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ANALGESIC EFFECTIVENESS OF THE NARCOTIC AGONIST–ANTAGONISTS

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1 Two fundamentally different types of narcotic–antogonists have been found to be very effective analgesics with relatively low dependence-producing potentials.
2 These two drug classes can be distinguished as being either morphine-like or nalorphine-like on the basis of their subjective and objective effects after single doses and on chronic administration, and by the character of their abstinence syndromes on abrupt withdrawal or on precipitation by other antagonists.
3 To explain differences in side effects associated with their analgesic actions, the existence of three types of receptors has been postulated: a μ receptor which is believed to be associated with euphoria and other typical morphine-like effects and a kappa (κ) and a sigma (σ) receptor which are believed to be associated with the sedative and psychotomimetic effects, respectively, of the nalorphine-like drugs.
4 The antagonist–analgesics of the morphine-type have the characteristics of being agonists of low intrinsic activity but with high affinity for the μ receptor. Representative analgesics of this type are profadol, propiram and buprenorphine.
5 The antagonist–analgesics of the nalorphine-type are drugs which are believed to have varying degrees of affinity and intrinsic activity at all three receptors, but characteristically seem to act merely as competitive antagonists with no intrinsic activity at the μ receptor. Representative analgesics of this type are pentazocine, nalbuphine and butorphanol.
6 There are considerable differences among the individual drugs of each type in terms of their analgesic and narcotic–antagonistic potencies. However, clear differences in analgesic efficacy among any of the antagonist–analgesics remain to be proved. All give evidence of being capable of relieving pain in nondependent patients in situations in which doses of morphine (or its surrogates) usually used would be effective.
7 The major advantages of the partial agonists of the morphine-type over the nalorphine-type drugs are that they have not been found to produce psychotomimetic reactions, and they seem to have fewer potentially deleterious effects in cardiac patients.

Introduction

DEVELOPMENTS in the field of narcotic–antagonists have given an exciting new dimension to the pharmacology of analgesics. Not only have these drugs provided specific antidotes for treating narcotic overdosage and toxicity, but many of them have also proven to be potent and effective analgesics without many of the undesired properties of the classical narcotics. The roles which these drugs have served in furthering our understanding of the physiology of pain and of the basic mechanisms of action of the narcotic analgesics, and the uses to which they have been put in the study, control and treatment of drug addiction, have already been presented in some detail. In this paper, we focus on the roles of narcotic antagonists in the clinical management of pain.

Classification of narcotic antagonists

A large number of narcotic–antagonists have been found to have antinociceptive properties in laboratory animals. Although only a select few have undergone definitive clinical trials for analgesic effectiveness in man, there are sufficient differences among them to speak of them as subclasses of narcotic antagonists.

A useful method of classifying these drugs in man has been based on their pharmacological characteristics both as antagonists of morphine and as agonists themselves (Jasinski, 1977). Measures of their antagonist properties in man have generally been assessed by their ability to precipitate an abstinence syndrome in non-withdrawn subjects stabilized on high (240 mg/daily) or low (60 mg/daily) doses of morphine; and by their capacities for precipitating abstinence in subjects stabilized on other narcotic antagonists, for worsening the morphine abstinence syndrome of withdrawn subjects, and for blocking the subjective and objective effects of a subsequently administered dose of morphine or another narcotic agonist. Measures of their agonist properties have generally been based on the spectra of objective and subjective signs and symptoms they produce on single dose

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administration, on their capacity for suppressing the abstinence syndrome in withdrawn morphine-dependent subjects, and, finally, on whether or not chronic administration will lead to the development of an abstinence syndrome and drug-seeking behaviour on withdrawal or precipitation with nalorphine and naloxone. From the results of such tests, the narcotic–antagonists can be categorized as (1) relatively pure antagonists; (2) mixed agonist–antagonists; or (3) partial agonists of the morphine type.

Martin (1967) has maintained that, to explain the complex pharmacology of these drug subclasses, more than one type of receptor must be involved in their analgesic actions, and he initially proposed the concept of 'receptor dualism' in which one receptor is associated with morphine-like effects and the other, with nalorphine-like effects. He and his associates (Martin *et al.*, 1976; Gilbert & Martin, 1976) have since hypothesized the presence of still a third receptor, so that it is presently conceived that there are μ, κ and σ receptors with which associated effects of euphoria, sedation and psychotomimetic reactions, respectively, can be identified. Martin (1967) has also pointed out that it is necessary to consider these drugs as varying in their affinities for and intrinsic activities at each of these receptors, so that, for example, antagonism can be the consequence of the displacement from the receptor of a drug of high intrinsic activity with one of lower activity (partial agonist) as well as by one with no agonist activity (a 'pure' or competitive antagonist).

It must be acknowledged that the actions and interactions of the narcotic agonists and antagonists are very complex and not fully understood. One might even question whether, with the possible exception of certain endogenous substances, there are, in fact, any pure narcotic agonists, for even morphine, which will be referred to as a 'pure agonist', has been shown, in isolated organ and receptor binding assays, also to have antagonistic activity (Kosterlitz *et al.*, 1973). Nevertheless, the concepts advanced by Martin and his associates do provide a basis for understanding some of the apparently paradoxical effects of the narcotic antagonist analgesics encountered in certain clinical situations.

Pure antagonists

Within the conceptual framework mentioned above, the 'pure antagonists' are those which have affinity for but no intrinsic activity at any of the postulated receptors. Actually, as with the agonists, there are no known pure narcotic antagonists, for even naloxone and naltrexone, which most closely fit this characterization, have been shown to have some agonist actions in animals (Blumberg & Dayton, 1973). In man, however, their only demonstrable effects seem to be those attributable to competing with and displacing drugs with any degree of agonist activity. They are virtually devoid of analgesic activity, produce no characteristic subjective symptoms, can precipitate abstinence in non-withdrawn narcotic–agonist — and mixed agonist–antagonist — dependent subjects, and can antagonize the analgesic, euphoric, miotic, emetic, constipating, sedative, dysphoric, psychotomimetic and presumably all effects of narcotic agonist and mixed antagonist drugs (Jasinski *et al.*, 1968; Blumberg & Dayton, 1973; Jasinski, 1977).

Naloxone

Naloxone is the prototype of this subclass of antagonists and, though less potent than naltrexone, shows the least evidence of intrinsic activity. Nevertheless, naloxone has been used in narcotic–analgesic mixtures on the premise (Foldes, 1964) that N-allyl derivatives of narcotics have a relatively greater affinity for receptors of the respiratory centre than for those of the sensory cortex. Foldes *et al.* (1963) have, for example, reported that, in postoperative patients, naloxone selectively antagonizes the respiratory effects, but not the analgesic effects, of oxymorphone. Similar claims have also been made for mixtures of other antagonists and narcotics (Swerdlow, 1964), but whether there are, in fact, substantial differences in sensitivity to competitive antagonists of neuronal systems subserving most of the undesired, as opposed to the analgesic, effects of narcotics remains to be proved.

From what is now known of the pharmacology of these drugs, there seems to be little justification for using fixed combinations of narcotic–agonists and narcotic–antagonists in the management of pain. As Swerdlow (1964) has cautioned, there are appreciable risks of complications when combining these drugs with substantial differences in potency and duration of action which may be additionally influenced by the patient's physical status and previous exposure to other narcotics. For example, it is well established that physical dependence to narcotics produces a heightened sensitivity to antagonists (Jaffe & Martin, 1975), and it is also well known that altered physical states, such as drug- or sleep-induced hypercapnia, can result in transient but sometimes misleading 'overshoot' phenomena when antagonists are given (Landmesser *et al.*, 1953; Lambertson, 1964). Moreover, from the evidence at hand, the 'pure antagonists' merely cause displacement of the dose–effect curves of agonists to the right. However, a by-product of these investigations, which is both of theoretical and practical interest, is that no

combination of doses of morphine and naloxone has been observed to have produced psychotomimetic reactions of the type seen with agonist/antagonist–analgesics of the nalorphine-type.

Mixed agonist/antagonist–analgesics

This subclass of antagonists has also been referred to as the 'partial agonists of the nalorphine-type' (Jaffe & Martin, 1975). Nalorphine is the archetype of this historically oldest and largest group of narcotic antagonists. It is considered to be both a 'pure', or competitive, antagonist at the μ or 'morphine receptor' and an agonist, or partial agonist, of the κ and σ receptors which constitute the 'nalorphine receptors'. Although drugs of this class vary considerably in their relative agonist and antagonist potencies, their dominant properties are that, on single dose administration, they produce subjective and objective symptoms and signs which are not morphine-like; and that, on chronic administration, they can induce a state of physical dependence which can be elicited by the precipitation of an abstinence syndrome by naloxone. These drugs are also capable of precipitating abstinence in non-withdrawn morphine-dependent subjects, and they do not suppress abstinence in withdrawn high-dose morphine-dependent subjects (Jasinski, 1977). Characteristically, analgesics of this type can produce acute dysphoric and psychotomimetic effects (Wikler, 1951; Lasagna & Beecher, 1954; Telford *et al.*, 1961; Houde *et al.*, 1976).

Nalorphine

The discovery of the remarkable ability of nalorphine to counteract the actions of narcotics overshadowed the observation that nalorphine itself had some analgesic properties (Unna, 1943; Hart & McCawley, 1944). Thus, most of the early studies of nalorphine were concerned with its combined administration with morphine in the hope of finding the 'ideal ratio' which would retain the analgesic properties of morphine but not its undesirable ones. Subsequently, many combinations of nalorphine and levallorphan with morphine, levorphanol, meperidine, alphaprodine, anileridine, oxymorphone and other narcotic analgesics were used as general anaesthetic supplements and for the control of post-operative pain. Reports of their effectiveness have, however, been conflicting (Swerdlow, 1964), and more recent efforts have concentrated on finding the desired characteristics within a single drug.

Lasagna & Beecher (1954) were the first to recognize and report that nalorphine had analgesic properties in man. However, they also observed, as did Houde & Wallenstein (1955) and Keats & Telford (1956, 1957), that analgesia was obtained with nalorphine only at the cost of an unacceptable risk of disturbing adverse mental effects. Meanwhile, Houde & Wallenstein (1956) found that biphasic analgesic dose–response curves were obtained when increasing doses of nalorphine were combined with morphine, and it became apparent that similar biphasic curves were obtained in studies in animals of the interactions of nalorphine and levallorphan with morphine and levorphanol (Gruber, 1954; Yim *et al.*, 1955; Rubin *et al.*, 1964). These observations, among others, led Martin (1967) to postulate his theory of 'receptor dualism'.

The finding that nalorphine was a potent analgesic which produced neither psychic dependence nor a morphine-like abstinence syndrome (Isbell & Fraser, 1950) suggested to Isbell (1956) that potent non-addicting analgesics might be found among drugs of the nalorphine type. A large number were subsequently produced and several have undergone clinical evaluation, primarily in patients with postoperative pain (Telford *et al.*, 1961; Archer *et al.*, 1962; Fraser & Harris, 1967). Many of these drugs were observed to have substantial analgesic activity (Telford *et al.*, 1961), and although some, like cyclazocine, are many times more potent than morphine (Lasagna *et al.*, 1964), the margin between the doses needed for effective analgesia and those producing distressing mental effects has been found to be too narrow to justify their introduction as analgesics in medical practice.

Pentazocine

Pentazocine is the first drug of this class which has been considered to have the proper attributes to be introduced into medical practice. However, its classification as a nalorphine-like drug has been questioned, for it also produces morphine-like subjective effects and physical dependence. In single-dose studies, parenteral doses of pentazocine 40 mg or less (per 70 kg) produced signs and symptoms which were indistinguishable from those of modest doses (10 mg/70 kg) of morphine, whereas in higher doses, the effects of pentazocine were distinctly nalorphine-like (Jasinski *et al.*, 1970). Pentazocine suppressed the abstinence syndrome of withdrawn subjects on doses of morphine 30 mg daily (Jasinski, 1977) but not that of subjects dependent on either 60 or 240 mg daily. Pentazocine was approximately 1/50th as potent as nalorphine in precipitating abstinence in non-withdrawn subjects dependent on morphine 240 mg daily (Jasinski *et al.*, 1970). In direct addiction studies in subjects stabilized on doses of pentazocine greater than 500 mg daily, abrupt withdrawal produced a mild abstinence syndrome with both morphine-like and nalorphine-like features. Naloxone, but not nalorphine, precipitated

a moderately severe abstinence syndrome in these subjects (Jasinski *et al.*, 1970). Overall, it seems that pentazocine is more nalorphine-like than morphine-like and thus has been properly considered with this group of drugs. Its abuse potential has been judged to be greater than that of nalorphine, but less than that of codeine or of propoxyphene; and that judgement seems to be sustained by the epidemiological data on drug abuse in the USA (Jasinski, 1977).

Pentazocine has been investigated as an analgesic in a variety of clinical settings and has been rather widely used in medical practice in America, most frequently for the treatment of severe chronic pain (Seitner *et al.*, 1975). Parenterally administered pentazocine has been variously estimated to be about one-half to one-sixth as potent as morphine in patients with postoperative pain and chronic pain due to cancer and of other aetiologies, the differences in estimates reflecting, by and large, the method of analysis and the fact that pentazocine is a shorter acting drug than morphine (Keats & Telford, 1964; Cass *et al.*, 1964; Gordon & Moran, 1965; Stoelting, 1965; Lasagna, 1964; Beaver *et al.*, 1966). Estimates of its oral potency have also varied, but in a controlled, double-blind crossover comparison in cancer patients, oral pentazocine was estimated to be one-third to one-quarter as potent as intramuscular pentazocine (Beaver *et al.*, 1968).

As an analgesic, pentazocine seems to be as effective as morphine in clinical situations in which doses (8-16 mg) of the latter usually used would suffice, that is, excepting those situations in which substitution of pentazocine for morphine would be inappropriate or contraindicated, such as in narcotic dependent patients (Houde, 1974) and in most patients with acute myocardial infarction (Alderman *et al.*, 1972). The adequacy of analgesia and the occurrence of undesired side-effects seem to be less predictable with pentazocine than with morphine, which may be due to the considerable variability among individuals in the rate of metabolism of pentazocine (Brogden *et al.*, 1973). Within the range of tolerated doses and the limits of sensitivity of clinical analgesic assays, the slopes of the dose–effect curves of pentazocine and morphine seem to be parallel (Beaver *et al.*, 1966) but whether or not this is true at higher dose levels is less certain. Engineer & Jennett (1972) have shown that increasing the dose of pentazocine beyond 30 mg does not produce proportional increases in respiratory depression, and Smith (1971) has reported that a 'ceiling effect' is reached at a dose equianalgesic with about morphine 0.4 mg/kg, which translates into an average parenteral dose of about 90 mg pentazocine. Tolerance to the analgesic and subjective effects of pentazocine is known to occur, but it is not clear if the rate of development is comparable to that seen with morphine-like drugs or is the same for all effects of the drug (Jaffe & Martin, 1975). On the other hand, the analgesic efficacy of pentazocine can be greatly influenced by the patient's narcotic history, for precipitated abstinence in opioid-dependent patients has been well documented in the clinical setting (Beaver *et al.*, 1966; Peltola, 1972). Moreover, it has been shown that in non-tolerant patients, the analgesic effects of the combined administration of graded doses (40 and 80 mg) of pentazocine and a fixed (8 mg) dose of morphine are additive, whereas, in narcotic tolerant patients, increasing doses (10, 20 and 40 mg) of pentazocine produced a progressive decrement in the analgesic effect of morphine (Houde *et al.*, 1972; Houde, 1974). In the narcotic tolerant patients, a shift to the left was also noted in the pentazocine dose–effect relationship for psychotomimetic reactions, indicating that narcotic dependence may unmask or produce a state of increased sensitivity to other nalorphine-like actions of pentazocine as well.

In early studies of the use of pentazocine in anaesthesia, surgery, obstetrics and gynecology, and internal medicine (Janzen *et al.*, 1972), psychotomimetic side-effects were reported only infrequently. However, Dundee (1972) noted that in studies which he and his colleagues (Hamilton *et al.*, 1967) had carried out in preoperative patients, 6% developed psychotomimetic reactions (2% severe) on parenterally administered doses of pentazocine 60 mg, and he commented that, in retrospect, many of the dysphoric side-effects which he had attributed to precipitated withdrawal in an earlier study of levorphanol/levallorphan combinations (Dundee, 1964) also may actually have been psychotomimetic reactions. Beaver *et al.* (1966) also commented on the difficulty in determining whether, in patients who have previously received narcotics, dysphoric reactions after pentazocine represent borderline precipitated withdrawal, agonistic effects of pentazocine, or a combination of both. Jasinski *et al.* (1970) observed disturbing dysphoric and psychotomimetic reactions with large doses of pentazocine in morphine-dependent subjects during their substitution and precipitation studies, and remarked that cross-tolerance to the nalorphine-like subjective effects of pentazocine does not seem to occur in morphine-tolerant subjects. They felt, however, that these adverse reactions were likely to be encountered only in parenterally administered doses of 60 mg or more, which they considered to be one and one-half to two times the usual dose used clinically for analgesia. Although it is evident that these adverse effects are dose-related, it also seems that susceptibility to these reactions varies appreciably among patients, that doses as high as or greater than 60 mg are often required for the control of severe pain, and that psychotomimetic reactions

have been encountered more frequently in patients with severe chronic pain (Beaver *et al.*, 1966, 1968; Houde, 1974; Houde *et al.*, 1976).

Nalbuphine

Nalbuphine is one of the antagonists of the noroxymorphone series, which is closely related structurally to naloxone and naltrexone, but differs from them in having substantially stronger agonistic and somewhat weaker antagonistic actions (Blumberg & Dayton, 1973). Its pharmacological profile in man has been found to resemble more closely that of pentazocine than that of its congeners but, more importantly, it seems to be less psychotomimetic than pentazocine. The subjective and objective effects of single 8 mg (per 70 kg) doses of nalbuphine were more barbiturate-like and weakly psychotomimetic, which are more characteristic of nalorphine-like activity. Nalbuphine was estimated to be one-quarter as potent as nalorphine in precipitating abstinence in subjects dependent on morphine 60 mg daily (Jasinski & Mansky, 1972). More recently, nalbuphine has been found to suppress abstinence in withdrawn subjects dependent on morphine 30 mg daily (Jasinski, 1977). Chronic administration of nalbuphine in doses over 200 mg daily produced physical dependence resembling that of pentazocine. Doses as high as 30 mg nalorphine did not precipitate abstinence, whereas doses of 4-6 mg naloxone produced an abrupt abstinence syndrome and associated drug-seeking behaviour (Jasinski & Mansky, 1972).

Nalbuphine has been evaluated as an analgesic in postoperative and cancer patients. In postoperative patients, in which intramuscular doses ranging from 3-12 mg nalbuphine were compared with 5 and 10 mg morphine, nalbuphine was found to be slightly (1.2 times) more potent than morphine (W.H. Forrest, personal communication). Side-effects of nalbuphine in this general hospital study were reported to be similar to those of morphine, and these results are in keeping with effects of single doses and short-term chronic administration of 10-mg doses in healthy subjects (Elliott *et al.*, 1970; Jasinski & Mansky, 1972). In a crossover study in non-tolerant cancer patients with postoperative and disease-related pain, intramuscular doses of from 1.25-20 mg nalbuphine were compared with 15-60 mg pentazocine (Houde *et al.*, 1976; Houde *et al.*, 1976). Nalbuphine was found to be approximately three to five times as potent as pentazocine depending on the method of analysis, as pentazocine was found to be a more rapid and shorter acting drug than nalbuphine. A high incidence of side-effects was encountered in this study, particularly with pentazocine. Seven of the 27 patients who received pentazocine 60 mg and one of the 104 patients who received pentazocine 30 mg developed either disturbing psychotomimetic reactions or frank hallucinations. By contrast, only one of the 10 patients who received nalbuphine 20 mg in this crossover study and two of the 48 patients who received nalbuphine 10 mg developed similar reactions. There were no appreciable differences in the responses of the postoperative and chronic pain patients in this study population and no precipitated abstinence occurred.

Butorphanol

Butorphanol is a structurally related drug of the morphinan series which has also been judged to be similar to pentazocine in its pharmacological profile. Single 2-8 mg parenterally administered doses produced subjective effects resembling those produced by nalorphine and pentazocine; and, in studies in subjects dependent on morphine 60 mg daily, butorphanol neither precipitated nor suppressed abstinence. In direct addiction studies in which the subjects were eventually stabilized on butorphanol 48 mg daily (12 mg four times daily), naloxone precipitated a moderately severe opiate-like abstinence syndrome, whereas very high dose nalorphine precipitated only very mild abstinence signs, and withdrawal produced a moderately severe syndrome with nalorphine-like features (Jasinski, 1977).

Butorphanol has been studied by a number of investigators in patients with postoperative pain. It has been compared by the intramuscular route to meperidine (Gilbert *et al.*, 1976), to pentazocine (Dobkin *et al.*, 1975; Gilbert *et al.*, 1976; Andrews, 1977), and to morphine (Tavakoli *et al.*, 1976). In intramuscular doses of up to 4 mg, butorphanol tartrate was found to be from 15-23 times as potent as pentazocine, 5-8 times more potent than morphine sulphate, and approximately 30-50 times as potent as meperidine. In patients with acute ureteral colic in which 2 and 4 mg intramuscular doses were compared with 80 mg meperidine, butorphanol was found to be approximately 40 times as potent as meperidine (F. S. Caruso, personal communication). Finally, in a study of the intravenous administration of butorphanol up to 2 mg compared with morphine sulphate 5 mg, Del Pizzo (1976) estimated that butorphanol was approximately 5-8 times more potent than morphine. In all of these studies, butorphanol is reported to have acted promptly and effectively, and to have produced no significant side-effects other than excessive drowsiness. There were scattered reports of essentially morphine-like side-effects, and it is reported that one patient did experience an episode of hallucinations and diaphoresis which was interpreted as possibly being a mild withdrawal syndrome.

The circulatory and respiratory effects of intravenous butorphanol and morphine have also been investigated in a crossover study by Nagashima *et al.* (1976). In intravenous doses of butorphanol up to 60 μg/kg and morphine up to 300 μg/kg, there were no significant changes in circulatory homeostatic mechanisms or in the various respiratory parameters except when the patient was subjected to a CO_2 challenge, at which time the minute volume/PA_{CO_2} regression lines became depressed. The data suggests that in contrast to morphine, the respiratory dose–response of butorphanol is flat, suggesting that butorphanol may be acting as a partial agonist with a low ceiling effect. The haemodynamic and respiratory effects of butorphanol and morphine were also studied in the course of diagnostic cardiac catheterization by Popio *et al.* (1978). In these patients, either morphine sulphate 125 μg/kg or butorphanol tartrate 25 μg/kg was administered intravenously. Butorphanol decreased the *p*H, P_{O_2} and systemic artery pressure, and increased P_{CO_2}, cardiac index and pulmonary artery pressure. Morphine caused similar changes in *p*H, P_{O_2}, systemic artery pressure and P_{CO_2} but much smaller changes in cardiac index and no change in pulmonary artery pressure. The major observed changes were interpreted to be the result of respiratory depression after administration of either drug, but the butorphanol-associated increases in pulmonary artery pressure, left ventricular-end diastolic pressure and cardiac index are reminiscent of those observed after pentazocine. Pentazocine is generally felt to be contraindicated in angina and myocardial infarction in that it may aggravate myocardial ischaemia by increasing myocardial oxygen consumption.

In a double-blind crossover study in cancer patients (Houde *et al.*, 1976), butorphanol was found to be approximately four times as potent as morphine. The time–effect curves of the two drugs were similar. However, in striking contrast to the experience of the investigators cited above, and others (F. S. Caruso, personal communication), a very high incidence of dysphoric and psychotomimetic reactions was encountered: in 6 out of 18 patients after butorphanol 4 mg and in 6 out of 33 patients after butorphanol 2 mg. None were observed after morphine. Although these patients were studied for postoperative pain after major cancer surgery, many of the patients in whom these reactions occurred had been receiving narcotics for pain before surgery. Houde *et al.* (1976) commented that although the reactions were more typical of psychotomimetic reactions observed after nalorphine and pentazocine than they were of the opiate abstinence syndrome, data showed some correlation between the occurrence of these reactions and the amount of narcotics pre- and postoperatively administered.

Partial agonists of the morphine-type

This class of antagonists consists of those whose actions are best expressed in terms of competitive antagonism (Ariëns *et al.*, 1964). Characteristically the effects of these drugs reach a plateau or 'ceiling' as their doses are increased. Their subjective and physiological effects are similar to morphine even though, at high doses, they also are capable of precipitating abstinence in narcotic-dependent subjects. Drugs which have been considered to fall in this category are profadol, propiram and buprenorphine. Psychotomimetic reactions have not been reported with any of these drugs.

Profadol

Profadol is a congener of meperidine which was not recognized to have antagonistic properties until it was later found that it did not suppress abstinence in morphine-dependent primates (McCarthy, 1973). In subsequent studies at the Addiction Research Center in Lexington (Jasinski *et al.*, 1971), profadol was found to have a typical morphine-like profile in single-dose studies and it was judged to be approximately one-half to one-third as potent as morphine. In subjects dependent on morphine 240 mg daily, profadol did not suppress abstinence and was about 1/50th as potent as nalorphine in precipitating abstinence. In subjects dependent on morphine 60 mg daily, profadol was approximately one-third as potent as morphine in suppressing abstinence. In direct addiction studies of daily doses of profadol greater than 500 mg, no nalorphine-like symptoms or signs were noted; abstinence was precipitated by nalorphine but only by relatively large doses; and the abstinence syndrome on withdrawal more closely resembled that of morphine than nalorphine.

There is a paucity of published clinical data on this drug. However, a study of its analgesic properties was carried out by Beaver *et al.* (1969) in which intramuscular doses of profadol 25 and 50 mg were compared with morphine sulphate 8 and 16 mg in patients with chronic pain due to cancer. Profadol was found to be approximately one-fifth to one-quarter as potent as morphine in this crossover study and the dose–effect slopes of the two drugs seemed to be parallel within this limited dose range. The two drugs were virtually indistinguishable in terms of the occurrence and patterns of side-effects, and no psychotomimetic reactions were observed.

Propiram

Propiram, a congener of phenampromide, has been found to have a similar pharmacological profile.

Like profadol, propiram produced dose-related morphine-like signs and symptoms in single-dose studies. In high doses (280 mg/70 kg), dysphoric reactions were observed but these were not characterized as nalorphine-like. In subjects dependent on morphine 240 mg daily, propiram precipitated abstinence but only at a dose about 200 times that of nalorphine, and it was judged to be about one-tenth as potent as morphine in suppressing abstinence in subjects dependent on morphine 60 mg daily. In direct addiction studies of doses of propiram ranging from over 500-1800 mg daily, nalorphine precipitated an opiate-like abstinence syndrome, whereas abrupt withdrawal produced a mild abstinence syndrome that was neither typically morphine- or nalorphine-like (Jasinski *et al.*, 1977). It was estimated that propiram would have significant abuse potential, less than that of morphine and profadol, but greater than that of pentazocine.

Studies of its analgesic properties have been carried out in a variety of clinical situations. In postoperative patients, Forrest *et al.* (1972) have reported that intramuscularly administered propiram was one-eleventh as potent as morphine and that its side effects were similar to morphine. In patients with chronic pain due to cancer, oral propiram was observed to be approximately two-thirds as potent as intramuscular propiram, and the time–effect curves for the two forms of medication were remarkably similar (Houde *et al.*, 1975). In a subsequent study in cancer patients with postoperative pain and in patients with chronic pain due to cancer, we had also observed that the onset, peak effect and duration of equianalgesic doses of orally administered propiram fumarate were very similar to those of parenterally administered morphine sulphate. Oral propiram was estimated to be one-eleventh as potent as intramuscular morphine in this study (Houde *et al.*, 1977). The side-effects noted were predominantly morphine-like. As was observed with profadol, no patient in these two studies experienced any psychotomimetic reaction, and there were no incidents of a precipitated abstinence syndrome.

Buprenorphine

Buprenorphine, a much more potent drug, is a member of the oripavine series and a close analogue of etorphine and diprenorphine. In laboratory animals, buprenorphine produces some morphine-like effects, but it shows little capacity to produce physical dependence, and it is an antagonist of both morphine and etorphine (Cowan *et al.*, 1977). In chronic spinal dogs, ceiling effects were noted to occur with graded single doses of buprenorphine and large doses of naloxone were required to precipitate abstinence in buprenorphine-dependent dogs. On the basis of these and other findings, buprenorphine was judged to be a morphine-like substance but with less intrinsic activity than morphine, and, accordingly, was considered to be a partial agonist of the morphine type (Martin *et al.*, 1976). In studies of its abuse potential in man, buprenorphine produced morphine-like subjective behavioural and physiological effects. The drug was estimated to be 25-50 times more potent than morphine and to have a longer duration of action. There were, however, two observations which distinguished buprenorphine from morphine and from methadone; these were that large doses of naloxone failed to precipitate abstinence during chronic administration of buprenorphine and that a delayed and very low intensity abstinence syndrome followed abrupt withdrawal of doses of buprenorphine potentially equal to morphine sulphate 200-400 mg based on single-dose studies (Jasinski *et al.*, 1978).

Buprenorphine has undergone extensive clinical evaluation, primarily in the treatment of postoperative and intractable (cancer) pain, but also in other painful states and in analgesic anaesthesia. In double-blind twin crossover studies (Wallenstein & Houde, 1975) carried out in cancer patients with postoperative or chronic pain in which intramuscular doses of from 0.1-1.6 mg buprenorphine hydrochloride were compared with 8 and 16 mg morphine sulphate, buprenorphine was found to be about 28 times as potent as morphine. The analgesic time–effect curves of the two drugs were similar. The side-effects observed after buprenorphine were predominantly morphine-like, although, in two postoperative patients with histories of chronic pain, signs and symptoms of precipitated narcotic withdrawal were observed after doses of 0.8 and 1.6 mg buprenorphine. Another patient who received 0.8 mg buprenorphine reported some symptoms suggesting depersonalization, but no other psychotomimetic effects were observed in the 136 patients who participated in this study (Houde *et al.*, 1977).

In analgesic anaesthesia, DeCastro & Parmentier (1976) found that doses of 0.4-1.8 mg buprenorphine produced analgesia sufficient for minor surgical procedures when reinforced with nitrous oxide or flunitrazepam, but it was generally unsatisfactory as the sole agent. When administered intravenously or intramuscularly in doses of 0.4-0.8 mg after analgesic anaesthesia with nitrous oxide and fentanyl or fentathienyl, buprenorphine acted as an antagonist of the narcotics but rarely induced suppression of analgesia; in fact, its own agonistic actions tended to extend the duration of analgesia. These investigators judged buprenorphine to be equipotent to naloxone as an antagonist but slower in onset and less disruptive in its actions.

In terms of its effect on respiration, Orwin *et al.*

(1976) have reported that buprenorphine is 44 times more potent than morphine in displacing the response curve to the right in normal volunteers and that doses as high as 16 mg of intravenously administered naloxone only partially reversed the shift in the respiratory response curve to CO_2-rebreathing produced by a single intravenous dose of buprenorphine 0.3 mg.

Intramuscular and intravenous doses from 0.1-1.6 mg buprenorphine have been evaluated in several controlled and open studies in postoperative patients after general, obstetric or gynecological procedures and have been compared with varying doses of either meperidine, pentazocine or morphine (Masson, 1976; Rolly & Versichelen, 1976; Dobkin *et al.*, 1977; Orwin, 1977). Buprenorphine has also been administered sublingually in single doses of up to 0.8 mg and multiple doses of up to 4.8 mg daily to patients with pain due to cancer and to women in labour (Adriaensen & Van de Walle, 1976; McQuillan, 1976). In the dose range of 0.3-0.6 mg, intramuscularly administered buprenorphine provided analgesia comparable to other commonly used narcotic analgesics and was judged to be about 35 times as potent as morphine (J.W. Lewis, personal communication). Except for the study of Houde *et al.* (1977) in which the time–effect curves for analgesia were found to be very similar to those of morphine, most investigators seem to have observed a much longer duration of action with buprenorphine. Jasinski *et al.* (1978) report, however, that the durations of euphoria produced by buprenorphine and morphine in their study were very similar, results which are in keeping with the analgesic data of Houde *et al.* (1977), whereas the miotic, sedative and narcotic 'blockade' effects were longer than even those of methadone. Side-effects reported by various investigators all seem to indicate that those of buprenorphine are morphine-like. There have been no reports of unequivocal psychotomimetic reactions (Ward, 1977).

Discussion and conclusions

The early clinical experience with adverse reactions to the archetypical antagonist–analgesics hardly seemed likely to generate great enthusiasm for the therapeutic potentials of these drugs as analgesics. Indeed, it would seem a strange twist of logic to look for better analgesics among drugs whose actions counteract or reverse those of proven highly effective analgesics. However, until the analgesic properties of the narcotic antagonists were recognized, the history of the search for non-addictive strong analgesics had been marked only by frustration after frustration (Isbell, 1977). The resulting efforts to explain the antagonist–analgesic paradox have served as a catalyst both for other research basic to understanding pain and its modification by drugs, and for new approaches to analgesic drug development.

Central to Martin's concept of how the narcotics and narcotic antagonists exert their effects is that analgesia can result from drug occupation of receptors of more than one type, and that antagonism is merely the consequence of the interaction of drugs with differing affinities for and intrinsic activities at one or more of three postulated receptors (μ, κ and σ). Within this theoretical framework, morphine and its surrogates are assumed to act almost solely on the μ receptors and to have little affinity for and intrinsic activity at the κ and σ receptors; whereas the pure antagonists, such as naloxone and naltrexone, are believed to have high affinity for, but virtually no intrinsic activity at, all three receptors. By definition, the partial agonists of the morphine type have pharmacological properties similar to morphine and act on μ receptors to produce their analgesic effects. On the other hand, the mixed agonist/antagonists are considered to have varying affinities and activities at all three receptors but are believed to exert their analgesic actions primarily by occupation of κ receptors.

The fundamental difference between the two clinically useful types of antagonist–analgesics is thus conceived to be that one produces analgesia by acting on μ receptors and the other by acting on κ receptors. Whether receptor occupancy of one type is equivalent in analgesic power to that of the other type cannot be inferred from the clinical studies, for the methods of measuring pain in that setting have lacked the precision for distinguishing even between relatively pure μ agonists and partial agonists of the same type in terms of theoretically predicted differences in their dose–effect slopes. In addition, limiting adverse side-effects have precluded using high enough doses of most of these drugs to demonstrate conclusively that the analgesic effects of the partial agonists do, in fact, plateau as their doses are increased. Although distinctions of this kind have been made in man in terms of the respiratory depressant actions of 'pure' and partial agonists (Smith, 1971; Engineer & Jennett, 1972), it does not necessarily follow that the same conditions apply with respect to analgesia.

If all of the narcotic antagonists–analgesics are, in fact, partial agonists of one type or another, no valid statement of 'relative potency' or 'relative efficacy' can be made without specifying the effect level at which the drugs are being compared. However, in most clinical studies of analgesics, this level of effect is usually defined, either directly or tacitly, as that produced by the doses of a reference or standard analgesic, such as morphine, which are conventionally used in that particular clinical setting.

Thus, even though most of these studies of analgesic effect have been insufficiently sensitive to show differences in dose–effect slopes and ceiling effects among the different drugs under consideration, they have provided a measure of clinically meaningful equianalgesic doses of these drugs which, in general, have correlated well with estimates of their agonist properties in studies of their subjective and objective effects in healthy subjects and postaddicts (Jasinski, 1977; Houde *et al.*, 1977; Jasinski *et al.*, 1978).

Differing estimates of the analgesic potency of some of these drugs have been reported by some investigators. In many instances, the disagreements are more apparent than real and are merely due to uses of different measures of effect or criteria of effectiveness when comparing drugs whose time–effect curves are dissimilar. In other cases, the discrepancies could be attributed to differences in some characteristic of the patient populations studied (as in degree of previous narcotic exposure) or to differences in ways in which the studies were carried out. Although there seems to be no substantial evidence that the morphine-type agonists, as a class, are any more or less effective than those of the nalorphine type for specific kinds of pain, there are substantial differences between the two types of drugs in some of their pharmacological properties, such as in their euphoria-producing attributes, haemodynamic actions and capacities for precipitating unnerving psychotomimetic effects.

Although the results of studies to date do not provide a firm basis for distinguishing between the partial agonists of the morphine-type and the mixed agonist–antagonists on the basis of efficacy, there are unquestionable marked differences both in analgesic and in antagonistic potencies among individual drugs of the two classes. For example, among the partial agonists, buprenorphine is conservatively estimated to be about 30 times as potent as morphine as an analgesic, and as potent as naloxone as an antagonist, whereas propiram has been judged to be less than 1/10th as potent an analgesic as morphine and 1/200th as potent as nalorphine in precipitating abstinence in morphine-dependent subjects. Thus, buprenorphine may be considered to be approximately 300 times as potent an agonist, and over 1500 times as potent as antagonist as propiram; but *per se*, neither the relative analgesic potency nor the ratios of agonist to antagonist potency (approximately 4 for buprenorphine and 20 for propiram) has yet been shown to be a reliable index of analgesic efficacy or of the potential therapeutic merits of these drugs.

Both propiram and buprenorphine have unique properties as analgesics. Orally administered propiram seems to be a remarkably effective and rapidly acting analgesic for, in their double-blind crossover study in cancer patients, Houde *et al.* (1977) found that, in equianalgesic doses, the time–effect curves of oral propiram and intramuscular morphine were virtually identical. As parenterally administered propiram had been estimated to have a potential for abuse greater than that of pentazocine, though less than that of morphine (Jasinski *et al.*, 1971), there remains a question of whether having an oral analgesic with the effectiveness and approximate speed of action of parenterally administered morphine will prove to be a greater disadvantage in terms of risk of abuse than a therapeutic advantage. Buprenorphine, on the other hand, is expected to have a poor oral/parenteral potency ratio from the preclinical data (J.W. Lewis, personal communication), but it has been found to have a very long duration of action by parenteral administration. It has proven to be a highly effective analgesic in a variety of clinical situations and sufficiently potent to be effectively used sublingually in patients in whom injections and the enteral routes of administration are either contraindicated or impossible. More importantly, its cardiovascular effects seem to be less hazardous to cardiac patients than the mixed agonist–antagonist analgesics and, despite its high agonist potency, it seems capable of producing only delayed and a very mild abstinence syndrome (Jasinski *et al.*, 1978).

Of the mixed agonist–antagonist analgesics, two of the more recently developed drugs, nalbuphine and butorphanol, have been reported to have distinct advantages over pentazocine in terms of their estimated lower abuse liability and, apparently, in showing some dissociation of presumed κ and σ receptor associated effects (Jasinski, 1977). Both have been found to be more potent than pentazocine, and at least as effective, even though their constellations of pharmacological effects are similar to those of pentazocine. Neither has been found to be devoid of the risk of producing psychotomimetic side-effects, although these reactions were observed to be significantly less common after nalbuphine than after pentazocine in a crossover study carried out by Houde *et al.* (1976), and they have not been reported to occur after butorphanol in patients who have not previously received narcotics (F.S. Caruso, personal communication).

Both the partial agonists of the morphine type and the mixed agonist/antagonists are capable of precipitating abstinence in narcotic-dependent subjects, and the greater the degree of physical dependence, the greater the degree of sensitivity to all antagonistic actions of these drugs. It is also evident that tolerance to narcotic agonists does not convey crosstolerance to the dysphoric and psychotomimetic actions of antagonist–analgesics with nalorphine-like properties; in fact, narcotic-tolerant patients may be more susceptible to these reactions. Nevertheless, when used before resorting to conventional narcotic–

analgesics, both the partial agonists of the morphine-type and the mixed agonist/antagonists should be effective analgesics in virtually all situations in which narcotics are used.

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