5-1-1976

Pacific Information Service on Street-Drugs May 1976

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

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

This review is an attempt to explain the current status of narcotic antagonists as they relate to drug therapy (treatment of opiate overdose) and drug abuse (management of the postwithdrawal opiate addict). All individuals using these agents should have a thorough understanding of their pharmacological actions. These narcotic antagonists are currently the most specific antidote available for heroin overdose and act within seconds of injection. They are life 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 clinically useful antagonists have resulted from the replacement of the N-methyl group on the parent narcotic with an N-allyl or N-methylcyclopropyl group. The structures and names of these narcotic antagonists that are currently available are given in Table I.

In general, antagonists with an N-methylcyclopropyl (as in cyclozocine) group have a longer duration of action than those with an N-allyl moiety (nalorphine, naloxone, and levallorphan). Introduction of hydroxyl at the 4-position of the morphine nucleus (as in naloxone) imparts a stronger and purer antagonistic activity. The 4-5 ether bridge in nalorphine or naloxone does
### Table I. Currently Marketed Narcotic Antagonists

<table>
<thead>
<tr>
<th>Structure</th>
<th>Parent Narcotic</th>
<th>Narcotic Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Nalorphine" /></td>
<td>Morphine</td>
<td>Nalorphine (Nalline)</td>
</tr>
<tr>
<td><img src="image" alt="Oxymorphone" /></td>
<td>Oxymorphone</td>
<td>Naloxone (Narcan)</td>
</tr>
<tr>
<td><img src="image" alt="Levorphanol" /></td>
<td>Levorphanol</td>
<td>Levallophan (Lorfan)</td>
</tr>
<tr>
<td><img src="image" alt="Metazocine" /></td>
<td>Metazocine</td>
<td>Pentazocine (Talwin)</td>
</tr>
</tbody>
</table>

**Numbering of Morphine Ring System**

### Pharmacology

Narcotic antagonists are capable of reversing effects such as analgesia, sedation, euphoria, gastrointestinal effects, and the frequently lethal respiratory depression caused by morphine and its surrogates. These antagonists are specific in that they will not reverse depressions resulting from other classes of drugs such as barbiturates. They are also worthless in treating overdosage with stimulants (such as cocaine and the amphetamines). However, naloxone has recently been reported to reverse the effects of large doses of diazepam (Valium)\(^8\)\(^7\).

Nalorphine and levallorphan are termed partial-antagonists or mixed agonist-antagonists for the following reasons. When these agents are administered to normal persons, they mimic to varying degrees the effects seen with morphine administration (agonist effects). However, when these agents are given to persons dependent on opiates or who have opiates present in their systems, these partial antagonists "reverse" the effects of the opiate. Naloxone displays very little if any agonist effects when given to normals and is therefore termed a pure antagonist. Although pentazocine is a mixed agonist-antagonist, its antagonist component is weak and it is not useful in cases of narcotic overdose. It is used primarily as an analgesic.

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

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

It should be emphasized again that these antagonists will not reverse respiratory depression caused by the barbiturates. In fact, nalorphine and levallorphan may even worsen barbiturate-induced or alcohol-induced respiratory depression because of their agonist activity. In overdosage, if the cause of respiratory depression is not clear, or if drugs in addition to barbiturates are suspected in the depression, naloxone is indicated since it produces no respiratory depression of its own. It should also be cautioned that administration of any antagonist to addicts may precipitate a severe withdrawal syndrome which can be more dangerous than the respiratory depression; however, administration of the antagonists in a period of 1 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 duration of the antagonist may be shorter than the narcotic causing the respiratory depression. The effects of the antagonist may wear off before those of the narcotic, and life-threatening respiratory depression may again result, requiring the administration of more antagonist. Overdosed patients should always be under qualified medical supervision.

Nalorphine (Nalline HCl\(^7\), Merck, Sharp and Dohme). Nalorphine shows little evidence of analgetic activity in most animal studies except in the rat. However, in man it is as potent analgetic as morphine\(^11\). As is typical of partial agonists, "addiction" liability is low compared to morphine or heroin. Unfortunately, the compound produces psychotomimetic effects at analgetic doses.

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

Nalorphine is useful in the treatment of narcotic overdose to combat the severe respiratory depression caused by morphine, codeine, heroin, and similar agents. Nalorphine has also...
Ideally, if these individuals are continuously taking sufficient amounts of a narcotic, vent withdrawal effects. An opiate-free period of 1-2 days before pentazocine administration will usually suffice. Dependence and the dose of pentazocine given. In patients receiving opiates on a regular basis, detoxification is present—the intensity of which is related to the level of side effects. The presence of opiate in the urine is preferable both medically and in courts of law.

Levallorphan (TartrateRoche). Levallorphan has twice the potency of nalorphine as an antagonist and has comparable analgesic potency. 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 (NarcanEndo). Naloxone is approximately 7 times more potent than nalorphine as an antagonist. It produces negligible side effects in normal subjects at therapeutic doses. Naloxone will inhibit or reverse the effects of all opiate agonists such as morphine, heroin, methadone, propoxyphene (Darvon) and meperidine (Demerol). Unlike nalorphine and levallorphan, naloxone is an effective antagonist of the respiratory depression caused by pentazocine and other agonists. 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) and poor oral activity (1-3 grams/day are required to protect against the effects of heroin for 24 hours) 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 (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 pleasurable effects caused by methadone, thereby reducing the attractiveness of the mixture for abuse by injection.

Pentazocine (TalwinWinthrop). The only antagonist currently marketed as an analgesic in penta-zocine. The potency of both agonist and antagonist activity in pentazocine has been demonstrated. As an analgesic it is 1/3 as potent as morphine on injection and roughly equipotent to codeine orally. 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. 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). 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.
Current research to develop antagonists of long duration through modification of the dosage 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 formulations of naloxone, the drug was suspended in small particles of polyacrylate plastic. In this way, 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 to slow the release 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 of side effects and without potential for dependence.

**REFERENCES**

- Weltjard, J. and Erickson, A.E., ibid., 64, 869 (1942).
10.


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.
Atlanta, 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.

H. R. 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:
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Pacific Information Service on Street-Drugs
Volume 5, No. 5
May, 1976