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Hussain

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[54] **METHOD OF ADMINISTERING NARCOTIC ANTAGONISTS AND ANALGESICS AND NOVEL DOSAGE FORMS CONTAINING SAME**

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[21] Appl. No.: **258,308**

[22] Filed: **Apr. 28, 1981**

[51] **Int. Cl.**[3] **A61K 31/485**

[52] **U.S. Cl.** ..... **424/260**; 260/239 BB; 546/44; 546/45; 546/46; 546/61

[58] **Field of Search** ..... 424/260; 260/239 BB

[56] **References Cited**

U.S. PATENT DOCUMENTS

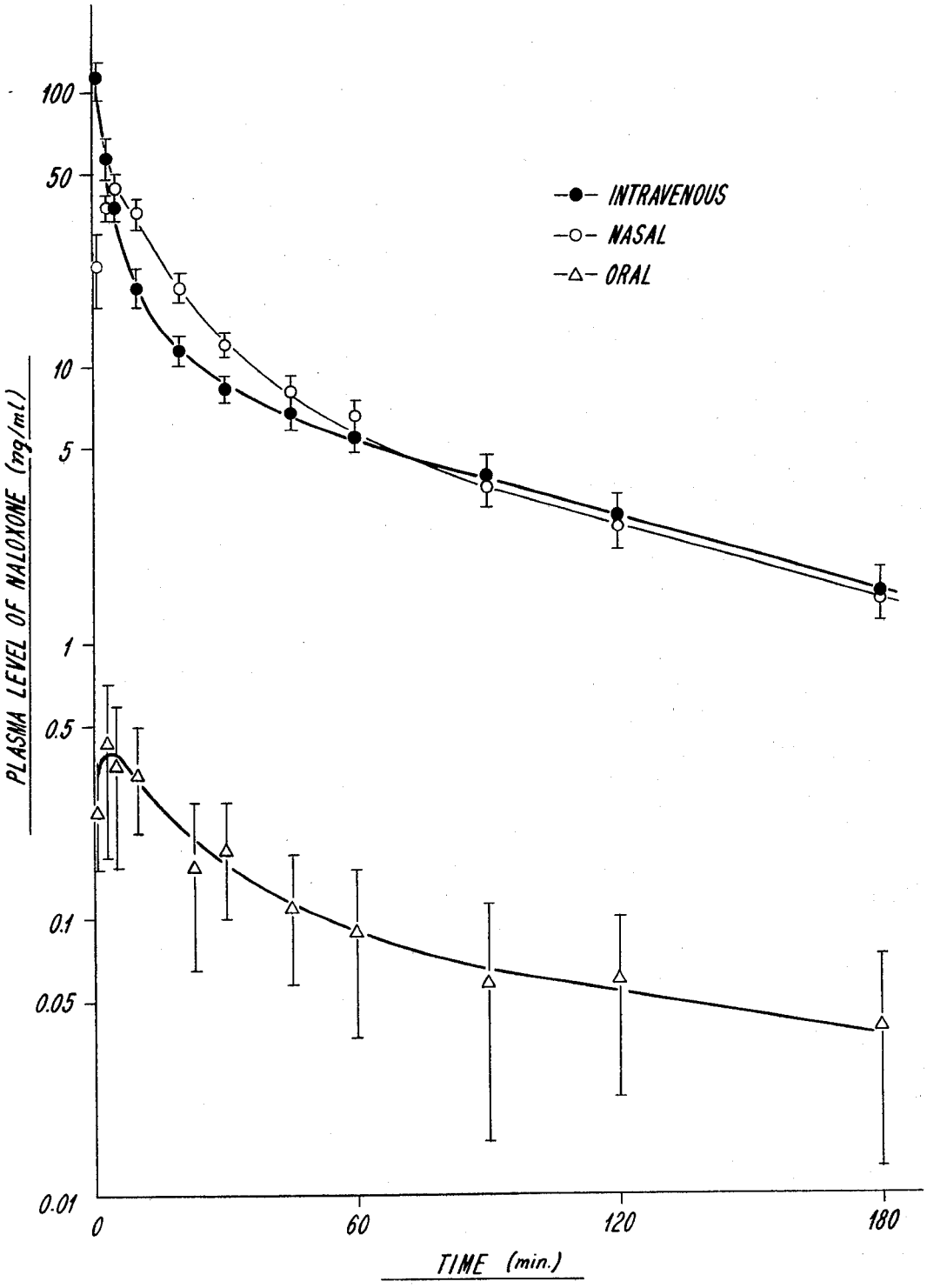
4,275,059 6/1981 Flora et al. 424/230

Primary Examiner—Stanley J. Friedman
Attorney, Agent, or Firm—Burns, Doane, Swecker & Mathis

[57] **ABSTRACT**

The invention provides a novel method of administering narcotic antagonists, narcotic analgesics and related compounds, and novel dosage forms containing those compounds which are adapted for nasal administration. The nasal dosage forms disclosed include solutions, suspensions, gels and ointments. Especially preferred compounds which can be advantageously administered in accordance with the invention include naloxone, naltrexone, nalbuphine, levorphanol, buprenorphine, butorphanol, Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD) and levonantradol.

51 Claims, 1 Drawing Figure



METHOD OF ADMINISTERING NARCOTIC ANTAGONISTS AND ANALGESICS AND NOVEL DOSAGE FORMS CONTAINING SAME

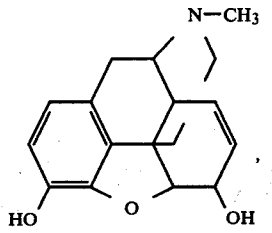
BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a novel method of administering narcotic antagonists, narcotic analgesics and related compounds, and to novel dosage forms containing such compounds adapted for nasal administration.

2. Background Art

Morphine, which has the structural formula



is a potent narcotic analgesic which is principally used to relieve pain; it is also used in the dyspnea of heart failure, in pulmonary edema and cough, as a sedative and in the control of diarrhea (chiefly in the form of paragoric). Morphine causes both depression and stimulation in the central nervous system and the gut, its most significant actions being analgesia, hypnosis, respiratory depression, smooth muscle spasm, nausea, vomiting and circulatory and other effects (especially miosis). The drug is well-absorbed by injection, but absorption via the oral route is inefficient and variable, probably because of metabolism in the liver, chiefly by conjugation with glucuronic acid. Abuse leads to habituation or addiction.

The morphine molecule has been subjected to a variety of structural modifications in efforts to enhance selected properties and/or to deemphasize others, as well as to produce drugs which actually antagonize the effects of morphine and other opioid analgesics. Such efforts have led to the development of a variety of classes of chemical compounds, such as the class of morphine analogues whose structures are very closely allied to that of morphine, retaining both the phenolic OH and the N-methyl substituent of morphine, such as apomorphine, levorphanol and oxymorphone, and which as a group have strong analgesic, respiratory depressant and smooth muscle stimulant activity but which also are highly addicting. Retention of the phenolic hydroxyl while replacing the methyl on the nitrogen atom with a larger alkyl or similar side-chain has afforded both morphine analogues which are relatively pure opioid antagonists (e.g. naloxone and naltrexone) and are used in the treatment of narcotic-induced respiratory depression (overdose), in the diagnosis of narcotic addiction and in the prophylaxis of narcotic abuse; and morphine analogues which are agonist-antagonists (e.g. buprenorphine, pentazocine, nalorphine and cyclazocine), which display varying degrees of morphine-like activity as well as of morphine-antagonist behavior, and which can therefore be used as analgesics as well as for the purposes for which the relatively pure antagonists are used. Buprenorphine appears to be a particularly valuable analogue because of its low physical dependence potential, as well as its potent narcotic antagonist and analgesic activity. See Cowan et al, *Br. J. Pharmac.* (1977), 60, 537–545; Jasinski et al, *Arch. Gen. Psychiatry,* Vol. 35, April 1978, 501–516; Mello et al, *Science,* Vol. 207, Feb. 8, 1980, 657–659.

Virtually all of the members of the groups of morphine analogues discussed supra are well-absorbed by injection, but are rarely used orally because of inefficient and variable absorption by that route. The low effectiveness of naloxone when taken orally has been attributed to the rapid and almost total formation of a less active metabolite in the first hepatic transit. See Fishman et al, *J. Pharmacol. Exp. Ther.* 187, 575–580 (1973). Also Berkowitz et al, *J. Pharmacol. Exp. Ther.* 195, 499–504, and the references cited therein.

Yet other structural modifications of the morphine molecule have resulted in codeine and its analogues; methadone and related compounds; and meperidine and related compounds such as profadol. Also see, generally, *Pharmacological Basis of Therapeutics,* ed. Goodman and Gilman, sixth edition, Chapter 22, "Opioid Analgesics and Antagonists", by Jaffe and Martin, pp. 494–534 (MACMILLAN PUBLISHING CO., INC., New York, 1980); *Cutting's Handbook of Pharmacology,* sixth edition, ed. T. Z. Czáky, M.D., Appleton-Century-Crofts/New York, Chapter 50, pp. 551–571.

Recent studies of THC, or Δ^9-tetrahydrocannabinol, which is the active ingredient in marijuana, or its derivatives (e.g. CBD or cannabidiol, and levonantradol) suggest that these compounds are potentially useful in a wide variety of therapeutic areas, such as in the prevention of narcotic withdrawal symptoms and as antiemetics, particularly in the treatment of cancer patients undergoing chemotherapy. Unfortunately, oral administration has been found to be much less effective than intramuscular injection. See, *Medical News,* Monday, Jan. 19, 1981, page 3, for a more detailed discussion of the various therapeutic uses of THC and its derivatives.

SUMMARY OF THE INVENTION

In view of the foregoing, it is apparent that a serious need exists for the improved delivery of narcotic antagonists, narcotic analgesics and related compounds which are not well-absorbed orally. Thus, it is an object of the present invention to provide novel dosage forms and a novel method of administering morphine or an analogue thereof bearing at least one phenolic hydroxyl substituent and having narcotic analgesic, antagonist or agonist-antagonist activity, or Δ^9-tetrahydrocannabinol or a pharmacologically active analogue thereof bearing at least one phenolic hydroxyl substituent, which will provide greatly enhanced bioavailability as compared to oral administration, while at the same time providing relative ease of administration when compared to intramuscular, subcutaneous or intravenous injection. This object is achieved by nasal administration of morphine, Δ^9-tetrahydrocannabinol, or one of their aforesaid phenolic, pharmacologically active analogues, advantageously formulated into a solution, suspension, ointment or gel adapted for nasal administration.

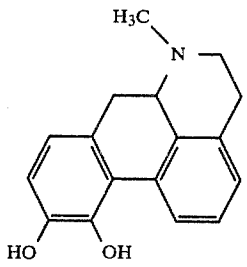
BRIEF DESCRIPTION OF THE DRAWING

The FIGURE of the drawing is a semi-logarithmic plot of mean plasma levels of naloxone after intravenous, nasal and oral administration of a dose of 30 μg of naloxone per rat.

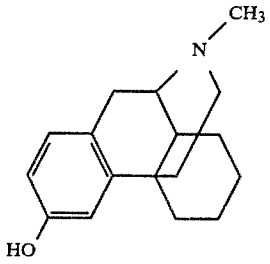
DETAILED DESCRIPTION OF THE INVENTION

The narcotic analgesics, narcotic antagonists and narcotic agonist-antagonists intended for use in the compositions and method of the present invention include morphine and pharmacologically active analogues thereof having at least one aromatic ring, said ring bearing at least one free OH group. Particularly significant morphine analogues contemplated by the present invention include morphine-like analgesics such as apomorphine, hydromorphone, levorphanol, metopon and oxymorphone; and narcotic antagonists and agonist-antagonists such as buprenorphine, diprenorphine, butorphanol, cyclazocine, pentazocine, phenazocine, levallorphan, nalorphine, naloxone, alazocine, nalbuphine, oxilorphan, nalmexone and naltrexone. Other analogues contemplated by the invention included ketobemidone, apocodeine, profadol, cyclorphan, cyprenorphine, desomorphine, dihydromorphine, 3-hydroxy-N-methylmorphinan, levophenacylmorphan, metazocine, norlevorphanol, oxymorphone, phenomorphan, pholcodine and hydroxypethidine. Especially preferred morphine analogues are those having antagonist or agonist-antagonist properties, especially naloxone, nalbuphine, naltrexone, buprenorphine and butorphanol. Any pharmaceutically acceptable form of morphine or of its phenolic analogues can be used, i.e. the free base or a pharmaceutically acceptable acid addition salt thereof (e.g. naloxone hydrochloride, nalbuphine hydrochloride, nalorphine hydrochloride, nalorphine hydrobromide, levallorphan tartrate, morphine sulfate, levorphanol tartrate, buprenorphine hydrochloride, butorphanol tartrate, pentazocine lactate, pentazocine hydrochloride, phenazocine hydrobromide, morphine hydrochloride, profadol hydrochloride, etc.); generally, the selected compound is employed in the instant compositions and method in the pharmaceutically acceptable form which has previously been found most advantageous for use by injection or orally. The structural formulae for representative free bases encompassed by the present invention are set forth below:

apomorphine



levorphanol



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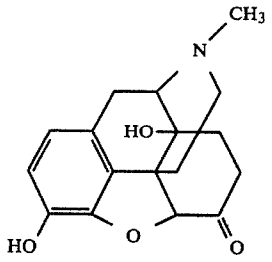
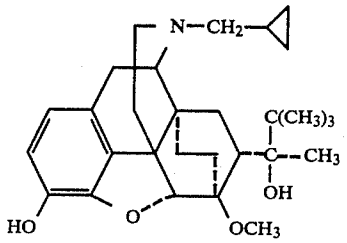
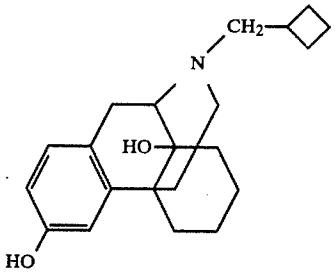
oxymorphone



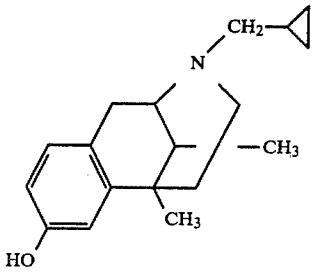
buprenorphine



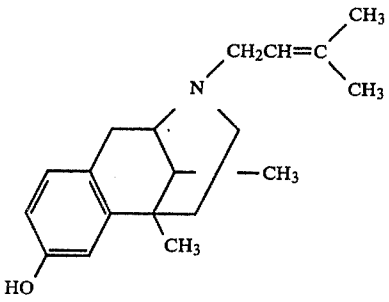
butorphanol



cyclazocine



pentazocine



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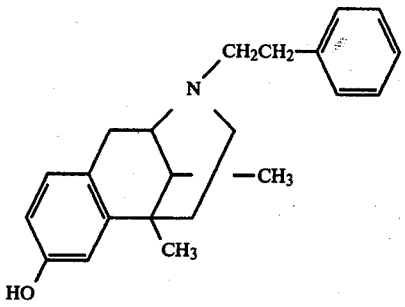
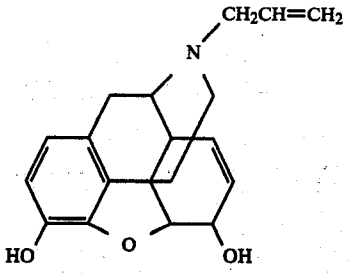
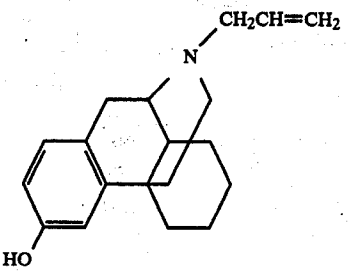
phenazocine



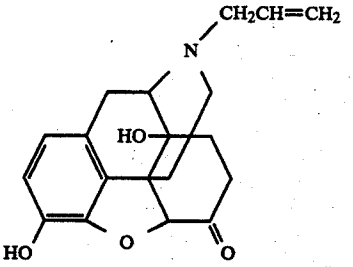
nalorphine



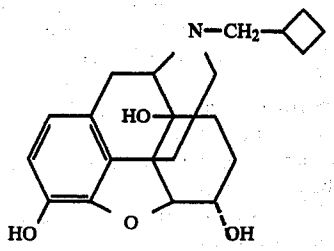
levallorphan



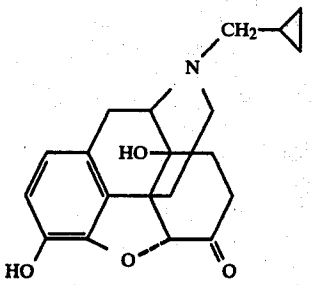
naloxone



nalbuphine



naltrexone



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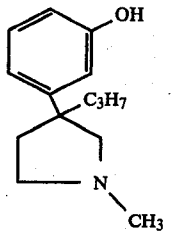
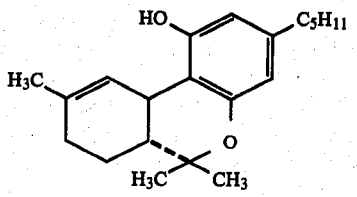
profadol



These morphine analogues and their salts can be prepared by well-known methods. Morphine itself can of course be isolated from natural sources and then converted, if desired, into a pharmaceutically acceptable acid addition salt.

The cannabinoids intended for use in the method and compositions of the present invention include Δ^9-tetrahydrocannabinol (THC) and pharmacologically active derivatives thereof having at least one free OH group on an aromatic ring thereof. Δ^9-Tetrahydrocannabinol has the structural formula



Preferred derivatives thereof for use in the present invention include cannabidiol (CBD) and levonantradol. These compounds can be prepared by known methods or, in the case of THC and CBD, isolated from natural sources.

In accord with the present invention, morphine, THC and their pharmacologically active phenolic analogues can be administered nasally with results considerably superior to those obtained with oral administration in terms of enhanced drug bioavailability and minimization of blood level variations, thus enabling use of these drugs at the dosage levels previously possible only by injection without the disadvantages inherent in subcutaneous, intrasmuscular or intravenous administration. It would appear that these drugs are rapidly absorbed from the nasal mucosa into systemic blood without extensive metabolism in the gastrointestinal tract and/or extensive first-pass metabolism.

The following study was undertaken to examine the bioavailability of a representative drug employed in the method and compositions of the invention, namely naloxone, administered nasally, in comparison with the bioavailability of that drug when administered orally and intraveneously.

Sprague-Dawley male rats, each weighing about 270 grams, were used in the study. Three groups of three rats each were employed, one group for each route of administration. The rats were anesthetized with pentobarbital (50 mg/kg) prior to administration of the drug. Naloxone was administered at a dose of 30 μg/rat (~40 μCi/rat) as ^{3}H-naloxone in 0.1 ml of isotonic saline. For intravenous administration, the drug was injected through the femoral vein. For oral (intraduodenal) administration, the abdomen of each rat was opened through a midline incision and the drug was injected

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