THE PHARMACOLOGY OF NALORPHINE (N-ALLYLNORMORPHINE)[1]

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INTRODUCTION

One of the exciting discoveries of recent years is the observation of the pharmacologic properties of nalorphine (N-allylnormorphine). This drug, which has a chemical structure closely akin to that of morphine, does not possess any unusual actions by itself, but it has the unique ability of antagonizing many of the pharmacologic effects of morphine and other potent analgesics. This remarkable antagonism is strikingly demonstrated by the intravenous injection of a small dose of nalorphine into a dog narcotized with morphine. Characteristically in about ninety seconds or less after the nalorphine injection, the dog stands, wags his tail and walks away, appearing to be quite normal in all respects. Conversely if the dog is morphine-tolerant, the administration of nalorphine precipitates an "abstinence syndrome" characteristic of the canine species. The acquisition of this specific antagonist for morphine has rekindled interest in the mechanisms of the pharmacologic actions of the latter drug. Nalorphine has become a very useful tool in the study of the development of tolerance and physical dependence to morphine. Evaluation of the addiction liability of morphine congeners and new synthetic analgesic agents has been greatly facilitated by the use of nalorphine. Practical applications of the antagonism of nalorphine against the opiate drugs are the treatment of acute poisoning with the potent analgesic agents and reversal of respiratory depression in newborn infants following maternal narcosis with morphine and related agents.

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The first observations that the substitution of the allyl group for methyl on nitrogen in the opiate series would yield an agent which would antagonize morphine were reported by Pohl (69) and von Braun (86) in 1916 for N-allylnorcodeine. This compound was shown to arouse temporarily a dog narcotized with morphine. About ten years later the morphine-antagonistic action of other N-substituted derivatives, including alicyclic as well as unsaturated aliphatic groups, of norcodeine were described to be similar but weaker than the N-allyl derivative (87). The significance of these results was not appreciated and interest lagged until 1941–1942 when the antagonism of morphine by N-allylnorcodeine was confirmed (43) and the synthesis of N-allylnormorphine was reported (59, 88). The remarkable antagonism of morphine by N-allylnormorphine (43, 44, 45, 84) stimulated further synthetic research and more recently a large number of N-alkyl derivatives of morphine, morphine congeners and synthetic analgesics have been synthesized and their morphine-antagonistic action evaluated (18, 36).

In this review the generic term nalorphine will be used throughout. Wherever doses are mentioned they will represent hydrochloride salt although only the term nalorphine will be given.

I. PHYSICAL-CHEMICAL PROPERTIES OF NALORPHINE

Nalorphine base melts at 208–209°C, is soluble in chloroform, ethanol and acetone but sparingly soluble in ether or water (88). The hydrobromide salt melts at 258–259°C, is water soluble and can be crystallized from ether (88). The hydrochloride salt melts at 265–270°C and exhibits a specific rotation, $[\alpha]_D^{25}$, of -115 to $-120°$ (6% w/v in methanol) (19, 22). An aqueous solution of nalorphine hydrochloride gives maximum absorption in ultraviolet light at 285 mμ [specific absorbency, E (1%, 1 cm), of about 44] and minimum absorption at about 260 mμ (22). Ultraviolet absorption is not specific for nalorphine, *i.e.*, does not differentiate from morphine, but can be used for the quantitative determination of pure material (73). Nalorphine possesses a characteristic infrared absorption pattern differing from that of morphine and gives a characteristic wave in the polarograph which is not shown by morphine or normorphine and presumably is dependent upon the reduction of the allyl group (73).

Information on the pK values of the amino and phenolic groups is not available in the literature at the present time, but presumably these values would be nearly the same as those of morphine. Accordingly at physiological pH nalorphine would exist predominantly as the cation (substituted ammonium ion), the phenolic group being relatively non-ionized. Buffer distribution studies on the *p*-nitrobenzoyl phenolic esters indicate that nalorphine is a weaker base than morphine (100).

II. PHARMACOLOGICAL ACTIONS OF NALORPHINE *PER SE*

The acute pharmacological actions of nalorphine in several animal species are summarized in Table 1. In general, the effects are qualitatively similar to morphine but of lower intensity. Only the general effects upon the central nervous

system (CNS), analgesic and respiratory effects, will be discussed in detail. The other actions of nalorphine are of minor theoretical or practical consideration and accordingly the information in Table 1 is adequate.

1. General CNS effects. In all animal species nalorphine is less of a CNS depressant than morphine and in the human is an atypical CNS stimulant. After high dosage in the human nalorphine produces disturbing day-dreams, acute visual hallucinations, anxiety, uncontrollable "thoughts racing through the head", pronounced dysphoria, and acute panic, all of which are promptly abolished by pentobarbital administered intravenously (89, 95). Some of these actions can appear in mild form if excessive dosage of nalorphine is administered for the antagonism of morphine (68). Individuals experiencing some of the above effects of nalorphine, especially the day-dreams and acute visual hallucinations, have compared these effects with those of mescaline or hyoscine (95).

It is not entirely clear whether nalorphine causes death by CNS depression or stimulation. Lethal doses in mice did not produce sedation and death was usually preceded by convulsions (45), although respiratory failure as a terminal event has been reported (84). The effect of lethal doses of nalorphine in the monkey is that of producing tremors and periodic clonic convulsions, simultaneous respiratory arrest and cardiovascular collapse being the terminal event (49). It would appear that CNS stimulation is the more prominent primary factor in the lethal effect of nalorphine, although certain CNS depressant effects undoubtedly play an important role.

2. Analgesic effects. With the exception of one report which indicated considerable potency in rats (45), studies on the analgesic effect in lower animal species showed nalorphine to be a weak analgesic agent. The experiments on rats were repeated with the same method of analgesic testing but after subcutaneous instead of intraperitoneal injection and showed very low analgesic potency for nalorphine (98). Nalorphine is nearly as effective as morphine for relieving postoperative pain in human patients (57), but the untoward side-effects make the analgesic use of nalorphine quite undesirable. Why nalorphine provides pain relief in human patients but is relatively impotent in the analgesic assay procedures performed in lower animals is a difficult question to answer. However, such differences do suggest that the transfer of results obtained with analgesic assay procedures on lower animals to the clinical relief of pain may not be valid.

3. Respiratory effects. In lower animal species nalorphine lacks the consistent respiratory depressant action of morphine, producing either mild stimulation or depression of respiration (Table 1). However, nalorphine administered in a dose of 5 mg to adult human subjects depresses respiration, the effect being primarily a reduction in minute volume with little change in rate (57).

Nalorphine has no significant effect on the respiration of newborn human infants when administered to the mother (30), although this drug after maternal administration does antagonize the depression of fetal respiration resulting from maternal narcosis with morphine (30). Accordingly nalorphine must gain access to the fetal circulation. Therefore, it appears that newborn infants have a higher threshold for the respiratory depressant action of nalorphine than adults.

TABLE 1

Pharmacological actions of nalorphine in several animal species

Species	Effect	Route of Admin.*	Observations	Reference
Mouse	CNS	h	Absence of restlessness or Straub reaction.	84
		ip, h	Death usually preceded by convulsions, Straub reaction not fully typical. No sedation with lethal doses.	45
		h	Increases sleeping time, but does not alter LD_{50} of secobarbital.	39
	Respiratory	h	Labored, irregular and then failure with lethal doses.	84
	Analgesic	h	Very little.	84
	LD_{50}	h	670 mg/kg.	84
		h	704 mg/kg.	45
		ip	492 mg/kg.	45
Rat	CNS	h	Much less depressant than morphine.	52
	Analgesic	ip	Greater than morphine?	45
		h	Very weak.	79, 98
Guinea-pig	Antitussive	h	Potency equal to codeine.	96
	Antispasmodic	To bath	Weak action on isolated ileum.	98
Rabbit	Respiratory	iv	Occasional brief stimulation of rate concomitant with fall in blood pressure and a slight decrease in tidal volume with doses of 2–20 mg/kg in unanesthetized animals or animals anesthetized with urethane.	45, 84
		iv	Failure with death after injection of 50 mg/kg.	84
	Circulatory	iv	Transient hypotension lasting 1–3 minutes after injection into animals anesthetized with urethane.	84
	Antispasmodic	To bath	Weak activity on isolated ileum.	98
Cat	CNS	h	In doses of 10–20 mg/kg did not show significant changes in behavior—no excitement as observed with morphine.	44, 45 84, 92
Dog	CNS	h	Doses of 10–30 mg/kg have little effect.	84, 98
	Analgesic	h	Doses of 10–30 mg/kg do not alter the pain threshold.	79, 84, 98
	Respiratory	h	No noticeable change in rate with doses of 10–30 mg/kg.	84, 98
		iv	Occasional increase of rate in barbitalized animals.	46

TABLE 1—*Continued*

Species	Effect	Route of Admin.*	Observations	Reference
Dog—*continued*	Respiratory —*continued*	iv	Doses of 30 mg/kg result in increased rate, total ventilation, and ventilatory equivalent of oxygen in animals anesthetized with chloralose-urethane or pentobarbital.	6, 85
	Circulatory	iv	In doses of 30 mg/kg produces hypotension in pentobarbitalized animals.	6
	Antispas-	iv	Slightly decreases tone and increases activity as recorded from Thiry-Vella loops after doses of 0.5 mg/kg.	45
	Antitussive	h	Potency equal to codeine.	96
	EEG	h	In unanesthetized uncurarized trained animals doses of 2.5–30 mg/kg produce changes which are identical with, or resemble closely, the "burst-slow waves" patterns which occur in natural sleep or during pentobarbital anesthesia.	90
	Reflexes, in chronic spinal dogs	h	Slightly depresses ipsilateral flexor and crossed extensor refleces, while the effects on knee jerks and extensor thrusts are variable and small.	94
Monkey	CNS	h	Slight drowsiness with doses of 1–50 mg/kg. Nausea and anorexia with 60–100 mg/kg. Doses above 100 mg/kg produce vomiting, apprehension, crying, intention tremors, ataxia, hallucinatory-like behavior and periodic clonic convulsions.	48, 49
	Respiratory	h	Occasional slowing of rate with doses of 1–50 mg/kg. Stimulation with doses of 100 mg/kg. Arrest (simultaneous with cardiovascular collapse) with lethal doses.	49
	Circulatory	h	Cardiovascular collapse as a terminal event with lethal doses.	49
	LD_{50}	h	Approximately 400 mg/kg.	49
		iv	Approximately 100–200 mg/kg.	49
Human	CNS	iv, h	Depressant in normal subjects and hospitalized patients in doses of 5–10 mg.	9, 26, 31
		h	Euphoria and dysphoria in normal subjects in doses of 5–10 mg.	57
		h	Relaxation and drowsiness in some post-addicts and nausea, giddiness, sweating, disturbing day-dreams or acute visual hallucinations in others with doses of 5–15 mg.	95

TABLE 1—*Continued*

Species	Effect	Route of Admin.*	Observations	Reference
Human—*continued*	CNS —*continued*	h	Lethargy, drowsiness, vivid day-dreams, pronounced dysphoria, anxiety, uncontrollable "thoughts roving through the head," and acute panic in post-addicts given 30–75 mg. Intravenous pentobarbital (250 mg), but not morphine (30 mg), promptly and permanently abolishes the dysphoria and day-dreaming but enhances the drowsiness.	89, 95
		iv	Hallucinations, crying and complaints of muscular weakness in obstetrical patients in labor after 10 mg.	30
	EEG	h	In post-addicts receiving 30–75 mg results in increased rhythmicity and slight slowing of alpha frequencies associated with relaxation and euphoria, and intermittent or continuous reduction in amplitude and decrease in rhythmicity associated with anxiety and slight drowsiness.	95
	Eye	h	Marked miosis and pseudoptosis in post-addicts after 60–75 mg.	95
	Analgesic	h	In hospital patients doses of 10–15 mg provide relief of postoperative pain.	57
	Respiratory	h, iv	Moderate depression in normal human subjects and hospitalized patients, primarily a reduction in minute volume with little change in rate.	26, 57, 72, 83
		iv	Lowers sensitivity of respiratory center to CO_2 by about 50%.	83
		—	No depression in newborn infants when drug administered to mother 5–15 minutes before birth.	30
	Circulatory	h	Slight but significant slowing of cardiac rate and elevation of systolic blood pressure in post-addicts after 14 mg.	95
		h	Postural hypotension.	66
	Antitussive	o	30 mg nearly as effective as 30 mg of codeine.	7a
	Antispasmodic	h	Diminished spontaneous motility of stomach, jejenum and colon, unlike morphine.	4
	Renal	h	Occasional copious diuresis after large doses.	95
	Body temperature	h	Slight lowering in post-addicts after 15 mg.	95
	Cerebrospinal fluid pressure	iv	Effects an increase.	53

TABLE 1—*Concluded*

Species	Effect	Route of Admin.*	Observations	Refereece
—	Inhibition of some enzyme systems *in vitro*	—	Slightly more potent inhibitor of the cholinesterases of mouse brain, bovine erythrocytes and horse serum than morphine. The minimal concentration for inhibition is 0.8×10^{-4}M. Inhibits serum cholinesterase more completely than brain or erythrocyte cholinesterase.	8
		—	67% inhibition of DPN-cytochrome c reductase activity in rat brain homogenates by a concentration of 1×10^{-3}M.	87a

* h = hypodermic, ip = intraperitoneal, iv = intravenous, o = oral.

III. EFFECT OF NALORPHINE ON THE RESPIRATORY DEPRESSION OF NON-NARCOTIC DRUGS

There is considerable difference of opinion regarding the efficacy of the administration of nalorphine for reversing the respiratory depression of non-narcotic drugs. Since the principal studies on this problem have been performed in the rat, dog, and human, only the results in these three species will be discussed.

The respiratory rate of rats anesthetized with pentobarbital is not altered with nalorphine (11) but the respiratory minute volume is restored to normal (21). It should be emphasized that the latter effect could be achieved only with doses of nalorphine twofold greater than those of pentobarbital which is an amount of nalorphine much greater than that needed to antagonize most of the actions of morphine.

Investigations on the dog have shown that nalorphine, administered intravenously in a dose of 30 mg/kg, significantly increases the respiratory rate, the total ventilation and ventilatory equivalent of oxygen in animals anesthetized with chloralose-urethane or pentobarbital (6, 85). Vivanti *et al.* (85) concluded that nalorphine probably acts centrally on the respiratory centers in overcoming the respiratory depression of pentobarbital. Stimulation of respiration was apparent after bilateral carotid denervation, bilateral vagotomy, and decerebration. Thus reflex action resulting from hypotension or stimulation of peripheral chemoreceptors, or indirect effect via the cerebral cortex, was precluded by the latter investigators (85). Nalorphine has no effect on the ventilation of the dog with acute respiratory depression resulting from carbon dioxide (40%) narcosis (83).

Eckenhoff *et al.* (26, 27, 29), Adriani and Kerr (3), and Solomon *et al.* (72) have stated that in the human nalorphine is of no value for antagonizing the respiratory depression produced by the barbiturates, thiobarbiturates, ether, or cyclopropane. Indeed it has been reported that nalorphine produces a 50% lowering

of the sensitivity of the respiratory center of the human to carbon dioxide (83). In contrast, antagonism by nalorphine of the respiratory depression produced by thiopental and thiamylal in two patients has been described (25).

On the basis of the divergent results in these three animal species, one must conclude either that there is a species variation, the dog being more sensitive to the respiratory stimulant action of nalorphine, or that the experimental techniques are sufficiently varied to account for the different results. It would appear that the latter is the more correct explanation. There seems to be no doubt that if given in doses of considerable magnitude nalorphine stimulates respiration in the dog and rat, and probably the human, depressed with barbiturates or other central nervous system depressant agents. It is equally apparent that this antagonism is not of the same quality as the antagonism of nalorphine against morphine. For example, a dog narcotized by the subcutaneous or intravenous injection of 30–40 mg/kg of morphine is aroused immediately by the intravenous injection of 1 mg/kg of nalorphine (62). After the nalorphine injection such an animal arises, walks around, drinks water, and appears to be quite normal in its behavior. This is to be contrasted with the effect of the intravenous injection of about thirty times the above dose of nalorphine into dogs anesthetized with pentobarbital, *viz.*, some respiratory stimulation but not complete awakening (85). Doses of nalorphine less than 30 mg/kg in these dogs do not consistently give successful respiratory stimulation. A comparison of the magnitude of the dose of nalorphine was well as the results of administration of this agent to dogs which have received morphine or pentobarbital, respectively, would indicate that we are dealing with two types of antagonism. The evidence suggests that the nalorphine-barbiturate type of antagonism is non-specific and is merely a reflection of the central nervous system stimulant action of nalorphine, an action which has been demonstrated by other studies. The nalorphine-morphine antagonism is more specific and restricted to the potent analgesic agents. The nature and characteristics of the nalorphine-morphine antagonism will be discussed in V, 5.

IV. DISTRIBUTION AND FATE OF NALORPHINE

Only preliminary information is available on the distribution and fate of nalorphine. Experiments on rats have shown that after subcutaneous injection, nalorphine is absorbed more rapidly and is found in lower concentrations in both free and conjugated forms in tissues (100) than found previously for morphine (99). Homogenates of rat liver with added amounts of cytochrome c oxidize nalorphine to a pseudomorphine-like material (13).

Apparently nalorphine passes rapidly through the placental barrier since the drug, when administered to the mother, quite promptly stimulates fetal respiration in both the rabbit (80, 81) and the human (30) when this respiration had been previously depressed by maternal administration of morphine.

Nalorphine is conjugated more rapidly and more completely by the intact dog than morphine (63). After subcutaneous administration of the identical dose (30 mg/kg) of drug to the dog, the concentration of nalorphine attains a three- to fourfold greater level in the brain than that of morphine (100). The rate of disap-

pearance of nalorphine from dog brain is more rapid than for morphine, at four hours after injection the level of nalorphine being one-half that of morphine (100). Accordingly, it is not surprising that the pharmacologic actions of morphine outlast the antagonistic effects of a single dose of nalorphine. At similar concentrations of drug, dog liver slices conjugate nalorphine at approximately the same rate as morphine (76).

V. ANTAGONISM OF NALORPHINE AGAINST MORPHINE

The most valuable and dramatic pharmacologic action of nalorphine is its antagonism of the effects of morphine. It should be emphasized that the extent of the antagonism of nalorphine for morphine is dependent on the particular action of morphine being considered, some being prevented or abolished completely and others altered only slightly, and the animal species being studied. Likewise, tolerance to morphine markedly alters the qualitative nature of the nalorphine-morphine antagonism and, indeed, the administration of nalorphine to a morphine-tolerant animal results in an "acute abstinence syndrome".

1. Non-tolerant animals. The effect of nalorphine on the actions of morphine in non-tolerant animals is summarized in Table 2. Nalorphine has little, if any, effect on the lethal or convulsant actions of morphine in the mouse or rat. Except for man after accidental overdosage, the antagonism of the lethal effect of morphine has not been well evaluated in any other animal species. It is well-known fact that morphine in large doses is a stimulant and convulsant to all animal species except man. Accordingly the above results on the absence of antagonism of the lethal effect of morphine in mice and rats by nalorphine, and the unquestionable life-saving effect of nalorphine in patients deeply narcotized with morphine, suggest that nalorphine antagonizes the CNS depressant, but not the stimulant, actions of morphine. Less than lethal doses of morphine in mice, rats, dogs, and monkeys, result in narcosis and analgesia. Nalorphine will effectively antagonize all of these effects of morphine in all four species thus providing additional evidence for the hypothesis that nalorphine antagonizes the CNS depressant actions of morphine even in the lower animal species. The excitation phenomenon produced by morphine in cats is quite effectively prevented or abolished by nalorphine (45, 84, 98). This antagonism might appear to be an exception to the above hypothesis. However, if the view is accepted that the excitation of the cat by morphine is the result of an atypical CNS depression, much like the pseudo "stimulation" of the human with alcohol, then the results with the cat can be reconciled with the other observations. That the overt excitation of the cat by morphine is in reality a CNS depressant effect is further suggested by the fact that less chloroform or ether is required to anesthetize cats premedicated with morphine (55a). Although nalorphine exhibits an analeptic effect in the rat, dog, and monkey narcotized with morphine, this drug has not uniformly demonstrated a complete analeptic action in the human depressed with morphine. The latter result may be due to the fact that usually only a sufficient quantity of nalorphine is administered to return respiration and blood pressure to normal in patients narcotized with morphine.

Depression of respiration by morphine, which is essentially a central effect, is

TABLE 2

Effect of nalorphine on the actions of morphine in non-tolerant animals

Species	Morphine Action	Result	Reference
Mouse	Lethality	Some protection	37, 38, 45, 61, 84
		No effect	55
	Convulsions	Incidence not reduced	55
	Analgesia	Prevents or abolishes	84
	Urinary excretion of morphine	Accelerates	1
	Concentration of morphine in liver and kidney	Reduced	2
Rat	Lethality	No effect	55
	Convulsant	No effect	55
	Narcosis	Antagonism	65
	Analgesia	Antagonism	21, 45, 79, 84, 98
		(Threshold of antagonism lowered by cortisone)	96a
	Respiratory depression	Antagonism	21, 79
	Catalepsy	Antagonism	79
	Anti-diuretic action	Antagonism	34a, 97
	N-Demethylation of morphine	Not blocked	57a
Rabbit	Respiratory depression in normal or anesthetized	Prevents or abolishes	43, 44, 45, 84
	Respiratory depression of fetus when morphine given to mother	Antagonism	80, 81
	Hyperglycemia	Prevents or abolishes	54, 102
Cat	Excitation phenomenon	Prevents or abolishes	45, 84, 98
	Hypotensive effect in pentobarbitalized cats	Antagonism	65
	Respiratory depression in pentobarbitalized cats	Antagonism	65
Dog	Narcosis and emesis	Prevents or abolishes	84
	Analgesia	Abolishes	79
	Respiratory depression	Abolishes	79
	Bradycardia	Abolishes	79
	Hypotension	Abolishes	42, 65
	Hypothermia	Abolishes	79
	Miosis	Abolishes	79
	Plasma levels of morphine	No significant effect	101
	Spasmodic action in trained unanesthetized dogs with Thiry-Vella or modified Mann loops	Incomplete antagonism	45
Monkey	Narcosis	Prevents	49
	Respiratory depression	Prevents	49

TABLE 2—*Continued*

Species	Morphine Action	Result	Reference
Human	Hypnosis	Little awakening	3, 25, 26, 27, 29, 58
		Analeptic in some	56
	Respiratory depression	Good antagonism	3, 25, 26, 27, 29, 58, 66, 72
		Only transient antagonism	68
	Hypotension	Antagonized if depressed	3, 25, 26, 27, 29, 58
	Intestinal spasmodic	Antagonism	4
	Biliary spasm	Prevents or abolishes	72a
	Respiratory depression in newborn	Antagonism	3, 15, 29
	Reduction of cerebral oxygen consumption	Returns to normal	70

prevented or abolished by nalorphine in all species investigated, *viz.*, the rat, rabbit, cat, dog, monkey, and human. This antagonism is of the greatest value in antidoting narcotic poisoning in man.

There is a difference in the threshold of the antagonism of the morphine effect by nalorphine depending on the individual action of morphine being considered. Orahovats *et al.* (65) have reported the antagonism of the hypnotic action of morphine in rats without reducing the analgesic effect. The optimum ratio for this differential effect seemed to be thirty-two parts of morphine to one part of nalorphine. Decrease of this ratio resulted in a considerable reduction of analgesia, and increase in the ratio showed no significant antagonism to the side effects of morphine. The same investigators (65) noted that in the dog the simultaneous administration of 2 mg/kg of morphine and 0.15 mg/kg of nalorphine produced analgesia of about the same degree and duration as that dose of morphine alone but without the morphine side-effects of marked general depression, emesis, transitory stimulation and then depression of respiration, bradycardia, hypothermia, and miosis.

Considerable controversy has developed as to the value of mixtures of nalorphine and morphine for clinical analgesia in the human. These mixtures were introduced with the hope that the untoward side-effects of morphine, but not the analgesic action, would be blocked by nalorphine as was observed in rats and dogs. The observations of Cappe and collaborators (14, 15) were confirmatory to the data in lower species and led to much optimism. These investigators administered equal amounts of nalorphine and morphine by fractional intravenous injection to seventy-five obstetrical patients in active labor, the total dose of each drug averaging 15.8 mg. The observations which were reported indicated the production of intense hypnosis and analgesia, the effects on respiratory rate, blood pressure, pulse rate, and rate of labor being negligible. Most of these patients were delivered under regional anesthesia, but when that was not possible plane I

cyclopropane anesthesia was used. It would seem that the observation of intense hypnosis in these patients without significant changes in respiratory rate, blood pressure, and pulse rate would be valid particularly since Payne (68) has reported that the intravenous administration of 10 mg of nalorphine to non-obstetrical patients or volunteers premedicated with 15 mg of morphine given intravenously or intramuscularly resulted in a marked intensification of hypnosis without a concomitant depression of respiratory minute volume. In view of the ancillary treatment of their obstetrical patients by Cappe *et al.* (15), their conclusion may not be valid that the mixture of equal amounts of nalorphine and morphine produced analgesia. Beecher and Lasagna (5, 57) did not observe any effect of 2 mg of nalorphine given simultaneously with 10 mg of morphine, either on the analgesic action or on the untoward side-effects of the latter drug. When 5 mg of nalorphine was administered together with 15 mg of morphine, the observations (57) indicated a trend toward greater respiratory depression than that produced by the same dose of morphine alone, results which are in disagreement with those of Cappe *et al.* (15). However, the latter investigators administered equal amounts of morphine and nalorphine, mixtures which Lasagna and Beecher (57) did not evaluate. Since nalorphine *per se* exhibits an analgesic action in the human (57) and approximately one-fifth to one-tenth of the nalorphine is involved in the antagonism of morphine (65), it is possible that the excess nalorphine was effective in producing analgesia. If the effect of a mixture of equal amounts of morphine and nalorphine is essentially the action of nalorphine, then the practical value of such a mixture as an analgesic preparation is low because of the excessive untoward side-effects of nalorphine (57). Nevertheless, additional studies should be performed on mixtures of equal amounts of morphine and nalorphine.

The salutary effect of nalorphine on severe respiratory depression induced in patients by morphine, or any potent analgesic agent, is a well-established fact. The intravenous injection of 5 to 10 mg of nalorphine is recommended as the initial treatment (72) which may be repeated, *if necessary*, every 15 minutes until pulmonary ventilation is adequate. Arousal of the patient should not be attempted. An alternative method of providing additional amounts of nalorphine, *if required* after the initial dose, is administration by slow intravenous drip in 5% glucose in water (72). The effect of the nalorphine persists for two to three hours so that the drug must be repeated in severe overdosage of morphine or other narcotic.

Orton *et al.* (66) have cautioned against the overdosage of nalorphine in the treatment of narcotic poisoning, the result being the production of symptoms very distressing to the patient. There may be considerable vaso-motor disturbances with postural hypotension. Likewise Payne (68) has reported that in human subjects premedicated with 15 mg of morphine by intravenous or intramuscular injection, the subsequent intravenous injection of 10 mg of nalorphine produced prolonged unpleasant side-effects as nausea, vomiting, sweating, pallor, and vertigo. In the treatment of narcotic poisoning Orton *et al.* (66) has recom-

mended that initially only 5 mg of nalorphine be given intravenously and more drug administered only in the presence of persistent profound depression. In view of the observation of Payne and Orton *et al.* noted above, the practice of administering the minimal, but still adequate, dosage of nalorphine is to be commended. Like many other aspects of clinical therapy, overzealous treatment can cause unnecessary difficulties.

Nalorphine should not be used in the treatment of overdosage of morphine, or other narcotic agents, in the addict. The resulting acute abstinence syndrome (see discussion in V, 2) may be more hazardous to the addict than the effect of the morphine. Therefore before nalorphine is administered to a morphine-narcotized subject it is essential to ascertain that the individual is not an addict. Measures other than the administration of nalorphine should be instituted if the latter is true.

Following the administration of narcotics to the mother the injection of nalorphine significantly shortens the interval between delivery and establishment of respiration in new-born infants (15, 29). This occurs whether nalorphine (10 mg) is administered intravenously to the mother just prior to delivery or injected into the umbilical cord in a dose of 0.1 to 0.2 mg (30). In these obstetrical patients the efficacy of nalorphine was reduced by nitrous oxide anesthesia and prevented by ether anesthesia. At the present time there is no adequate explanation for the latter effect.

2. Morphine-tolerant animals. Just as nalorphine antagonizes some, but not all, of the actions of morphine in non-tolerant animals, so does it antagonize only certain effects of morphine in the tolerant animal. The antagonism in the tolerant animal results in an acute "abstinence syndrome" or "withdrawal syndrome".

Rats tolerant to a high dosage of morphine (100 mg/kg of sulfate injected twice daily subcutaneously) show a definite change in behavior following the administration of nalorphine (injected subcutaneously in a dose of 10 mg/kg) (52). In these animals the action of morphine is seemingly reversed, the usual stimulation of morphine becoming an apparent sedation. However, these animals do demonstrate increased gastrointestinal motility, marked increase in fecal elimination and occasional diarrhea, signs which are characteristic of abstinence in higher species. Rats on a much smaller chronic dosage of morphine do not show any alteration of behavior when injected with nalorphine (95a). In this connection it has been reported that in rats, injected repeatedly with a mixture of morphine and nalorphine in which the dose of the latter was too small to inhibit completely the analgesic effect of the morphine, the analgesic effect of the mixture declined more rapidly than that of morphine alone (64). This result was shown to be due not to tolerance to the analgesic effect of morphine but to the potentiation of the inhibiting effect of nalorphine on morphine in partially tolerant as compared with non-tolerant rats. It was also demonstrated that rats injected chronically with nalorphine alone were more responsive to the analgesic effect of morphine than normal animals. The significance of these observations is difficult to interpret in the light of our present knowledge.

The injection of nalorphine into dogs tolerant to morphine results in the prompt appearance of an "abstinence syndrome" characterized by restlessness, salivation, vomiting, lacrimation, and muscle tremors (16, 52).

Nalorphine unmasks physical dependence in the addicted monkey and produces the typical signs of abstinence (48).

In human morphine addicts nalorphine induces an abrupt and explosive type of "abstinence syndrome" resembling strikingly that which is observed after abrupt withdrawal of morphine except that after nalorphine, withdrawal signs appear within fifteen minutes, may reach greater intensity (in forty-five minutes) and subside over a period of several hours (93). This result is another example of the fact that the effect of morphine outlasts that of nalorphine. Quantitative differences do exist between nalorphine-induced and morphine withdrawal "abstinence syndromes" and there is some evidence for minor qualitative differences. Human addicts receiving morphine chronically are unusually sensitive to nalorphine, relatively small doses being sufficient to produce the acute "abstinence syndrome" (95).

Signs and symptoms of a clear-cut "abstinence syndrome" in human subjects receiving 15 mg of morphine sulfate four times daily for as short a period as two or three days (95) have been produced by the subcutaneous injection of 15 mg of nalorphine. During this early period of addiction, physical dependence can be demonstrated with an injection of nalorphine but not with acute drug withdrawal.

3. Alterations in neurophysiological function in spinal animals. In the spinal cat nalorphine enhances the flexor and crossed extensor reflexes and blocks the depressant effects of morphine thereon, or reverses these effects if morphine was injected first (92). Morphine administered in sufficient doses to chronic spinal dogs depresses the flexor and crossed extensor reflexes, and nalorphine by itself possesses similar but much less intense actions. However, in spinal dogs which have received morphine repeatedly or as large single doses, nalorphine effects an "over-shooting" of the morphine-antagonistic actions on the spinal reflexes (94). The latter results indicate that some of the characteristics of physical dependence can develop even after single doses of morphine. This "over-shooting" is characterized by hyperactivity of the hind limb reflexes with spontaneous "running" movements resembling those which occur in the chronic spinal dog after abrupt withdrawal of morphine following a period of addiction. Pentobarbital in anesthetic doses, but not morphine, will antagonize this nalorphine-induced abstinence sign. After full recovery of reflexes following withdrawal of morphine, nalorphine fails to precipitate the "abstinence syndrome".

4. Structural requirements for optimal antagonism against morphine. Green *et al.* (36) determined the anti-analgesic action of a wide variety of N- and O-substituted normorphine derivatives against morphine. The N-allyl and N-propyl substituted normorphine possess the greatest antagonistic action, the N-butyl, N-crotyl, N-propargyl, and N-ethyl derivatives having a much weaker but still significant activity. Most of these agents exhibited very weak analgesic activity the N-ethyl and N-propargyl derivatives showing maximum activity. Alkylation

of the phenolic hydroxyl group reduces the activity of the N-allyl- and N-propylnormorphines. Esterification of both hydroxyl groups by acetic or propionic acid gives derivatives of nalorphine which are somewhat less potent than the parent compound but which still possess very marked morphine-antagonistic action. According to Clark *et al.* (18) N-substitution of allyl, methallyl, propyl, or isobutyl in normorphine, dihydro-, desoxy-, dihydrodesoxy-normorphine and dihydronormorphinone invariably produces compounds capable of counteracting the analgesic effect of morphine. N-Allylnormeperidine (18, 21), N-allylnordihydrothebanone methyl ether (18), and N-allylnorisomorphinan (18) are practically inactive as morphine antagonists. The parent compound of the latter derivative, N-methylnorisomorphinan, is also inactive as an analgesic agent. The *dl*- and *l*-3-hydroxy-N-allylmorphinans antagonize the actions of racemorphan or levorphan in producing respiratory depression in unanesthetized rabbits and analgesia in rats (7). The *l*-form (levallorphan) of the allyl derivative is twice as active as the *dl*-form, and the *d*-form is completely inactive. Levallorphan also antagonizes the respiratory depressant and analgesic actions of methadone and meperidine (21). It has been suggested that the margin between the anti-analgesic and the anti-asphyxial dose of nalorphine against morphine is smaller than the comparative margin of levallorphan against racemorphan (34). Levallorphan antagonizes the respiratory depression produced by levorphan, morphine or meperidine in rats (20, 21) and human subjects (32, 35, 41). It has also been claimed that a combination of levallorphan with levorphan in a ratio of 1:10 has maximal analgesic action without depression of respiration or blood pressure (23). However, the absence of respiratory depression with this mixture in normal human subjects has been denied by Eckenhoff *et al.* (28). Thomas and Tenney (83a) have reported that the administration of a 1 to 5 ratio of levallorphan to levorphan gives less respiratory depression than levorphan alone, particularly with high alveolar carbon dioxide tensions.

Morphine antagonism has been described for *p*-cyclohexyloxy-α-phenylethylallylamine (60). This N-allyl derivative abolished completely the analgesic action of 10 mg/kg of morphine and reduced but did not abolish the analgesia caused by 20 mg/kg of morphine in rats. The morphine-antagonistic action of this compound was of long duration, being approximately twenty-four hours. It remains to be seen whether or not the morphine-antagonistic action of this compound is of the same type as that of nalorphine.

The previous observations, with but few exceptions, suggest that there is a high degree of chemical specificity in the morphine-antagonistic actions. In the morphinan series of morphine-antagonistic agents stereoconfiguration is very important. Although certain facts are known about the planar configuration and the optical rotation of the inactive and active compounds, the significance of such observations in terms of mechanism of action is not clear at the present time.

The above observations lead to the conclusion that the maximum potency for morphine antagonism in the morphine and morphinan series is obtained when 1) a free phenolic group is present at the 3-position and 2) when a straight chain of three carbon atoms length is substituted on the nitrogen. Unsaturation of the

alkyl group on the nitrogen is not an essential requirement but increases potency to some extent. Substitution in the alpha position of the 3 carbon chain on the nitrogen (*i.e.*, methallyl or isobutyl) reduces but does not destroy activity. Apparently, the total size of the group substituted on the nitrogen is of less importance than the presence of the 3 carbon straight chain, *viz.*, isobutyl substitution results in a much better antagonist than *n*-butyl substitution.

5. Possible mechanisms. Unfortunately a discussion of the mechanism of the nalorphine-morphine antagonism must be largely conjecture because so little is known of the mechanism of morphine action. Also, the threshold for the morphine-antagonistic effect of nalorphine varies with the particular action of morphine and with the species. The existence of the "dual" actions of morphine of "stimulation" and "depression" makes the consideration even more complicated.

The first question to be answered with regard to mechanism is whether the nalorphine-morphine antagonism is specific or non-specific. On the basis of a) dramatic effect *in vivo* when nalorphine is administered in relatively small doses to animals narcotized with morphine, b) restricted requirements of chemical structure including optical rotation, and c) that no other agent or group of agents compares both in dosage and in dramatic effectiveness with that of nalorphine, the evidence at the present time is overwhelmingly in favor of this antagonism being specific. That nalorphine possesses CNS-stimulating properties is undeniable. Such stimulation can be demonstrated with and without prior central nervous system depression. However, the amounts of nalorphine necessary to demonstrate overt central stimulation is much greater than that needed to antagonize the actions of morphine. Furthermore, Costa and Bonnycastle (21) have recently reported that using doses which gave antagonism of respiratory depression, levallorphan had no effect on levorphan analgesia while nalorphine had no effect upon morphine analgesia in rats. However, both levallorphan and nalorphine were significantly effective as antagonists of analgesia produced by analgesics other than the parent compound.

Once the assumption is made that the nalorphine-morphine antagonism is specific, inquiry must be made as to the modus operandi of the interaction. Certain facts are known about the nature of this antagonism and are itemized below to serve as a basis for further consideration:

a. In all species tested the convulsant lethal effect (the ultimate of central "stimulation") is rather poorly antagonized by nalorphine. Statistically there is a significant protection, but quantitatively it is much *less* impressive than the ability of nalorphine to antagonize some of the central depressant actions of morphine.

b. The threshold of the antagonism of nalorphine *versus* morphine varies considerably with the particular action of morphine being considered. In some cases, such as the antitussive action, the pharmacological activity of nalorphine and of morphine appears to be additive.

c. Whatever action of morphine is responsible for the development of physical dependence, this action is not antagonized by nalorphine. By the same token, the actions of morphine responsible for preventing the appearance of the signs and symptoms of physical dependence are antagonized by nalorphine.

d. The very short latent period for the appearance of the morphine-antagonistic action of nalorphine which occurs after subcutaneous, but particularly after intravenous administration. Such speed of antagonism, thirty to ninety seconds, might suggest that we are dealing with a physico-chemical phenomenon at the cell surface.

e. In both non-tolerant and tolerant animals, the greater the dosage of morphine, the more sensitive the animals are to the morphine-antagonistic effect of nalorphine, *i.e.*, smaller doses being needed for antagonism.

Several possible mechanisms suggest themselves for this interaction: 1) chemical interaction of the *in vitro* type, 2) anticholinesterase action of nalorphine and 3) a competitive antagonism at the surface membrane of the axon or cell body particularly of the internuncial neurons.

Chemical interaction between morphine and nalorphine can be dismissed on the basis that optimal effects would be obtained with a one to one ratio of the two agents. Likewise, all the actions of morphine would be antagonized, and that is not the case.

The hypothesis that nalorphine is an effective antagonist because it inhibits cholinesterase is interesting, particularly since Shaw and Bentley (77, 78) and Brodie *et al.* (12) have reported that potent cholinesterase inhibitors antagonize morphine narcosis. There are a number of reasons why this theory is difficult to accept. Pharmacological agents which are much more potent anticholinesterase drugs than nalorphine are actually less effective in antagonizing morphine depression. When physostigmine and nalorphine are compared simultaneously in dogs narcotized with morphine, there is little similarity in the antagonistic actions of these two drugs against morphine.

An hypothesis which has been advanced by Seevers and Woods (75) and Seevers (74) is that of a competitive antagonism of a physico-chemical nature of nalorphine against morphine on the surface of the axon or cell body of the internuncial neurons. Nalorphine would be conceived of as occupying the receptors normally affected by morphine or displacing the morphine from the receptors if the latter drug had been previously administered. It would appear that nalorphine would have a greater affinity for these receptors than morphine. On the basis of present evidence it seems apparent that one molecule of nalorphine can displace several molecules of morphine from this receptor on the cell or axon surface. More strength is given to this hypothesis if one postulates that morphine is in a dynamic state of either penetrating or egressing from the interior of the cell and that the depressant actions of morphine are related to its presence on the receptors of the cell surface. It is conceivable that nalorphine has a predilection for the receptors on the surface and perhaps because of its greater molecular volume is unable to penetrate beyond a certain point through the cell surface or axon surface. If, as has been suggested (74, 75), physical dependence is related to the intracellular action of morphine, then if nalorphine were continuously present on the cell surface, one should not be able to develop a state of physical dependence with repeated administration of morphine. That nalorphine inhibits markedly the tolerance development to morphine in rats has been observed during chronic administration of nalorphine-morphine mixtures (64). Furthermore,

TABLE 3

Effect of nalorphine on the actions of potent analgesic drugs other than morphine

Drug	Species	Action of Drug	Result	Reference
Normorphine	Mouse	Lethality	Slight antagonism	61
Dihydromorphinone	Dog	Respiratory depression	Antagonism	46, 47
	Rabbit	Hyperglycemic effect	Prevents or abolishes	54
	Rat	Analgesic effect	Antagonism	98
	Human	Toxic effects	Antagonism	17, 29
	Dog	Increase in intestinal tonus	Prevents or reduces	40
Metopon	Dog	Respiratory depression	Antagonism	46, 47
	Dog	Increase in intestinal tonus	Prevents or reduces	40
	Monkey	Physical dependence	Acute "abstinence syndrome"	14
	Human	Effects of overdosage	Antagonism	31
6-Methyl-Δ^6-desoxymorphine	Rat	Hypnotic, exophthalmic and ataxic actions	Antagonism	65
	Rat	Analgesic action	Antagonism	65, 98
Heroin	Rat	Analgesic effect	Antagonism	98
	Human	Effects of overdosage	Antagonism	82
	Human	Physical dependence	Acute "abstinence syndrome"	93, 95
Codeine	Mouse	Lethality	No antagonism	61
	Rat	Analgesic effect	Antagonism	98
	Dog	Respiratory depression	Antagonism	46, 47
	Monkey	Chronic administration every 6 hours	Very mild "abstinence syndrome"	23a
	Human	Effects of overdosage	Antagonism	72
Norcodeine	Mouse	Lethality	Antagonism	61
Thebaine	Mouse and rat	Lethality and convulsions	No effect	55
Pantopon	Human	Effects of overdosage	Antagonism	29
N-Methyl-Δ^6-dehydroisomorphinan	Rat	Analgesic effect	Antagonism	98
Racemorphan	Rat	Analgesic effect	Antagonism	98
	Rabbit	Hyperglycemic effects	Antagonism	54
	Dog	Increase in intestinal tonus	Prevents or antagonizes	40
	Monkey	Physical dependence	Acute "abstinence syndrome"	48
	Human	Effects of overdosage	Antagonism	10, 17, 24

TABLE 3—*Continued*

Drug	Species	Action of Drug	Result	Reference
Levorphan	Human	Effects of overdosage	Antagonism	31
Meperidine	Mouse	Lethality	No antagonism	61
	Mouse	Lethality	Significant reduction	71
	Rat	Analgesic effect	Partial antagonism	79, 98
	Rabbit	Depression of fetal respiration	Antagonism	80
	Rabbit	Respiratory depression	Antagonism	98
	Dog	Respiratory depression	Antagonizes in unanesthetized animal	98
	Dog	Respiratory depression	No antagonism	46, 47
	Dog	Increase in intestinal tonus	Prevents or antagonizes	40
	Human	Respiratory depression	Antagonism	3, 9, 26, 29, 72
	Human	Neo-natal asphyxia	Antagonism	29, 30, 67
Normeperidine	Mouse	Lethality	Not antagonized	61
Alphaprodine (Nisentil)	Rat	Analgesic effect	Antagonism	98
	Rabbit	Hyperglycemic effect	Abolishes	54
	Dog	Increase in intestinal tonus	Prevents or abolishes	40
	Man	Effects of overdosage	Antagonism	31, 72
Ketobemidone	Monkey	Respiratory depression	Antagonism	48
	Monkey	Narcosis	Antagonism	48
	Monkey	Physical dependence	Acute "abstinence syndrome"	48
Methadone	Mouse	Lethality	Protection	79
	Rat	Analgesic effect, respiratory depression, catalepsy and lethality	Antagonism	79
	Rabbit	Depression of fetal respiration and reflexes when given to mother	Antagonism	80
	Dog	Respiratory depression	Prevents or antagonizes	46, 47
	Dog	Physical dependence	Acute "abstinence syndrome"	16
	Dog	Increase in intestinal tonus	Prevents or antagonizes	40
	Monkey	Respiratory depression and narcosis	Reversal	48
	Monkey	Physical dependence	Acute "abstinence syndrome"	48
	Human	Effects of overdosage	Antagonism	29, 33
	Human	Physical dependence	Acute "abstinence syndrome"	93, 95

TABLE 3—*Concluded*

Drug	Species	Action of Drug	Result	Reference
Isomethadone	Mice	Lethality	Antagonism	79
	Rat	Analgesia, respiratory depression, catalepsy and lethality	Antagonism	79, 98
	Monkey	Respiratory depression and narcosis	Antagonism	40
Heptazone	Mice	Lethality	Antagonism	79
	Rat	Analgesia, respiratory depression, catalepsy and lethality	Antagonism	79
Acetyl-*dl*-methadol	Mice	Lethality	Antagonism	79
	Rat	Analgesia, respiratory depression, catalepsy and lethality	Antagonism	79
	Rat	Analgesia	Antagonism	98
	Human	Physical dependence	Acute "abstinence syndrome"	50, 51

Wikler (91) has found that in chronic spinal dogs, concomitant administration of nalorphine retarded the development of tolerance to morphine and reduced the intensity of morphine abstinence phenomena following abrupt withdrawal of both drugs.

The foundation of this hypothesis of competitive antagonism of nalorphine against morphine on the axonal or cell body surface of the internuncial neurons can be established only when the cellular localization of morphine and nalorphine is ascertained with reliable histochemical procedures. Of course, that will still leave unanswered the question of the precise action (enzymatic, etc.) of nalorphine, or morphine, at any particular site.

VI. NALORPHINE ANTAGONISM AGAINST POTENT ANALGESIC AGENTS OTHER THAN MORPHINE

The effects of nalorphine on the pharmacological actions of potent analgesic agents other than morphine in various animal species are summarized in Table 3. Most of the actions of these analgesic agents are prevented or abolished. The antagonism by nalorphine is qualitatively similar to that against morphine but differs quantitatively with some of the other narcotic agents. As noted in Table 3 nalorphine will produce an acute "abstinence syndrome" in several animal species, including man, made tolerant to a variety of analgesic agents.

VII. CONCLUSIONS

The pharmacological properties of nalorphine which are of greatest theoretical and practical value relate to the antagonism of the effects of morphine and morphine-related narcotics. As a result of studies with nalorphine, it has been pos-

sible to obtain new information which adds to our knowledge of the mechanisms of development of tolerance and physical dependence to morphine. Nalorphine has become the drug of choice in treating acute overdosage of morphine and related analgesics in the human. The use of nalorphine in obstetrics has made possible the use of morphine for its analgesic action without the major undesirable side-effect of fetal respiratory depression. The administration of mixtures of nalorphine and morphine (or related analgesics) for the routine production of analgesia may offer considerable therapeutic possibilities. There seems to be no doubt that such mixtures can be used which still possess very respectable analgesic effects but the reports are controversial (see V, 1) as to whether the nalorphine in these mixtures prevents the undesirable side-effects of the morphine such as sedation, respiratory depression, etc. in the human. Even though there may prove to be no antagonism of the acute untoward side-effects, if the development of tolerance and physical dependence to morphine is inhibited as has been suggested (see V, 5), the use of such mixtures for clinical analgesia would be very definitely advantageous providing a parallel increased sensitivity to the analgesic inhibitory action of nalorphine does not develop as has been shown for rats.

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