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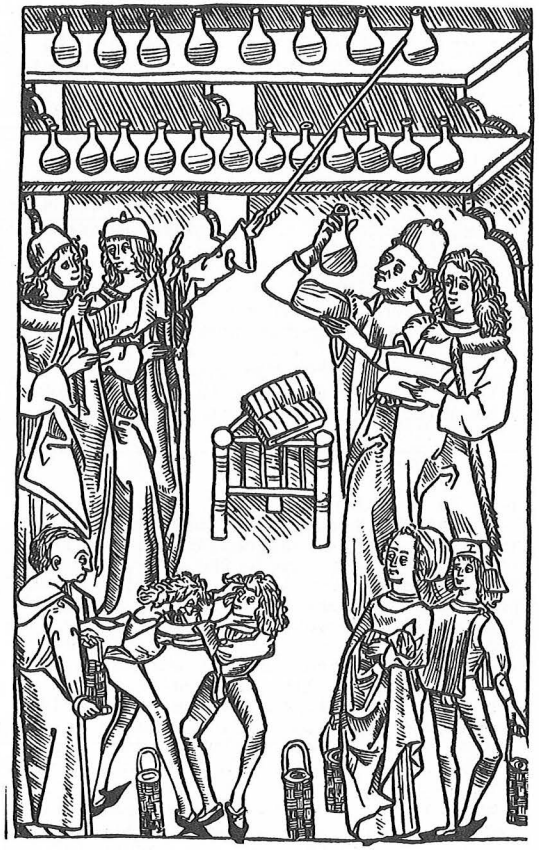
"Here in Singapore the abuse of heroin has increased alarmingly - a small epidemic to quote the Govt. Schoolchildren in their early teens are now involved. The govt. has brought in very tough legislation. A person found in possession of more than 3 g (Gm) morphine or 2 g heroin is presumed, until contrary is proved, to be a drug trafficker. Maximum sentence is 20 years and 20 strokes of the cane. For trafficking in more than 15 g of heroin (or 30 g morphine) the penalty is death. One such case will be coming up to the courts soon. Suspected abusers must supply urine samples for tests and if any controlled drug is found in the urine, the person is presumed to have consumed the drug and thus committed an offence. Thus it will not be a defence, as before, that the person may have been administered the drug without his knowledge in a drink, cigarette etc. He is guilty unless he can prove his innocence."

Personal Communication (AW to JKB) April 1976.



THE USE OF NARCOTIC ANTAGONISTS IN RELATION TO OPIATE-TYPE DRUG DEPENDENCE

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INTRODUCTION

Narcotic antagonists are drugs which reverse the pharmacological effects of morphine, roin and other narcotic analgetics. The first narcotic antagonist was reported by Pohl(1). an attempt to improve the analgetic (pain-killing) properties of codeine, he synthesized allylnorcodeine and found that it unexpectedly antagonized the respiratory depression and upor induced by morphine. This finding lay dormant until the synthesis of N-allylnormorphine alorphine)(2,3) which was found to antagonize most of the actions of morphine(4). The initial efulness of nalorphine was to test for physical dependence in individuals suspected to be ddicted" to heroin-like agents. Later nalorphine was realized to be life saving in cases of rcotic overdose. Continued studies also revealed nalorphine to have strong analgetic prop- ties in man. These interesting properties of nalorphine provided the impetus for development pure narcotic antagonists and also of other compounds possessing a mixture of analgetic and tagonist properties.

Recently narcotic antagonists have been studied for use in postdetoxification treatment of dicts, with the aim that pretreatment of individuals with an antagonist will provide protec- on against the pharmacological actions of those narcotics responsible for heroin-like drug pendence(5).

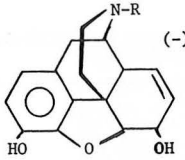
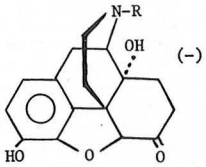
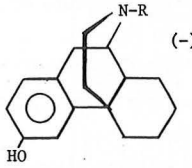
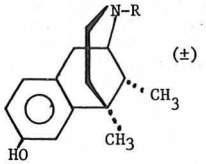
This review is an attempt to explain the current status of narcotic antagonists as they late to drug therapy (treatment of opiate overdosage) and drug abuse (management of the post thdrawal opiate addict). All individuals using these agents should have a thorough under- anding of their pharmacological actions. These narcotic antagonists are currently the most ecific antidote available for heroin overdosage and act within seconds of injection. They are ife saving compounds and are stocked in the emergency rooms of practically all hospitals today.

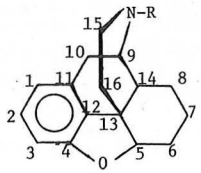
CHEMISTRY

Narcotic antagonists are structurally very similar to parent narcotic agents. At this time l clinically useful antagonists have resulted from the replacement of the N-methyl group on e parent narcotic with an N-allyl or N-methylcyclopropyl group. The structures and names of e narcotic antagonists that are currently available are given in Table I.

In general, antagonists with an N-methylcyclopropyl (as in cyclazocine) group have a longer ration of action than those with an N-allyl moiety (nalorphine, naloxone, and levallorphan). bstitution of hydroxyl at the 14-position of the morphine nucleus (as in naloxone) imparts ronger and purer antagonistic activity. The 4-5 ether bridge in nalorphine or naloxone does

Table I. Currently Marketed Narcotic Antagonists

STRUCTURE	PARENT NARCOTIC R	Name	NARCOTIC ANTAGONIST R	Name
	$-CH_3$	Morphine	$-CH_2-CH=CH_2$	Nalorphine (Nalline®)
	$-CH_3$	Oxomorphone	$-CH_2-CH=CH_2$	Naloxone (Narcan®)
	$-CH_3$	Levorphanol	$-CH_2-CH=CH_2$	Levallorphan (Lorfan®)
	$-CH_3$	Metazocine	$-CH_2-CH=C(CH_3)_2$	Pentazocine (Talwin®)



Numbering of Morphine Ring System

ot appear essential for antagonist activity and may promote faster metabolism at the C-3 posi-ion; its removal is a desirable feature in the design of longer acting antagonists(6).

PHARMACOLOGY

Narcotic antagonists are capable of reversing effects such as analgesia, sedation, eupho-ia, gastrointestinal effects, and the frequently lethal respiratory depression caused by mor-hine and its surrogates. These antagonists are specific in that they will not reverse depres-ion resulting from other classes of drugs such as barbiturates. They are also worthless in reating overdosage with stimulants (such as cocaine and the amphetamines). However, naloxone as recently been reported to reverse the effects of large doses of diazepam (Valium®)(7).

Nalorphine and levallorphan are termed partial-antagonists or mixed agonist-antagonists for he following reasons. When these agents are administered to normal persons, they mimic to arying degrees the effects seen with morphine administration (agonist effects). However, when hese agents are given to persons dependent on opiates or who have opiates present in their odies, these partial antagonists "reverse" the effects of the opiate. Naloxone displays very ittle if any agonist effects when given to normals and is therefore termed a pure antagonist. lthough pentazocine is a mixed agonist-antagonist, its antagonist component is weak and it is ot useful in cases of narcotic overdose. It is used primarily as an analgetic.

In general the agonist-antagonists have a low potential for drug dependence. In studies nvolving chronic administration of nalorphine, cyclazocine and pentazocine, abrupt withdrawal roduced an abstinence syndrome which was relatively mild compared to morphine(8,9,10). Asso-iated with their agonist component, these agents can produce significant respiratory depres-ion. Agents of this class can also produce psychotomimetic effects (disorientation, halluci-ations, etc.), particularly when both agonist and antagonist properties are strong(11).

The pure antagonists (naloxone) by definition have no agonist properties. They will not roduce analgesia, respiratory depression, pupillary constriction, or psychotomimetic effects nd physical dependence is not possible. Tolerance to the antagonist properties is also not bserved on chronic administration(11,12).

It should be emphasized again that these antagonists will not reverse respiratory depres-ion caused by the barbiturates. In fact, nalorphine and levallorphan may even worsen barbi-urate-induced or alcohol-induced respiratory depression because of their agonist activity. In verdosage, if the cause of respiratory depression is not clear, or if drugs in addition to piates are suspected in the depression, naloxone is indicated since it produces no respiratory epression of its own. It should also be cautioned that administration of any antagonist to ddicts may precipitate a severe withdrawal syndrome which can be more dangerous than the res-iratory depression; however, administration of the antagonists in small doses over a period of 5 to 30 minutes will reduce the chance of this happening. Further, narcotic overdose cases especially methadone) treated with antagonists should be observed periodically, since the dura-ion of the antagonist may be shorter than the narcotic causing the respiratory depression. The ffects of the antagonist may wear off before those of the narcotic, and life-threatening res-iratory depression may again result, requiring the administration of more antagonist. Over-osed patients should always be under qualified medical supervision.

Nalorphine (Nalline HCl®, Merck, Sharp and Dohme). Nalorphine shows little evidence of algetic activity in most animal studies except in the rat. However, in man it is as potent analgetic as morphine(13). As is typical of partial antagonists, "addiction" liability is ow compared to morphine or heroin. Unfortunately, the compound produces psychotomimetic ffects at analgetic doses.

Nalorphine is rapidly absorbed after subcutaneous administration and quickly crosses the lood-brain barrier to its site of action. It is excreted rapidly via the urine. Its duration f action is significantly shorter than its parent compound, morphine.

Nalorphine is useful in the treatment of narcotic overdosage to combat the severe respira-ry depression caused by morphine, codeine, heroin, and similar agents. Nalorphine has also

been used as a diagnostic agent for opiate abuse (Nalline test)--a positive response being indicated by a prompt increase in pupil size(14). Tests of this kind should only be done by physicians well acquainted with the procedure. The reliability of the test has been questioned and the use of sensitive chemical tests for the presence of opiates in the urine are preferable both medically and in courts of law(15).

Levallorphan (Lorphan Tartrate^{R}, Roche). Levallorphan has twice the potency of nalorphine as an antagonist and has comparable analgetic potency(16,17). As with nalorphine, its duration of action is significantly shorter than its parent, levorphanol. Its overall actions and uses are similar to those of nalorphine, and similar precautions should be taken in its use.

Naloxone (Narcan^{R}, Endo). Naloxone is approximately 7 times more potent than nalorphine as an antagonist. It produces negligible side effects in normal subjects at therapeutic doses(18). Naloxone will inhibit or reverse the effects of all opiate agonists such as morphine, heroin, methadone, propoxyphene (Darvon^{R}) and meperidine (Demerol^{R}). Unlike nalorphine and levallorphan naloxone is an effective antagonist of the respiratory depression caused by pentazocine and other antagonists(11). Because naloxone is a potent, fast-acting (effects noticed approximately 2 minutes following intravenous administration and slightly longer intramuscularly), pure narcotic antagonist that produces no respiratory depression, it is the drug of choice to combat respiratory depression resulting from opiate overdose. Since naloxone does not alter respiratory depression caused by barbiturates or other sedative-hypnotics, failure to get a response from naloxone is a good indication that the depression is not caused by an opiate.

Naloxone treatment has been proposed as a means to prevent addicts from returning to drug use, but its short duration of action (effective levels of naloxone can be maintained in man for only 4 hours)(17) and poor oral activity (1-3 grams/day are required to protect against the effects of heroin for 24 hours)(19) limit its use for this purpose.

The low oral activity of naloxone (50 times less potent orally than parenterally) is utilized in a preparation called Methenex^{R} (Bristol). This product is formulated to provide a ratio of 40 mg methadone HCl to 2 mg naloxone HCl. When given orally at the usual doses, the naloxone present does not interfere with the effects of methadone. However, administration of this mixture by injection results in significant reduction of the pleasing effects caused by methadone, thereby reducing the attractiveness of the mixture for abuse by injection(20).

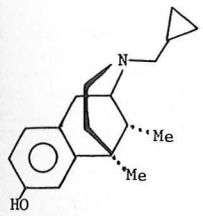
Pentazocine (Talwin^{R}, Winthrop). The only antagonist currently marketed as an analgetic is pentazocine. The presence of both agonist and antagonist activity in pentazocine has been demonstrated. As an analgetic it is 1/3 as potent as morphine on injection and roughly equipotent to codeine orally(21). Pentazocine has relatively weak antagonist activity, being 1/50 as potent as nalorphine in precipitating abstinence in subjects dependent on 240 mg/day of morphine(8). It is not used for treatment of narcotic overdoses. In general, pentazocine at the usual doses produces typical opiate CNS effects including analgesia, sedation and respiratory depression, but at higher doses produces nalorphine-like dysphoria (restlessness and anxiety)(10). It is well absorbed from the gastrointestinal tract and from subcutaneous and intramuscular sites. As is typical of mixed agonist-antagonists, pentazocine's dependence liability is low and withdrawal from chronically administered pentazocine has been judged 1/3 as severe as morphine. If pentazocine is administered to subjects dependent on opiates, the possibility of precipitating a withdrawal syndrome is present--the intensity of which is related to the level of dependence and the dose of pentazocine given. In patients receiving opiates on a regular basis, an opiate-free period of 1-2 days before pentazocine administration will usually suffice to prevent withdrawal effects. Pentazocine has the ability to depress respiration, and in cases of overdose the respiratory depression cannot be countered by nalorphine or levallorphan. Naloxone has been reported effective in this regard.

ANTAGONISTS IN NARCOTIC ADDICTION TREATMENT

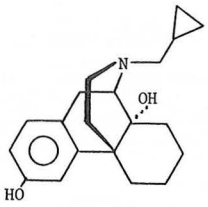
Narcotic antagonists were proposed some time ago for use by post-withdrawal addicts. Ideally, if these individuals are continuously taking sufficient amounts of a narcotic antagonist, the effects of ordinary doses of opiates are significantly reduced or blocked entirely.

duction of physical dependence is not possible in these circumstances. Further, if compulve opiate use is a result of reinforcement of drug seeking behavior due to euphoric effects of drugs, the use of antagonists should extinguish this behavior(22,23).

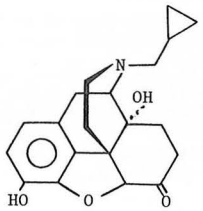
There are several unmarketed compounds presently being investigated as agents for treatment post-withdrawal addicts. These include cyclazocine, oxilorphan and naltrexone (see structures below).



Cyclazocine



Oxilorphan



Naltrexone

Cyclazocine. Cyclazocine has both potent agonist and antagonist activities. Cyclazocine injection is approximately 40 times more potent than morphine as an analgetic(24). Its agonist potency is slightly less than naloxone(16). Like nalorphine and levallorphan, cyclazocine is capable of producing marked respiratory depression. Although chronic administration of cyclazocine to human subjects produces an abstinence syndrome on abrupt withdrawal, the severity is mild compared to morphine.

In doses of approximately 4 mg/day orally, cyclazocine has been found to antagonize the effect of morphine administration for 24 hours--a mode of administration and duration of action suitable for use in post-withdrawal treatment programs(5,9,18). However, the compound produces dysphoria, hallucinations, irritability and sedation. Although these side effects increase in severity as the dose increases(25,26), they usually, but not always, disappear on continued administration. Tolerance does not develop to the antagonist activity(25). Cyclazocine's unpleasant side effects, particularly during induction, would appear to prevent its widespread clinical use(19,27).

Oxilorphan. Oxilorphan has weak agonist and predominant antagonist properties. It has an agonist potency similar to cyclazocine and it appears to have a long duration of action(28). It has been proposed for use in narcotic post-withdrawal treatment programs and studies are currently underway to determine the efficacy of oral administration, duration of antagonist activity and the level of side effects.

Naltrexone. Naltrexone is a pure antagonist with greater potency than naloxone. Having agonist properties, euphoria or physical dependence is not possible. In doses of 50-200 mg employed in clinical studies, negligible effects were observed(12,29). It is orally active and with moderate doses gives a duration of protection against opiate effects comparable to that achieved with cyclazocine(30). Little toxicity data is available for naltrexone, and studies are underway to determine its safety and utility for post-withdrawl treatment.

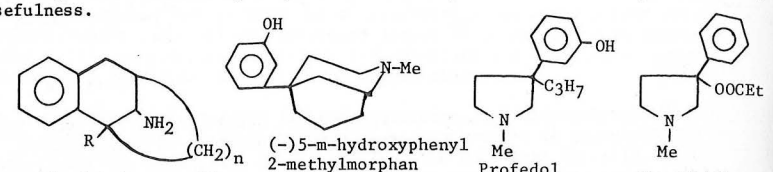
In summary, the results from studies investigating the efficacy of using an antagonist drug in the rehabilitation of addicts have not been impressive when compared to the methadone-maintenance approach--particularly with regard to the percentage of patients becoming socially productive and the attractiveness of the method to the addict population(18,27,31,38). Treat-

ment with antagonists appears to require a well motivated subject with a relatively moderate habit(27). The dysphoric effects of cyclazocine and oxilorphan probably will prevent these drugs from ever attaining widespread clinical use. Agents such as naloxone or naltrexone provide no euphoria or reinforcing properties for the former addict and, since this individual can no longer get relief from heroin when life seems intolerable, he may turn to other depressant drugs such as alcohol or barbiturates.

The authors can see two possible modes by which narcotic antagonists may someday become useful in drug rehabilitation therapy. The first of these would require that courts of law make participation in the programs mandatory for parolees whose criminal records are directly related to use of the opiate drugs. The second would require the development of a new antagonist which would both block the action of heroin, and induce pharmacological effects which are desirable enough to substitute for the drug response which the individual is seeking. Whether such a drug can be found remains to be seen.

CURRENT RESEARCH

All of the compounds discussed above have chemical structures closely related to morphine. In the continuing search for analgetics superior to morphine, simpler compounds with mixed agonist-antagonist properties are being investigated. The bridged aminotetralins(33), the levo-isomer of 5-m-hydroxyphenyl-2-methylmorphan(34), profedol(35), prodilidine(35), and viminol(36) are among these interesting compounds. However, none of these compounds have yet found clinical usefulness.

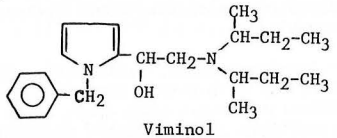


Bridged Aminotetralins

(-)5-m-hydroxyphenyl 2-methylmorphan

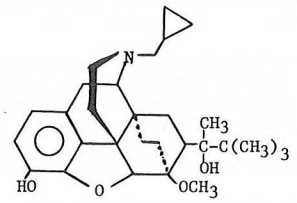
Profedol

Prodilidine



Viminol

Compounds of even more complex structure than morphine have been synthesized. Buprenorphine, a bridged derivative of thebaine, has been proposed for clinical trials because of promising pharmacological results in animals(37). The compound has shown potent agonist and antagonist activity in rodents. It does not produce physical dependence on chronic administration to mice or monkeys. In clinical studies at doses of 2 µg/kg intravenously or intramuscularly and 40 µg/kg orally, doses which have shown significant blockade of experimentally-induced pain, no signs of dysphoria were observed.



Buprenorphine

Current research to develop antagonists of long duration through modification of the dosage forms of existing antagonists is in progress. Most clinicians indicate a preference for an antagonist of several days or weeks duration, as this would require less motivation of former addicts in rehabilitation programs. In one study, to determine the feasibility of slow-release preparations of naltrexone, the drug was suspended in small particles of polylactide plastic. In dogs, a single dose blocked the effects of morphine for a period of 20-30 days(38). Alza Corporation, Palo Alto, California, is also examining the development of polymers that can be used with a variety of drugs, including naloxone, to provide slow release. At the present time, all these preparations require much further testing and clinical study to determine their safety and utility.

SUMMARY

The use of narcotic antagonists to counter life-threatening respiratory depression resulting from opiate overdose is well established. The role of antagonists in post-withdrawal management of the addict is yet to be determined. Certainly the antagonists should not be regarded as the answer to opiate abuse, but rather as a potentially powerful tool to aid the clinician and social worker in the overall treatment of narcotic drug dependence. Researchers continue to intensively investigate the antagonists not only with the hope of discovering more effective agents for the treatment of heroin-like drug dependence, but also of finding a strong analgetic, free of side effects and without potential for dependence.

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NEWS AND COMMENT

A new street-drug analysis laboratory. Further information may be obtained by writing to:

The Branan Drug Analysis and Toxicology Laboratory,
345 Boulevard, N. E.
Altlanta, Georgia 30312 Telephone (404) 688-4400

An excellent publication has just come to our attention and we are listing it because it does seem to fulfill a need in toxicology.

Charles L. Winek, Editor and Sydney P. Shanor, Assistant Editor

TOXICOLOGY ANNUAL 1974
New York NY: Marcel Dekker, Inc., 1975

A very interesting article related to the topic in this issue of the BULLETIN is in the above publication.

R. H. McDonald. "NARCOTIC DRUG DEPENDENCE." In TOXICOLOGY ANNUAL 1974. pp. 91-127.

Another publication has come to our attention (we have not seen a copy) that could be very useful in street-drug analysis.

N. H. Choulis. IDENTIFICATION PROCEDURES OF DRUGS OF ABUSE.

Publisher etc., not available - - write to:

Professor N. H. Choulis
School of Pharmacy
West Virginia University
Morgantown, West Virginia 26506