purpose of warning the individual and is a useful diagnostic aid for the physician, chronic pathological pain often imposes severe emotional, physical and economic stresses on the patient, on his family, and on society.

The ubiquity of pain as a signal of tissue damage leads most of us to expect its occurrence after injury. We take it for granted that the intensity of pain we feel is proportional to the extent of damage. In fact, there is much evidence (Beecher, 1956; Petrie, 1967; Melzack, 1973; Melzack and Chapman, 1973) that pain is not simply a function of the amount of bodily damage alone. Rather, the amount and quality of pain we feel are determined by a number of factors, including cultural values, past experiences and how well we remember them, the meaning of the pain-producing situation, together with other influences such as attention, distraction, anxiety and suggestion.

Burke (quoted by Beecher, 1959 a: p. 62) has said "Pain and pleasure are simple ideas incapable of definition". Bishop (quoted by Beecher 1959 a: p 62) defined pain as "what the subject says hurts". A so-called operational definition of pain, where criteria such as the subject's statement, a cry, a skeletal withdrawal, or other reflex are employed to denote the presence or absence of pain, is still not a definition in any asatisfactory sense. Pain refers to an experience, not to the behaviour produced by that experience.

Melzack (1967) has perhaps formulated the most successful definition of pain. He defined pain as a perceptual experience whose quality and intensity are influenced by the unique past history of the individual, by the meaning he gives to the pain-producing situation and by his "state of mind" at the moment. In this way,

pain becomes a function of the whole individual, including his present thoughts and fears as well as his hopes for the future. Pain, therefore, can be said to represent the results of at least three neurophysiological processes:

1) a sensory-discriminative process whereby stimuli are localized in space, time and along an intensity continuum.

2) a motivational-affective component which provides the powerful drive and unpleasant effect that triggers the organism's protective mechanisms, and

3) cognitive influences such as anxiety, anticipation or memory of past experiences.

There are several possible approaches to the symptomatic relief of severe pain including: interruption of afferent pathways, either chemically or surgically; "dissociation" of the patient from his pain as achieved by such psychological devices as suggestion or hypnosis; interruption of perceptual pathways by pharmacological means. Today the most widely used method of treating pain, both acute or chronic, is pharmacotherapeutic intervention.

Pharmacological intervention may involve the utilization of narcotic or of non-narcotic analgesics. While the opiates and opioids as a group are reliable and powerful analgesics they possess features which lead to tolerance and possess a high potential for psychic and physical dependence. The non-narcotic analgesics generally available today have other disadvantages, the two most important being:

1) Their inefficacy against severe pain.
2) Their high incidence of side-effects, particularly in causing gastrointestinal reactions.

There is thus a continuing need for a pain-relieving drug which:

1. produces analgesia of a quality similar to that of morphine.
2. is effective when administered orally i.e. has adequate gastrointestinal absorption.
3. causes little or no respiratory or circulatory depression.
4. has a low side-effect potential especially in regard to the central nervous system, the gastrointestinal tract and renal functions.
5. is non-addicting.
6. causes little or no development of tolerance to the analgesic effect (Foldes, 1974; Houde, 1974)

Pharmacological relief of pain may be assessed in man or animals, although clinical assessment is the ultimate test of any analgesic (Houde and Wallenstein, 1956). Nontheless, much controversy exists concerning the best means of clinical assessment of analgesics, especially when judging the efficacy of oral analgesics. It has been long-accepted that the patient's verbal statement is the best indication of pain relief (Beecher, 1959 a; Lutterbeck and Triay, 1972). The behavioural (or objective) approach has received very little attention. As there is some evidence that the behavioural approach may be at least as sensitive as the subjective approach (Parkhouse and Holmes, 1963) these two methods of assessment will be compared in the present study.

B. MEASUREMENT OF ANALGESIC ACTIVITY

The analgesic activity of drugs has been evaluated using three different approaches;

1) by the measurement of relief of experimentally-induced "pain" in animals.
2) by the measurement of relief of experimentally-induced pain in man, and
3) by clinical assessment or the measurement of relief of pathological pain in man.

Most of the early studies done using experimentally-induced pain were done on man; the use of animals as subjects is more recent. Miller (1948) has commented that since pain is a subjective phenomenon, it should be more easily characterized in man than in an animals. Somewhat paradoxically the opposite seems to be the case as far as experimental pain is concerned. In any case, final appraisal of analgesic action must be based on the capacity of the agent to relieve naturally occurring pain such as is a result of disease or trauma.

1. Utilization of Experimentally-Induced Pain in Animals

Powerful analgesic drugs such as morphine and meperidine relieve pain arising from almost all pathological sources. They do not reliably raise pain threshold in man but they do raise the reaction threshold in animals. The pain threshold can be defined as the first barely perceptible pain to be reported in an instructed subject under given conditions of noxious stimulation. The human subject exposed to experimental pain realizes that the experience poses no real threat to him, while with pathological pain the consequences are potentially serious, possibly threatening life itself.

An animal, on the other hand, can scarcely be expected to make such a distinction. When a potentially painful stimulus is given to an animal, the experimenter commonly takes as an end-point a reflex movement of some sort, although it can not be said with assurance that the animal feels pain at this point. The point at which the animal responds is therefore more properly referred to as a "reaction threshold" rather than a "pain threshold". As Beecher (1962: p. 143) says "Pain is pain to an animal, presumably, and all pain (is) serious and significant". Elevations in reaction thresholds in animals may thereforebe regarded as very different from changes in pain tolerance in man, but may correspond more closely to pathological pain.

The ultimate value of analgesic assays in animals is based on how well the results can be used to predict clinical therapeutic activity. The finding that nalorphine was nearly equivalent in clinical analgesic potency to morphine was at first greeted with surprise because nalorphine was inactive in animal analgesic assays, such as the hot plate and tail flick tests commonly used at that time. In fact, nearly a decade later, inactivity in the mouse hot-plate test was a criterion employed that led to the characterization of pentazocine as a 'non-addicting' analgesic, because activity in this test was thought to be more nearly related to addiction liability than to analgesic utility. (Archer et al, 1964).

Houser and Paré (1973) have outlined the characteristics of an acceptable pharmacological test for analgesia as the following:

1. sensitivity - the ability to detect various classes of drugs at relatively low doses known to be analgesic in man
2. specificity - responsive to only those agents that are active in man
3. objectivity - response measured should not rely on a subjective evaluation

4. the procedure should reflect higher nervous function - not simply spinal reflexes
5. simplicity of behavioral response - so that cognitive processes are not involved
6. reliability - the test should give nearly identical results when repeated.

Animal experiments offer advantages that make them an indispensable preliminary and complement to clinical trials. These advantages include:

1) the abundance and ready availability of experimental animals.
2) the method is relatively inexpensive and permits rapid accumulation of results suitable for statistical analysis
3) the histories of the animals in a particular sample can be much more alike than is possible in a human sample, that is, there is a possibility of working on genetically homogeneous subjects, and
4) the fact that the animal experiments are not subject to the same ethical restrictions as experimentation in man (Harris, 1956).

Unfortunately, the correlation of analgesic performance in animals with that in man has left much to be desired, although some methods are more successful than others. While most methods are responsive to the effects of the narcotic analgesic agents, many fail in the evaluation of the salicylate (ASA) class of compounds and/or the narcotic antagonist analgesics.

One special problem with pain is that the "adequate stimulus" for it, is said to produce tissue damage with possible errors ensuing when subsequent measurements are made. A second problem is the assumption that the response in animals is truly a measure of pain. Many of the responses employed in animal studies are merely spinal reflexes which may not accurately reflect cortical and thalamic evaluation of pathological pain in humans. There is also the problem of the conditioning

of animals when they are used more than once; hence appropriate controls in technique of stimulus application and in sequence of agent administration are necessary.

The existing methods of algesimetry in animals can be divided into five categories - thermal, mechanical, chemical, electrical, and behavioural.

a. Thermal Methods

Of the thermal methods, the mouse hot-plate test (Woolfe and MacDonald, 1944); and rat tail-flick test (D'Amour and Smith, 1941) have found the greatest use. Thermal methods, though, reflect the ability of these drugs to inhibit spinal reflexes associated with thermal stimulation. Since pain in man is known to be mediated by higher centres, these tests may not provide a relevant animal model even for the narcotic analgesics. The tests are easy to perform, require little instrumentation and have a well-defined end-point. In one case, the response is paw licking, withdrawal, or escape attempts of mice when placed on a heated plate maintained at 55°C. and in the other, the tail movement of rats in response to radiant heat exposure. Repeated tests can be performed affording the advantage of using the animal as its own control and establishing time-response relationships in the same subjects.

These tests have generally been shown to be reproducible in determining relative potencies of narcotic analgesics at doses approximately ten times higher than those used in man. The mouse hot-plate test is useful only for narcotic analgesics. ASA-like drugs only prolong hot plate reaction times in mice at near toxic doses. Nalorphine-like drugs, are also ineffective in the mouse hot-plate test (Harris and Pierson, 1964).

The rat tail-flick test has been shown to be capable of detecting analgesic activity with both ASA and nalorphine-like drugs, although these findings are not consistent with all investigators. (Harris and Pierson, 1964; Winter et al, 1959).

The tail-flick test has been used less frequently with mice. As in the rat, ASA-like drugs are active only at near-toxic dose levels. Nalorphine-like drugs show a transient effect at high dose levels only (Taber, 1973).

b. Mechanical Studies

Pressure-induced pain was used for analgesic testing before the advent of the thermal methods. In its simplest form, pressure is applied to a rodent's tail with a forceps or artery clamp and the end-point is the animal's biting, squeaking or attempts of escape (Bianchi and Francheschini, 1954). Since this response is assumed to be mediated in the CNS at supra-spinal centres, it is more analagous to human pain. Unfortunately, it lacks complete objectivity as measurement involves a subjective judgement on the part of the experimenter. This method also has the drawbacks of lack of precision in measuring the amount of applied pressure and inability to use repeated stimuli because the tails become hypersensitive after a few tests. Several other methods have sought to gain more precision and repeatability by using a controlled gradual increase in pressure (Green, Young 1951).

Enhanced sensitivity can be achieved by measuring the reaction threshold after pressure is applied to inflamed tissue. Hyperaesthesia can be induced by inflaming a rat's paw with a subplantar injection of a yeast suspension (Randall and Selitto, 1957). Comparing drug-induced alteration in the thresholds of the inflamed and normal paws was originally thought to provide a means of discriminating narcotic from anti-inflammatory analgesics. Narcotics would be expected to raise the threshold of both paws; anti-inflammatory analgesics would affect only the inflamed paw. The narcotic antagonists, however, have no anti-inflammatory action yet they too raise only inflamed paw thresholds. (Winter and Flataker, 1965). Moreover, even ASA-type drugs can produce

analgesia in these tests under conditions in which their anti-inflammatory activity cannot be detected. (Gilfoil, Klavens and Grumbach, 1963).

c. Chemical Methods.

Since the initial observation that an intraperitoneal injection of a radio-opaque dye could elicit a syndrome characterized by squirming, stretching, cramping or writhing which could be blocked by various analgesics (Vander Wende and Margolin, 1956), a wide variety of chemicals with similar effects have been proposed as potential challenges for analgesic tests in mice and rats. A writhe is commonly considered to represent a combination or a sequence of arching of the back, pelvic rotation and hind limb extension. Perhaps the most widely used writhing agents have been phenylquinone and acetic acid. Other writhing agonists shown to be antagonized by analgesics in mice inlcude bradykinin, aconitine, ATP, potassium chloride, acetylcholine, epinephrine, oxytocin and hydrochloric acid (Taber, 1973). The agents differ in their time-response curves. It should be noted that there exist considerable strain differences in mice in response to writhing agents and differences in the sensitivity of the different writhing agents to the action of analgesics (Bhalla et al, 1973).

The chemical methods are simple to perform and require no instrumentation. Their major drawback is that many drugs with no proven clinical analgesic activity may be detected as "false positives" (Chernov et al, 1967). Adrenergic blocking agents, antihistamines, cholinomimetics, muscle relaxants, psychomotor stimulants, serotonin antagonists, MAO inhibitors, and neuroleptics have all been shown to be potent writhing inhibitors. Many of these false positives can be eliminated with careful scrutiny since all the drugs produced other performance decrements at doses equal to, or less than, those blocking writhing.

d. Electrical Methods

Although electric shock has been widely used as a nociceptive stimulus in conditioning experiments in animals it has found little use in analgesic screening tests until recently.

In a procedure developed by Evans (1961), the successive intensities at which a rat first flinches and then jumps after its paws are shocked on a grid serve as a measure of pain. It might be speculated that the flinch response reflects the first perception of pain by the animal and the jump response reflects an emotionally influenced reaction of the animal to pain. No drugs affect the flinch threshold but morphine, nalorphine, pentazocine and ASA all raise the jump threshold (Evans, 1962 and 1964).

In another procedure developed by Carroll and Lim (1960), vocalization and vocalization that persists after termination of the stimulus are determined by shocking a rat's tail. The vocalization "after discharge" threshold, that is vocalization after the cessation of the stimulus, has been claimed to be most sensitive for detecting the activity of all but the salicylate class of analgesics (Taber, 1973). A squeak response involves the participation of higher centres in the CNS than those of the heat methods.

Carroll and Lim (1960) found that morphine blocked vocalization after the shock at very low doses; but larger doses were required to block vocalization during stimulation. Lesions superior or rostral to the thalamus produced little effect on the response to shock, but transections of the thalamus blocked vocalizations after shock without affecting vocalizations during the shock. These findings seem to add more support to the notion that analgesic testing must use methods in which the response is governed by more complex levels of integration than required for simple reflexes.

Recently, procedures using tail-shock-evoked vocalization in mice have been used with greater frequency. By using the animals as their own controls to reduce individual variation and by implanting the electrodes subcutaneously to minimize impedance, as in the Nilsen procedure, more reproducible results have been obtained (Perrine et al, 1972). Drug sensitivity is comparable with that of thermal methods in mice. Narcotic analgesics are active in the tail shock test at virtually the same doses as in the hot plate tests. ASA-like drugs are only effective at near-toxic dose levels.

The thermal, mechanical, chemical and electrical methods have been compared in the following table to assess their effectiveness in predicting a therapeutic human dose of narcotics, narcotic antagonists and anti-inflammatory analgesics.

Table 1

Analgesic potency assayed with different nociceptive stimuli.
(data from Taber, 1973: p. 202)

	Thermal (rat tail-flick)	Mechanical (rat paw yeast)	Chemical (mouse phenyl-quinone writhing)	Electric (mouse tail-shock)
NARCOTICS				
Morphine	2	2	1	1
Codeine	2	2	1	1
NARCOTIC ANTAGONISTS				
Pentazocine	2 - 4	1	1	2
Nalorphine	2 - 4	1	1	2
ANTI-INFLAMMATORY				
Acetylsalicylic acid	3- 4	3	2	3
Aminopyrine	3- 4	2	2	3

Legend:
1 = active at 1 to 5 x human dose
2 = active at 6 to 25 x human dose
3 = active at 26 to 125 x human dose
4 = active at ≥125 x human dose

e. Behavioural Methods

The use of operant behavioural techniques for testing analgesic drugs is relatively new. In essence, this approach consists of administering a nociceptive stimulus to the animal which can be graded in intensity from subthreshold levels to a level which becomes aversive. The animal can decrease the intensity by the appropriate behavioural response. The "aversive threshold" can then be obtained.

Behavioral methods are probably best exemplified by the titration procedure designed by Weiss and Laties (1961). Their method utilized a titration schedule in which animals are trained to press a lever in order to decrease the current intensity of an electric shock applied through the floor of the experimental chamber. This method can be completely automated and detects narcotic and non-narcotic analgesics. Certain difficulties seem inherent in the use of this procedure. The very complexity of the behavior requires a considerable number of controls to ensure that the action of the drugs is upon the pain sense alone. Another difficulty is the determination as to whether the animal's response is due to an anticipation of the pain to come or the pain experience itself. A low shock stimulus may serve as a conditioned stimulus preceding a higher shock level (Evans, 1964).

A similar procedure has been developed by Weitzman and others (1961) for measuring pain in the monkey also with a titration schedule and electric shock. They noted that while barbiturates and chlorpromazine produced a shift in the shock level accepted, they also produced a change in the variability of the animal's response.

Rodriguez and Pardo (1968) determined the antinociceptive activity of various analgesics in the dog using the pain-induced functional impairment procedure. These authors state that perhaps one reason for the lack of correlation of results from experimental animal methods with clinical data is that current animal methods measure the capacity of the drug to increase the minimal stimulus required to elicit a nociceptive response. Clinically the efficacy of drugs can be measured in terms of their ability to reduce the effects of suprathreshold painful stimulation. (Beecher, 1959 a, Houde, Wallenstein and Rogers, 1960). The method of Rodriguez and Pardo takes advantage of an experimental situation which is analagous to clinical conditions in which analgesics are used, and considers the degree of utilization of the painful limb in ambulation as a non-verbal statement of the degree of pain or of its suppression by analgesic agents.

A weakness of these behavioral procedures lies in the degree of training and sophistication necessary for both the experimenters and the animals. The very complexity of the behaviour requires a considerable number of controls to ensure that the action of the drug are upon the pain sense alone as opposed to timing, memory or some other aspect of the schedule, such as negative reinforcement. Therefore, these methods are perhaps of greater theoretical interest than they are of practical importance as screening devices. However, the complete objectivity of the recorded response and the advantage of being able to obtain a continuing measurement of the animal's performance during the action of the drug partially compensates for the limitations of the method.

2. Utilization of experimentally-induced pain in man

The need for a method of experimentally-contriving pain in man to test the analgesic power of new and potentially useful drugs has resulted in many approaches but results obtained with each of these methods have not been able to dependably predict analgesic effectiveness against pathological pain.

The assumption of all methods using experimentally-induced pain in man to measure the effectiveness of analgesics is basically that analgesics will raise the normal pain threshold. Hardy, Wolff and Goodell have long advocated the view that the pain threshold represents perception of pain and that the threshold for perception of the pain under normal circumstances is approximately the same in all subjects and in the same subject at varying times of the day. There is a notable lack of confirmation of this view, not only with their own radiant heat technique but by other methods as well (Beecher, 1959a).

The variability of the pain threshold may well be accounted for by the reaction or processing component influencing the pain threshold. Beecher (1959a) has summarized considerable evidence for the importance of the reaction component in analgesic studies demonstrating:

1) effectiveness of emotion in blocking pain, for example that of euphoria or that of anger in combat, or fear.
2) significance of the wound in determining the pain experienced
3) the powerful effect of placebos, and
4) the evidence for the greater effect of placebos in the presence of increased stress.

Many other factors may affect the pain threshold including age, sex, race, diurnal variation, fatigue, adaptation and suggestion, just to name a few (Beecher 1959a). It is difficult, if not impossible, to reproduce in the laboratory the reaction component produced by the pain of disease or trauma. This has imposed a very great limitation on experimental pain to the present time. The very fact that powerful analgesics have not clearly been shown to produce a dependable elevation of experimental pain threshold in man, yet are universally found to be effective in treating pain of pathological origin indicates a difference between experimentally-induced pain and pain of pathological origin. (Beecher, 1962).

In comparing experimental pain in man to that of animals, there are obvious advantages in working with humans rather than animals. The subject can report and describe his pain. Also the fate and action of the drug can be compared to its fate and action in humans with pathological pain (Harris, 1956).

There are however distinct disadvantages in working with humans in the laboratory. Susceptibility of humans to distraction, diversion, and distortion of the truth is almost certainly greater than in animals. Reliable controls are therefore necessary. Control of humans between experiments is also far less satisfactory than with animals. The subjects who are ambulatory may be more influenced by nauseant, emetic or sedative effects of a drug (Harris, 1956). The acquisition of subjects is an important practical problem. It is legally desirable to call on volunteers although Lasagna (1954) in an analysis of this problem has shown that the volunteer is by no means representative of the average subject.

Numerous thermal, mechanical, electrical and chemical methods have been used to induce experimental pain in man.

Hardy, Wolff and Goodell (1940) produced pain by focusing radiant heat of increasing intensity on the forehead and measured changes in the pain threshold reported. There have been many failures in attempts to confirm constancy of pain threshold in man using radiant heat methods.

Wolff, Kantor, Jarvik and Laska (1969) compared two analgesic assays, namely electrical stimulation of two fingers and ice-water (cold-pressor) stimulation of each hand. They found that both methods are valid instruments for analgesic assay and that pain tolerance is a more sensitive instrument of analgesic efficacy than pain threshold. Secobarbital influenced the pain responses to electrical stimulation but had no significant effect on those to cold-pressor stimulation.

Tibial pressure algesimetry has been used for assessing analgesia. Thorpe (1966) feels it can be used successfully provided adequate numbers of subjects are investigated and results are compared to a control group simultaneously investigated under blind conditions.

Harris (1956) favours the tooth pulp as a site for stimulation. This, he believes, contains only pain fibres although he and others have

reported a pre-pain sensation from electrical stimulation. Evidence has been presented by Reynolds and Hutchins (1948) that painful stimulation of teeth produces a hyper-irritable central state which persists from months to years. What influence this might have on repeated determinations of pain threshold by electrical stimulation of teeth is not known but very suspect.

Isbell and Frank (quoted by Beecher, 1959a), found no consistently reproducible threshold in man with electric shocks to teeth, nor did Bishop. Beecher (1959a: p. 81) states "In view of the remarkable inconclusiveness of the method of electrical shocks to teeth in man, it is difficult to accept work which depends upon the method and technique". Threshold changes in dogs, though, using tooth pulp stimulation are more impressive than in man.

Possibly one difficulty with experimental pain methods is that the experimental pain produced is usually sudden and fleeting, "pricks", "jabs", "stabs" of pain and so on, whereas most clinical pain, aside from some of the colics, is much more sustained. Moreover it is difficult or impossible to control the pain aroused by sudden pressure on a wound or colicky pain with even large doses of powerful narcotics.

Beecher and certain other authors do not exclude the use of experimental pain and suggest that it can be related to clinical pain if it is induced slowly, for instance by means of a tourniquet on the arm.

In the sub-maximum effort tourniquet technique pain is produced by having the subject squeeze a hand exerciser 20 times after a tourniquet had been inflated around his upper arm. Time is recorded for pain to build up to levels designated as slight, moderately distressing, very distressing and unbearable. The number of squeezes is fixed rather than variable and is fixed at a number fewer than the number that the subject could give under maximum effort instructions. Smith and co-workers found significant differences between placebo, 7.5 and 15 mg. of

intravenous morphine using this technique (Smith et al, 1968).

In a further study Smith and colleagues (1969) found that they could distinguish between placebo and ASA 600 mg using this technique but this was only significant for moderately distressing and very distressing pain. These results have yet to be confirmed by others, though. Further study is needed using this technique in order to determine its value as a tool in algesimetry.

3. Clinical Assessment

Despite periodic waves of interest in experimental pain, clinical pain has become more widely used in the assessment of analgesic activity. Unfortunately, the clinical yardstick has not in itself been a completely reliable standard, for the medical literature is replete with conflicting reports of the efficacy of many analgesic drugs but there is still considerable division of opinion on many aspects of analgesic testing in man (Houde and Wallenstein, 1956).

a) Factors Affecting the Response to Analgesics in Pathological Pain.

The response to analgesics in patients with pain of pathological origin may be affected by patient, drug or observer variables (Keats, Beecher, Mosteller, 1950; Houde and Wallenstein, 1956 and others).

The need for standardization of the population is shown by many variables such as personality, previous experience and upbringing or continued psychological stress which may affect man's reaction to pain. Conflicting evidence has been produced relating to the influence of sex and age on response to pain.

It is often believed that women withstand pain better than men although there is virtually no experimental evidence to back this widely-held notion. Woodrow and associates (1972) using experimentally-induced pain in 41,119 subjects found that men tolerated more pain than women. The difference was highly significant. In addition, pain tolerance

varied less among women than men. Wolff and his associates (1966) also, have found sex differences with women giving lower mean pain threshold and pain tolerance responses than men when age and ethnic groups were help constant, although there were large interindividual differences. Parkhouse, Lambrechts and Simpson (1961) compared drug requirements of men and women following appendectomies but found no statistical differences. Loan, Morrison and Dundee (1968) when studying postoperative pain concluded that the sex of the subject did not appear to influence response to treatment.

Old people, also, are generally thought to be relatively tolerant of pain although Loan, Morrison and Dundee (1968) have found that age does not appear to influence response to treatment. Wolff (1966) have found there to be a direct correlation between age and pain response; pain threshold to a greater and pain tolerance to a lesser degree increasing with age, particularly from the fifth decade of life, and more significantly for men than women. Parkhouse, Lambrechts and Simpson (1961) when studying requirements following upper and lower abdominal operations found a significant difference between patients below the age of 50 and patients above this age. In clinical practise the difference is small, although it is noteworthy that in Parkhouse's survey, in the abdominal cases, no patient below the age of 50 managed without postoperative drugs. Bellville and associates (1971) studied 712 postoperative patients and found age to be highly correlated with pain relief reports in that the older age group reported more pain relief. They concluded from the results of the survey that age is one of the most important variables in determining the degree of pain relief following the intramuscular administration of a potent analgesic.

It is also recognized that the type or cause of pain and clinical setting are potential sources of patient variability. Malignant disease can be highly variable depending on the extent of the disease and on other therapeutic measures that have been taken. With postoperative patients, it is desirable to choose from a group with a single operative procedure since pain varies with different

operative sites (Swerdlow et al, 1964). The type of operation also may affect the patient's attitude towards their pain. For example, many women do not complain of pain following childbirth due to the emotional factors involved. The meaning of the operation is a factor determining the pain that the patient experiences (Beecher, 1956 b).

Drug variables include the effects of concurrent or previous therapy. Some drugs given for other symptoms may influence pain or potentiate analgesics. For example Keats and Beecher (1959) have contended that barbiturates are analgesics in their own right, while Sadove (1971) and Fennessy and Sawynok (1973) have reported that tranquilizers are capable of potentiating analgesics. Most investigators consider it wise to eliminate such medication during the course of the study.

The patient's previous experiences with analgesics are also capable of influencing responses to study drugs. His expectancy of relief or particular side effects and his prejudices for or against a particular form of medication are all molded by previous drug experience.

Observer variables can also affect the results. In order to decrease observer variables, the method of choice is the use of full-time, trained observers who can maintain an objective interest in carrying out the experiment. (Lutterbeck and Triay, 1972; Loan and Dundee, 1967). It is best to use just one observer, to avoid the introduction of more variables into the study.

b) General Requirements in Analgesic Testing.

i) Subjective and objective evaluation.

Two methods have been used to evaluate analgesic activity, namely the subjective method and the behavioral or objective method.

Lutterbeck and Triay (1972), Houde (1960), and others have stated that the best estimates of intensity of pain are made verbally by the patients themselves. Although we might admit that pain is what the subject feels, we might hesitate to agree with the patient's quantification of his pain. The patient is an unskilled assessor and has very little experience of how mild or severe pain can be. The interviewer may have a wide experience of assessing pain but he is faced with the problem of "how to get inside the patient's mind". Some patients do exaggerate while others are reluctant to reveal their suffering. If the interviewer records his own impression of the severity of the patient's pain, this is still a purely subjective assessment, involving two subjects instead of one.

To assess pain at the second interview period, one of two questions must be asked:

1. How severe is your pain? This will be followed by subtraction on paper.
2. How has your pain changed? In this case, the patient does the subtraction which can be called "mental subtraction".

"Mental subtraction and "subtraction on paper" are not the same process and will not always yield the same result. If the patient is asked to estimate the change in his pain he must cast his mind back and recall an experience from the past. This is retrospection with all the usual pitfalls. Patients often underestimate the pain of an hour ago.

Keats, Beecher and Mosteller (1950) assess pain relief in terms of "more than half" relieved or "less than half" relieved, that is to say, that at postinjection interviews the patient was asked to state whether his pain was more or less than half the preinjection severity. This assumes that the patient could remember what the pain had been like at the previous interview. It has been found that even if the patient was not asleep immediately prior to the interview he frequently had difficulty in

remembering past pain intensity.

"Subtraction on paper" can be performed either with the patient's unmodified introspective assessment, or with the interviewer's opinion. In either case the difficulty in having to compare a present experience with a memory is avoided. Two immediate impressions, obtained at different times, are available for comparison; but one thing is essential: the patient must be seen by the same interviewer before and after the drug is given.

Present difficulties encountered in these procedures are:

1. in the formulation of uniform questioning methods, and
2. in the formulation of good rating scales. In forming rating scales the problems involved are:
   a) semantic presentation
   b) the half-life of this scale (how long it can be applied before the people who are responding lose interest and simply respond in a haphazard way without thought or consideration).
   c) demonstrating reliability of the scale (how well the scale gives the same coherent results under the same conditions).
   d) demonstrating validity (how well the scale succeeds in measuring what it is intended to measure).
   e) the number of points that should be along the scale; too few confer a lack of sensitivity, too many and the differentiation becomes unreliable.
   f) comprehensiveness - there are many determinants of pain, all of which have been reduced to a few scaled items - items which do not fit might be lost. (Beecher, 1959a).

When the investigator asks the patient to take a deep breath and to cough he is then seeking objective, or behavioural, information. Parkhouse and Holmes (1963) have stated that a graded record of these efforts is probably the closest approach that can be made to a truly

objective assessment without the use of a measuring instrument. These authors have demonstrated the usefulness of respiratory function measurements in assessing the effectiveness of postoperative analgesics. Vital capacity (VC) and peak expiratory flow rate (PEFR) are easy to measure but not all forms of pain interfere with respiratory activity. Clinical experience with VC and PEFR has been disappointing (Loan and Dundee, 1967). Although these methods can reflect the analgesic action of known pain-relieving drugs, they do not necessarily do so in a quantitative manner. Apart from those who have concentrated on measuring VC, most workers who have used postoperative pain for comparing drugs have confined their studies to pain at rest.

Parkhouse and Holmes (1963) compared pain relief following administration of morphine and saline to postoperative patients (upper abdominal cases) after pain induced by movement or coughing were taken into account, to that of the pain present while at rest. They hoped that a study of movement-and coughing-induced pain would magnify the difference between morphine and saline but this was not so, although the results compared well to the subjective results.

Table 2 Subjective Assessment Compared to Behavioral Assessment of Postoperative Pain Relief. (from Parkhouse and Holmes, 1963; p. 583).

Rest pain only (Investigator's assessment)

	Improved	Not improved	Total
Morphine	22	4	26
Saline	10	12	22
Total	32	16	48

$P \simeq 0.01$

Rest pain and pain induced by movement and coughing

	Improved	Not improved	Total
Morphine	22	4	26
Saline	11	11	22
Total	33	15	48

$P \simeq 0.02$

Figures are number of patients.

ii) Crossover and Noncrossover Studies.

Experiments in the clinical evaluation of drugs have used 2 methods for the allocation of patients to treatments - crossover ('within patient') and noncrossover ('between patient') designs. The crossover comparison uses each patient as his own control by giving him sequentially more than 1 treatment.

The notable advantage of crossover design lies in eliminating the variation introduced in the experimental results by the unequal distribution of patient variables among treatment groups. The decreased variation yields an economy in the number of patients required to demonstrate a significant difference between treatments.

Unfortunately, the use of the patient as his own control does not assure that the pain will return to the same baseline prior to each treatment. If the pain fluctuates with time in a relatively random way, this poses no greater source of variation in the crossover than in the non-crossover study. However, if there is a definite time trend in the pain severity, interpretation of crossover studies becomes more of a problem.

Crossover comparisons carry with them possible complications of carry-over, order or learning effects among doses within the study. This may represent pharmacologic potentiation or antagonism of the action of one drug by another. Carry over may also be purely psychological and represent a positive or negative reinforcement of the following dose. Kantor and coworkers (1966) found that the potency of placebo depended on the previous medication when pharmacological interaction was probably not a factor.

The noncrossover studies, while free from carryover effects within the study, are subject to errors inherent in the variability of patient groups, which in some clinical settings can be considerable. (Loan and Dundee, 1967; Lutterbeck and Triay, 1972).

iii) Standards and Controls.

Bias or prejudice is an effect arising from sources other than pharmacological action of drugs.

Modell (1963) has classified these errors and their controls as follows:

a) Experimental and subject bias: controlled by double blind administration
b) Psychic, symbolic and cultural implications of medication: controlled by the administration of placebo.
c) Extraneous factors: controlled by randomization.

a) Double Blind Technique

The double blind technique is a control device to prevent bias from influencing results. It rules out the effects of the hopes and anxieties of the patient by giving both the drug under investigation and a placebo (or standard drug) of identical appearance in such a way that the subject (the first "blind" man) does not know what he is receiving. It also rules out the influence of preconceived hopes of, and unconscious communication by, the investigator or observer by keeping him (the second "blind" man) ignorant of whether he is prescribing a placebo (or standard drug) or the investigational drug. At the same time, the technique provides another control, a means of comparison with the magnitude of

placebo effects (Modell and Houde, 1958).

b) Placebos.

A placebo is a control for 2 types of phenomena:

1) for the effect of suggestibility, personality, attitudes, anticipations and other biases on the part of the patient, investigator or observer in double-blind studies, and

2) for spontaneous changes in the course of the disease or in the symptoms under study, as well as for events that are independent of the treatments under study.

An inert preparation may appear to relieve pain by a genuine placebo response, and may reflect the insensitivity of the method of assessment.

Beecher (1962) has tabulated the results of 10 clinical studies involving 831 patients and found that on the average 35% obtained some pain relief following placebo administration. This can be contrasted with the 3% of patients in experimental pain studies who were relieved by placebo. An ethical question can be raised when an inert preparation is used in organic pain studies. From an ethical standpoint it is difficult to rationalize the use of a placebo when a standard agent of known potency is also available to serve as a reference yardstick. If it happened that the supposedly active drug were inactive, that is, if all agents including the placebos were inactive, patients might be allowed to suffer unduly, lacking effective treatment for an unreasonably long time.

c) Randomization

Randomization is another necessary control. Prescribing medicament and placebo by a scheme of random distribution. decreases the tendency of extraneous forces to influence results. These extraneous forces include all external influences which affect the state of the subject's physical and psychic state. Randomization does not eliminate external forces but attempts to spread them equally. (Modell and Houde, 1958).

The random, uncontrolled variations that occur in the clinical situation dictate that a difference between treatments as compared with variability between subjects must be found significant by some statistical test before it can be accepted as a true drug effect.

iv) Internal Controls.

A significant difference between an analgesic standard and a placebo is a measure of the sensitivity of the method. When a test medication does not differ significantly from placebo this does not mean very much if no difference can be found between the standard and placebo. Thus, a standard and a placebo control serve as an internal measure of the discriminatory ability of the subjects and of the experimental procedure and allow us to interpret differences or lack of differences in the light of the sensitivity of the method we have employed.

A failure to establish statistical difference need not imply that the effects are equal; it may, of course, be due to the limitations of the clinical experiment itself. On the other hand, statistically significant differences do not necessarily imply clinically meaningful differences.

The ability to discriminate between graded doses of a standard medication is in itself an index of sensitivity and often a more sensitive one than the use of a placebo and a single dose of a standard. (Modell and Houde, 1958; Houde, Wallenstein and Rogers, 1960).

v) Testing Utilizing Different Types of Pain

A new drug alleged to have pain relieving properties must be studied in controlled conditions in a variety of types of pain. Clinical analgesic trials often involve chronic pain due to malignant disease or post-operative pain. Malignant disease can be highly variable depending on the extent of the disease and on other therapeutic measures that have been taken. The patient's psychic modification of the painful stimulus may be of considerable magnitude. Also, the patient's previous experience with analgesics and the possibility of tolerance may impede proper assessment if these are not taken into account. (Lutterbeck and Triay, 1972).

Post-operative pain is a viable alternative but the patients must be chosen from a single operative entity. Swerdlow and his colleagues (1964) found that after upper abdominal operations patients required more analgesics and obtained shorter periods of pain relief than those in the lower abdominal group, while Parkhouse and his co-workers (1961) found a marked diminution in the number of doses of pain-relieving drugs required as the operation site moved down from the subcostal to the inguinal region.

It is also important that the operative entity be so chosen that pain does not decrease linearly during the study period.

c) Methods of Study

Three basic methods have been used in analgesic evaluations in the clinical setting (Beecher, 1959 a):

i) Beecher group's method

The Beecher group, beginning in 1946, were the first to systematize the use of pathological pain for the study of analgesic agents. He recorded whether or not there was 50% pain relief at 45 and 90 minutes following drug injection. His controls included the double-blind technique, use of a placebo and a reference standard, randomization of drug order and a cross-over design. They utilized postoperative wound pain and demonstrated the discriminatory ability of the postoperative subjects involved. This group felt that the cooperative statement by the subject must take first rank as an indication of the existence of a subjective response or of change in it. Trained technicians were utilized as observers throughout the 24 hours of the day.

ii) Houde group's method

Houde's group directed their attention to the use of patients with chronic pain for the screening and appraisal of analgesic agents. In the selection of patients, only well-orientated patients capable of communicating their subjective experiences, and to whom the drugs could be given safely, were chosen. They employed a full-time nurse who works 8 hours a day, 5 days a week. The single individual working for a limited time undoubtedly obtains more consistent results and has a more constant relationship with her patients than several individuals could; on the other hand, 24-hour observation probably includes cyclic changes in the patients' analgesic needs not obtained with the limited observation period. In common with the Beecher group they do not accept sleep as proof of the absence of pain. Houde's group classified pain as none, slight, moderate, severe or agony i.e. a scale of 1 to 5. They also utilized 50% pain relief scores. Like Beecher, their methodology included cross over designs, double blind technique, the use of placebo and reference standards. They also employed graded doses of the test drugs. Pain relief scores were

recorded hourly. When agents were compared, one of which was to be administered orally, for example ASA, and others parenterally for example morphine, patients were given both an oral medication and a hypodermic injection at the same time. They do not consider it advisable to screen out poor discriminators but by the use of cross-over studies have consistently been able to show significant differences between ASA or morphine and placebo with 10 - 25 patients.

The excellent agreement of data obtained by Beecher's and Houde's groups demonstrates that postoperative patients are able to discriminate as well as patients suffering from chronic pain.

iii) Keele's method

Keele planned what amounts to a time-intensity curve; a pain chart to be kept at regular intervals by the patient with chronic pain. Pain was to be graded as none, slight, moderate, severe or agonizing by the patient at hourly intervals. The variations found in their results stress the unsatisfactory nature of the patient's own pain chart. Keele reported that the task of charting their pain was welcomed by the patient; however, others, who had tried a similar method did not agree (Houde and Wallenstein, 1953). Keele changed from his earlier method when dealing with acute pain and utilized questioning by an observer who then kept a pain chart. This modification differs from Beecher's method since:

1) They ulilized only a single blind technique since they felt that the observer was obliged to be on the lookout for toxic effects of the untried agent and the group did not consider the use of unknowns safe.

2) They did not consider it justifiable to use saline controls.

3) They regarded sleep as indicating complete relief of pain. Most investigators agree that sleep may not be accepted as evidence of analgesia (Beecher, 1959a).

C. FLOCTAFENINE

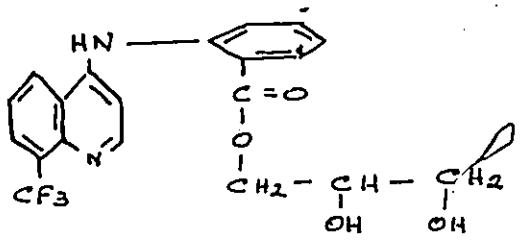
1. Introduction

In the nineteen sixties Roussel Laboratories in France examined a series of synthetic compounds of the anthranilic acid group. Several compounds were found to possess analgesic properties during pharmacological screening. Floctafenine (RU 15750) was believed to represent the best compound of the analgesic group and also a significant advance on other analgesics.

Floctafenine is a non-narcotic analgesic; some structural resemblance to mefenamic acid (Ponstan) and flufenamic acid may be present.

Figure 1

CHEMICAL STRUCTURES OF FLOCTAFENINE FLOCTAFENIC ACID, MEFENAMIC ACID AND FLUFENAMIC ACID



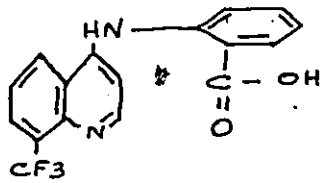
FLOCTAFENINE

the ∝ glyceryl ester of N- (8-trifluoromethyl 4 quinolyl) anthranilate.
Also described as:

2,3-dihydroxypropyl N-(8-trifluoromethyl 4 quinolyl) anthranilate.

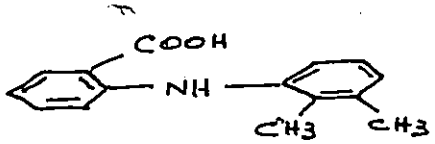
Molecular formula: C_{20} H_{17} O_2 N_2 F_3

Proposed British approved name: FLOCTAFENINE

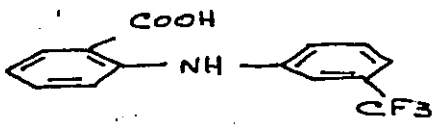


FLOCTAFENIC ACID (RU 4320) - main metabolite of Floctafenine

2 - (8-trifluoromethyl-4 quinolyl) anthranilate



MEFENAMIC ACID



FLUFENAMIC ACID

2. Analgesic screening in animals.

The analgesic activity of floctafenine has been studied in animals using the following methods (Allais et al, 1973; unpublished data, Roussel Laboratories Ltd):

a. Mouse Anti-writhing test (Koster, 1959)

An intraperitoneal injection of acetic acid in mice causes characteristic repeated movements of stretching and writhing which persist more than 6 hours. Analgesics, including the ASA class of analgesics, can prevent or attenuate this syndrome.

The test was applied in two different ways:

i) administering floctafenine half an hour before the i.p. injection of acetic acid, comparing it with acetylsalicylic acid (ASA), dextropropoxyphene and indomethacin.

ii) administering floctafenine at various times before acetic acid injection to determine its duration of action.

The results indicate that floctafenine is more potent than ASA or dextropropoxyphene and less potent than indomethacin (see tables 3 and 4). It had significant effect at 4 hours after administration of 1,2,5 or 10 mg/kg and activity was still present at 7 hours after a dose of 20 mg/kg.

Table 3

ANALGESIC POTENCY OF ORALLY ADMINISTERED FLOCTAFENINE, ASA, AND DEXTROPROPOXYPHENE DETERMINED BY THE WRITHING TEST OF KOSTER IN MICE.

(unpublished data, Roussel Laboratories)

Substance	Dose mg/kg	ED_{50} mg/kg (95% confidence limits)
Control	0	-
Floctafenine	1,2,5,10	2,3 (1.39 to 3.79)
ASA	50,100,200	60.0 (37.9 to 94.8)
d-Propoxyphene	20,50,100	46.0 (33.3 to 63.4)

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Table 4

ANALGESIC POTENCY OF ORALLY ADMINISTERED FLOCTAFENINE AND INDOMETHACIN DETERMINED BY THE WRITHING TEST OF KOSTER IN MICE.

(unpublished data, Roussel Laboratories)

Substance	Dose mg/kg	(95% ED_{50} confidence limits) mg/kg
Vehicle control	0	-
Floctafenine	2,5,10	4.6 (2.7 to 7.5)
Indomethacin	0.2,0.5, 1, 2	0.45 (0.23 to 0.87)

b. Mouse tail heat stimulation test (D'Amour and Smith's test, 1941).

This test consists of the application of a light beam to the tails of rats and mice to produce a constant heat stimulus. To avoid the burn caused by the beam, the animal moves its tail to one side.

The results indicate that floctafenine was inactive in this test even in doses of 50 mg/kg.

c. Mouse Hot Plate Test.

Floctafenine was shown by this test to have no statistically significant activity.

Both the tail-flick test and the hot plate test have been shown to be reproducible only in detecting an analgesic action with the narcotic analgesics. ASA-like drugs are active only at near toxic dose levels.

d. Pressure-pain Threshold of Yeast-inflamed Tissue.

This test is based on the reduction of the threshold of sensitivity to pain by inflammation and the raising of this threshold by analgesics.

Like the ASA class of analgesics and the narcotic antagonist analgesics, floctafenine was found only to have an effect on inflamed paws. The narcotic analgesics act also on intact paws.

3. Other Pharmacological Effects

a. Anti-inflammatory activity.

The anti-inflammatory activity of floctafenine was compared with that of indomethacin and ASA by using the following methods:

i) ultraviolet erythema test in guinea pigs.

In this test, it was shown that there was 50% protection in guinea pigs dosed with 26 mg/kg floctafenine, 6.7 mg/kg indomethacin and 170 mg/kg ASA. All drugs were administered orally. Floctafenine, therefore, showed an anti-inflammatory potency approximately 4 times lower than indomethacin and 7 times higher than acetylsalicylic acid.

ii) carageenin-induced edema in rats.

In this test, there was 40% protection in rats dosed with 72 mg/kg floctafenine, 4.1 mg/kg indomethacin, and 115 mg/kg ASA. All were administered orally. Therefore, floctafenine was approximately twice as active as ASA and 17 times less active than indomethacin.

b) Antipyretic effect

The antipyretic effect of floctafenine in rats, made pyrexial by means of subcutaneous injections of 2 ml of 15% suspensions of brewer's yeast, was moderate. Oral doses of 100 and 200 mg/kg of floctafenine were needed to observe a significant drop in temperature (approximately 1^{o}).

c) Pharmacological Effects on the Cardiovascular and Respiratory System

At a dose of 20 mg/kg, intravenous floctafenine was devoid of effect on the blood pressure of the normal or experimentally-induced hypertensive rat. In anesthetised dogs, transient respiratory excitation was noted only after the 20 mg/kg dose. The blood pressure response to adrenaline, noradrenaline, acetylcholine and histamine was not modified by administration of floctafenine. The product did not modify the electrocardiographic tracings of the animals.

The effect of floctafenine alone, or in combination with warfarin, on coagulation was assessed by measuring prothrombin time in rats. Results indicated that floctafenine had no anticoagulant effect up to the dose of 200 mg/kg., although, at the dose of 200 mg/kg, it was found to potentiate the anticoagulant effect of warfarin.

d. Central nervous system effects.

Several tests were used to study the possible effect of floctafenine on the central nervous system: actography test, duration of barbiturate sleep, pentetrazolic attack in mice, threshold of cortical excitability and maximum attack induced by electric shock in rats. All test results were negative, even at doses of 50 to 100 mg/kg.

e. Ulcerogenic Effects.

The ulcerogenic activity of floctafenine was studied in acute experimentation in rats and compared with that of ASA. At doses of 400 mg/kg, ASA and floctafenine were found to be equally ulcerogenic. However, at lower doses, ASA was more ulcerogenic eg. 100 mg/kg ASA produced greater ulceration than 300 mg/kg floctafenine.

Therefore, from animal testing, floctafenine has been shown to possess analgesic potency greater than that of acetylsalicylic acid. In the acetic acid-induced writhing test, it exerted its analgesic action at approximately 1/26 the dose of ASA. Floctafenine is ineffective in the hot plate and radiant heat tests which only reliably detect narcotic analgesics. (Taber, 1973).

The drug has been shown to have some effect in acute inflammation and to have a moderate antipyrexial effect.

No other pharmacological activity worthy of note was observed with this derivative; in particular there was no effect on the central nervous system or on coagulation.

4. Pharmacokinetics

The pharmacokinetics of floctafenine have been studied in man and animals (Pottier et al, 1975; unpublished data, Roussel Laboratories).

In animals (mice, rats and dogs), absorption was rapid with peak levels obtained 1/2 to 1 hour after administration. The levels then decreased rapidly for 2 hours and more slowly, thereafter. The plasma clearance was practically complete within 24 hours. The major part of the drug was hydrolyzed in the liver into floctafenic acid (RU 4320), its main circulating metabolite in all species studied (see Figure 1). The diffusion of floctafenic acid to tissues was poor due to its polarity and albumin binding; floctafenine diffuses more widely into tissues. The brain contained only minimal quantities of floctafenine or its metabolites. No floctafenic acid was excreted in the free state; the major derivative observed was the β D-glucuronate ester. The main excretory route was via the bile, biliary excretion being largely prominent in dogs and rats, and somewhat less so in man and mice.

Pharmacokinetic studies in man using ^{14}C-labelled floctafenine have led to the following general conclusions:

1. Plasma activities decreased rapidly (by a factor of 30 on the first day) and the radioactivity was almost completely eliminated within 4 to 5 days.

2. Approximately 40% of the administered dose was excreted through the urine and approximately 60% through the bile and then the feces. (see Table 5).

3. There is little difference in the metabolic behaviour between oral and intravenous administration. The main metabolite recovered is floctafenic acid, but a so-called "non-identified" fraction (more polar) is quite large. The conjugated fraction of the metabolites is generally smaller than the free fraction; however, the proportions are reversed in the case of urinary

excretion after oral administration. The amount of floctafenine free or conjugated, in the excreted products represents only 12% (I.V. administration) or 15% (oral administration) of the administered quantity. (see Tables 6 and 7).

4. There are few inter-patient differences concerning the overall rates of excretion.

5. Absorption of the product following oral administration is higher than 80%. The state of the gastric milieu did not seem to play a major role in controlling absorption: concomitant administration of floctafenine and oxyphencyclimine, an anticholinergic, or that or floctafenine and pentagastrin failed to alter the proportion of floctafenine absorbed.

Table 5

OVERALL RECOVERY OF EXCRETED RADIOACTIVITY IN PERCENTAGE OF THE ADMINISTERED ACTIVITY

(unpublished data Roussel Laboratories)

Time (hours)	I.V. administration		Oral administration	
	urines	faeces	urines	faeces
0 - 24	32.5	0.9	34.5	2.4
24 - 48	3.6	25.1	3.5	2.0
48 - 72	1.0	31.9	1.9	31.4
72 - 96	<0.1	3.0	0.4	17.4
96 - 120	-	-	0.2	1.7
Sums	37.1	60.9	40.7	54.9
Totals	98.0		95.6	

Table 6

EXCRETION OF ^{14}C-FLOCTAFENINE AND METABOLITES FOLLOWING I.V. ADMINISTRATION IN MAN*

(unpublished data, Roussel Laboratories)

OVERALL ELIMINATION (98% over 4 days)

- Urines (37.1%)
  - Free Fraction (27.6%)
  - Conjugated Fraction (9.5%)
- Faeces (60.9%)
  - Free Fraction (47.0%)
  - Conjugated Fraction (13.9%)

	Urines: Free Fraction (27.6%)	Urines: Conjugated Fraction (9.5%)	Faeces: Free Fraction (47.0%)	Faeces: Conjugated Fraction (13.9%)	Total Elimination Metabolites
FLOCTAFENINE	1.7%	1.3%	8.6%	1.4%	13.0%
FLOCTAFENIC ACID	8.1%	3.4%	21.2%	2.9%	35.6%
NON-IDENTIFIED	17.8%	4.8%	17.2%	9.6%	49.4%

*All values are expressed as percentages of administered activity.

Table 7

EXCRETION OF ^{14}C-FLOCTAFENINE AND METABOLITES FOLLOWING ORAL ADMINISTRATION IN MAN* (unpublished data, Roussel Laboratories).

OVERALL ELIMINATION (95.6% over 5 days)

Urines (40.7%) — Faeces (54.9%)

	Urines: Free Fraction (6.8%)	Urines: Conjugated Fraction (33.9%)	Faeces: Free Fraction (51.2%)	Faeces: Conjugated Fraction (3.8%)	Total Elimination Metabolites
FLOCTAFENINE	1.7%	0.7%	12.8%	0.5%	15.7%
FLOCTAFENIC ACID	2.0%	24.6%	21.9%	0.5%	49.0%
NON-IDENTIFIED	3.1%	8.6%	16.5%	2.8%	30.1%

*All values are expressed as percentages of administered activity.

5. Toxicology

Floctafenine was investigated for acute toxicity in the mouse, rat and rabbit (unpublished data, Roussel Laboratories) (see Table 8).

Six month chronic toxicity studies were performed in rats and dogs. In rats at 80 mg/kg daily, the mortality rate was 5/60 and a decrease in the number of erythrocytes and hemoglobin concentration was noted although no histological signs of toxicity were observed. In dogs, at 150 mg/kg daily, there was no mortality but there was a slight increase in the sedimentation rate plus small areas of ulceration occurred in the pyloric region in 2 out of 6 dogs. At 450 mg/kg, again there was no mortality but a moderate increase in sedimentation rate occurred plus areas of ulceration in the pyloric region in 5 out of 6 dogs. No significant change in morphology was seen in any of the other tissues examined.

Acetylsalicylic acid in doses of 3 - 4 g/day may decrease hemoglobin and in some patients increase the sedimentation rate. Exacerbation of peptic ulcer symptoms, gastrointestinal hemorrhage, and erosive gastritis have all been reported in patients on high dose therapy of ASA (Woodbury, 1970).

No teratogenic effects were observed in mice, rats or rabbits at doses up to 320 mg/kg daily.

Table 8

SUMMARY OF LD_{50} VALUES
(unpublished data, Roussel Laboratories)

Animal Species	Sex	Oral	I.V.	i.p.
Swiss mice	Male	3.40 g/kg		
	Female	2.25 g/kg	192 mg/kg	395 mg/kg
Sprague-Dawley rats	Male	960 mg/kg		
	Female	1100 mg/kg		
Russian rabbits	Male	700 mg/kg		

6. Physical Dependence Liability

Floctafenine has been examined for its ability to alleviate the withdrawal signs which occur in morphine-dependent rhesus monkeys from which morphine has been withdrawn. At no dose level tested (up to 2400 mg/kg) was any alleviation of withdrawal signs observed in any of the monkeys tested.

Floctafenine was also assessed for its capacity to produce physical dependence following chronic administration in naive rhesus monkeys. Rhesus monkeys received floctafenine or morphine sulphate by oral gavage for a period of 30 days. The dose for each compound was maintained at a level producing toxic side effects. The nalorphine challenge failed to produce any withdrawal signs in the monkeys receiving floctafenine; nor were withdrawal signs observed during the seven days following cessation of dosing with floctafenine. In both of these studies, floctafenine was assessed as being devoid of physical dependence capacity. (Roussel laboratories, unpublished data).

7. Comparison with two post-operative Analgesics; Meperidine and Dextropropoxyphene

Animal studies on floctafenine have demonstrated analgesic activity as well as some anti-inflammatory activity and moderate antipyrexial effects. No other pharmacological effects were observed. In particular, its lack of toxicity on the central nervous system, its very low ulcerogenic activity and its lack of renal toxicity suggest advantages of this compound over presently marketed analgesics. Thus the drug appears to be a desirable compound to further investigate as a possible new non-narcotic analgesic.

Due to the unacceptability of the use of a placebo in an organic pain study, two commonly-used oral analgesics namely meperidine and dextropropoxyphene (propoxyphene) with proven differences in analgesic activity were compared in the present study with the investigational drug. Propoxyphene 65 mg has been shown to be a weak analgesic relative to meperidine 75 mg. (Miller et al, 1970). Therefore these two drugs, besides being able to pinpoint the analgesic effectiveness of floctafenine, also serve as an internal control. Pain relief differences must be found between

meperidine and propoxyphene in order to demonstrate that the study is sensitive enough to detect analgesic differences.

Propoxyphene has enjoyed widespread popularity because the manufacturer claims the same analgesic potency as codeine without addiction potential and with significantly lower incidence of undesirable side effects. After a thorough review of the literature involving a critical evaluation of study methodology, Miller and co-workers (1970) concluded that propoxyphene is no more effective than ASA or codeine and may even be inferior to these analgesics. Two previous reviews are in essential agreement with the conclusion of these authors. Beaver (1966) concluded that adequate doses of propoxyphene are superior to placebo: doses of less than 65 mg. are of questionable activity. He estimates the potency of propoxyphene to be one-half to one-third that of codeine and he believes that 32 mg. or 65 mg of propoxyphene is no more and possibly less effective than the commonly used doses of ASA when taken alone or when in combination with phenacetin and caffeine.

Propoxyphene (only the d-isomer has analgesic properties) is a congener of methadone (see Figure 2). Lim et al (1964) have demonstrated that propoxyphene acts both centrally and peripherally.

The side effects noted with propoxyphene have been qualitatively quite similar to those associated with the use of codeine, i.e. nausea, vomiting, sedation, dizziness, constipation, and occasionally skin rashes.

The analgesic effect, after oral administration, appears within 15 minutes to one hour and persists for 4 to 6 hours. Peak serum levels are usually obtained within two hours. Propoxyphene's biological half-life is of the order of 3.5 to 4 hours (Reilly, 1975).

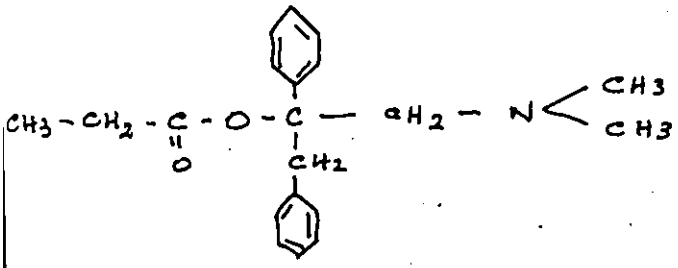
Meperidine (pethidine) is the prototype of the phenylpiperidine-derivative narcotic analgesics (see Figure 2). Narcotic analgesics act on the central nervous system to cause analgesia although the precise mechanism of their action is still unknown (Jaffe 1970; Reilly, 1975).

Meperidine causes vomiting nearly as frequently as morphine; it induces atropine-like effects, including dry mouth and blurred vision, and causes sedation. It has an advantage over morphine in that the effectiveness of the drug by the oral route is not reduced to the same degree as is that of morphine (Jaffe, 1970).

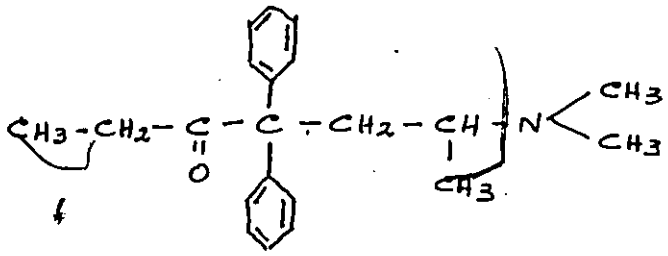
After oral administration of meperidine, peak analgesia occurs within one hour and gradually declines over two to four hours. (Reilly, 1975).

Figure 2

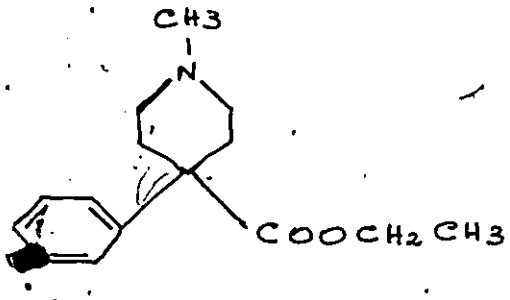
CHEMICAL STRUCTURES OF DEXTROPROPOXYPHENE, METHADONE AND MEPERIDINE



PROPOXYPHENE



METHADONE



MEPERIDINE

II STUDY PROTOCOL

A. Objectives

The objectives of this study were two-fold:

1) To confirm the analgesic activity of floctafenine in post-operative pain and to compare the efficacy of floctafenine with that of established and acceptable post-operative analgesic treatments (meperidine 75 mg. or propoxyphene 65 mg.) in post-cholecystectomy patients at the Ottawa General Hospital.

2) To compare the usefulness of a behavioural approach i.e. the measurement of pain on movement and coughing to that of the accepted subjective approach for the measurement of pain relief.

B. Design

The study was of a double-blind cross-over nature with each patient receiving meperidine (75 mg.), propoxyphene (65 mg.) and floctafenine (200 mg.) in an order determined by a multiple permutation of a 3 x 3 orthogonal Latin squares randomization.[1]

Each patient, on the second or third day post-operatively, received one of the test medications every four hours during a single day so that the entire study for her/him did not exceed 12 hours. All three drugs were prepared in identical dosage forms and labelled with the patient study number and either A,B, or C referring to the first, second, or third dose respectively. Each dose consisted of one white capsule plus one white tablet.

[1]Permutations provided by Dr. M. MacConaill, Dept. of Pharmacology, University of Ottawa.

Patients could receive the three drugs in any of the six orders, namely.

1) Meperidine, Floctafenine, Propoxyphene
2) Meperidine, Propoxyphene, Floctafenine
3) Propoxyphene, Meperidine, Floctafenine
4) Propoxyphene, Floctafenine, Meperidine
5) Floctafenine, Propoxyphene, Meperidine
6) Floctafenine, Meperidine, Propoxyphene

C. Patient Selection

Post-cholecystectomy patients between 18 and 65 years old, weighing more than 100 lbs (45 kg.) and able to take oral medication were eligible for inclusion in this study.

Lutterbeck and Triay (1972) have stressed that patients should be chosen from a group with a single operative procedure. A uniform site of operation produces a more homogeneous population. Cholecystectomy was chosen as the operative procedure for this study for several reasons:

1. Moderate pain lasts for several days following the operation: this facilitates the testing of an oral analgesic. In a study done by Parkhouse and co-workers (1961) on postoperative analgesic medication, the greatest number of postoperative injections were required after gastric surgery. Cholecystectomy showed the next highest analgesic requirement demonstrating the painful post-operative condition of this group of patients. Post-cholecystectomy patients in Parkhouse's study had a more compact distribution in their requirements for postoperative analgesics than had most other operative entities.

2. There are less psychological factors involved with such an operation as compared with childbirth, hysterectomies, or operations which necessitate a change in lifestyle (Wolf, 1970).

3. The operation is a common enough one so it would not be difficult to obtain an adequately large population.

Informed consent was obtained from each patient who agreed to participate in the investigation (See consent form in Appendix A). Each patient was interviewed prior to surgery in order to assess that the patient was sufficiently intelligent and well-orientated to give reliable information and to ensure that no medical contraindications to the study existed. The essential nature of the study was explained to each patient; he or she was informed that a new analgesic as well as older agents with known pain relieving actions would be used and that he or she could withdraw from the study if adequate pain relief was not achieved.

Patients accepted into the investigation had not received tranquilizers, sedatives, hypnotics, nor analgesics for at least 4 hours preceding the initial administration of the test medication. Such drugs were also not allowed during the study period. Keats and Beecher (1959) have contended that barbiturates are analgesics in their own right. Chapman and Feather (1973) feel that diazepam is analgesic in that it reduces the aversive drive associated with continuing pain. Sadove (1971) and Fennessy and Sawynok (1973) have reported that tranquilizers are capable of potentiating analgesics.

D. Method

1. Patients' Evaluation (Subjective Evaluation)

The patient was asked to evaluate his own pain by means of a wooden ruler calibrated from 0 to 10. The nurse-observer explained to the patient that 0 represented no pain and 10 represented very severe pain. The patient, therefore, evaluates his own pain, while at rest, between 0 and 10 using the visual scale on the ruler.

The usual scale which is used in analgesic studies judging the patient's pain at rest is the following:

0 = no pain
1 = mild pain
2 = moderate pain
3 = severe pain

In testing an oral non-narcotic analgesic, a scale more sensitive than 0 to 3 is probably necessary since the changes in pain intensity are often not as dramatic as those following parenteral analgesic administration. Also, the initial pain level of patients on the second or third day post-cholecystectomy may only be moderate and not severe. The scale would thus range only from 0 to 2 and therefore would be quite insensitive to small changes.

2. Nurse's Evaluation (Objective Evaluation)

The nurse-observer recorded:

a. The patient's own evaluation of this pain while at rest, and
b. her evaluation of the patient's pain on movement or coughing i.e. while under some stress. This was done by evaluating the ability of the patient to carry out a series of simple tasks, including deep breathing, coughing, walking on the flat, sitting up, leaving bed, entering bed and putting on a dressing gown (dressing). Each task

was scored from 0 to 4 with 0 representing no apparent pain, 1 for mild pain, 2 for moderate pain, 3 for severe pain and 4 for unbearable pain. The scale used in this part of the evaluation was smaller because the patient's pain when the patient was under stress and not at rest varied from no apparent pain to unbearable pain. A larger scale would cause the evaluation to be more difficult for the nurse since each point on the scale would not represent a well-defined level of pain severity.

The final score for the nurse's (objective) evaluations was determined by summing the scores for the individual tasks for each patient and so could range from 0 to 28 for the 7 tasks. In order to make it possible to compare these results with those of the subjective evaluation, the final results were normalized to a 0-10 scale by dividing by 2.8.

Both types of evaluation were completed at every interview period: these were before each drug was given and 1/2, 1, 2, 3 and 4 hours later. For the second and third drugs the 'before drug' interview corresponded also to that 4 hours after the previous drug: thus there was a total of 16 (3 x 6 - 2) interviews.

Interview periods:

0 hours (before drug A)
Drug A was given
1/2 hour
1
2
3
4 (0 hour before drug B)

Drug B was given.
1/2 hour
1
2
3
4 (0 hour before drug C)

Drug C was given.
1/2 hour
1
2
3
4

The times of the evaluations and the times of the administration of the doses were recorded by the nurse.

Sleep was not accepted as an indication that the medication may have produced an analgesic effect. Patients were awakened if necessary at the evaluation period.

The nurse-observer did not specifically ask about side-effects unless they were volunteered or clearly observed. Direct questioning was avoided to minimize the possibility of suggestion. If side-effects were reported these were recorded on the evaluation sheet under the appropriate time slot and the patient was questioned on subsequent visits concerning their severity or persistence.

Failure to obtain adequate analgesia caused the study to be terminated at that point. It was possible to break the code in the occurrence of disturbing side-effects.

E. Evaluation

The results were examined by examining the:

1. Pain Intensity Differences using only data obtained for the first drugs administered to each patient
2. Analysis of Variance results using all data obtained during the 12-hour periods.
3. Covariance Analysis results using first only the data obtained for the first drugs administered to each patient, then for all data obtained during the 12-hour periods.

1. Pain Intensity Differences.

The results were first examined by examining the Maximum Pain Intensity Difference (MPID) and the Summed Pain Intensity Difference (SPID) (Beecher, 1959a; Belleville, Forrest and Brown, 1968; Lutterbeck and Triay, 1972 and others). In the analyses the first medication results for non-completers were used as well as those where the crossover design had been completed.

a) MPID

The MPID rating was derived by subtracting the lowest pain score that was reported for the patient from the patient's initial pain score. This value, therefore, represents the peak effect of the drugs; carry-over effects would not be significant since only data obtained for the first drugs administered to each patient were used.

b) SPID

The SPID rating was derived by summing the PID values calculated at 1, 2, 3 and 4 hours. The 1/2 hour values were not used because of the possibility of varying absorption rates with the different medications. The SPID values could be positive or negative. Patients who discontinued the study during the first period due to severe unrelieved pain were given the highest pain score values which were experienced by patients in the study i.e. a subjective rating of 9 and an objective rating of 28 and their PID's were derived using these values.

2. Analysis of Variance

Mosteller in Beecher's publication on "Measurement of Pain" (1959a: p. 112) stated that "In the study of responses to drugs, the analysis of variance is widely used in the assessment of effects and in the allocation of variability to its source". Most workers including Houde and co-workers (1960) and Belleville and co-workers (1968) have used this statistical test in their investigations. Using the analysis of variance, the total variation in a set of data may be reduced to components associated with possible sources of

variability whose relative importance can then be assessed (Moroney, 1951). This is of particular importance in the clinical evaluation of analgesics.

3. Covariance analysis

A covariance analysis was done to examine the effects of the patient's initial pain on the pain relief achieved. Effects due to age, sex, residual drug effects and period effects were also examined. Both the first 4-hour period and the 12-hour period for each patient was analyzed.

III. RESULTS

A. Description of Patients.

Forty-three post-cholecystectomy patients were studied over a period of 5 months.

Table 9

Description of Patients in the Investigation

Age	18 - 30	31 - 40	41 - 50	51 - 60	61 - 65	Total
Female	11	7	7	8	3	36
Male	1	1	3	2	0	7
Total	12	8	10	10	3	43

Complete trials	40
Incomplete trials	3

Of the forty completed trials, three were used in the evaluation of first drug effects only for the following reasons:

1. Patient # 2 did not receive dose B until she asked for pain relief.
2. Patient # 6 received her dose B one hour late due to a miscalculation by the nurse-observer.
3. Patient # 22 received 2 doses of diazepam (Valium) 5 mg. during the trial period.

Incomplete trials:

Patients # 3 and # 30 did not complete the first round due to severe, unrelieved pain. Patient # 16 did not complete the second round for the same reason. All 3 patients were on propoxyphene when they requested discontinuation of the study.

B. Side Effects

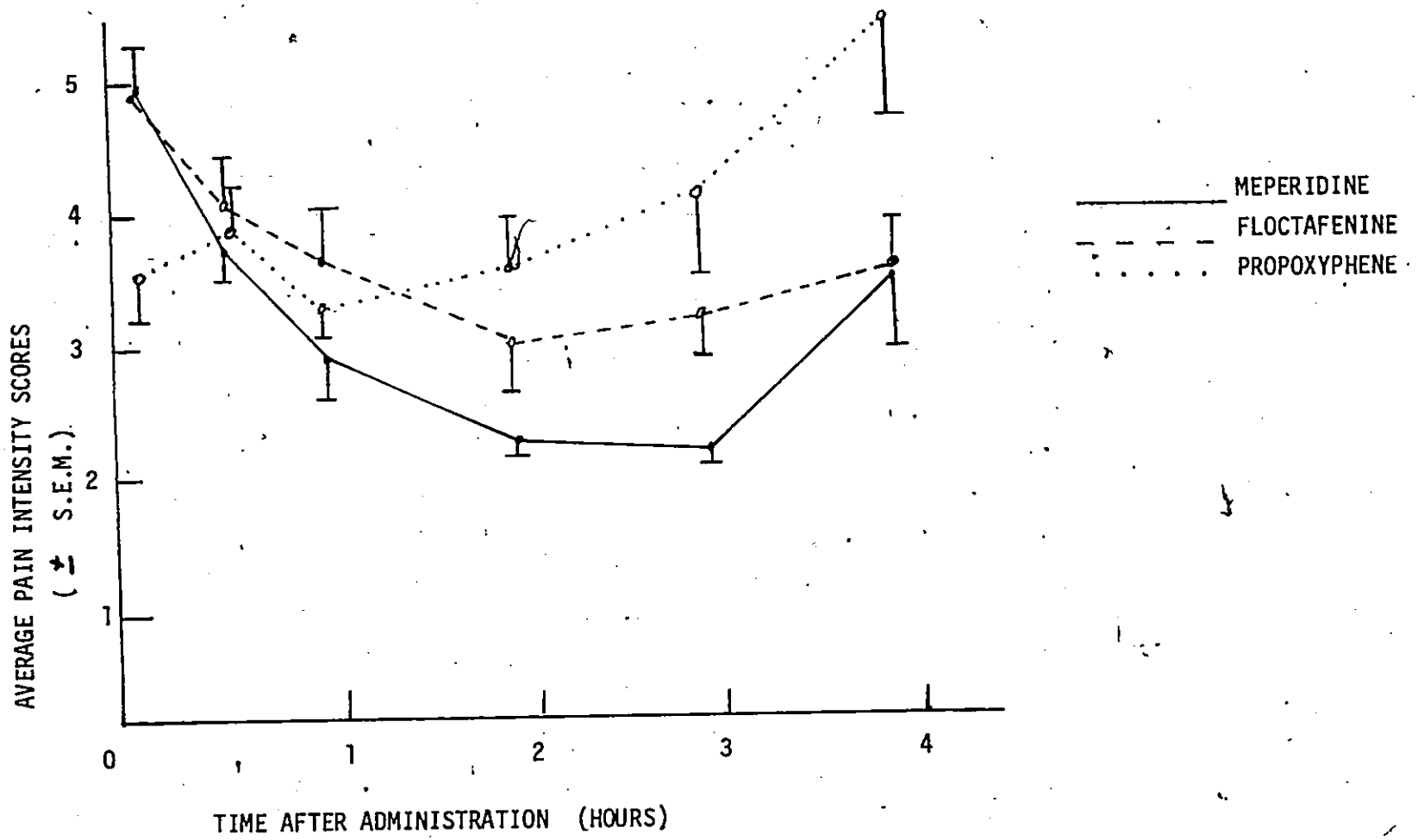
Nineteen of the 43 patients reported some side effects during the study period. The most commonly-reported side effect with all three drugs was drowsiness.

Table 10.

SIDE EFFECTS OF MEPERIDINE, FLOCTAFENINE AND PROPOXYPHENE

	Meperidine	Floctafenine	Propoxyphene
Drowsiness	10	5	7
Dizziness	2	1	3
Thirst	1	1	1
Dry mouth	2	1	0
Nausea	(1)	1	1
Vomiting	1	0	0
Diarrhea	0	1	0
Feeling of warmth, perspiration	1	0	2
Congested and slightly short of breath.	1	0	0
Total side effects	18	10	14
Total patients	13	6	12

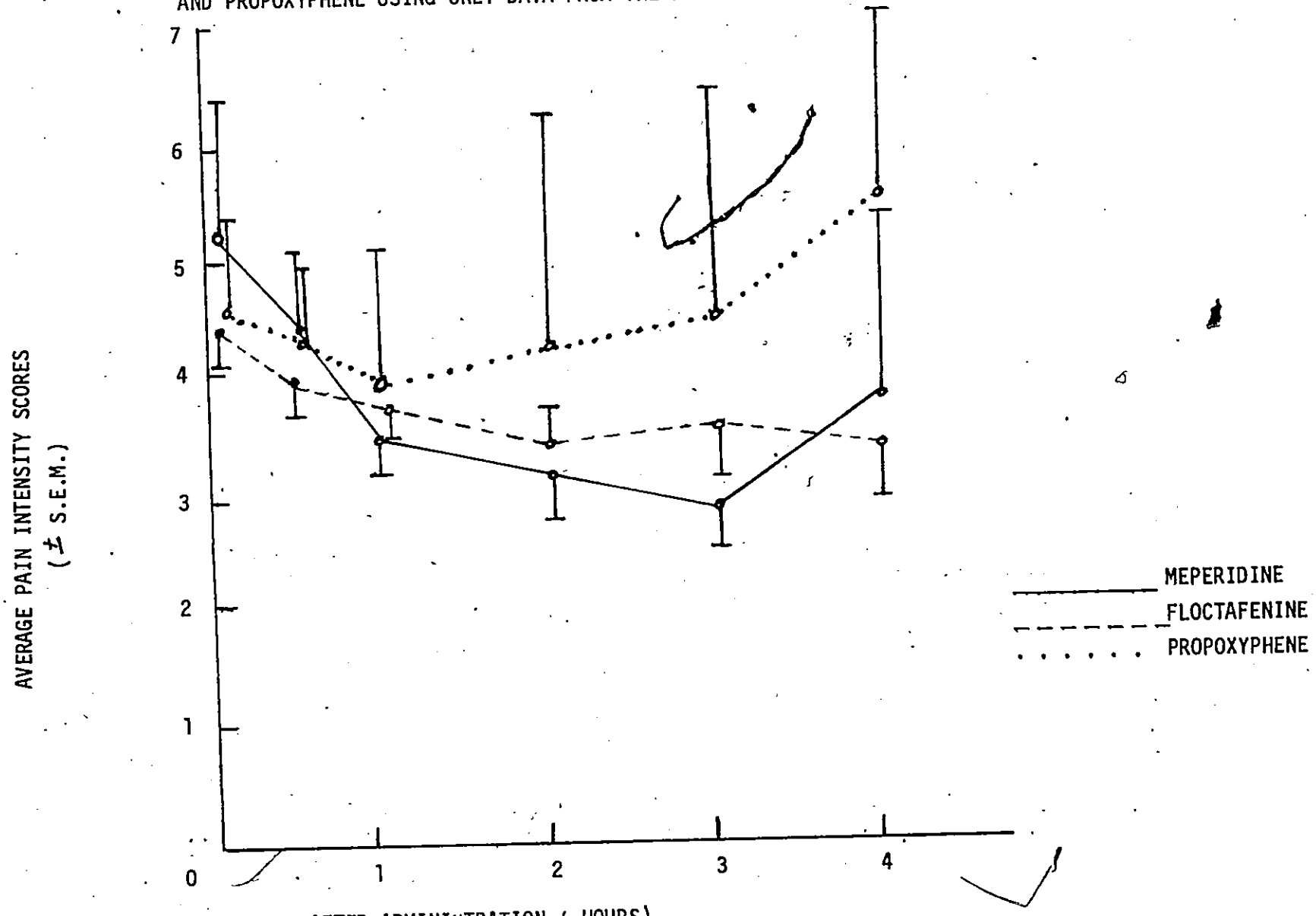
FIG. 3 AVERAGE PAIN INTENSITY SCORES FOLLOWING MEPERIDINE, FLOCTAFENINE, AND PROPOXYPHENE ADMINISTRATION USING ONLY DATA FROM THE FIRST FOUR-HOUR PERIOD * (SUBJECTIVE EVALUATION)



3.58 for propoxyphene not 2.58

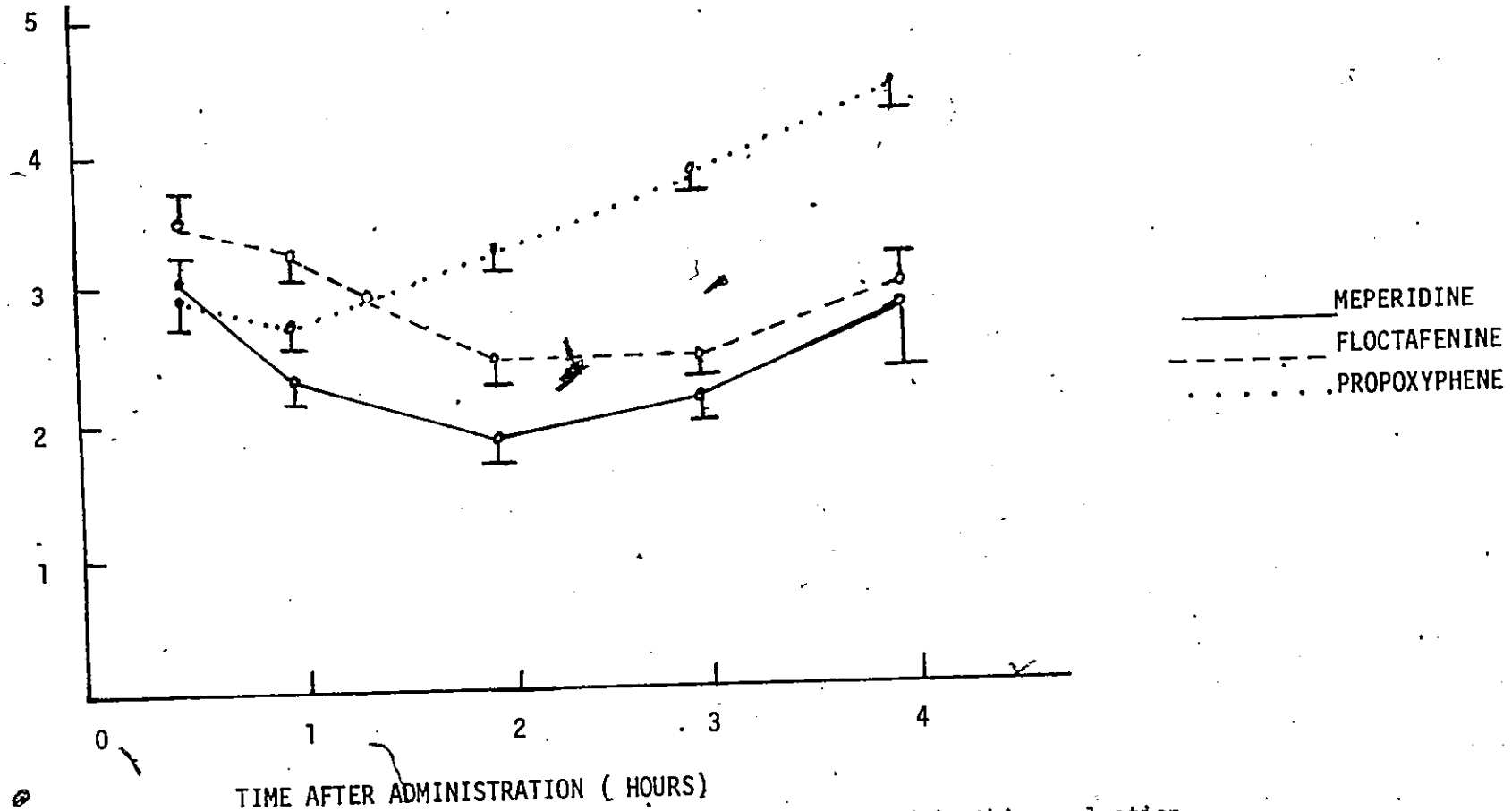
* Only data obtained from the first drug administered to each patient were used.

FIG. 4 AVERAGE PAIN INTENSITY SCORES FOLLOWING MEPERIDINE, FLOCTAFENINE AND PROPOXYPHENE USING ONLY DATA FROM THE FIRST FOUR-HOUR PERIOD * (OBJECTIVE EVALUATION)



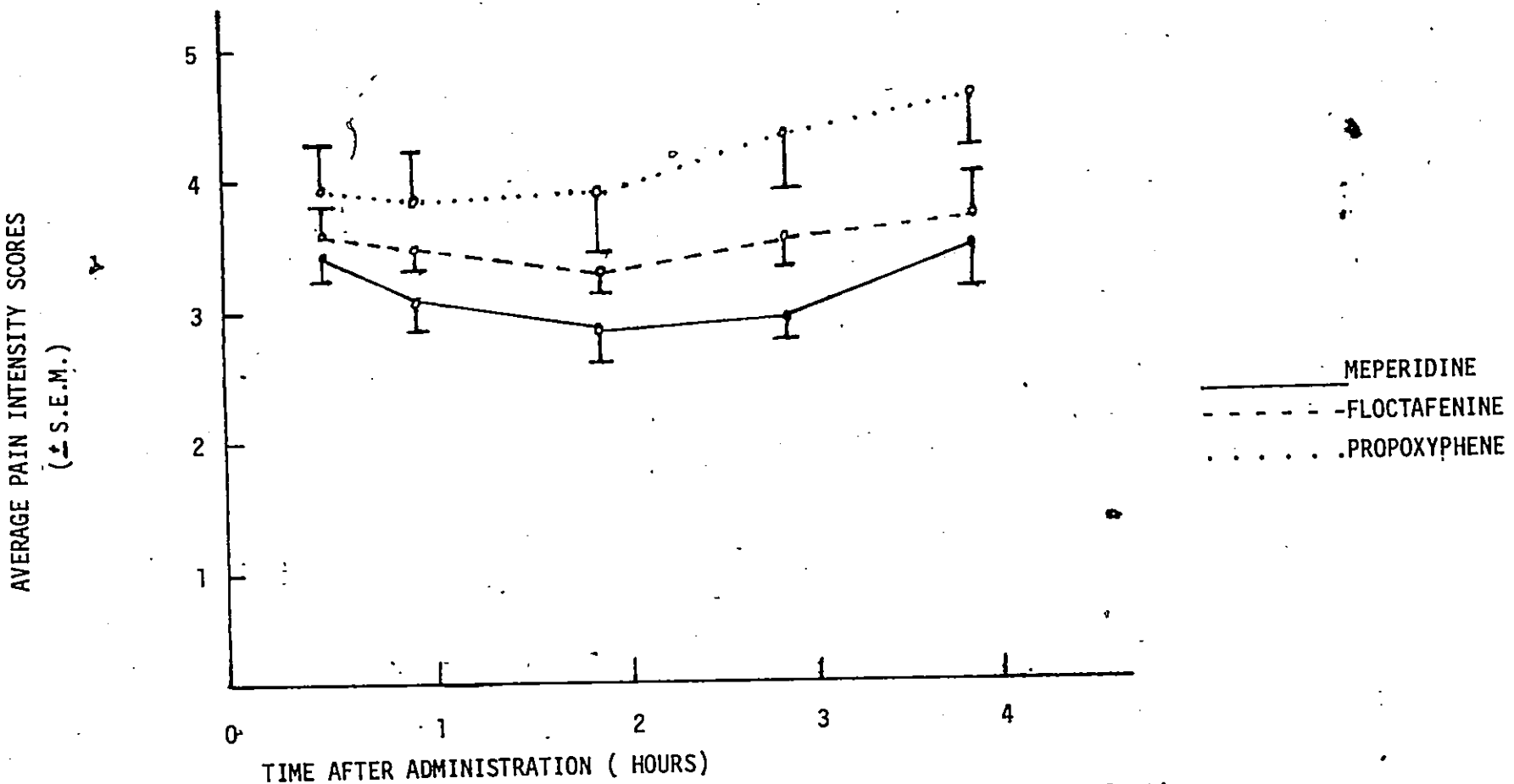
*Only data obtained from the first drug administered to each patient were used.

FIG. 5 AVERAGE PAIN INTENSITY SCORES FOLLOWING MEPERIDINE, FLOCTAFENINE AND PROPOXYPHENE ADMINISTRATION USING ALL DATA * (SUBJECTIVE EVALUATION)



* All data obtained during the twelve-hour periods were used in this evaluation.

FIG. 6 AVERAGE PAIN INTENSITY SCORES FOLLOWING MEPERIDINE, FLOCTAFENINE AND PROPOXYPHENE ADMINISTRATION USING ALL DATA* (OBJECTIVE EVALUATION)



* All data obtained during the twelve-hour periods were used in this evaluation.

C. Onset and Peak Effects

The onset of action (see figures 3 and 4) for all three drugs occurred within 1/2 hour after administration. Since the patient was only interviewed 1/2 hour following administration of the medication, this is as accurate as a determination for onset effects can be made. Peak effects occurred between 2 and 3 hours following administration. Duration of action could not be determined since patients were only studied for a 4 hour period. Floctafenine may be longer acting than meperidine and propoxyphene (see figures 3 and 4). Figures 5 and 6 show the average pain intensity scores of the three drugs using all the data obtained throughout the 12-hour study periods i.e. regardless of whether the drugs were administered as dose A, B or C.

D. Analysis of Results

1. Pain Intensity Differences.

The results were first examined by looking at the maximum pain intensity differences (MPID) and at summed pain intensity differences (SPID) during the first 4-hour period. In the analyses, the first medication results from those not completing the four hour period were used as well as from the patients who completed the crossover design. The results from patients 7, 10 and 11 were not used in view of the initial low pain scores seen in these patients. Patients who withdrew from the study due to severe unrelieved pain were given a subjective score of 9 and an objective score of 28 for the remaining interview times of the first period. These patients had to be included in the analysis, otherwise the data would have been biased in favour of the drug which failed to produce any pain relief. This is an important factor to consider when looking at the results of the analysis of variance and covariance analysis of all three periods when the results of only the completely crossed-over patients were utilized. It is hoped, though, that because of the large number of patient trials that this factor is not of too great consideration.

MPID

In the subjective or patient's evaluation, significant differences were found between meperidine and propoxyphene ($F = 9.91$, $p \leq 0.01$) and between floctafenine and propoxyphene ($F = 5.44$, $p \leq 0.01$). No significant difference between meperidine and floctafenine was found ($F = 0.67$). A patient population of 53 per group would have been necessary in order to have been able to detect differences at the 5% level of confidence.

For a patient population of 13 per group, the variance ratio necessary to demonstrate significant differences ($p \leq 0.05$) in drug effects between groups (assuming the same variability between patients as found in the sample tested) would be 2.69. From this can be calculated the number of patients per group necessary to demonstrate significant drug differences.

In the objective or nurse's evaluation, significant differences were found between meperidine and propoxyphene ($F = 5.70$, $p \leq 0.01$) and between meperidine and floctafenine ($F = 2.70$, $p \leq 0.05$). No difference was detected between floctafenine and propoxyphene. A larger patient population consisting of 64 patients per group would have been necessary in order to detect differences between these two drugs (see Table 11).

SPID

The subjective SPID results were similar to the MPID results. Meperidine was superior to propoxyphene ($F = 13.29$, $p \leq 0.01$) and floctafenine was superior to propoxyphene ($F = 7.07$, $p \leq 0.01$). No difference was seen between floctafenine and meperidine. A patient population of 37 per group would have been necessary to achieve a F-ratio above the $F_{5\%}$ value.

The objective SPID results were also similar to the objective MPID results. Meperidine produced significantly better pain relief than propoxyphene ($F = 7.71$, $p < 0.01$). In order to demonstrate significant differences between meperidine and floctafenine, a patient population of 17 patients per group would have been required. To show significant differences between floctafenine and propoxyphene, 21 patients per group would have been necessary (see Table 11).

Table 11

MAXIMUM PAIN INTENSITY DIFFERENCES (MPID) AND SUMMED PAIN INTENSITY DIFFERENCES (SPID) OF MEPERIDINE, FLOCTAFENINE AND PROPOXYPHENE DURING THE FIRST FOUR-HOUR PERIOD.

		SUBJECTIVE						OBJECTIVE					
		MPID			SPID			MPID			SPID		
FACTOR	DF	MS	F	P	MS	F	P	MS	F	P	MS	F	P
MEAN	1	217.03			1000.16			798.78			5215.41		
BETWEEN DRUGS	2	15.10	5.34	<0.01	472.36	7.11	<0.01	59.81	2.98	NS	987.43	3.86	<0.05
OVER DRUGS	3	82,41			648.29			306.13			2396.76		
WITHIN DRUGS	36	2.83			66.41			20.05			255.78		
OVER PATIENTS	39	8.95			111.17			42.06			420.47		

		SUBJECTIVE		OBJECTIVE	
DRUG	N	MPID	SPID	MPID	SPID
MEPERIDINE	13	3.23 ± 0.47	10.00 ± 2.26	6.88 ± 1.24	20.42 ± 4.44
FLOCTAFENINE	13	2.69 ± 0.47	6.86 ± 2.26	4.00 ± 1.24	11.27 ± 4.44
PROPOXYPHENE	13	1.15 ± 0.47	-1.65 ± 2.26	2.69 ± 1.24	3.00 ± 4.44

	SUBJECTIVE						OBJECTIVE					
	MPID			SPID			MPID			SPID		
F/P	Mep.	Floc.	Prop.	Mep.	Floc	Prop.	Mep.	Floc.	Prop.	Mep.	Floc.	Prop.
Mep.		0.67	9.91		0.97	13.29		2.70	5.70		2.13	7.71
Floc.			5.44			7.07			0.55			1.74
Prop.												

2. Analysis of Variance

A two-way analysis of variance, crossed (APL program ANOVA 2) was done to crudely compare the effectiveness of the various drugs, and to look for evidence that the pain score might be influenced by age or sex. The values for the 37 patients who completed the cross-over study were used. The means of the 2nd and 3rd hour values were compared in order to minimize carry-over effects (both pharmacological and psychological) and also in order to allow for time for absorption of the orally-administered medications. From the data it had been observed that the peak effects of the three drugs generally were obtained at 2 - 3 hours after administration. The subjective (patients' evaluations) and objective (nurse's evaluations) results were analyzed separately. The patients' evaluations could vary in magnitude from 0 to 10 while the nurse's evaluations could vary from 0 to 28. The nurse's evaluation was obtained by summing the recorded values for the 7 tasks. The results of the nurse's evaluations were normalized to a scale of 0 - 10 by dividing by 2.8 in order to facilitate comparison with the subjective results.

These results (see Table 12) demonstrate the significant variability between patients and the significant interaction between patients and treatments. The residual error is large. This again stresses the subjective nature of pain and the great variability of pain perceived or tolerated and pain relief obtained which have been reported in the literature. This variability necessitates the study of a relatively large population of patients in order to overcome this patient variability and to detect significant treatment effects, as seen in the MPID and SPID evaluations.

Significant differences between meperidine and propoxyphene could betdetected utilizing either the subjective ($F = 13.28$, $p < 0.01$) or objective ($F = 16.55$, $p < 0.01$) data. Meperidine was only marginally better than floctafenine after evaluation of the subjective results. It was statistically significantly better than floctafenine when utilizing the objective results ($F = 10.00$, $p < 0.01$). Floctafenine was not significantly different from propoxyphene by either the subjective or objective evaluations.

Using ANOVA 2 sex and age differences were then examined in order to determine if sex or age affected the results and if a more homogeneous population could be produced by using, besides only one operative entity, one sex or one age group.

Evaluation of Sex Differences

Males (See Table 13)

The variability among patients decreased when we regard the male population studied but because of the small number of males involved in the study ($n = 7$), no statistical difference between meperidine and propoxyphene could be detected.

To demonstrate a significant difference between meperidine and propoxyphene with the objective results a patient population of 9 would have been required if the variability between patients remained constant and with the subjective results a patient population of 20 would have been required.

Females (See Table 14).

Meperidine produced significantly lower pain scores than floctafenine (subjective results: $F = 5.71$, $p < 0.05$; objective results: $F = 7.54$, $p < 0.05$) and than propoxyphene (subjective results: $F = 11.09$, $p < 0.01$; objective results: $F = 11.63$, $p < 0.01$) when only the results of the female patients involved in the investigation were evaluated. No statistical

difference between floctafenine and propoxyphene was found.

Evaluation of Age Differences.

Three age groups, namely 18 - 30 years, 31 - 50 years, and 51 - 65 years, consisting of 10, 16 and 11 patients respectively were examined to see if there was any evidence at all for differences in pain relief with different age groups.

In the 18 - 30 age group no significant differences between drugs could be detected probably due to the small number of patients (n = 10) studied. (See Table 15).

In the 31 - 50 age group, although we are looking at the results from 16 patients, no significant differences were seen. There was a tendency for the patients not to be able to discriminate between the 3 drugs as can be seen by the similar values of the subjective means of the three drugs.

In the 51 - 65 age group, the patients appeared to be able to discriminate between drugs somewhat better than the 31 - 50 years old group, and the variance between patients tended to be not significant. (See Table 17).

This analysis suggests that age may have some influence on pain relief since the three age groups examined were not completely similar in their response to the three test analgesics and in their intrinsic variability. A more detailed analysis is necessary to clarify the importance of age on pain relief as well as the influence of certain other factors including initial pain score on the pain scores recorded.

Table 12

ANALYSIS OF VARIANCE FOR COMPLETE SAMPLE FOR THE TWELVE-HOUR PERIOD

	SUBJECTIVE				OBJECTIVE		
Meperidine and Floctafenine	D.F.	MS	F/AB	P	MS	F/AB	P
Between Drugs	1	8.28	3.32	NS	13.68	10.00	<0.01
Between Patients	36	7.92	3.18	<0.01	5.28	3.86	<0.01
Interaction	36	2.50			1.37		
Residual	74	0.791			0.219		
Meperidine and Propoxyphene							
Between Drugs	1	34.54	13.28	<0.01	32.10	16.55	<0.01
Between Patients	36	9.62	3.70	<0.01	4.64	2.39	<0.01
Interaction	36	2.60			1.94		
Residual	74	1.17			0.648		
Floctafenine and Propoxyphene							
Between Drugs	1	9.00	2.73	NS	3.87	1.95	NS
Between Patients	36	9.46	2.87	<0.01	5.08	2.56	<0.01
Interaction	36	3.30			1.98		
Residual	74	1.01			0.777		

MEANS ± S.E.	Subjective	Objective
Meperidine	1.78 ± .067	2.55 ± 0.117
Floctafenine	2.26 ± .074	3.16 ± 0.135
Propoxyphene	2.75 ± .099	3.47 ± 0.132

Table 13

ANALYSIS OF VARIANCE FOR MALE SAMPLE FOR THE TWELVE-HOUR PERIOD

		SUBJECTIVE			OBJECTIVE		
Meperidine and Floctafenine	D.F.	MS	F/AB	P	MS	F/AB	P
Between drugs	1	1.29	0.659	NS	1.48	6.35	<0.05
Between patients	6	8.23	4.21	NS	4.62	19.89	<0.01
Interaction	6	1.95			0.232		
Residual	14	0.161			0.009		
Meperidine and Propoxyphene							
Between drugs	1	9.72	2.13	NS	8.42	5.07	NS
Between patients	6	8.93	1.96	NS	4.49	2.70	NS
Interaction	6	4.56			1.66		
Residual	14	0.330			0.068		
Floctafenine and Propoxyphene							
Between drugs	1	18.08	2.89	NS	2.85	2.71	NS
Between patients	6	11.93	1.91	NS	5.17	5.92	<0.05
Interaction	6	6.25			1.05		
Residual	14	0.259			0.068		

MEANS ± S.E.	SUBJECTIVE	OBJECTIVE
Meperidine	2.39 ± 0.196	2.12 ± 0.48
Floctafenine	1.96 ± 0.531	2.58 ± 0.49
Propoxyphene	3.57 ± 0.769	3.21 ± 0.75

Table 14

ANALYSIS OF VARIANCE FOR THE FEMALE SAMPLE FOR THE TWELVE-HOUR PERIOD

		SUBJECTIVE			OBJECTIVE		
Meperidine and Floctafenine	D.F.	MS	F/AB	P	MS	F/AB	P
Between drugs	1	14.01	5.71	<0.05	12.40	7.54	<0.05
Between patients	29	8.11	3.30	<0.01	5.29	3.22	<0.01
Interaction	29	2.45			1.64		
Residual	60	0.938			0.268		
Meperidine and Propoxyphene							
Between drugs	1	25.21	11.09	<0.01	23.92	11.63	<0.01
Between patients	29	9.48	4.17	<0.01	4.69	2.28	<0.05
Interaction	29	2.27			2.06		
Residual	60	1.36			0.783		
Floctafenine and Propoxyphene							
Between drugs	1	1.63	0.672	NS	1.88	0.847	NS
Between patients	29	9.20	3.78	<0.01	5.02	2.27	<0.05
Interaction	29	2.43			2.21		
Residual	60	1.18			0.943		

MEANS ± S.E.	SUBJECTIVE	OBJECTIVE
Meperidine	1.64 ± .089	2.65 ± 0.150
Floctafenine	2.33 ± .088	3.30 ± 0.173
Propoxyphene	2.56 ± .107	3.55 ± 0.165

Table 15

ANALYSIS OF VARIANCE FOR THE SAMPLE 18 - 30 YEARS OF AGE FOR THE TWELVE-HOUR PERIOD.

		SUBJECTIVE			OBJECTIVE		
Meperidine and Floctafenine	D.F.	MS	F/AB	P	MS	F/AB	P
Between drugs	1	3.91	3.64	NS	0.459	2.51	NS
Between patients	9	11.39	10.62	<0.01	3.17	17.33	<0.01
Interaction	9	1.07			0.183		
Residual	20	0.506			0.172		
Meperidine and Propoxyphene							
Between drugs	1	9.03	3.83	NS	8.62	4.32	NS.
Between patients	9	10.45	4.43	<0.01	4.32	2.16	NS
Interaction	9	2.36			2.00		
Residual	20	0.80			0.191		
Floctafenine and Propoxyphene							
Between drugs	1	1.06	0.36	NS	5.10	2.47	NS
Between patients	9	13.01	4.46	<0.05	3.56	1.72	NS
Interaction	9	2.92			2.07		
Residual	20	1.06			0.359		

MEANS ± S.E.	SUBJECTIVE	OBJECTIVE
Meperidine	1.85 ± .234	2.34 ± 0.100
Floctafenine	2.48 ± .191	2.55 ± 0.082
Propoxyphene	2.80 ± .408	3.27 ± 0.146

Table 16

ANALYSIS OF VARIANCE FOR THE SAMPLE 31 - 50 YEARS OF AGE FOR THE TWELVE-HOUR PERIOD.

		OBJECTIVE			SUBJECTIVE		
Meperidine and Floctafenine	D.F.	MS	F/AB	P	MS	F/AB	P
Between drugs	1	0.016	5.42	NS	2.44	3.15	NS
Between patients	15	9.21	3.19	<0.05	8.10	10.46	<0.01
Interaction	15	2.88			0.775		
Residual	32	1.36			0.253		
Meperidine and Propoxyphene							
Between drugs	1	3.52	1.40	NS	15.43	6.94	<0.05
Between patients	15	9.77	3.89	<0.01	5.51	2.48	<0.01
Interaction	15	2.52			2.22		
Residual	32	1.83			1.33		
Floctafenine and Propoxyphene							
Between drugs	1	4.0	3.33	NS	5.60	2.85	NS
Between patients	15	9.25	7.71	<0.01	6.48	3.30	<0.05
Interaction	15	1.20			1.96		
Residual	32	1.28			1.44		

MEANS $\pm$ S.E.	SUBJECTIVE	OBJECTIVE
Meperidine	$1.97 \pm .219$	2.64 ± 0.36
Floctafenine	$1.94 \pm .160$	2.70 ± 0.43
Propoxyphene	$2.44 \pm .166$	3.62 ± 0.60

Table 17

ANALYSIS OF VARIANCE FOR THE SAMPLE 51 - 65 YEARS OF AGE FOR THE TWELVE-HOUR PERIOD.

		OBJECTIVE			SUBJECTIVE		
Meperidine and Floctafenine	DF	MS	F/AB	P	MS	F/AB	P
Between drugs	1	12.55	4.36	NS	18.09	6.31	<0.05
Between patients	10	4.36	1.51	NS	2.57	0.897	NS
Interaction	10	2.88			2.87		
Residual	22	0.223			0.212		
Meperidine and Propoxyphene							
Between drugs	1	31.96	12.93	<0.01	8.14	4.42	NS
Between patients	10	10.50	4.25	<0.05	4.30	2.33	NS
Interaction	10	2.47			1.84		
Residual	22	0.540			0.075		
Floctafenine and Propoxyphene							
Between drugs	1	4.45	0.603	NS	1.96	1.35	NS
Between patients	10	7.28	0.984	NS	4.06	2.8	NS
Interaction	10	7.39			1.45		
Residual	22	0.557			0.188		

MEANS ± S.E.	SUBJECTIVE	OBJECTIVE
Meperidine	1.41 ± .126	2.63 ± 0.386
Floctafenine	2.52 ± .203	3.91 ± 0.306
Propoxyphene	3.16 ± .464	3.49 ± 0.395

3. Covariance Analysis

A covariance analysis was done on the results of the first four-hour period in order to examine the effects of initial pain intensity on the change in pain score obtained and on the final pain score reported. The entire sample was examined first and then the group consisting of only the females in the investigation was examined in order to determine if a more homogeneous group could be produced by excluding the male population. This possibility was suggested from the results of the analysis of variance.

The results from patient trials 7, 10 and 11 were not included in view of their low initial pain scores. The results from patients who discontinued the study during the first period due to severe unrelieved pain were given a subjective pain score of 9 and an objective pain score of 28 for the remaining interviews in the period. These scores were chosen because they were the highest scores reported by other patients in the study.

The nurse's evaluations or objective results were normalized to a scale of 0 - 10 by dividing by 2.8.

The original means for the three drugs were not found to be significantly different for the pooled sexes ($F = 2.05$ for the subjective data and 2.41 for the objective data). The original means, though, were significantly different in the female sample when examining the subjective data ($F = 4.04$, $p < 0.05$); they did not differ significantly when examining the objective data ($F = 0.46$).

The final pain scores following meperidine and floctafenine appeared to have approximately a 50% dependence on the initial pain level and to have approximately a 50% constant change. Post-propoxyphene scores, on the other hand, did not show dependence on the initial pain level. (See Tables 18 and 19).

No significant differences were found between the female sample and the pooled sexes sample. The female sample did not appear to be a more homogeneous group than that of the pooled sexes. (See Table 20).

Table 18

EFFECT OF ORIGINAL PAIN ON CHANGE AND FINAL LEVEL DURING FIRST PERIOD (POOLED SEXES)

	SUBJECTIVE			OBJECTIVE		
	Meperidine	Floctafenine	Propoxyphene	Meperidine	Floctafenine	Propoxyphene
Number in group	13	13	13	13	13	13
Mean original score	4.96 ± 0.40	4.92 ± 0.54	3.58 ± 0.59	5.25 ± 0.62	4.61 ± 0.39	4.81 ± 0.43
Mean final score	1.98 ± 0.37	2.83 ± 0.44	3.40 ± 0.66	2.99 ± 0.35	3.53 ± 0.33	4.41 ± 0.73
Slope: final/original	0.49 ± 0.23	0.39 ± 0.22	0.22 ± 0.41	0.35 ± 0.13	0.43 ± 0.22	1.24 ± 0.35
Slope: change/original	0.51 ± 0.23	0.61 ± 0.22	0.78 ± 0.41	0.65 ± 0.13	0.57 ± 0.22	-0.24 ± 0.35
Adjusted original	3.58	3.58	3.58	4.89	4.89	4.89
Adjusted final	1.30 ± 0.46	2.31 ± 0.49	3.40 ± 0.66	2.87 ± 0.29	3.65 ± 0.30	4.51 ± 0.52
Adjusted change	-2.88 ± 0.46	-1.27 ± 0.49	-0.18 ± 0.66	-2.02 ± 0.29	-1.24 ± 0.30	-0.38 ± 0.52
Bartletts M (X^2) for homogeneity of variance (df= 2)						
originals	1.80			3.19		
finals	12.90			5.37		
F for linear regression	4.32	3.28	0.03	7.04	3.87	12.39
F for differences in original means	2.05			2.41		

Table 19

EFFECT OF ORIGINAL PAIN ON CHANGE AND FINAL LEVEL DURING FIRST PERIOD (FEMALES)

	SUBJECTIVE			OBJECTIVE		
	Meperidine	Floctafenine	Propoxyphene	Meperidine	Floctafenine	Propoxyphene
Number in group	10	12	11	10	12	11
Mean original score	5.10 ± 0.50	4.83 ± 0.58	3.05 ± 0.56	5.39 ± 0.74	4.70 ± 0.41	5.06 ± 0.47
Mean final score	1.88 ± 0.48	2.71 ± 0.46	3.20 ± 0.93	3.30 ± 0.34	3.56 ± 0.36	4.59 ± 0.85
Slope: final/original	0.55 ± 0.27	0.36 ± 0.22	0.09 ± 0.55	0.36 ± 0.13	0.44 ± 0.24	1.34 ± 0.42
Slope: change/original	0.45 ± 0.27	0.64 ± 0.22	0.91 ± 0.55	0.64 ± 0.13	0.58 ± 0.24	-0.34 ± 0.42
Adjusted original	3.05	3.05	3.05	5.03	5.03	5.03
Adjusted final	0.75 ± 0.69	2.07 ± 0.58	3.20 ± 0.93	3.18 ± 0.29	3.70 ± 0.33	4.55 ± 0.61
Adjusted change	-2.30 ± 0.69	-0.98 ± 0.58	+0.15 ± 0.93	-1.86 ± 0.29	-1.33 ± 0.33	-0.48 ± 0.61
Bartlett's $M(X^2)$ for homogeneity of variance (df = 2) originals	0.51			2.86		
finals	9.27			6.52		
F: for linear regression	4.14	2.65	0.03	7.92	3.45	10.31
F: for difference in original means.	4.04			0.46		

Table 20

COMPARISON OF ADJUSTED PAIN SCORES* OF THE FEMALE AND POOLED SEXES SAMPLES.

(FISHER-BEHRENS TEST)

	FEMALE SAMPLE		POOLED SAMPLE	
	SUBJECTIVE	OBJECTIVE	SUBJECTIVE	OBJECTIVE
t' F/P**	0.99	1.22	1.15	1.44
p	NS	NS	NS	NS
t' M/P+	2.15	2.03	2.25	2.75
p	≈ 0.05	> 0.05	< 0.05	< 0.05

* Corrected for originals

** for floctafenine and propoxyphene

\+ for meperidine and propoxyphene

For this test, the adjusted pain scores for the female sample were taken from Table 19, line 7 and those for the pooled sample from Table 18, line 7

(Fisher, R.A. and Yates, F., 1963 p. 3-4)

x^2 test for homogeneity of variance between drug groups - Bartlett's M test (Finney, D.J., 1964).

In applying the experimental design of the investigation it had been assumed that the variances of each treatment group taken separately were the same. To test this hypothesis, Bartlett's M test was used to compare the variance of the pain scores within each group. When all the data for the first four-hour period were considered, significant differences in the variance between groups was found. The variance within the propoxyphene group was significantly greater than within the other two groups. Then the data was re-examined leaving out the two patients in the propoxyphene group who had dropped out due to unrelieved pain and had been assigned scores. The variance within groups was now not significantly different in the three groups. The two patients who dropped out of the study in the first period due to severe unrelieved pain, can not be excluded, though, from the analysis, since this would bias the results in favour of propoxyphene. It appears from this test that the large variation within the propoxyphene group may be due partly to the pain scores assigned to these dropouts i.e. a subjective score of 9 and an objective score of 28. This again raises the problem of what scores should be assigned to patients who drop out of the investigation.

Table 21

'X^2' FOR HOMOGENEITY OF VARIANCE BETWEEN DRUG GROUPS (BARTLETT'S M-TEST)

	All data	Two Patients Excluded*
Unadjusted:		
Patients	6.76	0.918
Nurse	10.25	0.225
Adjusted for 'slope' (dependence of final on original)		
Patients	7.55	0.861
Nurse	6.52	0.810

($X^2 = 5.99$, $p = 0.05$)

* The two patients dropped out of the study in the first period due to severe unrelieved pain.

Table 22

VARIANCE OF FINAL SCORES FOR PATIENTS IN THE PROPOXYPHENE GROUP DURING THE FIRST PERIOD.

	SUBJECTIVE	OBJECTIVE
Excluding 2 drop-outs	2.81	0.88
Including 2 drop-outs	7.63	6.38

Covariance Analysis over the 12-hour period.

A covariance analysis was done based on the following model:

y = mean + period effect + current drug effect
+ residual (previous) drug effect + effect due to
initial pain level + age effect.

"y" represents the average of the 2nd and 3rd hour pain scores.

The results of 34 patients who completed the crossover design were used in these analyses. The results of patients trials 7, 10 and 11 were not included in view of their low initial pain levels.

Analysis 1

In analysis 1, the effects due to the initial pain levels, current drug administered and period of the day were examined. With the subjective results, a significant F-ratio was found only for the initial pain levels. The drug effect borders on the level of significance of $p = 0.05$. Significant differences were found between meperidine and propoxyphene ($t = 2.3$; $p < 0.05$). Period effects were not significant.

Examining the objective results, significant F-values were found for both the current drug and initial pain effects. Meperidine and propoxyphene were found to be significantly different ($t = 2.87$; $p < 0.01$) as well as meperidine and floctafenine ($t = 2.40$; $p < 0.05$). No difference was found between floctafenine and propoxyphene. Period effects again were not significant.

Analysis 2

In analysis 2, the carryover effects or effects due to previous medication were also examined.

The results of the subjective analysis were similar to those of analysis 1. Period effects showed the same trend but were of no statistical significance. Current drug effects demonstrated a significant difference only between meperidine and propoxyphene ($t = 2.79$; $p < 0.01$). The carryover effects did not reach significant levels but were in the same order as the drug effects although of smaller magnitude.

With the objective results, the period effects and drug effects were similar to those previously seen in analysis 1. Meperidine was superior to propoxyphene ($t = 3.31$; $p < 0.01$) and to floctafenine ($t = 2.24$; $p < 0.05$). No statistical difference between floctafenine and propoxyphene was found. The carryover effects were in the same order as the drug effects but no statistically significant differences were seen between the carryover values of the three drugs.

Analysis 3

In analysis 3, the effect of the patients' ages were considered. Age appeared to have a very small effect of no statistical significance.

Mean slope of pain scores due to age $\pm$ S.E.

Subjective = $-.011 \pm .012$
Objective = $+.005 \pm .008$

Table 23

COVARIANCE ANALYSIS FOR TWELVE-HOUR PERIOD EXAMINING INITIAL PAIN, PERIOD AND DRUG EFFECTS.

		SUBJECTIVE			OBJECTIVE		
Variation	D.F.	MS	F-RATIO	P	MS	F-RATIO	P
Initial pain	1	49.40	19.76	<0.01	25.56	22.29	<0.01
Period	2	0.304	0.12	NS	0.679	0.59	NS
Drug	2	6.53	2.61		5.49	4.79	<0.05
Residual	96	2.50			1.15		
Total	101	3.00			1.47		

MEAN EFFECTS ON PAIN SCORES $\pm$ S.E.

	SUBJECTIVE	OBJECTIVE
Initial pain level	2.80 ± 0.09	3.31 ± 0.03
Drug effects (change from initial level)		
Floctafenine	-0.40 ± 0.22	$+0.05 \pm 0.15$
Meperidine	-0.82 ± 0.82	-0.58 ± 0.15
Propoxyphene	$+0.06 \pm 0.22$	$+0.17 \pm 0.15$
Period effects (change from mean level)		
1st	$+0.11 \pm 0.22$	$+0.01 \pm 0.15$
2nd	-0.08 ± 0.22	-0.15 ± 0.15
3rd	-0.03 ± 0.22	$+0.14 \pm 0.15$

Table 24

COVARIANCE ANALYSIS FOR TWELVE-HOUR PERIOD EXAMINING INITIAL PAIN, PERIOD, DRUG AND CARRY-OVER EFFECTS.

		SUBJECTIVE			OBJECTIVE		
Variation	D.F.	MS	F-RATIO	P	MS	F-RATIO	P
Initial pain	1	53.30	21.63	<0.01	27.72	24.44	<0.01
Period	2	0.253	0.10	NS	0.624	0.55	NS
Drug	2	9.88	4.02	<0.05	6.44	5.68	<0.01
Carryover	2	4.42	1.80	<0.25	1.73	1.53	<0.25
Residual	94	2.46			1.13		
Total	101	3.00			1.47		

Mean effects on pain scores $\pm$ S.E.

	Subjective	Objective
Initial pain level	2.82 ± 0.09	3.32 ± 0.03
Drug effects (change from initial level)		
Floctafenine	$+0.50 \pm 0.25$	-0.00 ± 0.17
Meperidine	-0.95 ± 0.24	-0.65 ± 0.17
Propoxyphene	$+0.22 \pm 0.24$	$+0.78 \pm 0.16$
Period effects (change from mean level)		
1st	$+0.10 \pm 0.22$	0.00 ± 0.15
2nd	-0.06 ± 0.22	-0.14 ± 0.15
3rd	-0.03 ± 0.22	$+0.14 \pm 0.15$
Carryover effects (change from mean level)		
Floctafenine	-0.06 ± 0.30	-0.04 ± 0.20
Meperidine	-0.46 ± 0.30	-0.29 ± 0.20
Propoxyphene	$+0.52 \pm 0.31$	$+0.33 \pm 0.21$

IV DISCUSSION OF RESULTS

In the present investigation, floctafenine 200 mg, administered orally was shown to be less effective than meperidine 75 mg administered orally and marginally better than propoxyphene 65 mg. in relieving post-cholecystectomy pain. Pain relief differences were found between meperidine and floctafenine, the two drugs acting as an internal control. This was a necessary requirement of the study in order to demonstrate that the study was sensitive enough to detect analgesic differences. From the evaluation of the subjective results, no statistical difference was found between meperidine and floctafenine although a difference was found after the evaluation of the objective results.

The results of the investigation were analyzed by comparing the maximum pain intensity differences (MPID), the summed pain intensity differences (SPID) and the mean pain intensity scores of the second and third hours after administration. The MPID and SPID evaluations could only utilize the first 4-hour period due to the fact that pain scores did not return to their initial levels inbetween drug administration. By utilizing the means of the second and third hours after administration pain scores, time is allowed for the absorption of the drugs plus carry-over effects are largely eliminated.

The MPID and SPID values were found to be sensitive methods for evaluating pain relief differences as significant differences were seen between meperidine and propoxyphene and between meperidine and floctafenine when the patients' reports were evaluated. The nurse's evaluation showed less significant differences i.e. the F values were smaller, but tended to demonstrate more of a difference between meperidine and floctafenine. This could be due to the fact that pain, while the patients are being stressed, is harder to relieve and necessitates the use of a stronger analgesic. A narcotic analgesic may relief pain to a greater degree when the patient is being stressed while its pain relief might not be distinguishable from that of a non-narcotic analgesic when the patient is at rest. The fact that propoxyphene is a congener of methadone, although it only has weak analgesic activity, may account for its better performance in the nurse's evaluations when the patient

must perform certain tasks. Its mechanism of action may be predominantly central like the narcotic analgesics and therefore superior to a non-narcotic analgesic with its mainly peripheral mechanism of action (Lim, 1967)

In the MPID and SPID evaluations, the patients who discontinued the investigation due to severe unrelieved pain were included. These patients were given a subjective score of 9 and an objective score of 28 for each interview time in the first period after they discontinued the study. These values were chosen since they were the highest pain scores reported by a number of other patients in the study. Both patients who dropped out during the first period were being treated with propoxyphene. By leaving the results of these patients out, the results would be biased in favour of propoxyphene. By including these patients one is faced with the problem of what values to assign to these patients after they have discontinued the study. By using the values of 9 and 28, the variance within the propoxyphene group increased greatly. This variance contributed to the lack of statistical differences between groups.

It is important to note that the results suggest that floctafenine appears to have a longer duration of action than meperidine and propoxyphene from the results of this investigation. If this is true, then the results of the SPID analysis may be biased in favour of floctafenine since the analysis measures the pain intensity differences over a four-hour period. Any drug with a duration of action less than four hours would have low PID values for the last interview time and this would lower the SPID value for the drug.

The initial pain levels were not found to vary significantly between the different groups of patients receiving either meperidine, floctafenine or propoxyphene as a first medication in the pooled sexes sample. Three patients who had low initial pain scores were excluded from the analyses.

The Bartlett's M test for homogeneity of variance demonstrated that the variance within the propoxyphene group when the drop-outs were included was significantly greater than that within the meperidine or floctafenine groups, for the first period. When the two patients who had dropped out were excluded, the variance within each group was not significantly different between the three groups. This raises the problems of whether or not to include drop-outs in the analyses of results and if including them, what pain intensity scores to assign to them. Patients dropping out of the study should be included in order to prevent biasing the results in favour of the ineffective drug. A high pain intensity score must be assigned to these patients although this will cause an increase variance within the group.

The analysis of variance demonstrated significant differences in the analgesic effects of meperidine and propoxyphene and of meperidine and floctafenine, using the means of the pain scores of the second and third hours after administration. No significant differences were found between floctafenine and propoxyphene. The nurse's evaluation in this analysis appeared to be a more sensitive method for evaluating pain relief due to the larger F-values obtained. Age and sex differences were examined but no significant differences in drug effects between groups was evident.

A covariance analysis examined the effects of initial pain, drug effects, period effects, carryover effects and age effects on the final pain score. The initial pain and drug effects were significant with the drug effects being similar to those seen with the analysis of variance. The period effects, carry over effects and age effects were all non-significant.

Floctafenine appeared in this study to have a duration of action longer than that of meperidine or propoxyphene. The new drug had the lowest number of reported side effects in this study (10), while meperidine had the greatest number (18); propoxyphene was intermediate (14). Drowsiness was the most commonly reported side effect with all three drugs. These results compare favourably with some recently published clinical investigations involving floctafenine.

a) Vickers and Akbar (1975) conducted a double-blind crossover trial with 23 patients comparing the analgesic effect of floctafenine (F) 200 mg with placebo (P) in chronic pain. Each drug was self-administered by the patients for a period of one week during which time the patients utilized daily record cards. Patients were allowed to take up to 2 tablets on each occasion that they needed an analgesic. Other analgesics could be administered if adequate analgesia was not obtained. From the results, floctafenine showed significantly greater pain relief in a number of parameters, including patient's assessment of pain relief ($F = 7.38$; $P = 4.54$), use of additional or usual analgesics, ($F = 10.6$; $P = 13.5$), and patient's own preference ($F \geq 10$; $P = 1$: No difference = 5). The numbers in parentheses represent weekly pain relief scores except for those following patient's own preference which are numbers of patients. Frequency of side effects was similar in both groups which agrees with the low incidence of side effects reported in the present investigation. However, several problems are inherent in this study.

The use of patient record cards introduces the problems of patient compliance and patient recall (Beecher, 1959a). Each day's pain relief was recorded as excellent, good, poor or none. This rating includes the effects of alternate analgesics the patient was ingesting and so is not a measure of the pain relief by placebo or floctafenine. Also, patients with varying types of chronic pain were involved in this study. Besides the psychological aspects present with chronic pain plus the varying experience with analgesics that all chronic pain patients have, the daily variability of various types of chronic pain must be taken into account. Although, it is difficult to interpret the results of this study in view of the above factors, the fact that side effects of floctafenine were not different from those of placebo may be of some significance.

b) Stenport (1975) in a double-blind crossover study compared floctafenine 200 mg. with placebo in orthopedic post-operative patients. Pain was rated by the patient between 0 and 3. The second drug could be administered as soon as 1 hour after the first medication if pain relief was not obtained within that time. The SPID values for a 6 hour period were compared, and showed floctafenine to be superior to placebo. These results are in agreement with the present study in which floctafenine was shown to have an analgesic activity between that of meperidine and propoxyphene.

Stenport (1975) also compared floctafenine 200 mg to its soluble HCl salt and to ASA 600 mg in 60 orthopedic post-operative patients in a doubleblind, non-crossover study. Pain was rated between 0 and 3 and the SPID values for 8 hours were compared. No differences were found between any of the drugs. It is not known, though, if the study methodology was sensitive enough to detect differences since no internal control was utilized. Gastric side effects were minimal with all drugs and occasional drowsiness was similar among the three groups. The low incidence of side effects found is consistent with the results of the present investigation.

c) Lipton and Akbar (1975) executed a double-blind, crossover study comparing floctafenine 200 mg and dihydrocodeine 60 mg. in 72 patients suffering from post-operative pain. Pain levels were scored as being between 0 and 3. No significant difference in the pain relief score for floctafenine (3.5) and dihydrocodeine (3.9) was found. There was also no significant difference in the duration of analgesia seen with floctafenine (4.03 hours) or dihydrocodeine (3.74 hours). Of the 65 patients receiving both drugs, seven complained of side effects following floctafenine but not following dihydrocodeine. However, 20 patients complained of side-effects following dihydrocodeine but not following floctafenine. This difference was statistically significant. Again, various types of post-operative pain were used and the study did not demonstrate that significant differences could be found between drugs using this method. The length of duration of analgesia and low incidence of reported side effects is again consistent with the present investigation.

d) Lipton, Conway and Akbar (1975a) carried out a double-blind crossover study comparing floctafenine 200 mg with pentazocine 50 mg in 70 patients suffering from postoperative pain. Pain was again evaluated on a scale of 0 to 3. No significant difference was found between the mean pain relief score (SPID) of floctafenine (3.1) and pentazocine (2.9). Of the 65 patients who received both drugs, 11 complained of side effects following floctafenine but not following pentazocine and 18 complained of side effects following pentazocine but not floctafenine. The difference was not statistically significant. Examination of the time between the administration of the 2 trial doses showed no significant difference between the two compounds although the mean duration of relief afforded by floctafenine was longer. As before, the study involved post-operative pain of diverse etiology and contained no internal control to ensure sensitivity. Although this study could not demonstrate the analgesic activity of floctafenine it did demonstrate the low side effect potential and long duration of action of the drug.

e) Lipton, Conway and Akbar (1975b) performed a double blind crossover study comparing floctafenine 200 mg with ASA 600 mg or propoxyphene 130 mg in 77 post-operative patients. Pain relief scores were recorded at hourly intervals and the SPID values for a 6-hour period calculated. For the first dose, the difference between the mean pain relief score for patients receiving floctafenine (12.8) and that for patients receiving propoxyphene (6.2) was significant ($p < 0.05$) but the difference between the mean score for ASA (9.2) and that for propoxyphene or for floctafenine were not significant. These results compare favourably with the results of the present investigation since differences between floctafenine and propoxyphene 65 mg. were found between the SPID values from the subjective evaluation. This, though could be partly due to the shorter duration of action of propoxyphene. Considering the combined data for both doses, the mean pain relief score for floctafenine was 11.3, for ASA 9.3 and for propoxyphene 9.4. The differences in mean scores was not significant. The lowest number of side effects were reported following

floctafenine which agrees with the present investigation and other reported studies (Vickers and Akbar, 1975; Lipton and Akbar, 1975; Lipton, Conway and Akbar, 1975a; Stenport, 1975)

These recently published investigations stress the low side effect potential of floctafenine. Although floctafenine is a congener of mefenamic acid it does not appear to share mefenamic acid's propensity for frequent and severe side effects i.e. severe diarrhea, gastrointestinal ulceration and bleeding, headache, drowsiness, nausea, nervousness and autoimmune hemolytic anemia (Medical Letter, 1972). A much larger study is required, though, in order to quantify the side effects of floctafenine, given acutely and chronically.

No placebo was utilized in this investigation due to the ethical problems involved when treating a patient having organic pain with a placebo. It was felt that more meaningful results could be obtained if the new drug was compared with two standard analgesics. If floctafenine proved to be as good as or superior to meperidine 75 mg., the results would have meaning; the drug would then be of some clinical value.

The inclusion of a placebo would increase the number of patients who would drop out of the study due to unrelieved pain. Then, pain scores would have to be assigned to these patients in order that these patient trials could be included in the analyses so the results would not be biased in favour of the placebo. This would introduce the problem of what scores to assign to these patients and increase the variability of the group as was seen with the patients who dropped out of the present investigation while on propoxyphene.

Thus floctafenine 200 mg. was shown in the present investigation to be an analgesic effective against mild to moderate pain at the studied dosage but possessing a longer duration of action and producing a lower number of side effects than either meperidine or propoxyphene. Its activity appears to be intermediate to that of meperidine and propoxyphene. These results concur with recently reported investigations of floctafenine.

SUBJECTIVE VS. OBJECTIVE (BEHAVIOURAL) APPROACH TO THE MEASUREMENT OF PAIN RELIEF.

In this investigation the objective evaluation was a more sensitive measure of pain relief than the subjective results when analyzed by covariance analysis. This can be seen by the larger F-values obtained and the significant differences which may be found between meperidine and floctafenine during the statistical evaluation utilizing data obtained by the objective assessment of pain relief (see Tables 23 and 24).

Although the two evaluations correlate well it may be noted that in the subjective evaluation the mean pain levels are lower than in the objective evaluation. This could be due to the fact that the subjective approach is measuring the pain levels at rest while the objective approach measures the pain level produced by movement and coughing which is harder to relieve with analgesics (Keats, 1956; Parkhouse and Holmes, 1963).

Parkhouse and Holmes (1963) administered morphine or saline intravenously to post-operative (upper abdominal) patients and recorded their pain as being improved or not improved. They found that pain induced by movement or coughing was as good a measure as that of pain on rest but not better i.e. it did not magnify the differences between drugs. There are several differences between their study and the present study which could account for the different results. Parkhouse and Holmes's patients had more severe pain, since they were studied on the first day post-operatively, than the patients in the present study, so that movement or coughing would be more difficult for their patients. While morphine might distract the patient from his pain while at rest a high dose of morphine would be necessary to obliviate pain on movement. Also, they rated pain levels as being improved or not improved. This is a crude measure of pain relief and could serve to decrease the differences found between the two drugs.

It has been accepted up to the present date that the best estimate of a patient's pain relief is that of a verbal statement by the patient (Lutterbeck and Triay, 1972, Beecher, 1959a). Bishop's definition of pain (as quoted by Beecher, 1959a) as being what the subject says hurts has been used as the basis for the evaluation of analgesics in clinical investigations. Patients, though, are unskilled assessors of pain and their assessments of pain are influenced by many factors including their personality, their environment, their racial background, and their past experiences, and the type and cause of pain.

In the present study evaluation of pain relief following movement or coughing was as sensitive a method if not a more sensitive method detecting analgesic activity than the subjective evaluation following the oral administration of analgesics in post-cholecystectomy patients. It is possible that this type of evaluation may be used in other types of post-operative pain with similar success.

OPERATIVE SITE

Lutterbeck and Triay (1972) have stated that patients should be chosen from a group with a single operative procedure in order to obtain a more homogeneous patient population. Cholecystectomy was chosen as the operative procedure for this investigation. Forty-three patients were studied over a 4 1/2 month period in a 540 bed general hospital. Even though the study was scheduled over the summer months when the problem of surgeons taking summer holidays is encountered there was no difficulty in obtaining the desired patient population. At the Ottawa General Hospital there were 361 cholecystectomies performed in 1972, 326 in 1973, and 216 in 1974, demonstrating the frequency of the operation. The nurse-observer was only employed on a 5 day week basis so patients who would be suitable for the investigation on a weekend were not studied. Approximately one-quarter to one-third of the patients who were approached concerning the investigation did not give their consent. Only two patients in the specified age group were not approached concerning the study due to medical contraindications - one due to a malignancy and one due to a severe cardiac condition.

Cholecystectomy proved to be a reasonable choice in that moderate pain lasts for several days following the operation and allows the testing of an oral analgesic. The average stay for a patient admitted for a cholecystectomy at the Ottawa General Hospital in 1974 was 12.8 days. The operation is welcomed by patients as a long-awaited escape from their gastrointestional distress. The mortality rate from cholecystectomy in 1956 at the Massachusetts General Hospital was 0.6% (Warren, 1963). In the present study no marked progressive changes in pain levels over the twelve-hour investigation period could be detected as could be seen in the covariance analysis when period effects were very small and not significantly different. Whether progressive changes in pain levels existed could not be evaluated, though, since all patients were on analgesics throughout the twelve hour periods.

In order to obtain a larger sample of post-cholecystectomy patients for future studies, it would be necessary to:

a) work a 7-day week. (This would require more than one observer), or
b) use a larger hospital or more than one hospital, or
c) extend the study over a longer period of time.

The site of the operation has been shown to be the most important single factor determining severity of post-operative pain. (Swerdlow et al, 1964; Parkhouse et al, 1961). In view of these findings, the results of studies using post-operative pain of diverse etiology must be regarded with some caution.

SEX DIFFERENCES

Sex differences in this study were examined in order to determine if there were differences in pain relief due to sex. Unfortunately, since cholecystectomies are performed predominantly in females there were only seven males to compare to the thirty females in this study.

Ackerman and Rosai (1974) quote the ratio of women: men who undergo cholecystectomy to be 4:1.

No significant differences between drugs were seen in the males. We were now able to detect statistical differences between meperidine and floctafenine in the female patients which were not present in the whole population. This suggests the possibility that the female patients were a slightly more homogeneous group than the whole sample studied. This possibility was examined by comparing the covariance analysis of the first period of the pooled sexes to that of the females but no significant differences were noted.

Most of the studies which have examined sex differences (Woodrow, et al, 1972; Wolff et al, 1969) have utilized pain tolerance following the production of experimentally-contrived pain. Parkhouse, Lambrechts and Simpson (1961) and Loan, Morrison and Dundee (1968) studied pain relief in post-operative patients and concluded that the sex of the patient did not appear to influence response to treatment. Therefore, the present time there is no good evidence indicating that only one sex should be used in organic pain studies in order to produce a more homogeneous population.

AGE DIFFERENCES

In this study age differences were examined. In the covariance analysis of the first period, pain scores tended to decrease very slightly as age increased. This effect of age is in no way significant but suggests the possibility that a limited age group may produce a more homogenous population.

Old people are generally thought to be more tolerant of pain than younger people but there remains much controversy concerning the effect of age on pain relief. Again, many of the studies on age effects utilize experimentally-contrived pain which only tends to confuse the issue. Parkhouse, Lambrechts and Simpson (1961), when studying analgesic

requirements following upper and lower abdominal operations found a significant difference between patients below the age of 50 and patients above this age. Belleville and associates (1971) studied 712 post-operative patients and found age to be highly correlated with pain relief reports in that the older age group reported more pain relief.

It has been stated that there is, in general, an increasing effect of all drugs in older age groups (Bender 1964). The change in pain relief with age may be due to alterations which affect the body's absorption, distribution, metabolism and elimination of the drug. It seems logical to postulate that the effect of age on the pain relief obtained from administration of a narcotic analgesic may differ from that of a non-narcotic due to their different mechanisms of action. The perception of pain has been reported as diminished in aging patients so decreased pain sensitivity may be related to changes in other modalities. For instance, it is well documented that the protective airway reflex is decreased with aging. (Pontoppidan and Beecher, 1960).

Also environmental factors may play a significant role. Older patients may have grown up in a harsher environment i.e. during the depression and this could influence their overall view of pain and what they consider pain relief.

Belleville and associates (1971) concluded from the results of the survey that age is one of the most important variables in determining the degree of pain relief following the intramuscular injection of a potent analgesic. A decrease in the variability between patients was not seen in the present study, though, when three age groups, namely 18-30 years, 21-50 years, and 51-65 years were examined (see Tables 15, 16, 17). This may be due to the small number of patients in each age group.

PERIOD EFFECTS

The period effects were not significant throughout the analyses. The patients, though, felt that they fared best during the second period of the day and the nurse agreed with this opinion.

Changes in the patient's pain relief through different periods of the day could be due to the changing environment of the patient in the hospital. Visitors present during visiting hours in the afternoon and evening could affect the psychological state of the patient. Change of nursing staff on the ward, conversations with other patients and other personnel or a physician's visit may affect the pain relief that the patient obtains in a certain period of the day. Increased fatigue on the part of the patient or altered standards or even boredom on the part of the assessor could affect the nurse's evaluation of pain relief (Swerdlow et al, 1963).

Neither the patients' or nurse's evaluations of the period effects demonstrate that pain is decreasing linearly during the 12 hour period as one would expect with postoperative pain of short duration. It appears, therefore, that during the 12 hour period studied the pain level remained fairly constant in these patients.

Man's subjective evaluation of pain has long been suspect of rhythmic responses. A rhythm has been found in mice in that maximum sensitivity to pain occurs while the mouse is at rest and the converse is true while the mouse is active. Another significant observation was that mouse susceptibility to morphine analgesia is low while pain sensitivity is high (while at rest), whereas maximum sensitivity to morphine occurred when pain response was low (mouse awake and alert) (Morris and Lutsch, 1969). Grabfield and Martin (1912-1913 in Beecher, 1959a) when studying variations in the sensory threshold for faradic stimulation in normal human subjects found peaks of irritability at 10-11 o'clock in the morning and another rise beginning in the late afternoon. This would correspond to the first and third periods of this study. Procacci and coworkers (1974)found that a circadian rhythm of the cutaneous pain threshold is present in both men and women.

RESIDUAL DRUG EFFECTS

The data has been examined for evidence of effects that depend on the patient's experience with the previous analgesic. Crossover studies are often difficult to interpret due to pharmacologically-produced carryover and expectation effects caused by preceding drugs (Kantor et al, 1966). The residual drug effects in this investigation were not significant but tend to be in the same order as the current drug effects although generally of smaller magnitude. Some interesting trends however can be seen.

Meperidine, when it followed floctafenine produced a lower mean pain intensity score than when it was given alone. This was not as evident when the drugs were given in reverse order; neither was this evident when propoxyphene follows floctafenine. Floctafenine may have a longer duration of action than meperidine or propoxyphene so pharmacological carryover may be the cause of the increased effect of meperidine when it follows floctafenine.

The carry-over effects of meperidine are mainly seen in the first 1/2 to one hour following the administration of the next drug. The duration of effective action of oral meperidine is 2 to 4 hours but it is possible that this carry-over effect is partially psychological. The patient had an effective analgesic so he expects the succeeding analgesic to be effective as well (Kantor et al, 1966).

Propoxyphene does not appear to exert much of a carry-over effect. If anything, the scores of the succeeding drug are slightly higher implying a negative carry-over effect. It is possible that because a person received a relatively ineffective drug, that person expects the next drug to produce similar effects.

LIMITATIONS OF THE PRESENT STUDY

In retrospect, several limitations of this study and suggestions for implementation in future studies have become evident.

The initial pain levels varied in this study. A lower limit should have been set and no patients admitted with pain below this level since the pain relief score has been shown to be correlated to the initial pain level.

The study of each drug's effects were done over a 4-hour period. Although meperidine and propoxyphene are short-acting, floctafenine appears to have a longer duration of action, as seen both from the results of this investigation and from that of recently published studies (Lipton and Akbar, 1975; Stenport, 1975). If a 6-hour investigation period had been used pain may have returned to the initial level between drugs but then only 2 drugs could have been compared on the same day, eliminating the internal control. A 6-hour investigation period also would have decreased physician and patient cooperation due to the increased cases of unsuccessful analgesia. This is an important consideration in clinical investigations.

Seven tasks were used for the behavioural evaluation of pain. This could have been reduced to 5 tasks, namely, getting out of bed, walking on flat, sitting up, coughing and deep breathing. Entering bed and dressing could have been eliminated with essentially similar results obtained and less work and effort on the patient's part, since these 2 tasks tended to yield similar results to the others tested.

Patients involved in this study were any consenting post-cholecystectomy patients fulfilling the requirements listed in the section on Patient Selection. They occupied 4-bed, 2-bed and private hospital rooms. This could be a possible source of variability since the patient's attitude may be greatly modified by previous hospital experiences and by the behaviour of neighbouring patients who have already undergone surgery. The patient should be isolated from other patients in order to minimize the influence exerted by other patients (Parkhouse and Holmes, 1963).

Other sources of variation which have not been controlled include the type of incision, length of incision and previous experience with abdominal surgery. The importance of controlling these variables in clinical analgesic studies have not yet been determined.

CONCLUSION AND SUMMARY

Floctafenine 200 mg is a non-narcotic analgesic which when given orally has activity intermediate to that of oral propoxyphene 65 mg and oral meperidine 75 mg. in relieving post-cholecystectomy pain.* Patients in the investigation reported substantially more side effects following meperidine than following floctafenine administration. This low side effect potential of floctafenine is in agreement with other recently reported studies.

In this investigation the initial pain level was found to have a significant influence on the final pain score reported. The influences of age, sex, period and previous medication on the pain relief obtained were examined and all found not to be statistically significant.

A behavioural approach for evaluating pain relief was compared with the normally-used subjective approach. There appears to be good correlation between the two methods although pain scores were somewhat higher using the behavioural approach. This method has been demonstrated to be a sensitive method for evaluating new oral analgesics in post-operative pain.

* Significant differences between floctafenine plus meperidine were found in 4 out of the 5 evaluations (MPDI, SPID, Analysis of Variance, Covariance analyses (2)) using the objective data but not seen in the evaluations using the subjective analyses. Significant differences between floctafenine and propoxyphene were found in 2 out the 5 analyses using the subjective data and 1 out of the 5 analyses using the objective data.

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In this study, the protocol was set up by the candidate in cooperation with Dr. I.W.D. Henderson and Dr. MacConaill. The candidate was responsible for the hiring and training of the nurses involved in the study; the choice of the patients used involving a review of their physical examination and history and an interview in which consent was requested; the obtainment of approval for the consenting patient by the surgeon in charge; the decision as to the appropriate day for each patient study; the education of the surgical residents and interns plus the nurses on the surgical wards as to the nature of the study; and the solving of any problems that arose during the study period.

Dr. Henderson was responsible for obtaining approval by the Department of Surgery and the Human Ethics Committee in the Ottawa General Hospital.

Dr. MacConaill aided the candidate in the statistical evaluation of the results of the study.

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APPENDIX A

OTTAWA GENERAL HOSPITAL
DECLARATION OF CONSENT TO THE
ADMINISTRATION OF SPECIAL DRUGS

I HEREBY CONSENT TO THE ADMINISTRATION AT THE OTTAWA GENERAL HOSPITAL OF THE SPECIAL DRUG(S) _____ PRESCRIBED FOR
(NAME OF THE DRUG(S)

_____ BY DR. _____.
(INSERT "ME" OR NAME OF PATIENT)

THE DOCTOR HAS GIVEN ME AN EXPLANATION OF THE POSSIBLE UNFAVOURABLE EFFECTS THAT MIGHT ARISE BY THE DRUG(S) BEING TAKEN BY ME / THE PATIENT BUT I UNDERSTAND THAT UNDER THE PRESENT CIRCUMSTANCES, THIS (THESE) SPECIAL DRUG(S) MAY BE THE ONLY ONE(S) TO HELP ~~MY~~ THE PATIENT'S CONDITION. I ALSO UNDERSTAND THAT THIS (THESE) DRUG(S) ARE RELATIVELY NEW, AND NOT ALL UNFAVOURABLE SIDE EFFECTS ARE AS YET FULLY KNOWN.

DATE _____

WITNESS _____ SIGNATURE _____

_____
RELATIONSHIP TO PATIENT

NOTE: IF THE PATIENT IS UNABLE TO SIGN BY REASON OF MENTAL OR PHYSICAL DISABILITY, THIS CONSENT IS TO BE SIGNED BY HIS SPOUSE, PARENT OR ONE OF HIS NEXT OF KIN.

IF THE PATIENT IS UNMARRIED AND UNDER EIGHTEEN YEARS OF AGE, THIS CONSENT IS TO BE SIGNED BY HIS PARENT OR GUARDIAN.

HÔPITAL GÉNÉRAL D'OTTAWA
DÉCLARATION DE CONSENTEMENT À
L'ADMINISTRATION DE MÉDICAMENTS SPÉCIAUX

JE, SOUSSIGNÉ(E) CONSENS À L'ADMINISTRATION, À L'HÔPITAL GÉNÉRAL D'OTTAWA, DE MÉDICAMENT(S) SPÉCIAUX _____ ORDONNÉ(S)
INDIQUER LE(S) MÉDICAMENT(S)
POUR _____ PAR LE DR. _____
INSÉRER "MOI-MÊME" OU LE NOM DU MALADE
_____.

JE DÉCLARE QUE LE DOCTEUR M'A EXPLIQUÉ, QUE CE OU CES MÉDICAMENTS SONT SUSCEPTIBLES DE PRODUIRE DES EFFETS NOCIFS DANS L'ORGANISME. JE RÉALISE CEPENDANT, QU'ÉTANT DONNÉ LES CIRCONSTANCES ACTUELLES, CE OU CES MÉDICAMENTS SPÉCIAUX SONT POSSIBLEMENT LES SEULS QUI PUISSENT AMÉLIORER MA OU LA CONDITION DE _____.
INSÉRER LE NOM DU MALADE

JE RÉALISE ÉGALEMENT QUE CE OU CES MÉDICAMENTS SONT RELATIVEMENT NOUVEAUX, ET QUE TOUS LES EFFETS SECONDAIRES NOCIFS NE SONT PAS ENCORE TOTALEMENT RECONNUS.

DATE _____

TÉMOIN _____ SIGNATURE _____

_____
LIEN DE PARENTÉ

NOTE: SI LE MALADE NE PEUT SIGNER EN RAISON D'UNE INCAPACITÉ MENTALE OU PHYSIQUE, CETTE AUTORISATION DEVRA ÊTRE SIGNÉE PAR SON ÉPOUX(SE) OU UN PARENT RESPONSABLE.

SI LE MALADE EST CÉLIBATAIRE ET N'A PAS DIX-HUIT ANS, CETTE AUTORISATION DEVRA ÊTRE SIGNÉE PAR SON PÈRE, SA MÈRE OU SON TUTEUR.

ANALGESIC PAIN STUDY

NAME _____ AGE ____ SEX ____ STUDY NO. _____

WEIGHT _____

TIME OF LAST ANALGESIC _____ NAME OF LAST ANALGESIC _____

DOSE _____

DIAGNOSIS:

			a.m. 7	8	9	10	11	12	p.m. 1	2	3	4	5	6	7
Drug given															
Pain site															
Pain	Severe	10													
		9													
	Moderate	8													
		7													
		6													
		5													
	Mild	4													
		3													
		2													
		1													
	None	0													
SCORE	Sitting position														
	Leaving bed														
	Dressing														
	Walking on flat														
	Entering bed														
	Deep breathing														
	Coughing														
Side-effects															

Score	
Unbearable	4
Severe	3
Moderate	2
Mild	1
None	0

Pain site

1.
2.
3.
4.

Side-effects

1.
2.
3.
4.

Observer's Signature .....

APPENDIX B

DATA

APPENDIX B

Subjective

No.	Sex	Age	Drugs	0	1/2	1	2	3	4
1	F	50	FMP	5	4	2.5	1	1	1
2	F	35	MPF	5	2	2	2	1	0.5
3	F	30	P	2	5	5	D/C		
4	F	61	MFP	6	5.5	5	3	3	6
5	F	27	PFM	2	2	1	1	1	4
6	F	55	FPM	8	7	7	5	5	5
7	F	43	PFM	0	0	0	0	0	4
8	F	53	MPF	3	3	2.5	2.5	1	2
9	F	46	PMF	4	10	7	2	2	8
10	M	48	FMP	0	0	0	0	0	0
11	F	32	MFP	2	0	0	0	0	1
12	F	63	FPM	3	3	1	1	2	2
13	F	53	PFM	4	2.5	2.5	2.5	0	1
14	F	54	FMP	4	2	4	4	4	3
15	M	55	MFP	5.5	5.5	3.5	3	2	2
16	F	61	FPM	2	2	2	5	2	5
17	F	53	MPF	7	3	1	1	2	10
18	F	19	PMF	1	1	0.5	0.5	0.5	1
19	F	42	FPM	5	3	1	0	1	1
20	F	29	MFP	3	2	1	1	1	4
21	F	24	FPM	3	3	3	3	1	1
22	F	44	PMF	6	3	3	1.5	1.5	
23	F	31	MPF	4	4	3	0	0	0
24	F	26	PFM	2	2	0	1	5	6
25	F	41	MFP	7	3	2	2	2	4
26	F	37	MPF	4	2	0	0	0	0
27	F	32	FPM	3	1	1	1	5	6
28	F	54	FMP	7	5	5	2	2	1
29	F	53	PFM	2	2	2	2	1	1
30	F	25	PMF	2	1.75	4	D/C		

1/2	1	2	3	4
0	0	1	0	2
Error				
6	6	3	3	5
4	3	0	1	5
Error				
4	4	2	0	0
1	5	6	6	0
2	1	1	7	4
0	0	0	0	0
1	3	1	1	1
2	2	1	4	4
1	2	2	2	2
0	0	0	0	2
0	0	0	0	0
4	7	9	D/C	
8	0	4	4	5
0	0	0	0	0
0	9	0	1	3
3	2	1	1	5
1	0	0	0	0
Error				
0	4	4	4	6
5	4	3	1	1
3	2	1	1	1
0	0	0	0	0
6	2	2	2	6
2	1	1	1	2
1	1	1	1	1

1/2	1	2	3	4
0	0	0	4	7
5	5	5	5	5
5	5	2	0	2
0	0	0	0	0
0	0	5	5	5
1	1	1	1	1
0	0	3	1	1
4	3	0	2	2
1	1	1	1	1
1	0	0	0	1
2	0	0	0	0
0	0	7	7	7
3	3	3	1	4
0	1	0	0	0
0	1	1	2	1
4	5	4	7	7
0	0	0	0	0
9	9	4	4	4
1	1	1	2	2
1	1	1	3	4
0	0	0	0	6
5	4	2	2	4
1	1	1	2	2
0	0	0	0	0

Objective

0	1/2	1	2	3	4
14	10	6	2	2	2
28	14	14	14	7	7
23	23		D/C		
18	17.5	14.75	11.5	11.5	9.5
14	10	6	6	6	13
15	14	13.5	12	12	6.5
4	3	2	2	2	7
9	9	5.5	4	1	5
21	21	17	15	15	21
4	4	4	2	2	2
7	4	4	1	1	10
7	7	7	7	8	8
12	8.5	10	10	8	10
16	15	13	11	11	6
21	21	14	7	7	7
14	14	14	14	14	21
21	17.5	13	12	12	28
14	16	11	12	15	20
18	15	13	11	19	13
11	11	7	7	7	11
9	9	9	9	9	9
22	15	15	12	12	
11	11	11	9	9	11
14	14	8	8	8	14
21	21	15	15	15	21
9	9	8	8	8	11
18	14	13	11	12	14
18	13	13	12	11	11
10	10	7	7	7	7
16	16	16	D/C		

1/2	1	2	3	4
2	1	5	1	6
Error				
9.5	11.5	11.5	11.5	8.5
13	13	0	7	6.5
Error				
6	4	2	1	2
4	11	9	9	7
14	10	10	12	13
2	1	1	1	1
8	10	5	5	6
8	8	8	10	10
10	10	8	10	10
5	1	0	2	8
7	7	11	11	11
21	21	21	D/C	
21	17	17	17	16
12	12	6	6	6
8	8	8	8	14
11	7	8	8	15
9	6	6	9	9
Error				
7	10	10	11	21
14	14	7	7	8
15	15	15	15	15
11	11	11	11	11
14	15	11	14	14
11	11	7	7	8.5
7	8	8	8	8

1/2	1	2	3	4
6	10	7	5	8
8.5	10.5	10	9	9
4.5	2.5	1	1	2
2	2	2	2	2
4	5	13	20	20
9	9	11	11	11
1	1	10	7	7
5	4	28	7	10
8	8	8	10	11
10	10	10	10	14
8	8	8	8	8
16	16	16	16	17
16	16	16	17	16
6	6	5	5	5
14	13	7	14	14
15	15	15	21	21
9	9	9	9	9
21	21	14	14	14
8	8	8	8	8
12	12	12	19	19
11	8	8	13	28
14	14	11	14	14
8.5	8.5	6	6	8
5	5	5	5	3.5

No	Sex	Age	Drugs	Subjective															Objective														
				0	1/2	1	2	3	4	1/2	1	2	3	4	1/2	1	2	3	4	0	1/2	1	2	3	4	1/2	1	2	3	4	1/2	1	2	3	4
31	M	24	MPF	4	4	2	2	2	2	2	1	1	1	3	3	3	1	1	1	10	9	3	2	2	3	3	3	3	3	4	6	6	4	4	3
32	F	34	PMF	2	2	1	2	7	7	7	5	4	6	5	5	3	2	2	2	11	11	6	6	14	14	11	9	9	11	8	8	8	8	7	8
33	F	24	FMP	5	5	4.5	4	4	6	5	5	3	3	3	3	3	5	4	4	9	9	9	7	7	10	8	7	7	8	7	7	8	9	8	8
34	F	61	FPM	5	5	4.5	3	3	2	2	2	1	2	5	5	5	2	2	2	10	10	9	9	9	9	9	9	8	8	10	10	10	8	8	8
35	M	46	PFM	6	5	5	3	3	3	3	3	3	3	3	3	3	3	4	4	9	9	9	9	9	9	9	9	8	8	8	8	8	8	8	8
36	F	23	MFP	5	5	5	3	3	3	3	5	4	4	4	4	3	4	3	3	10	10	8	8	8	8	9	9	8	9	9	9	6	6	6	6
37	F	43	FPM	8	7	7	4	6	5	4	4	3	4	6	5	3	3	7	7	9	9	9	8	8	8	8	8	9	9	9	9	9	8	8	8
38	F	27	PFM	5.5	5.5	4	4	4	8	8	8	5	3.5	3.5	3.5	2	2	2	2	10	10	9	9	9	11	11	11	9	9	9	8	8	8	8	8
39	F	31	PMF	7	5	5	4	4	4	4	4	4	3	3	3	3	3	3	3	11	9	9	8	8	9	8	8	8	8	8	8	8	9	9	10
40	M	60	FMP	6	6	5	4.5	4	4	4	3.5	3.5	3	2	2	4	4	5	5	10	9	9	9	9	8	9	11	10	9	10	9	9	11	9	9
41	F	22	MFP	7	6	6	5	5	5	5	6	7	5	4	4	4	5	5	4	13	10	10	9	9	10	8	8	8	8	8	8	8	8	8	8
42	M	47	MPF	4	3	3	3	2	2	2	2	2	1	1	1	1	1	1	1	9	8	8	7	8	8	11	10	9	8	9	8	8	8	8	8
43	M	31	PFM	7	6	6	6	6	6	6	5	5	4	4	4	3	3	3	3	10	9	9	9	11	11										