Psychopharmacology (1987) 91:273–278

Psychopharmacology

A comparative assay of nefopam, morphine and *d*-amphetamine

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Abstract. Nefopam is a non-opioid analgesic reported to have some stimulant properties. The subjective, behavioral and physiological effects of nefopam, morphine and *d*-amphetamine were compared in seven non-dependent substance abusers to assess the abuse potential of nefopam. Morphine and *d*-amphetamine had significant effects on a number of measures generally consistent with the effects of drugs of the opioid and psychomotor stimulant drug classes. Subjects correctly discriminated between morphine and *d*-amphetamine. Nefopam was most frequently identified by subjects as being amphetamine-like, though several measures indicated that nefopam produced some sedation. Little or no "liking" of the effects of nefopam was reported by subjects. Overall, nefopam was one fifth as potent as morphine and one quarter as potent as *d*-amphetamine in producing subjective and physiological effects. The results indicate that nefopam is neither entirely morphine-like nor *d*-amphetamine-like. In our opinion, nefopam has a lesser potential to be abused than morphine or *d*-amphetamine.

Key words: Nefopam – Morphine – *d*-Amphetamine – Abuse potential

Nefopam hydrochloride, a cyclized analogue of diphenhydramine, is a novel analgesic which is active both orally and parenterally (Gassel et al. 1976). Nefopam was initially studied for antiparkinsonian effects under the name fenazoxine (Bassett et al. 1969) and was later renamed nefopam and tested for muscle relaxant properties (Klohs et al. 1972; Tobin and Gold 1972). Subsequently, nefopam was demonstrated to relieve clinical pathological pain (Sunshine and Laska 1975).

The mechanism of the analgesic activity of nefopam is unknown. Nefopam does not appear to act directly through opioid receptors, since it is a weak inhibitor of ^{3}[H]naloxone binding, does not exhibit cross tolerance to morphine, and does not antagonize morphine analgesia (Conway and Mitchell 1977; Tresnak-Rustad and Wood 1981). In addition, naloxone does not antagonize nefopam-induced analgesia (Piercey and Schroeder 1981; Vonvoightlander et al. 1983). Nefopam also does not act as an anti-inflammatory analgesic, since it does not inhibit prostaglandin synthesis except at very high doses (Conway and Mitchell 1977). Biochemically, nefopam is more similar to the psychomotor stimulants and antidepressants than to the opioids (Bassett et al. 1969; Tresnak-Rustad and Wood 1981). Nefopam blocks the synaptosomal uptake of dopamine, norepinephrine and serotonin (Tresnak-Rustad and Wood 1981), and its analgesic effects are blocked by reserpine (Vonvoightlander et al. 1983). Although nefopam blocks biogenic amine uptake, its spectrum of analgesic activity in a variety of experimental pain models in animals is more similar to that of amphetamine than to that of the tricyclic antidepressants or serotonin uptake blockers (Vonvoightlander et al. 1983).

The purpose of the present study was to evaluate the euphorigenic potential and other subjective, behavioral and physiological effects of nefopam in substance abusers and to compare its effects to those of morphine, a prototypic opioid analgesic, and *d*-amphetamine, a prototypic psychomotor stimulant in order to assess the abuse potential of nefopam.

Materials and methods

Subjects. Subjects were non-dependent, adult, male, volunteer prisoners. All subjects had histories of long-term polydrug abuse predominated by opioid abuse. At the time of this study they were incarcerated at the Addiction Research Center at Lexington, Kentucky. On the basis of physical examination, history, and laboratory chemistries, subjects were found to be without significant medical or psychiatric disturbance other than their drug abuse. Subjects participated in experimental sessions in pairs and were brought to the research ward the evening before and returned to their regular quarters within the prison the day after each experimental session. Subjects gave their informed consent prior to beginning the study and were paid for their participation. Ten subjects were enrolled in the study. Seven subjects completed the study.

General methods. Subjects were each given the seven following treatments under double-blind conditions: nefopam hydrochloride (40 and 80 mg), morphine sulfate (10 and

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Table 1. Items on the MBG, PCAG, and LSD scales from the Addiction Research Center Inventory (Jasinski 1977). Items are answered as true or false. Items marked with an asterisk are contained in more than one scale but are scored for the appropriate scale depending upon the positive or negative answers

Morphine-Benzedrine group (MBG) – 16 items
*I would be happy all the time if I felt as I do now
I feel as if I would be more popular with people today
Today I say things in the easiest possible way
*I feel more clear-headed than dreamy
Things around me seem more pleasing than usual
I have a pleasant feeling in my stomach
I feel a very pleasant emptiness
I fear that I will lose the contentment I now have
I feel in complete harmony with the world and those about me
I feel less discouraged than usual
I can completely appreciate what others are saying when I am in this mood
I would be happy all the time if I felt as I feel now
*I am full of energy
I am in the mood to talk about the feeling I have
I feel so good that I know other people can tell it
I feel as if something pleasant had just happened to me
Pentobarbital-Chlorpromazine-Alcohol group (PCAG) – 15 items
*My speech is slurred
I am not as active as usual
I have a feeling of just dragging along rather than coasting
*I feel more clear-headed that dreamy (answered negatively)
I feel sluggish
*A thrill has gone through me one or more times since I started the test (answered negatively)
My head feels heavy
I feel like avoiding people although I usually do not feel this way
I feel dizzy
*I am full of energy (answered negatively)
People might say that I am a little dull today
It seems harder than usual to move around
I feel more excited than dreamy (answered negatively)
I am moody
*I feel drowsy
LSD-Specific (LSD) – 14 items
I have a weird feeling
I have a disturbance in my stomach
*I would be happy all the time if I felt as I do now
*A thrill has gone through me one or more times since I started the test
My movements are free, relaxed, and pleasurable
I feel very patient (answered negatively)
I have unusual weakness of my muscles
Some parts of my body are tingling
It seems I'm spending longer than I should on each of these questions
My hands feel clumsy
I notice my hand shakes when I try to write
*I feel drowsy (answered negatively)
I feel an increasing awareness of bodily sensations

20 mg), *d*-amphetamine sulfate (15 and 30 mg) and saline placebo. Drugs were administered intramuscularly in randomized order at intervals of not less than 7 days.

Miosis and subjective and behavioral effects were measured using standard procedures previously described (Jasinski 1977). Baseline observations consisting of rectal temperature, respiratory rate, pulse rate, blood pressure, and pupil photographs for determination of baseline pupil diameter were obtained at 0800 and 0830 hours each test day. At 0900 hours, the drug treatment was administered. At 0930, 1000, 1100, 1200, 1300, 1400, 2100 hours and again at 0900 hours the following morning, physiological measures were repeated. At these same post-drug intervals, subjective and behavioral effects were measured.

Subjective effects were measured by the following questionnaires completed by the subjects: the Single Dose Questionnaire and a 40-item true/false questionnaire containing three scales from the Addiction Research Center Inventory, the Morphine-Benzedrine Group (MBG) which measures euphoria, Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) which measures sedation, lethargy, etc., and the LSD specific group (LSD) which measures dysphoric effects. Items on the MBG, PCAG and LSD scales are listed in Table 1. Behavioral effects were assessed with the observers' Single Dose Questionnaire. The subjects' and observers' Single Dose Questionnaires consisted of (1) a "feel drug" question [to indicate whether or not the subject had received an active drug; answered yes or no], (2) a drug identifica-

Table 2. Total cumulative drug identifications by subjects and observers in the single dose opiate questionnaires for the comparison of nefopam, morphine, *d*-amphetamine, and placebo. The maximum number of responses for each drug category is 42 (seven subjects and six post-drug observations for each condition)

		Morphine		*d*-Amphetamine		Nefopam	
	Placebo	10 mg	20 mg	15 mg	30 mg	40 mg	80 mg
Subjects identification							
Blank (placebo)	41	21	4	34	10	31	19
Dope (opiate)	–	12	17	–	1	3	–
Amphetamine	–	6	9	8	21	2	17
Other	1	4	14	–	10	6	6
Observers identification							
Blank (placebo)	28	13	4	18	1	18	7
Dope (opiate)	14	24	35	2	11	16	4
Amphetamine	–	5	–	21	28	4	29
Other	–	1	5	8	6	6	3

There were no cocaine, marijuana, barbiturate, alcohol, LSD, thorazine, or Librium identifications by subjects or observers. More than one drug category could have been identified at each observation

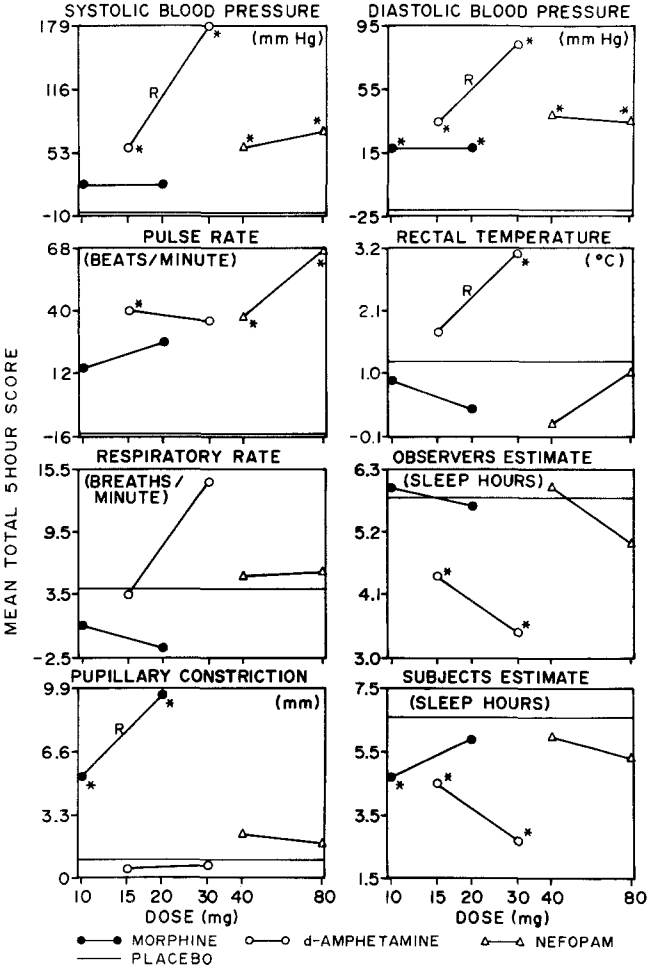

Fig. 1. Dose response curves for intramuscularly administered placebo, nefopam, morphine, and *d*-amphetamine. Each point represents the mean total 5 h change from control for blood pressure, pulse rate, respiratory rate, rectal temperature, and pupillary constriction or mean total hours subjects were judged asleep by observers or subjects. *Asterisks* represent a significant difference ($P<0.05$) from placebo. *R* represents a significant ($P<0.05$) regression of response on dose

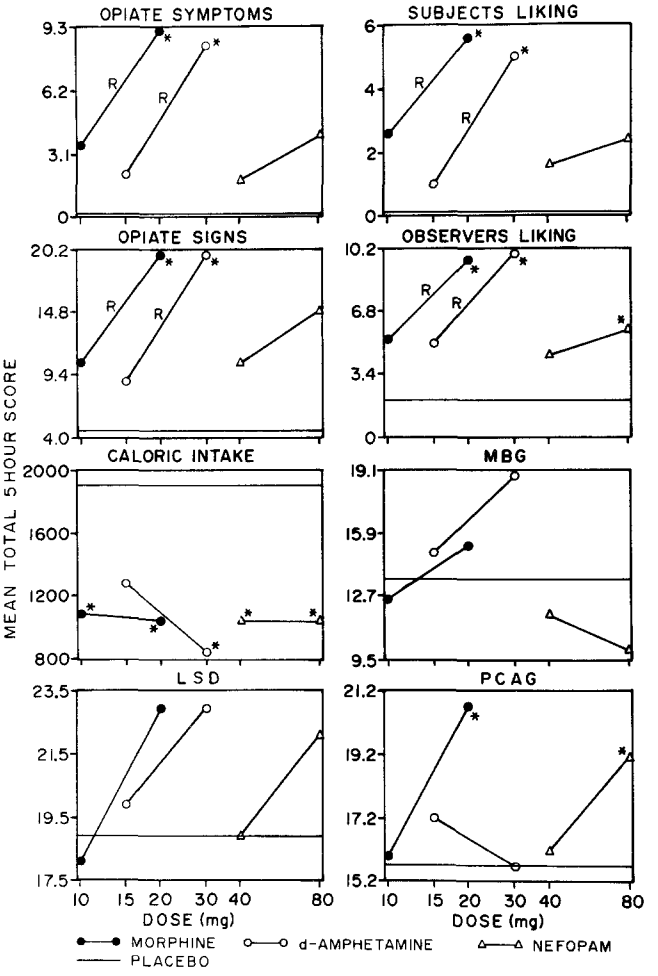

Fig. 2. Dose response curves for intramuscularly administered placebo, nefopam, morphine, and *d*-amphetamine. For all measures except caloric intake, each point represents the mean total 5 h score. Caloric intake represents the mean number of calories estimated in the three meals following drug administration. *Asterisks* represent a significant difference ($P<0.05$) from placebo. *R* represents a significant ($P<0.05$) regression of response on dose

Table 3. Total cumulative responses by subjects and observers to individual symptom and sign items in the single dose questionnaires for the comparison of nefopam, morphine, *d*-amphetamine, and placebo. The maximum number of responses for any category is 42 (seven subjects and six post-drug observations for each drug condition

		Morphine		*d*-Amphetamine		Nefopam	
	Placebo	10 mg	20 mg	15 mg	30 mg	40 mg	80 mg
Symptoms							
Normal	41	21	4	34	10	31	19
Turning of the stomach	–	–	21	6	8	1	5
Skin itchy	–	–	10	–	–	–	–
Relaxed	–	17	14	7	19	11	10
Coasting	–	–	6	1	8	–	1
Soapbox	–	–	6	–	6	–	–
Pleasant sick	–	–	–	–	7	–	–
Drive	–	–	6	–	7	1	2
Sleepy	–	1	–	–	–	–	–
Drunk	–	–	–	–	–	–	5
Nervous	–	–	–	1	–	1	3
Other	1	7	1	–	5	–	–
Signs							
Normal	28	13	4	18	1	18	7
Scratching	1	10	25	–	11	2	7
Red eyes	–	5	8	2	–	8	3
Relaxed	14	28	38	24	40	24	32
Coasting	–	3	15	2	13	9	11
Soapbox	10	9	22	14	28	14	10
Vomiting	–	–	1	–	–	1	–
Nodding	–	–	–	–	–	–	1
Sleepy	–	3	4	–	5	6	10
Nervous	4	6	11	13	19	8	23
Drunken	–	–	–	–	–	–	–
Other	3	8	14	8	20	1	7

tion question [to indicate what kind of drug had been given; answered by checking the appropriate drug on a list of drugs], (3) a list of opiate symptoms (subject form) and signs (observer form) [answered by placing a check mark next to the appropriate symptom or sign to indicate its presence], and (4) a liking scale [rated on a scale from 0 (not at all) to 4 (an awful lot) or as "other"]. The items on the subjects' opiate symptoms scale and observers' opiate signs scale from the Single Dose Questionnaires are listed in Table 2. In addition, on the day of each session observers recorded the caloric value of food chosen by each subject and the amount of food eaten at the noon meal, evening meal, and again at breakfast the next day. This information was used to estimate caloric intake (Jasinski et al. 1974). Sleep time was estimated by observing patients at 30 min intervals between 2200 and 0600 hours the night following drug administration. Subjects were asked to estimate sleep time the morning following drug administration.

Drugs. Doses of morphine sulfate, nefopam hydrochloride, and *d*-amphetamine sulfate, weighed as the salts, were dissolved in normal saline. Doses were administered in a constant volume of 2 ml. Normal saline (2 ml) served as placebo.

Data analysis. To measure drug effects, responses for the first six observations following drug administration were summed and expressed as total 5-h scores for the questionnaire measures and as total 5-h changes from the mean of two control measures for the physiologic observations. Observers' sleep estimates are given in mean total hours that subjects were judged asleep by observers in 17 observations made at 30 min intervals the night following drug administration. Caloric intake is reported as mean estimated number of calories consumed in the three meals following drug administration (lunch, dinner, breakfast). Mean responses for each measure were compared with a repeated measures analysis of variance; relative potencies were then calculated using methods for parallel line assays (Finney 1964). An approximation of the average response over the first 5 h can be calculated by dividing by 6 the values shown on the graphs of mean total 5 h scores.

Results

Figure 1 shows the dose-response curves for the effects of morphine, *d*-amphetamine and nefopam on the physiological and sleep measures. Nefopam and *d*-amphetamine significantly increased systolic blood pressure and pulse rate; morphine had no effect on these measures. All three drugs increased diastolic blood pressure. None of the drugs changed respiratory rate. Morphine produced pupil constriction, while *d*-amphetamine and nefopam had no significant effect on pupil size. Only *d*-amphetamine increased body temperature and decreased both subjects' and observers' estimates of hours of sleep. Morphine 10 mg significantly decreased subjects' estimate of sleep time; otherwise, however, neither morphine nor nefopam had significant effects on body temperature or on sleep time estimates. Both doses of each of the three active drugs significantly decreased caloric intake during the first meal (lunch) following drug administration. Over the 24-h period following drug

Table 4. Potencies with 95% confidence limits of nefopam relative to morphine and *d*-amphetamine. Relative potencies expressed as mgs of morphine and *d*-amphetamine equivalent to 1 mg nefopam. All assays met the statistical criteria for validity

Measures	Morphine	*d*-Amphetamine
Symptoms	0.13 (0.01–0.25)	0.25 (0.03–0.46)
Signs	0.19 (0.01–0.46)	0.32 (0.09–0.66)
LSD	0.25 (0.15–0.41)	0.30 (0.06–0.61)
PCAG	0.22 (0.10–0.39)	–
Subject's liking	–	0.28 (0.06–0.51)
Observer's liking	0.22 (0.02–0.38)	0.21 (0.02–0.38)
Mean potency[a]	0.20	0.27

[a] Calculated as the geometric mean of the valid potency estimates for the measures listed above

adminstration (Fig. 2) *d*-amphetamine did so only at the higher dose (30 mg).

On the Single Dose Opiate questionnaire subjects consistently distinguished *d*-amphetamine from morphine (Table 2). Nefopam was identified more frequently as an amphetamine than as an opiate. Total cumulative responses by subjects and observers to individual symptom and sign items in the single dose questionnaires are shown in Table 3. There were only minor differences in the profiles of symptoms and sign responses among nefopam, morphine and *d*-amphetamine. Nefopam produced fewer "coasting" (a street term for feelings of detachment) and "soapbox" (a street term for talkativeness or feeling a "need to talk") responses and more "drunk" responses than morphine or *d*-amphetamine on the symptoms list.

Overall, morphine and *d*-amphetamine, but not nefopam, significantly increased scores on the opiate symptom, opiate sign, and subjects' liking scales (Fig. 2). Nefopam, like morphine and *d*-amphetamine, did produce significant scores on the observers' liking scale. None of the drugs produced significant changes in MBG or LSD scale scores; however, nefopam and morphine did produce significant increases on the PCAG scale. Relative potencies calculated from the mean total 5 h scores indicated that nefopam was approximately one fifth to one quarter as potent as morphine and one quarter to one third as potent as *d*-amphetamine in producing subjective and behavioral effects (Table 4). Nefopam produced only very low subjects' liking scale scores and did not meet the statistical criteria for the determination of a valid relative potency to morphine.

The time course of the effects of nefopam was shorter than the time courses of morphine and *d*-amphetamine (Fig. 3). Nefopam's effects on most measures peaked at 1–2 h and dissipated by 3–4 h. In contrast, the effects of morphine and *d*-amphetamine were well maintained through the first 5 h after drug administration. Only the time course of the observer-rated opiate signs showed a similar time course for all three study drugs.

Discussion

The results of this study indicate that nefopam produces a profile of effects which is similar in some respects to both *d*-amphetamine and to morphine, but identical to neither. Nefopam produced increased systolic and diastolic blood pressure and pulse, lacked an effect on pupillary constriction and was identified by subjects as amphetamine. On the other hand, like morphine, nefopam differed from *d*-amphetamine in that nefopam had little or no effects on estimated sleep time and body temperature, and increased PCAG (sedative) scale scores. Overall, however, nefopam appeared to be more similar to *d*-amphetamine than to morphine.

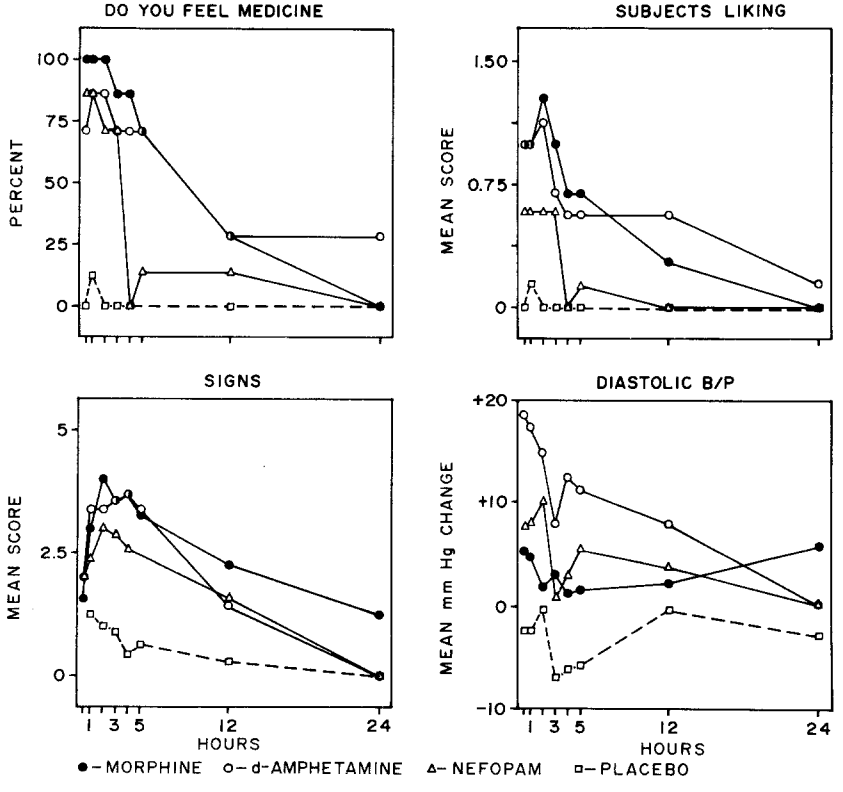

Fig. 3. Time action curves for comparison of nefopam 80 mg, *d*-amphetamine 30 mg, morphine 20 mg, and placebo. For the "do you feel medicine" question, subjects's liking and opiate signs, each point represents the mean response. For diastolic blood pressure (B/P), each point represents the mean change in blood pressure from pre-drug controls

Nefopam did not produce significant subjects' liking scores and produced opiate signs, symptoms and observers' liking scores which were generally lower than those produced by morphine and *d*-amphetamine. Overall, nefopam was one fifth as potent as morphine in producing morphine-like effects as measured in the present study. In previous studies of intramuscularly administered nefopam and morphine in the treatment of postoperative and related pain, nefopam has been shown to be one half to one third as potent as morphine in reducing pain (Sunshine and Laska 1975; Beaver and Fiese 1977). At the doses tested nefopam, therefore, is relatively less potent in producing morphine-like subjective effects than in producing analgesia. Nefopam was identified by subjects as an opiate on only three out of 42 occasions in the present study. Using a behavioral pharmacology paradigm, Frey and Winter (1979) showed that rats trained to discriminate between saline and morphine did not identify nefopam as being like morphine. Based on available experimental evidence, in our opinion, nefopam does not produce a profile of effects typical of morphine-like drugs and at equianalgesic doses has less potential for abuse than morphine.

Although nefopam was frequently identified as amphetamine, it was much less potent than *d*-amphetamine in producing subjective and behavioral effects (approximately one quarter as potent overall). In addition, nefopam, but not *d*-amphetamine, increased scores on the PCAG scale, indicating the production of sedation. It is not clear from these data which effects of nefopam resulted in its identification as amphetamine.

Other experimental studies comparing nefopam and amphetamine in humans have found substantial differences between the effects of the two compounds. Cole and his colleagues (1978) tested the subjective effects of orally given nefopam (90 mg), placebo, caffeine (300 mg), and amphetamine (10 mg) in "casual" drug users with previous experience using amphetamines. In these subjects nefopam was mildly dysphoric, was not identified as amphetamine, and showed few differences from placebo and caffeine. Belleville and his colleagues (1979) tested the effects of nefopam (15 and 30 mg), *d*-amphetamine (5 and 10 mg), pentazocine (22.5 and 45 mg), and placebo on visual tracking and subjective effects in sleep-deprived subjects. Nefopam had no effect on tracking or subjective effects. In contrast, *d*-amphetamine improved and pentazocine impaired tracking, and both drugs produced significant changes in subjective effects measures.

Some of the effects of nefopam found in the present study have previously been reported as side effects found in other clinical studies. These side effects include loss of appetite (Klotz 1974; Gassel et al. 1976), sleepiness (Klotz 1974; Beaver and Feise 1977; Bloomfield et al. 1980), and increased pulse rate and diastolic blood pressure (Bloomfield et al. 1980). Decreased respiration (Bhatt et al. 1981) and body temperature (Compos and Solis 1980; Bhatt et al. 1981) following nefopam administration have also been reported, but these effects were not demonstrated in the present study.

In summary, nefopam, given in single doses, produced a profile of effects which was neither entirely morphine-like nor entirely *d*-amphetamine-like. Nefopam did not produce significant scores on the subjects' liking scale nor on opioid sign and symptom scales, indicating that nefopam has a lesser euphorigenic potential than morphine or *d*-amphetamine. Nefopam was, however, frequently identified by subjects as amphetamine. In our opinion, nefopam has a lesser potential than that or morphine or *d*-amphetamine.

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Received May 5, 1986/Final version September 19, 1986