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## NEWER OPIUM ANTAGONISTS, THEIR ACTIONS AND USE

PAUL R. DUMKE, M.D.\*

Early in the history of medicine, opium was found to be a reliable and potent agent for the relief of pain. Through purification morphine has become popular as a potent and superior analgesic agent. Morphine and all of its derivatives are effective because they elevate the pain threshold, produce sleep, alleviate fear and produce relaxation. Respiratory depression and not infrequently circulatory depression are not uncommon when these drugs are exhibited in an attempt to attain maximum therapeutic effect and are a most dangerous symptom of opiate intoxication. These deleterious effects have in many instances precluded their use in geriatric, pediatric and obstetric patients.

Demethylation of morphine, codeine and other related alkaloids diminishes their analgesic potency. In 1915 Pohl<sup>1</sup> by substitution of an allyl for a methyl group in codeine, produced a compound called N-allylnorcodeine that counteracted to some extent the respiratory depressant effect of morphine. McCawley, Hart and Marsh<sup>2</sup> in 1941 substituted an allyl for a methyl group in morphine. This compound known as N-allylnormorphine was shown to have marked stimulatory effects on respiration and circulation in animals depressed by morphine. In 1943 Unna<sup>3</sup> reported its use in antagonizing the effects of morphine injected into mice. The data remained in the literature as a pharmacological curiosity until 1952 when Eckenhoff, Elder and King<sup>4</sup> reported the use of N-allylnormorphine in the treatment of morphine and demerol narcosis and overdose.

N-allylnormorphine is structurally identical with morphine except for the replacement of a methyl group. (Fig. 1) Meperidine is structurally different from morphine when the formula is written on paper, and the relationship between the two molecules is obscure; but when three-dimensional models are constructed there is a close similarity of pattern, so we can expect N-allylnormorphine to antagonize meperidine. Recent clinical studies have shown N-allylnormorphine to be effective against depression produced by dilaudid, metapon, methadon, morphine and meperidine.

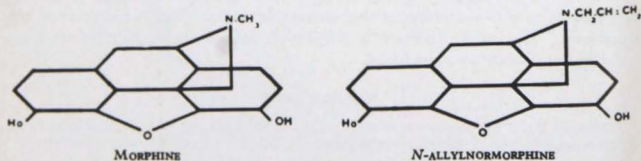


Fig. 1—Outline diagrams of molecules of morphine and nalorphine.

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N-allylnormorphine is quite interesting. Injected intravenously into a normal unpremedicated individual, it acts as a respiratory and circulatory depressant. Evidence presented by Tenney et. al.<sup>5</sup> points to the fact that N-allylnormorphine changes the threshold response of the respiratory center to carbon dioxide tension or pH. The sensitivity of the respiratory center is lowered by approximately 50 percent.

When the drug is injected into man, prior to the administration of a large dose of morphine, it inhibits the respiratory and circulatory depressant actions of the opiate; injected into a patient narcotized from large doses of the opiates, it causes a strong respiratory stimulation as well as a moderate circulatory stimulation. In spite of the stimulatory actions following opiate depression N-allylnormorphine seems to do little to counteract the sedation and analgesia produced by the opiates.

Injection of N-allylnormorphine into a subject deeply narcotized by morphine or any of its derivatives produces a dramatic effect as far as respiratory stimulation is concerned. The respiratory stimulation when 5 mgm. of the drug is exhibited intravenously in a patient narcotized with 60 mgm. of intravenous morphine is striking. The deep slow respirations that characterize opiate poisoning abruptly change after the antagonist is exhibited. In 15 or 20 seconds respiratory rate is increased 3-4 fold with regular less deep breathing. The change is not gradual as one sees after picrotoxin antagonism of barbiturate intoxication, nor is it an intense stimulation such as that seen with nikethamide or metrazol. Intense stimulation and then the gradual decline in respiratory rate and minute volume is not a characteristic of the new antagonist.

The effect of the antagonism on the circulation of the narcotized patient is not dramatic. If the blood pressure is depressed, it returns toward normal levels. If the pressure is normal the drug causes no marked change. The pulse rate is uniformly slowed.

The site of action of N-allylnormorphine has not been defined, but it is probably central. It may act in a competitive fashion with the opiates for certain receptors on cells of the central nervous system. It is possible for the drug to either occupy the receptor and block the action of the opiate, or it may displace the opiate. This is probably a nonspecific action because the sedative effect of the opiate is not blocked or completely displaced.

Another drug capable of the same effects against some of the opiates is levallorphan tartrate (3-hydroxy-n-allyl-morphinan). It bears a relationship to dromoran similar to that of N-allylnormorphine to morphine. It is an effective antagonist against respiratory depression produced by dromoran, nisentil, morphine, and demerol. Here then, we have two drugs which can be used intravenously to combat toxic effects of narcotics.

Some anesthetists have been using these drugs prophylactically in an attempt to eliminate the respiratory depressant and hypotensive effects that intravenous opiates possess. Obstetricians are using the drugs prior to delivery of an infant from a mother who is unduly depressed by opiates.<sup>7</sup> The respiratory depression in the newborn due to placental transfer of opiates is prevented by the antagonists.

The drug may also be given in 2 mgm. doses directly into the infant's umbilical vein if the depression of the newborn is thought to be due to opiates. Used this way the analeptic effect is quite dramatic.

It is important to remember that these drugs have no effect on depression of circulation or respiration caused by the barbiturates or any of the anesthetic agents. They are specific antagonists of opiates. N-allylnormorphine or levallorphan in persons not under the influence of narcotics produces lethargy, mild drowsiness, vivid daydreams, and dysphoria varying in intensity from vague anxiety to acute panic. All subjects complained of inability to repress such daydreams.

Of course, it goes without saying that these two drugs are life saving in the presence of severe opiate overdose, be it self-induced or accidental. The drugs are specific and are used in a 10 mgm. dose intravenously after the usual clear airway and adequate oxygenation of the patient is obtained. Repeated injections of the drug every 4-5 minutes, until 60 mgm. or more have been given, may be required to effect a stimulation of respiration and circulation in a severely poisoned individual.

It would be interesting to know what specific structural unit of N-allylnormorphine and levallorphan causes the antagonism of the opiates. If such a unit is found the chemists might be able to synthesize drugs which could have the same effect of antagonizing the respiratory depressant effects of barbiturates or cyclopropane.

Progress is being made in this direction. A wide number of drugs have been reported to have analeptic properties against the opiates. All of these analeptic drugs have either a muscarine like action or are anti-choline esterase drugs. A common chemical link in all of these drugs is a 2-4 diamino 5 phenyl thiazole.

When drugs with this linkage were tried against barbiturate intoxicated dogs they were roused. A report of successful trials in animals and in 20 cases of barbiturate poisoning in man of a new drug incorporating the 2-4 diamino 5 phenyl thiazole linkage\* has recently been made. This may be the linkage which is common to analeptics of this type. It will be interesting to see if the specific structural

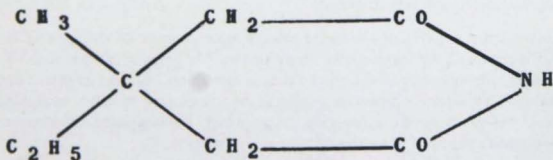


Fig. 2—bb METHYL ETHYL GLUTARIMIDE  
(N P 13)

unit can be isolated and used successfully. The barbiturate antagonist increased respiration and as the dose was increased produced wakening. If the drug is used in normal subjects it produces convulsions which can be controlled with barbiturates. The new drug (Fig. 2) is designated N P 13. Chemically it is bb methyl ethyl glutarimide and is quite specific against barbiturates.

The opiate antagonists are proving their usefulness everyday. Barbiturate antagonists with as much specificity as N-allylnormorphine would be a great advance in treatment of barbiturate toxicity.

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