HUMAN PHARMACOLOGY OF NARCOTIC ANTAGONISTS

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- 1 Human studies at the Addiction Research Center enable narcotic antagonists to be classified into three subgroups: (1) nalorphine-like agents; (2) pure antagonists; and (3) morphine-like agents.
- 2 Six narcotic antagonists (pentazocine, nalbuphine, cyclazocine, butorphanol, propiram and buprenorphine) developed in recent years seem to have a lesser abuse potential than codeine or propoxyphene.
- 3 When adjusted for relative availability of the agents, epidemiological data shows that pentazocine is abused less than codeine or propoxyphene in the US.
- 4 Recent studies with buprenorphine indicate that this agent would find application both as an analgesic of low abuse potential and as a new type of drug for the treatment of addiction.

Introduction

STUDIES of the human pharmacology of narcotics and narcotic antagonists at the Addiction Research Center have been primarily directed towards assessing the liability of analgesics to produce morphine-like abuse (Jasinski, 1977). These studies were carried out using volunteer prisoners with histories of abuse of heroin and other opioids. Acute administration of morphine and other opioids to non-tolerant members of this population results in a characteristic alteration of mood, feeling states, and perceptions that include feelings of well-being termed 'euphoria'. Chronic administration results in a state of physical dependence such that withdrawal of the drug results in characteristic physiological and psychological changes that are discomforting and lead to drug-seeking behaviour. Methods have been developed to measure validly these two effects of morphine in the addict population, and valid predictions of the relative abuse liability of morphine-like drugs can be made from the results of such studies (Jasinski, 1977).

On the other hand, studies of the two prototypic narcotic antagonists nalorphine and cyclazocine have indicated that these two drugs do not produce morphine-like effects in addicts (Martin *et al.*, 1965). Acute administration most often produces apathetic sedation accompanied by nervousness, thought disorders, and irritability which can progress to a toxic psychosis. Chronic administration produces a type of physical dependence distinct from that produced by morphine in that the withdrawal symptoms are not discomforting and do not lead to drug-seeking behaviour in the addict population. Unlike morphine-like drugs, nalorphine and cyclazocine will not suppress morphine abstinence but will precipitate morphine abstinence.

From human studies at the Addiction Research Center, the narcotic antagonists can be grouped into three classes (Jasinski, 1977): (1) those compounds which produce agonistic effects that resemble nalorphine and cyclazocine; (2) those compounds that do not produce agonistic effects (naloxone and naltrexone); and (3) those antagonists that produce agonistic effects that resemble those of morphine (the partial agonists of morphine).

Six narcotic antagonists have been introduced into therapeutics as analgesics of low abuse potential (Figure 1). With the exception of propiram, all are structural congeners of morphine containing substitutions on the nitrogen. Pentazocine, nalbuphine, cyclazocine and butorphanol produce nalorphine-like subjective effects and physical dependence. Propiram and buprenorphine are partial agonists of morphine.

All six drugs are effective clinical analgesics but differ in milligram-for-milligram relative potency (Table 1). With the exception of butorphanol, all drugs are antagonists of morphine in man, again differing in milligram-for-milligram potency (Table 1). In our studies, the morphine antagonistic activity of butorphanol could not be demonstrated (Jasinski *et al.*, 1975). Doses of butorphanol to 8 mg did not precipitate abstinence in morphine-dependent subjects, and larger doses could not be administered because of limiting psychotomimetic effects.

Conclusions from assessment studies at the Addiction Research Center have indicated that all six drugs (pentazocine, nalbuphine, cyclazocine, butorphanol, propiram and buprenorphine) have a lesser abuse potential than codeine or propoxyphene

Figure 1 a, Pentazocine; b, cyclazocine; c, nalbuphine; d, butorphanol; e, propiram; f, buprenorphine.

(Jasinski *et al.*, 1976; Jasinski, 1977; Jasinski *et al.*, 1978).

With this background, the remainder of this presentation will discuss three topics of both clinical and theoretical importance: (1) the abuse of

pentazocine; (2) the differences among the agonistic effects of nalorphine-like drugs; and (3) the pharmacology of buprenorphine, the most recent drug to be studied.

Originally Fraser *et al.* (1964) have concluded that pentazocine does not produce morphine-like effects in addicts and has an abuse potential less than that of morphine and equal to that of propoxyphene. Shortly after the introduction of pentazocine into clinical practice, case reports detailing its abuse appeared. Jasinski *et al.* (1970) re-evaluated the abuse liability of pentazocine and found that, in contrast to nalorphine, therapeutic doses of pentazocine produced morphine-like euphoria in addicts and withdrawal symptoms that produced a slight degree of discomfort and led to some drug-seeking behaviour. Jasinski *et al.* (1970) concluded that pentazocine had an abuse potential greater than that of nalorphine or cyclazocine but less than that of propoxyphene and codeine.

Jasinski (1977) has reviewed the reported incidence of abuse of morphine-like drugs to validate the methods used for assessing morphine-like abuse potential. A critical factor in interpreting data on abuse incidence is the availability of the drug relative to the standard agent (Jasinski, 1977). This estimated relative

Table 1 Relative potency estimates for clinical analgesia and morphine antagonist activity in man

	Equivalent analgesic doses (mg)	Equivalent morphine antagonist doses (mg)
Morphine*	1.0	—
Nalorphine*	1.0	1.0
Cyclazocine*	0.025 (approx.)	0.2
Nalbuphine*	1.0	4.0
Butorphanol†	0.2	?
Pentazocine*	4.0	50.0
Propiram*	9.0	192.0
Buprenorphine‡	0.04	0.1 (approx.)

* See Jasinski (1977) for reference.

† See Jasinski *et al.* (1975) for reference.

‡ See Jasinski *et al.* (1978) for reference.

availability was calculated by adjusting the aggregate US production by parenteral potency estimates and expressing the aggregate US production in terms of morphine equivalence. Examination of these data for codeine, propoxyphene and pentazocine indicates that, when adjusted for relative availability, the abuse of pentazocine is less than that of codeine or propoxyphene (Table 2). The one exception is the report from the Mayo Clinic of prescription drug abuse (Table 2). However, the numbers of cases in this survey (codeine 17; propoxyphene 14; pentazocine 32) are small and the data emanated only from one institution. The most recent report from the DAWN system (Project DAWN V, May 1976 to April 1977) has indicated that the incidence of mentioning pentazocine emanating from crisis centres, emergency rooms and medical examiners continues to be less than that for codeine or propoxyphene (Table 3).

Studies of the subjective effects of morphine-like, amphetamine-like and pentobarbital-like drugs indicate that within each of these three classes of drugs there is little difference among the subjective changes (Martin *et al.*, 1971; Jasinski *et al.*, 1976; Jasinski, 1977; Jasinski *et al.*, 1977). In contrast, drugs having nalorphine-like agonistic effects can be distinguished in terms of their subjective effects even though all

produce the sedative and psychotomimetic profile of nalorphine and cyclazocine. First, pentazocine is more reliably euphorogenic than nalorphine (Jasinski *et al.*, 1970). Secondly, 8 mg nalbuphine produces a degree of subjective changes, miosis and analgesia equivalent to that produced by 10 mg morphine (Jasinski & Mansky, 1972). Increasing the dose of nalbuphine ninefold to 72 mg produces only minimal psychotomimetic effects (Jasinski & Mansky, 1972), whereas a two- to three-fold increase in doses of pentazocine (Jasinski *et al.*, 1970), cyclazocine (Martin *et al.*, 1965), butorphanol (Jasinski *et al.*, 1975) and nalorphine (Martin *et al.*, 1965) that are equianalgesic and equimiotic to 10 mg morphine produces dose-limiting psychotomimetic effects. Thirdly, a crossover comparison of subjective effects of pentazocine, butorphanol and cyclazocine has indicated that there is no concordance in potency estimates for simultaneously measured sedation, euphoria, psychotomimetic effects and miosis, suggesting differences among these three agents (Jasinski *et al.*, 1975). Another observation indicated that this class of agents can differ in intrinsic activity in man. The administration of a large dose of nalorphine (40 mg) precipitated abstinence in subjects physically dependent on butorphanol (48 mg daily) (Jasinski *et al.*, 1976).

Table 2 Estimated relative availability and relative abuse incidence of pentazocine, propoxyphene and codeine *

	Pentazocine	Propoxyphene	Codeine
Availability (1973)†	0.9	1.9	1.0
DAWN mentions (1973-1975)‡	0.4	2.2	1.0
General population of men age 20-30 yr (1974-1975)‡	0.1	1.3	1.0
Mayo Clinic admissions (1966-1972)‡	1.8	1.2	1.0
Lexington civilly committed addicts (1968-1969)‡	0.2	1.0	1.0

* See Jasinski (1977) for original data and references.

† Availability expressed as ratio of morphine equivalence 1973 US aggregate production of pentazocine and propoxyphene to morphine equivalence 1973 US aggregate production of codeine.

‡ Relative abuse incidence expressed as ratio of total mentions for pentazocine and propoxyphene to total mentions for codeine.

Table 3 Relative abuse incidence of pentazocine, propoxyphene and codeine reported in project DAWN V (May 1976 to April 1977) *

	Pentazocine	Propoxyphene	Codeine
Emergency rooms	0.9	4.0	1.0
Crisis centres	0.6	1.9	1.0
Medical examiners	0.2	2.6	1.0

Numbers represent the ratio of mentions for pentazocine and propoxyphene to mentions for codeine. Relative availability data for this period have not been determined.

* See US Department of Justice, Drug Enforcement Administration (1977) for reference.

Taken together, these observations indicate that: (1) drugs having nalorphine-like effects are not a homogeneous class; (2) among these drugs, there are inherent differences in their abilities to produce euphoria, sedation and psychotomimetic effects; and (3) these agents can differ in intrinsic activities in man.

Recent studies of the partial agonist buprenorphine have indicated that this drug has an especially unique pharmacology in man (Jasinski *et al.*, 1978). In single doses, buprenorphine constricts pupils and produces morphine-like subjective effects and euphoria. In a dose range of 0.2-0.8 mg, buprenorphine is 25-30 times more potent than morphine. Larger doses of buprenorphine may be less effective relative to morphine. Like methadone, a single dose of buprenorphine constricts pupils and produces sedation for 72 h, but is an

effective analgesic and euphoriant for only 4-6 hours. When given chronically, buprenorphine produces very little physical dependence with clinically significant withdrawal symptoms and signs occurring only after 14 d of abrupt withdrawal. These findings indicate that buprenorphine would not only have a therapeutic application as an analgesic of low abuse potential but also as a new type of drug for treatment of narcotic addiction (Jasinski *et al.*, 1978).

In summary, this survey of the human pharmacology of the morphine antagonists has attempted to convey the practical conclusion that six drugs from this class have been introduced into therapeutics, all with a low abuse potential but each with a unique pharmacology.

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