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Note: Relevant information begins on p 139

PROGRESS REPORT FROM THE CLINICAL PHARMACOLOGY SECTION OF THE NIDA ADDICTION RESEARCH CENTER

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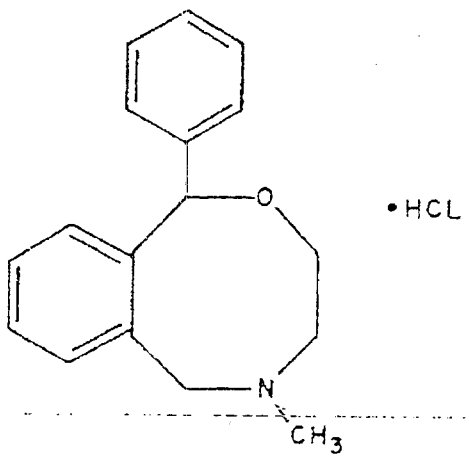
For almost 45 years, the ARC has collaborated with the Committee on Problems of Drug Dependence in assessing analgesics for morphinelike abuse potential. These studies were conducted in volunteer prisoner addicts. The Director of the Bureau of Prisons prohibited the use of federal prisoners as research subjects; and as of December 31, 1976, the ARC research program using prisoner subjects was discontinued. This report, therefore, will be the last report from the Clinical Pharmacology Section concerned with these collaborative studies.

This report will describe (1) the assessment of nefopam, (2) the determination of the relative potency of dilaudid as a euphoriant, (3) studies of the comparative metabolism of hydrocodone and hydromorphone, (4) the development of methods to assess the abuse potential of sedative hypnotics, and (5) the assessment of methaqualone.

Nefopam. This drug is a benzoxazocine derivative (Fig. 1) demonstrated to be an effective analgesic in man 1/2[1] to 1/3[2] as potent as morphine. In animals, the pharmacologic profile of nefopam more closely resembles amphetamine or procaine rather than morphine.[3,4,5] In monkeys, nefopam has reinforcing properties.[6]

The present study assessed the profile of subjective, behavioral and physiologic effects produced by nefopam in non-tolerant, non-dependent narcotic addicts. Nefopam 40 and 80 mg, d-amphetamine 15 and 30 mg, morphine 10 and 20 mg, and placebo were administered intramuscularly to 7 subjects in random order



NEFOPAM

Fig. 1. Structure diagram of nefopam (5-methyl-1-phenyl-3,4,5,6-tetrahydro-1H-2,5-benzoxazocine hydrochloride).

utilizing a double blind crossover design. Seven day intervals separated each drug administration. Drug effects were measured with our standard procedures for morphine[7,8,9,10,11] and amphetamine-like drugs.[12,13,14]

Nefopam and d-amphetamine increased systolic blood pressure and pulse rate (Fig. 2). All three drugs increased diastolic blood pressure. Only morphine changed pupil size (constriction) and only d-amphetamine changed body temperature (increased). None of the drugs changed respiratory rate (Fig. 2). Only d-amphetamine affected both subjects and observers estimates of hours of sleep (Fig. 2). All three drugs produced decreases in caloric intake (Fig. 3).

Subjects distinguished amphetamine from morphine (Table 1). Nefopam was identified as amphetamine rather than morphine (Table 1). Analysis of the responses to individual symptoms and sign items in the single dose opiate questionnaires indicate only minor differences in the profile of symptom and sign responses among nefopam, morphine, and d-amphetamine (Table 2). The most

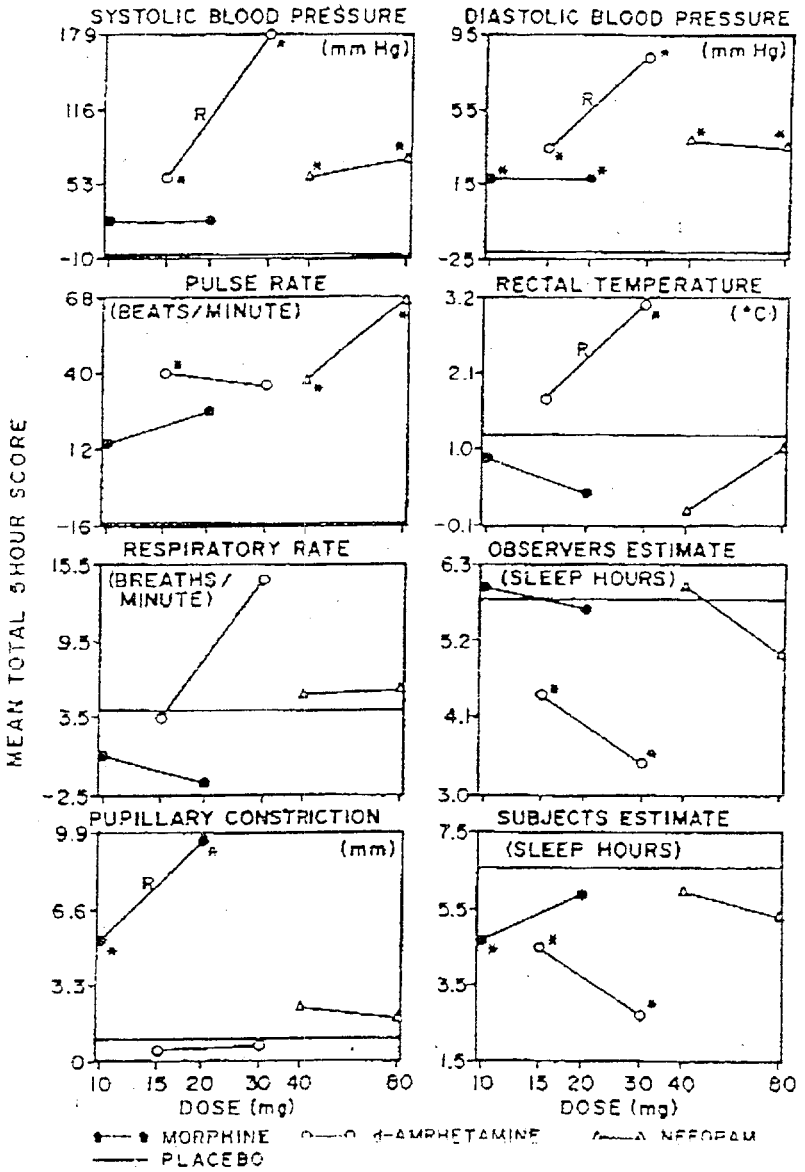


Fig. 2. Dose response curves for intramuscularly administered placebo, nefopam, morphine, and d-amphetamine. Each point represents the mean total 5 hour change from control for blood pressure, pulse rate, respiratory rate, rectal temperature, and pupillary constriction. Observers' sleep estimates represent mean total hours subjects were judged asleep (10 pm to 6 am) by observers checking subjects every 1/2 hour the night following drug administration. Subjects' estimates of sleep were determined the morning of the day following drug administration. Asterisks represent a significant difference ($p < .05$) from placebo. "R" represents a significant ($p < .05$) regression of response on dose.

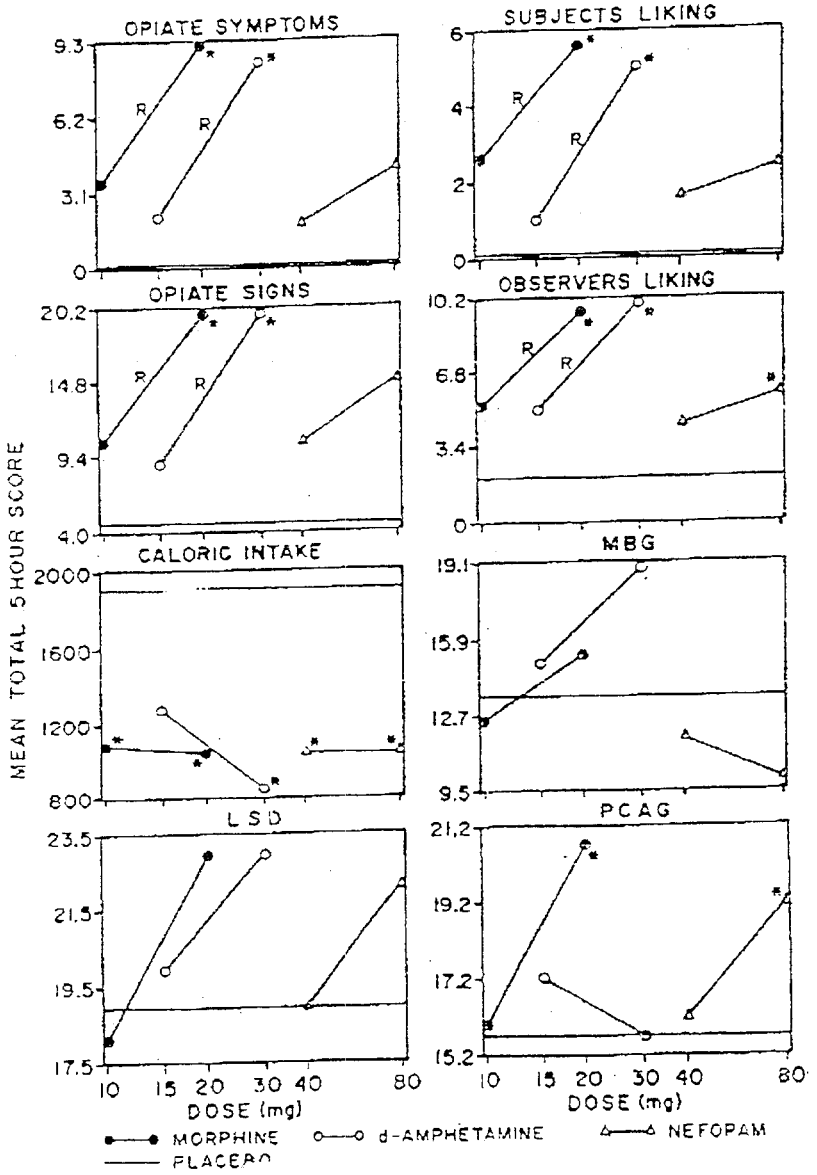


Fig. 3. Dose response curves for intramuscularly administered placebo, nefopam, morphine, and d-amphetamine. For all measures except caloric intake, each point represents the mean total 5 hour score. Caloric intake represents the mean number of calories estimated in the 3 meals following drug administration (lunch, dinner, breakfast). Asterisks represent a significant difference ($p < .05$) from placebo. "R" represents a significant ($p < .05$) regression of response on dose.

TABLE 1. 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 (7 subjects and 6 post-drug observations for each condition).

Subjects Identification	Placebo	Morphine 10 mg	Morphine 20 mg	d-amphetamine 15 mg	d-amphetamine 30 mg	Nefopam 40 mg	Nefopam 80 mg
Blank	41	21	4	34	10	30	19
Dope (opiate)	--	12	17	--	1	3	--
Amphetamine	--	6	9	8	21	2	17
Other	1	4	14	--	10	6	6
Observers Identification							
Blank	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, marihuana, barbiturate, alcohol, LSD, thorazine, or Librium identifications by subjects or observers.

TABLE 2. 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 (7 subjects and 6 post-drug observations for each drug condition).

		Morphine		d-amphetamine		Nefopam	
Symptoms	Placebo	10 mg	20 mg	15 mg	30 mg	40 mg	80 mg
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

noticeable difference is the responses on the symptom "drunk" with nefopam. Morphine and d-amphetamine, but not nefopam, produced significant scores on the opiate symptom, opiate sign, and subjects liking scales (Fig. 3). Nefopam, like morphine and d-amphetamine, did produce significant scores on the observers liking scale. None of the drugs produced significant MBG or LSD scale scores; however, nefopam and morphine did produce significant PCAG responses (Fig. 3). Relative potency calculations indicate that nefopam is about 1/4 as potent as morphine and 1/5 as potent as d-amphetamine in producing subjective effects (Table 3).

These studies indicate that nefopam produces a profile of effects more similar to those of d-amphetamine rather than morphine. In contrast to d-amphetamine, nefopam, like morphine, produces a degree of sedation and does not disturb sleep. Further, nefopam did not produce significant subjects liking or MBG scale scores; hence, significant euphoria was not demonstrated.

The indication in these studies that nefopam can produce subjective effects similar to those of d-amphetamine and the observations of Fishman and her colleagues[15] that cocaine also produces similar subjective effects to amphetamine indicates that structures unrelated to phenethylamine can produce amphetamine-like effects.

Assessment of hydromorphone (Dilaudid)

A single dose study was initiated to determine the relative euphorigenic potency of dilaudid to morphine when both drugs were administered subcutaneously and orally. The study utilized our standard procedure which involved a crossover design. Drugs were administered double blind in random order and with 7 day intervals between drug administration. Effects were measured at 1/2, 1, 2, 3, 4, and 5 hours after drug administration. The measures of drug effect utilized were changes in diameter of pupil photographs,[9] Subjects and Observers Single Dose Opiate Questionnaires,[7,8] and the Subjective Drug Effect Questionnaire.[10,11] The drugs administered were placebo, hydromorphine 1.5, 3, and 6 mg subcutaneously, hydromorphone 7, 14, 28 mg orally, morphine 10 and 20 mg subcutaneously, and morphine 130 and 260 mg orally. Not all subjects completed the crossover because of withdrawal from the study and the termination of the use of prisoners by the Bureau of Prisons. As a result, we proceeded to analyze the data utilizing the methods for the analysis of variance of unbalanced incomplete block designs[16,17] and calculation of relative potencies from the dose response curves of the resultant adjusted means (Fig. 4 and Table 4). All drug conditions produced dose related miosis and scale scores on the scales measuring morphinelike subjective effects. Relative potencies meeting the statistical criteria for validity were obtained and indicated that subcutaneously administered dilaudid was 1/9 as potent as subcutaneously administered morphine;

TABLE 3. Potencies with 95% confidence limits of nefopam relative to morphine and d-amphetamine. Relative potencies expressed as mgs of nefopam equivalent to 1 mg of morphine and 1 mg of d-amphetamine. All assays met the statistical criteria for validity.

Measure	Morphine	d-amphetamine
Symptoms	.13 (.01 - .25)	.25 (.03 - .46)
Signs	.19 (.01 - .46)	.32 (.09 - .66)
LSD	.25 (.15 - .41)	.30 (.06 - .61)
PCAG	.22 (.10 - .39)	—
Subject's Liking	—	.28 (.06 - .51)
Observer's Liking	.22 (.02 - .38)	.21 (.02 - .38)
Mean Potency	.20	.27

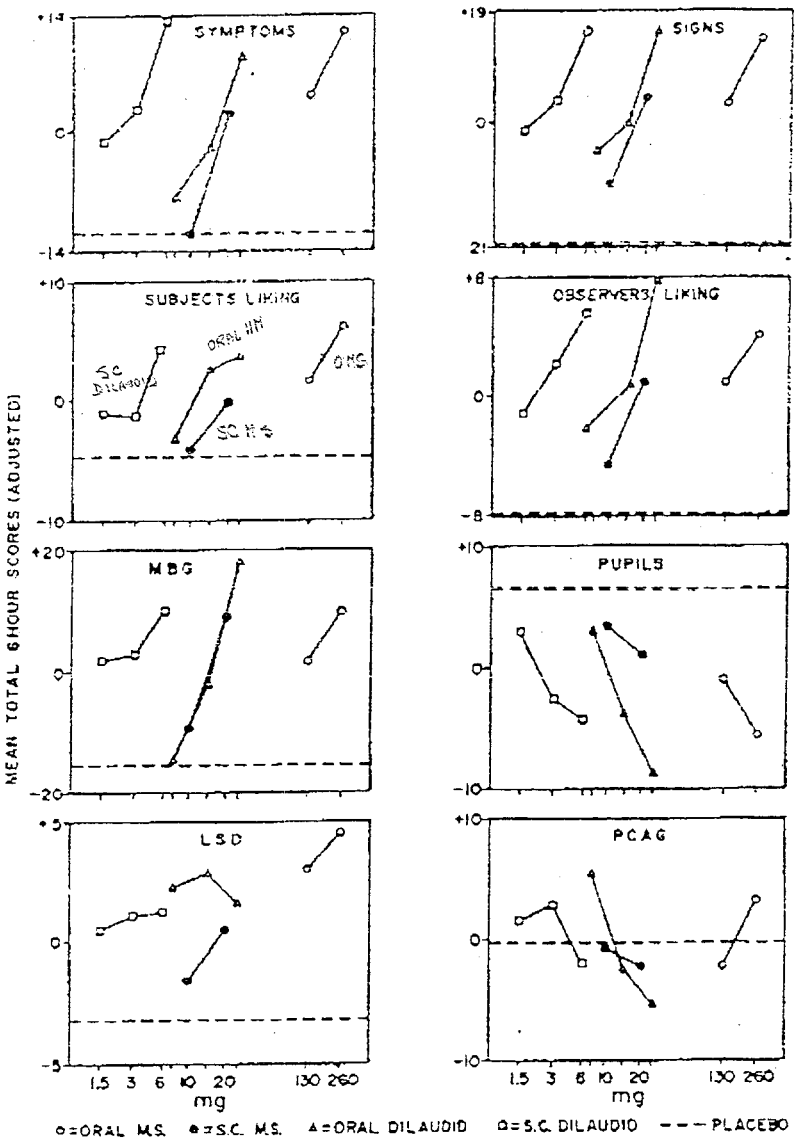


Fig. 4. Dose response curves for the comparison of subcutaneously and orally administered hydromorphone (dilaudid). Each point represents the mean total 5 hour score adjusted from the incomplete unbalanced randomized block analysis of variance. Means are expressed in terms of deviations of the grand mean.

TABLE 4. Relative potencies from the comparison of orally and subcutaneously administered hydromorphone (Dilaudid). Potencies with 95% confidence limits in parentheses are expressed as mg of first drug equivalent to 1 mg of the second. All assays listed met the statistical criteria for validity.

	Dilaudid subcutaneous to Morphine subcutaneous	Dilaudid oral to Dilaudid subcutaneous	Morphine oral to Dilaudid oral
Pupils	10.0 (5.6 - 173)	3.6 (2.0 - 6.4)	13.0 (6.8 - 23.4)
Opiate symptoms	9.7 (5.1 - 1055)	7.2 (3.7 - 26.6)	6.1 (0 - 15.0)
Opiate signs	8.7 (5.1 - 35.3)	5.6 (3.2 - 11.8)	9.1 (2.1 - 18.4)
Subjects' liking	--	6.3 (2.3 - 92.6)	6.8 (0 - 18.4)
Observers' liking	9.4 (5.9 - 32.1)	4.9 (2.9 - 9.2)	11.7 (4.9 - 22.3)
MBG	--	--	9.6 (0 - 35.8)
Mean potency	9.4	5.4	9.0

oral dilaudid was 1/5 as potent as subcutaneous dilaudid; and oral morphine was approximately 1/10 as potent as oral dilaudid. Thus, oral morphine is 1/5 as potent as subcutaneous morphine. These potencies are consistent with those of other investigators. As an analgesic, Mahler and Forrest[18] found a potency of 8.6 relating intramuscular dilaudid to intramuscular morphine. Wallenstein, Houde and Beaver[19] found that a potency of 6 to 1 for oral to subcutaneous morphine in relieving pain in cancer patients. Consequently, these results also indicate that useful relative potency data may be calculated from unbalanced incomplete block designs and suggests that this technique might be useful in other circumstances where complete crossover studies cannot be completed or conducted.

Comparative metabolism of hydrocodone and hydromorphone in man and laboratory animals

As part of a continuing effort to delineate appropriate animal models for use in the *in vivo* study of analgetics, we have examined the metabolic profile of hydromorphone (HM) and hydrocodone (HC) in man and several animal species. Single oral doses of HC or HM were administered to 6 human subjects from whom informed consent had been obtained. Total urine collections were made at timed intervals ending at 0, 2, 4, 8, 12, 24, 48, 72, and 96 hours following drug administration. Single doses of HC or HM (subcutaneous) were administered to animals housed in metal cages fitted with stainless steel collector pans. Urine collections were made at 0, 24 and 48 hours. Drug and metabolite content of the urine samples were determined using gas chromatography and/or gas chromatography-mass spectrometry (operating in the chemical ionization mode with methane as the reagent gas). Cyclazocine was used as an internal standard for quantitation.

The metabolites of HC and HM which were identified in this study are shown in Figure 5. HM was metabolized by conjugation (presumably glucuronide) and/or keto reduction to give the 6α- and 6β-hydroxymetabolites (6αHM and 6βHM). HC was metabolized by keto reduction to the analagous 6α- and 6β-hydroxymetabolites (6αHC and 6βHC) and by N- and O-demethylation. The latter biotransformation pathway led to the formation of HM which was metabolized similarly to HM administered as a single dose.

Quantitation of drug and metabolite for each species is shown in Table 5. The data is presented as the total % administered dose recovered from urine and represent a mean of three determinations. Conjugated drug was determined by subtraction of % free from % total drug (acid-hydrolyzed). The major drug or metabolite of each species is indicated by an asterisk.

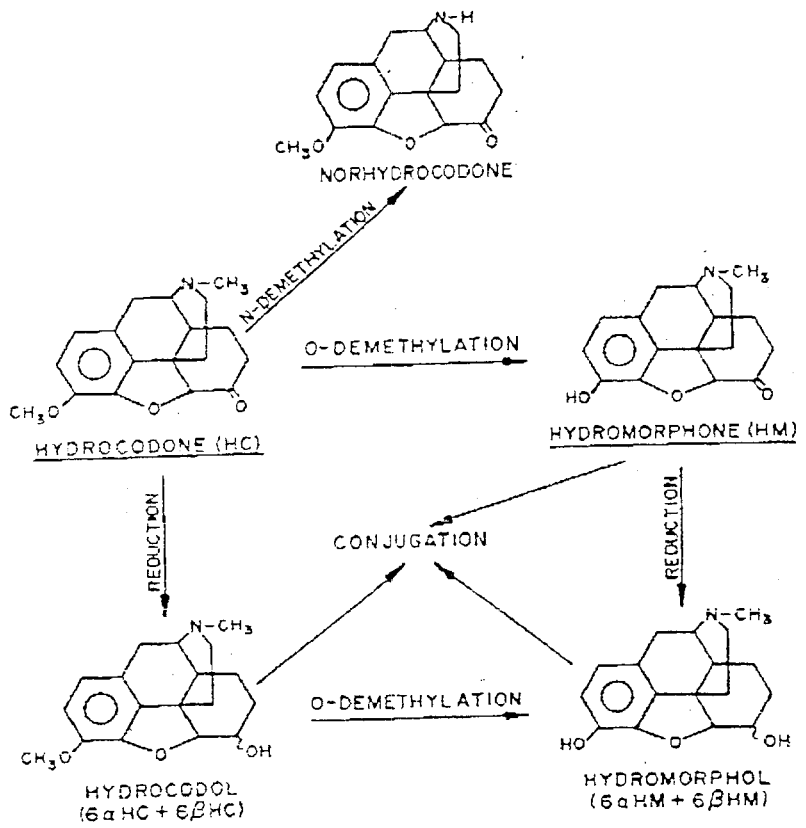


Fig. 5. Metabolism of hydrocodone and hydromorphone.

It is evident from Table 5 that both HC and HM were metabolized extensively in man and animals. All species differed considerably in the metabolism of HC. Man excreted the largest amount of parent compound (11.6%) whereas rat excreted relatively large amounts of conjugated 6βHM (4.8%) and free 6βHC (4.5%). The major metabolites in the guinea pig, dog, and rabbit were free 6βHC (32.9%), free NC (15.0%), and conjugated HM (6.0%), respectively.

For HM there was a much greater similarity in the patterns of metabolism between man and the other animal species. Man as well as rat, dog, and rabbit excreted relatively large amounts of conjugated HM (13-50%) and small amounts

TABLE 5. Average percent recovery of drug and metabolites from urine of man and animals administered hydrocodone or hydromorphone.

Species (N)	Avg. Wgt. (kg)	Dose (mg)	6αHC	6βHC	HC	NC[1]	6αHM	6βHM	HM	Total
			% Administered Dose, Free/Conjugated							
HYDROCODONE										
Man (6)	83.2	15	1.6/0.2	1.6/0.6	11.6*/0	5.2/1.3	0.02[2]	0.13[2]	3.52[2]	25.97
Rat (6)	0.46	5	0.12/0	4.48/0	3.60/0	0/0	0.05/0.02	2.13/4.76*	0.78/0.64	16.58
G. Pig (6)	1.02	5	2.36/0	32.92*/0	3.55/0	0/0	0.63/0	3.86/0	3.42/0	46.74
Dog (2)	8.20	10	0/0	0/0	3.58/0	14.96*/4.47	0/0	0/0	0.15/1.18	24.34
Rabbit (4)	4.40	5	0/0	0/0	0.66/0	0/0	0/0.35	0.06/2.79	0.62/6.00*	10.48
HYDROMORPHONE										
Man (6)	83.2	4	–	–	–	–	0.19[2]	2.37[2]	5.60/36.80*	44.96
Rat (6)	0.39	5	–	–	–	–	1.10/0.50	0.7 /1.10	9.1/19.4*	31.90
G. Pig (6)	1.00	5	–	–	–	–	8.30/0	19.10/0.20	34.00*/11.30	72.90
Dog (2)	7.75	10	–	–	–	–	0.60/1.00	1.10/1.00	11.20/50.50*	65.40
Rabbit (4)	4.15	5	–	–	–	–	0.30/0.80	2.20/4.70	7.60/13.00*	28.60

*Indicates major drug or metabolite in the urine.

[1]Analyzed separately by GC.

[2]Analyzed as total drug (free + acid-hydrolyzed), from two subjects.

of 6αHM (0.2%-1.1%) and 6βHM (0.7%-4.7%). In contrast, the guinea pig differed by producing large amounts of free 6αHM (8.3%), free 6βHM (19.1%) and free HM (34.0%).

Within these species some limited generalizations regarding metabolism of compounds having the hydromorphone structure can be made. Man, rat, and rabbit appear able to metabolize opiates through a variety of metabolic pathways including conjugation, reduction and N- and O-demethylation where any one of these processes may predominate for a given drug. Drugs with free phenolic groups are likely to be highly conjugated by the dog. Methylation of the phenolic group effectively blocks conjugation and N-demethylation then may become the predominant metabolic pathway. Reduction plays a major role in metabolism of 6-keto-compounds by the guinea pig whereas conjugation appears to be rather limited.

The importance of these species differences in influencing the overall pharmacologic activity of the drug is a complex issue. Each of the biotransformations described herein with the exception of conjugation presumably results in the formation of a metabolite whose activity may be greater or less than that of the parent compound. Their rate of formation, distribution, metabolism and excretion should ultimately decide their relative contribution to the activity of the drug.

Development of methods to assess sedative-hypnotics

In a series of studies, Martin and his colleagues[20,21] demonstrated that non-tolerant narcotic addicts (1) distinguish pentobarbital from placebo and morphine, and (2) report euphoria with pentobarbital. These investigators further observed that pentobarbital produced a dose-related facilitation of post-rotatory nystagmus and subsequently utilized the electro-oculogram and bioassay techniques to compare the increased frequency and duration of post-rotatory nystagmus produced by pentobarbital and meprobamate.

These studies by Martin and his colleagues suggested that sedative hypnotics might be evaluated for barbiturate-like abuse potential by assessing their ability to produce pentobarbital-like subjective effects, euphoria, and facilitation of post-rotatory nystagmus in non-tolerant non-dependent addicts. On this basis, studies were conducted to (1) compare intramuscularly administered morphine, pentobarbital, d-amphetamine, and placebo, (2) compare intramuscularly administered pentobarbital, secobarbital, phenobarbital, and placebo, and (3) compare orally administered pentobarbital, secobarbital, and placebo (Table 6). The purpose of these studies was to develop a scale to measure barbiturate-like euphoria, to determine if these measures could be used to determine relative potencies of sedative hypnotics in producing subjective effects and euphoria, and to evaluate if such studies could be conducted with orally administered drugs.

TABLE 6. Characteristics of three studies conducted to evaluate the potential to assay drugs for pentobarbital-like subjective effects and facilitation of post-rotatory nystagmus.

STUDY	I	II	III
SUBJECTS	11	10	9
DESIGN	Randomized Block	Latin Square	Randomized Block
ROUTE	Intramuscular	Intramuscular	Oral
DRUGS	(A) Placebo	(A) Placebo	(A) Placebo
	(B) Pentobarbital	(B) Pentobarbital	(B) Pentobarbital
	125 mg 250 mg 175 mg*	50 mg 120 mg 288 mg	60 mg 120 mg 240 mg
	(C) Morphine	(C) Secobarbital	(C) Secobarbital
	10 mg 20 mg	75 mg 180 mg 432 mg	60 mg 120 mg 240 mg
	(D) d-amphetamine	(D) Phenobarbital	
	15 mg 30 mg	150 mg 360 mg 557.1 mg	

The measures of drug effect were, with slight modification, those developed by Martin and his colleagues[19,20] to measure the effects of pentobarbital. These were (1) electro-oculographs of post-rotational nystagmus, (2) the "subjects' and observers' single dose opiate questionnaires" and (3) a subjective drug effect questionnaire containing 40 items from the Addiction Research Center Inventory.[10,11] This questionnaire contained subsets from the Morphine-Benzedrine Group Scale (MBG), the Pentobarbital-Chlorpromazine-Alcohol Group Scale (PCAG), and the LSD Specific Scale. The subset of items in this particular questionnaire had been chosen to distinguish the subjective effects of morphine from those of cyclazocine.[10,11] The items in the MBG Scale and the PCAG Scale subsets were, with one or two exceptions, different from those utilized by McClane and Martin[21] in their comparison of pentobarbital and morphine. From the responses to pentobarbital in the three present studies, a euphoria scale was derived from the MBG scale and a sedation scale was derived from the PCAG items (Table 7). This was done by analyzing to responses individual items and only those MBG items that showed a dose related response to pentobarbital, morphine, and d-amphetamine placed in the euphoria scale and those PCAG items that showed dose response related increases with morphine and pentobarbital were placed in the sedation scale (Table 7). There were no dose related sedation items with d-amphetamine.

In Study 1, subjects and observers correctly identified pentobarbital and distinguished it from morphine and d-amphetamine (Table 8) and the symptom and sign items "sleepy" and "drunk" were high response items with pentobarbital but not morphine or d-amphetamine (Table 9). All three drugs produced responses on the sign, symptom, and liking scales of the single dose questionnaire (Fig. 6). All three drugs produced significant responses in the euphoria scale but only pentobarbital and morphine produced significant responses on the sedation scale. Dextroamphetamine was 1.5 to 2 times less potent than amphetamine in producing subjective effects and pentobarbital is 1/3 to 1/2 as potent (Fig. 6).

In Study 2, the responses on the subjective scales and the measures in frequency and duration of post-rotational nystagmus indicated that pentobarbital, secobarbital, and phenobarbital had a similar onset and duration of action although the questionnaire responses at 24 hours suggest less of a decrement in response from 12 to 24 hours for phenobarbital.

Pentobarbital, secobarbital, and phenobarbital produced dose-related increases on scale scores and dose-related increases in the frequency and duration of post-rotatory nystagmus (Fig. 7). On all measures, secobarbital was equipotent to pentobarbital. On the other hand, phenobarbital was 1/4 to 1/5 as potent as pentobarbital as determined from scale scores but 1/2 to 1/6 as potent

TABLE 7. Items in the Euphoria Scale and the Sedation Scale derived from the MBG and PCAG scales of the ARCI.

EUPHORIA SCALE

1. I FEEL AS IF I WOULD BE MORE POPULAR WITH PEOPLE TODAY.
2. THINGS AROUND ME SEEM MORE PLEASING THAN USUAL.
3. I FEEL I WILL LOSE THE CONTENTMENT I NOW HAVE.
4. I FEEL LESS DISCOURAGED THAN USUAL.
5. I AM IN A MOOD TO TALK ABOUT THE FEELING I HAVE.
6. I FEEL SO GOOD I KNOW OTHER PEOPLE CAN TELL IT.
7. I FEEL AS IF SOMETHING PLEASANT JUST HAPPENED TO ME.

SEDATION SCALE

1. MY SPEECH IS SLURRED.
2. I AM NOT AS ACTIVE AS USUAL.
3. I HAVE A FEELING OF JUST DRAGGING ALONG RATHER THAN COASTING.
4. I FEEL SLUGGISH.
5. MY HEAD FEELS HEAVY.
6. I FEEL LIKE AVOIDING PEOPLE ALTHOUGH I USUALLY DO NOT FEEL THIS WAY.
7. I FEEL DIZZY.
8. PEOPLE MIGHT SAY I AM A LITTLE DULL TODAY.
9. IT SEEMS HARDER THAN USUAL TO MOVE AROUND.
10. I AM MOODY.
11. I FEEL DROWSY.

TABLE 8. Cumulative drug identifications by subjects and observers in the Single Dose Opiate Questionnaire for the comparison of intramuscularly administered pentobarbital, morphine, d-amphetamine, and placebo. Maximum number of responses in any category is 66 (11 subjects x 6 observations).

Subjects Identification	Placebo	Pentobarbital 125 mg	Pentobarbital 175 mg	Pentobarbital 250 mg	Morphine 10 mg	Morphine 20 mg	d-amphetamine 15 mg	d-amphetamine 30 mg
Blank	61	26	17	8	30	13	36	19
Dope	3	4	5	--	26	51	--	--
Cocaine	--	--	--	--	12	--	--	--
Barbiturate	--	46	45	63	--	7	5	7
Alcohol	--	2	--	--	--	--	--	--
Benzedrine (amphetamine)	--	--	--	--	3	9	26	43
Thorazine	--	3	6	--	--	--	--	--
Miltown or Librium	2	--	--	--	--	--	3	--
Others	--	--	4	1	4	--	4	7
Observers Identification								
Blank	50	9	10	10	27	13	32	9
Dope	3	--	--	--	38	55	7	10
Barbiturate	6	53	49	62	2	2	4	--
Benzedrine (amphetamine)	3	9	5	--	5	--	19	45
Others	1	2	3	1	3	6	18	10

There were no marijuana or LSD identifications by subjects or observers. There were no cocaine, alcohol, Thorazine, or Miltown and Librium identifications by observers.

TABLE 9. Cumulative responses by subjects and observers on individual symptom and sign items in the Single Dose Opiate Questionnaires for the comparison of intramuscularly administered pentobarbital, morphine, d-amphetamine, and placebo (Study I). Maximum number of responses in any category is 66 (11 subjects x 6 post-drug observations).

Symptoms	Placebo	Pentobarbital 125 mg	Pentobarbital 175 mg	Pentobarbital 250 mg	Morphine 10 mg	Morphine 20 mg	d-amphetamine 15 mg	d-amphetamine 30 mg
Normal	61	30	17	8	30	13	40	19
Turning of stomach	--	--	--	--	4	21	--	3
Skin itchy	--	--	--	--	4	29	--	1
Relaxed	2	5	8	12	27	21	9	21
Coasting	--	8	6	8	1	13	--	--
Soapbox	--	--	--	6	1	--	7	6
Pleasant sick	--	--	--	4	6	19	1	6
Drive	--	--	--	5	--	--	10	25
Sleepy	--	30	38	38	--	5	--	--
Drunken	--	19	28	24	--	1	--	3
Nervous	2	1	--	--	6	1	11	14
Other	--	--	1	1	1	3	8	2
Signs								
Normal	54	9	13	10	27	13	32	8
Scratching	2	--	--	--	28	4	8	9
Red eyes	1	32	27	41	20	9	6	20
Relaxed	12	55	53	59	45	58	30	60
Coasting	3	15	2	4	11	18	--	3
Soapbox	--	16	4	13	20	34	23	36
Vomiting	--	--	--	--	--	--	--	1
Nodding	--	4	1	--	8	--	--	--
Sleepy	8	29	43	47	--	7	--	2
Nervous	2	3	9	12	6	2	21	32
Drunken	3	29	25	46	--	5	5	1
Other	--	--	2	--	--	3	--	--

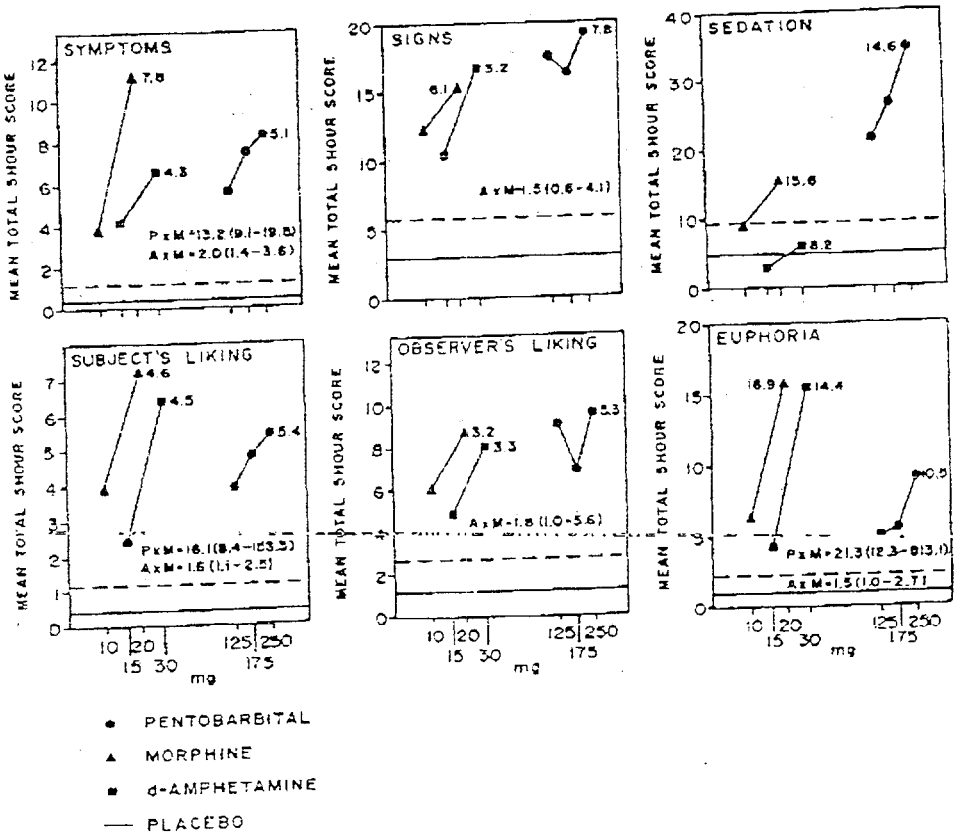


Fig. 6. Dose response curves for the comparison of intramuscularly administered pentobarbital, morphine, d-amphetamine, and placebo (Study I). Each point represents the mean total 5 hour score. Numbers at the top of each dose response curve are the standard deviations for responses to the large dose of that drug. Potencies expressed as mg of pentobarbital relative to 1 mg of morphine (P x M) or mg of amphetamine equivalent to 1 mg of morphine (A x M). Numbers in brackets represent 95% confidence limits. Broken line represents 95% confidence limits of mean placebo response.

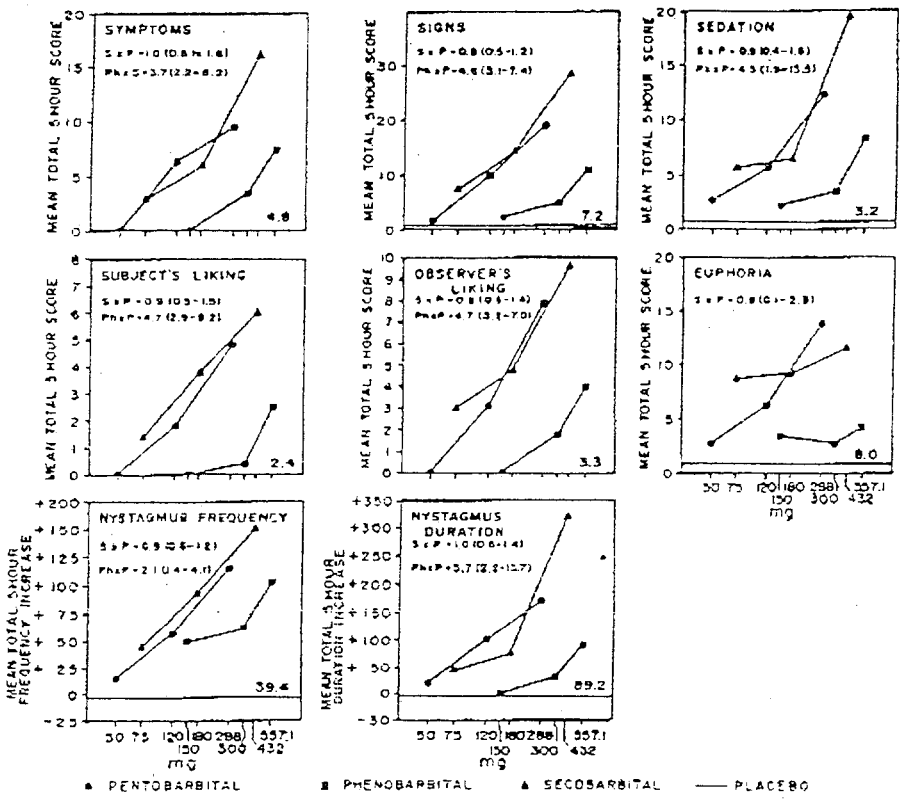


Fig. 7. Dose response curves for the comparison of intramuscularly administered pentobarbital, secobarbital, phenobarbital, and placebo (Study II). The potency of secobarbital (S x P) and phenobarbital (Ph x P) relative to pentobarbital are shown for those bioassays meeting the statistical criteria for validity. Numbers represent mg of drug and 95% confidence limits equivalent to 1 mg of pentobarbital. Numbers in lower right hand corner of each graph represent the standard deviation calculated as the square root of the error mean square in the analysis of variance.

as measured by the increase in frequency and duration of post-rotatory nystagmus (Fig. 7). Significant increases in dysphoria scale scores were observed but valid bioassays were not obtained.

Subjects and observers identified all three drugs predominantly as barbiturates (goofballs) (Table 10) and reported similar signs and symptoms (Table 11).

In Study 3, pentobarbital and secobarbital administered orally had similar onsets and similar durations of action through 12 hours. Comparison of dose response curves utilizing total 5 hour scores and relative potencies indicated that secobarbital is approximately equipotent to pentobarbital although there was a tendency for secobarbital to be less effective in producing the responses on the sedation scale (Fig. 8). Again subjects and observers identified both secobarbital and pentobarbital or goofballs (Table 12) and reported similar symptoms or signs (Table 13).

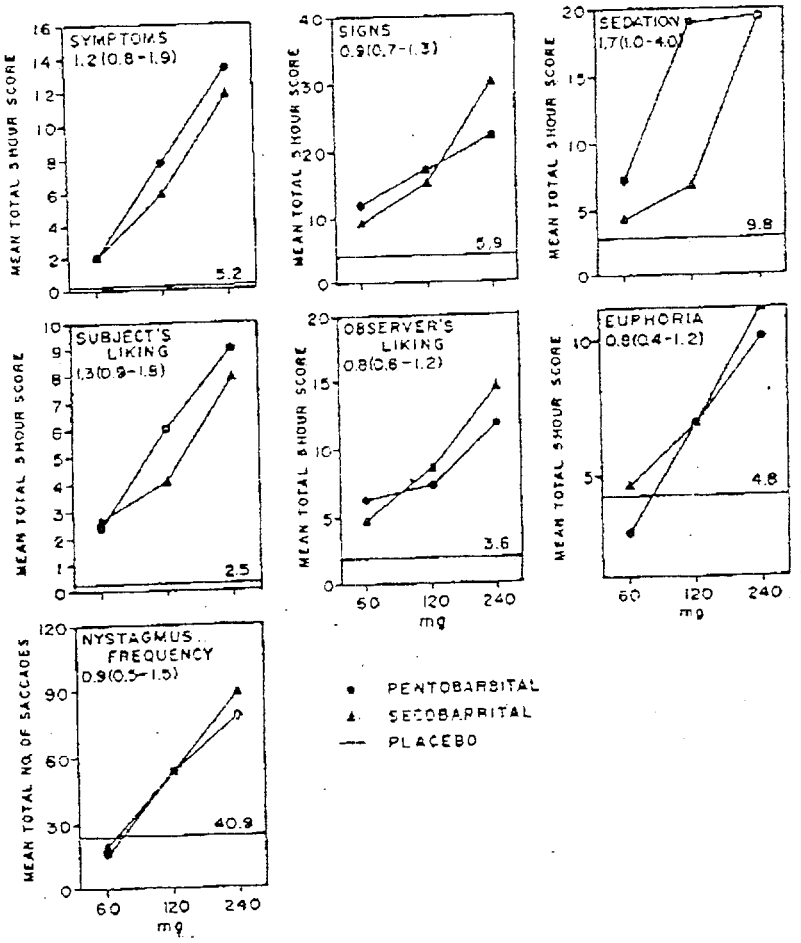


Fig. 8. Dose response curves for the comparison of orally administered pentobarbital, secobarbital, and placebo. Numbers represent mg of secobarbital equivalent to 1 mg pentobarbital and 95% confidence limits. Numbers in lower right hand corner of each graph represents the standard deviation calculated as the square root of the error mean square in the analysis of variance.

TABLE 10. Cumulative drug identifications by subjects and observers in the Single Dose Questionnaire for the comparison of intramuscularly administered pentobarbital, secobarbital, phenobarbital, and placebo (Study II). Maximum number of responses in any category is 60 (10 subjects x 6 post-drug observations).

Subjects Identification	Placebo	Pentobarbital 50 mg	Pentobarbital 120 mg	Pentobarbital 288 mg	Secobarbital 75 mg	Secobarbital 180 mg	Secobarbital 432 mg	Phenobarbital 150 mg	Phenobarbital 360 mg	Phenobarbital 557.1 mg
Blank	60	60	38	25	48	28	4	60	46	34
Goofballs	--	--	12	19	7	19	33	--	10	22
Benzedrine (amphetamine)	--	--	6	--	--	--	--	--	--	--
Other	--	--	4	16	8	13	24	--	4	4
Observers Identification										
Blank	54	53	33	12	39	10	3	50	43	24
Dope (opiate)	2	--	--	6	5	6	6	--	--	--
Goofballs	--	4	21	37	16	41	49	10	13	36
Benzedrine (amphetamine)	--	--	--	--	--	--	--	--	--	--
Other	4	3	1	4	--	3	2	--	3	--

There were no cocaine or marijuana identifications by subjects or observers and no dope ("opiate") identifications by subjects.

TABLE 11. Cumulative responses by subjects and observers on individual symptom and sign items in the Single Dose Opiate Questionnaires for the comparison of intramuscularly administered pentobarbital, secobarbital, phenobarbital, and placebo (Study II). Maximum number of responses in any category is 60 (10 subjects x 6 post-drug observations).

		Pentobarbital			Secobarbital			Phenobarbital		
Symptoms	Placebo	50 mg	120 mg	288 mg	75 mg	180 mg	432 mg	150 mg	360 mg	557.1 mg
Normal	60	60	58	24	48	29	4	60	46	31
Turning of stomach	--	--	--	--	--	--	1	--	--	--
Skin itchy	--	--	--	--	--	--	--	--	--	--
Relaxed	--	--	15	23	9	18	28	--	7	18
Coasting	--	--	--	7	--	5	8	--	--	3
Soapbox	--	--	3	4	--	6	1	--	--	--
Pleasant sick	--	--	--	--	--	--	--	--	--	--
Drive	--	--	6	--	--	--	2	--	--	10
Sleepy	--	--	13	15	7	9	24	--	6	12
Drunken	--	--	5	16	3	6	34	--	--	7
Nervous	--	--	--	--	--	--	--	--	--	--
Other	--	--	5	--	2	1	6	--	4	--
Signs										
Normal	54	53	34	12	39	10	3	--	42	24
Scratching	--	--	2	2	4	--	--	51	--	--
Red eyes	--	3	5	14	11	17	41	--	6	12
Relaxed	6	7	26	48	21	50	57	6	14	36
Coasting	--	3	9	16	7	10	13	9	6	5
Soapbox	2	--	3	19	6	4	29	--	1	1
Vomiting	--	--	--	--	--	--	3	--	--	--
Nodding	--	--	--	1	--	--	2	--	--	--
Sleepy	--	3	21	26	10	22	36	7	10	24
Nervous	--	--	--	--	--	--	--	--	--	--
Drunken	--	--	7	19	3	7	35	--	--	6
Other	--	--	--	--	--	--	--	--	3	--

LE 12. Cumulative drug identifications by subj s and observers in the Single Dose Opiate Questionnaire for the comparison of orally administered pentobarbital, secobarbital, and placebo (Study III). Maximum number of responses in any category is 54 (9 subjects x 6 post-drug observations).

Subjects Identification	Placebo	Pentobarbital 60 mg	Pentobarbital 120 mg	Pentobarbital 240 mg	Secobarbital 60 mg	Secobarbital 120 mg	Secobarbital 240 mg
Blank	52	35	17	10	37	25	9
Dope (opiate)	--	1	--	1	--	--	1
Marijuana	--	--	--	4	--	--	--
Barbiturate	--	6	33	37	7	16	41
Alcohol	--	--	--	1	6	7	--
Benzedrine (amphetamine)	--	--	--	--	--	--	1
Thorazine	--	--	--	1	--	--	--
Miltown or Librium	2	7	5	--	2	6	1
Others	--	--	--	6	2	--	1
Observers Identification							
Blank	41	23	13	6	26	8	3
Dope	4	4	--	--	--	6	4
Barbiturate	9	24	35	48	22	40	51
Benzedrine (amphetamine)	--	--	--	--	1	--	--
Miltown	--	3	--	--	--	--	--
Others	--	--	2	--	5	5	2

There were no cocaine or LSD identifications by subjects or observers. In addition, there were no marijuana, alcohol, or Thorazine observations by observers.

TABLE 13. Cumulative responses by subjects and observers on individual symptom and sign items in the Single Dose Opiate Questionnaires for the comparison of orally administered pentobarbital, secobarbital, and placebo (Study III). Maximum number of responses in any category is 54 (9 subjects x 6 post-drug responses).

Symptoms	Placebo	Pentobarbital 60 mg	Pentobarbital 120 mg	Pentobarbital 240 mg	Secobarbital 60 mg	Secobarbital 120 mg	Secobarbital 240 mg
Normal	52	35	17	8	37	24	7
Turning of stomach	--	--	6	5	1	5	4
Skin itchy	--	--	1	--	--	--	--
Relaxed	2	8	21	31	16	21	16
Coasting	--	--	5	16	2	4	8
Soapbox	--	--	--	5	--	--	6
Pleasant sick	--	6	3	--	--	3	6
Drive	--	--	1	7	--	--	6
Sleepy	--	5	15	15	3	10	16
Drunken	--	--	1	12	--	1	14
Nervous	--	--	--	--	--	--	--
Other	--	--	--	--	1	--	--
Signs							
Normal	41	23	17	6	26	8	3
Scratching	--	--	--	--	--	4	7
Red eyes	4	20	22	25	14	30	42
Relaxed	13	31	42	48	28	45	51
Coasting	1	9	7	21	5	12	29
Soapbox	3	12	13	20	9	19	27
Vomiting	--	--	--	--	--	--	--
Nodding	--	--	3	3	--	--	10
Sleepy	4	15	27	28	11	9	19
Nervous	--	--	--	--	--	--	--
Drunken	4	--	6	9	1	2	20
Other	--	3	4	7	1	7	17

The results of these three studies confirm the observations of Martin and his colleagues[20,21] that pentobarbital produces a type of euphoria, that the subjective effects are distinct from those of morphine or d-amphetamine, and that the facilitation of post-rotatory nystagmus can be used to assay for the relative potency of sedative hypnotics. In addition, these studies suggest that the abuse potential of sedative hypnotic agents can be evaluated by assessing their ability to produce the characteristic profile of a prototypic drug (pentobarbital) when administered acutely.

Assessment of methaqualone

The introduction of methaqualone following its introduction into the United States resulted in a number of cases of abuse. Gerald and his colleagues[22] summarized the pertinent literature and reported the results of a survey of methaqualone users. His results indicated that methaqualone appeared to produce a euphoric state and subjective effects which were barbiturate-like. On the other hand, there is little documentation of barbiturate-like physical dependence although there are case reports of withdrawal syndromes in the literature. Acute poisoning with methaqualone produces coma but unlike barbiturate poisoning there is little respiratory or cardiovascular depression, muscle tone is increased, and chronic convulsions occur.

These considerations indicate that the classification of methaqualone as a barbiturate-like drug is uncertain. A study was conducted to compare methaqualone, pentobarbital, and placebo utilizing the methods described above for assessing pentobarbital-like effects. This study (Methaqualone Study I) involved the oral administration of methaqualone 100, 200, and 400 mg, pentobarbital 100 and 200 mg, and placebo to 7 subjects.

In these studies, the onset and duration of the effects of methaqualone and pentobarbital were similar (Fig. 9). Subjects and observers identified methaqualone as a barbiturate (Table 14) and reported similar symptoms and signs for both drugs (Table 15). Methaqualone produced dose related responses on the scales measuring the pentobarbital-like subjective effects including euphoria and sedation and a dose related facilitation of post-rotatory nystagmus (Fig. 10). Methaqualone was 1.5 to 4 times less potent than pentobarbital. Some of the subjects reported generalized numbness and tingling with the larger doses of methaqualone but not pentobarbital. Although not significant, the dose response curves in Fig. 10 suggested that methaqualone produced more euphoria with less sedation and less facilitation of post-rotatory nystagmus than pentobarbital. The study was repeated (Methaqualone Study II) but the doses were changed on the basis of the relative potencies obtained in Study I. In Study 2, methaqualone 160 and 320 mg and pentobarbital 50, 100, and 200 mg were administered orally to 6 subjects. As an additional measure of drug effect,

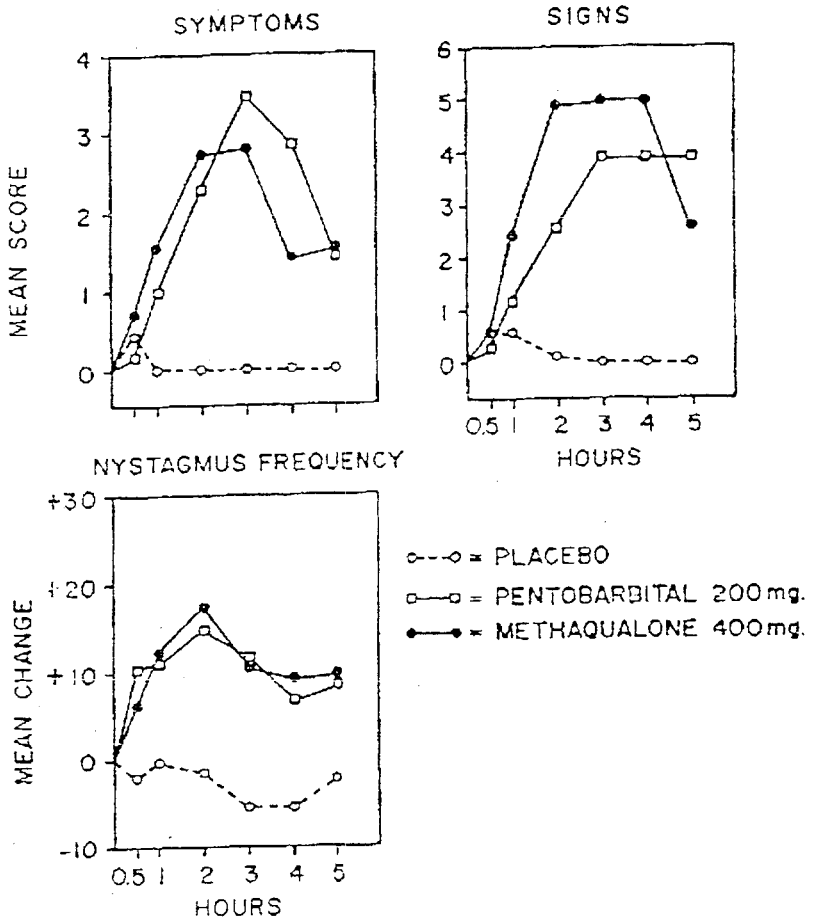


Fig. 9. Time action curves for orally administered pentobarbital, methaqualone, and placebo on the symptom and sign scales and the increase in frequency of post-rotational nystagmus (Methaqualone Study I).

one minute EEG samples from unilateral bipolar (frontal temporal) derivation were collected during eyes open and eyes closed conditions. These samples were taken twice prior to drug and three times post-drug at 1, 2, and 3 hours. This was done to determine if the increase in relative beta frequency bands could be used to assay for barbiturate-like effects.

In this second study, methaqualone was again identified as a barbiturate (Table 16), produced similar symptom and sign responses (Table 17), and produced dose related responses on the various scale and facilitated post-rotatory nystagmus. In this study, there was no evidence of an ability of methaqualone

TABLE 14. Total cumulative drug identifications in the single dose questionnaire by subjects and observers for the comparison of methaqualone, pentobarbital, and placebo (methaqualone Study I). Maximum responses in any category is 42 (7 subjects x 6 observations).

Subjects Identification	Placebo	Pentobarbital 100 mg	Pentobarbital 200 mg	Methaqualone 100 mg	Methaqualone 200 mg	Methaqualone 400 mg
Blank	40	30	18	38	22	14
Dope (opiate)	—	—	—	—	1	—
Goofball (barbiturate)	2	11	22	4	17	27
Alcohol	—	—	2	—	2	—
Thorazine	—	—	4	—	—	3
Other	—	—	—	—	—	—
Observers Identification						
Blank		17	14	21	9	13
Dope (opiate)		1	—	1	—	—
Goofball (barbiturate)		24	28	20	31	31
Other		1	3	—	7	—

There were no cocaine, marihuana, benzedrine (amphetamine), LSD, Thorazine, Miltown, or Librium identifications by subjects or observers. In addition, there were no alcohol or Thorazine identifications by observers.

TABLE 15. Total cumulative responses on symptom and sign items in single dose questionnaires by subjects and observers in the comparison of methaqualone, pentobarbital, and placebo (methaqualone Study I). Maximum responses in any category is 42 (7 subjects and 6 observations).

Symptoms	Placebo	Pentobarbital 100 mg	Pentobarbital 200 mg	Methaqualone 100 mg	Methaqualone 200 mg	Methaqualone 400 mg
Normal	40	31	17	38	23	17
Stomach turning	--	3	--	--	2	2
Skin itchy	--	--	--	--	--	1
Relaxed	1	4	7	1	5	9
Coasting	--	--	4	--	3	3
Soapbox	--	--	1	1	--	3
Pleasant sick	--	--	--	--	--	--
Drive	--	--	--	--	--	--
Sleepy	1	6	18	3	6	19
Drunken	--	7	14	2	11	9
Nervous	--	--	2	--	--	--
Other	--	1	--	1	1	--
Signs						
Normal	37	16	14	21	8	9
Scratching	--	--	1	1	4	2
Red eyes	--	11	10	6	16	13
Relaxed	1	23	28	19	35	31
Coasting	--	3	5	--	13	14
Soapbox	--	7	8	3	12	15
Vomiting	--	--	--	1	--	--
Nodding	--	2	4	--	--	3
Sleepy	1	14	19	6	9	20
Nervous	--	--	--	1	6	5
Drunken	--	11	8	3	1	10
Other	--	3	2	--	2	3

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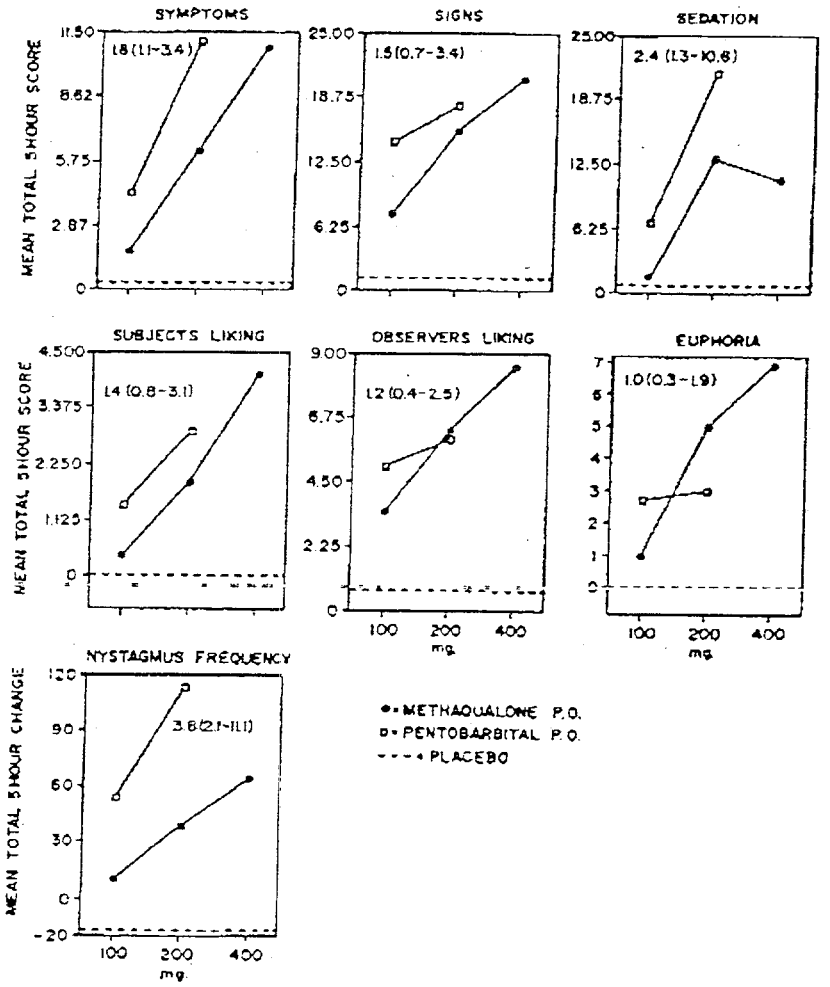

Fig. 10. Dose response curves for the comparison of orally administered methaqualone, pentobarbital, and placebo (Methaqualone Study I). Numbers in upper left hand corner of each graph represent mg of methaqualone equivalent to 1 mg of pentobarbital and 95% confidence limits.

to be more euphorigenic and less sedating than pentobarbital (Fig. 11). On all measures, methaqualone was about 1/2 as potent as pentobarbital. Both pentobarbital and methaqualone produced a relative increase in beta activity and a decrease in delta activity with eyes closed (Fig. 11) and relative potencies calculated from dose response curves for these EEG changes were similar to those calculated for subjective effects and facilitation of post-rotatory nystagmus.

TABLE 16. Total cumulative drug identifications in the single dose questionnaires by subjects and observers for the comparison of methaqualone, pentobarbital, and placebo (methaqualone Study II).

Subjects Identification	Pentobarbital 50 mg	Pentobarbital 100 mg	Pentobarbital 200 mg	Methaqualone 160 mg	Methaqualone 320 mg
Blank	25	15	6	16	7
Dope (opiate)	--	--	--	--	2
Marihuana	3	3	--	--	6
Goofball (barbiturate)	4	16	30	17	23
Alcohol	4	7	--	--	4
Other	1	--	--	3	5
Observers Identification					
Blank	26	3	2	11	1
Goofball (barbiturate)	10	33	34	25	33
Other	--	2	3	--	3

There were no cocaine, benzedrine (amphetamine), LSD, Thorazine, Miltown or Librium identifications by subjects or observers. In addition, there were no dope (opiate), marihuana, or alcohol identifications by observers.

TABLE 17. Cumulative responses on symptom and sign items in the single dose questionnaires by subjects and observers in the comparison of methaqualone and pentobarbital (methaqualone Study II). Maximum number of responses in any category is 36 (6 subjects for 6 post-drug observations).

	Pentobarbital			Methaqualone	
Symptoms	50 mg	100 mg	200 mg	160 mg	320 mg
Normal	28	15	6	16	7
Stomach turning	--	--	--	--	--
Skin itchy	--	--	1	--	--
Relaxed	3	8	20	6	17
Coasting	--	3	4	3	11
Soapbox	3	--	2	--	5
Pleasant sick	--	--	--	--	--
Drive	--	5	--	--	--
Sleepy	5	6	10	10	12
Drunken	--	3	1	--	12
Nervous	1	2	1	--	--
Other	2	4	5	8	5
Signs					
Normal	23	3	2	11	2
Scratching	--	1	4	--	1
Red eyes	--	7	23	6	18
Relaxed	7	28	33	25	33
Coasting	--	6	7	3	7
Soapbox	1	10	9	8	8
Vomiting	--	--	--	--	2
Nodding	--	3	6	--	--
Sleepy	3	23	17	10	26
Nervous	1	6	--	1	7
Drunken	3	7	21	6	18
Other	7	3	8	--	9

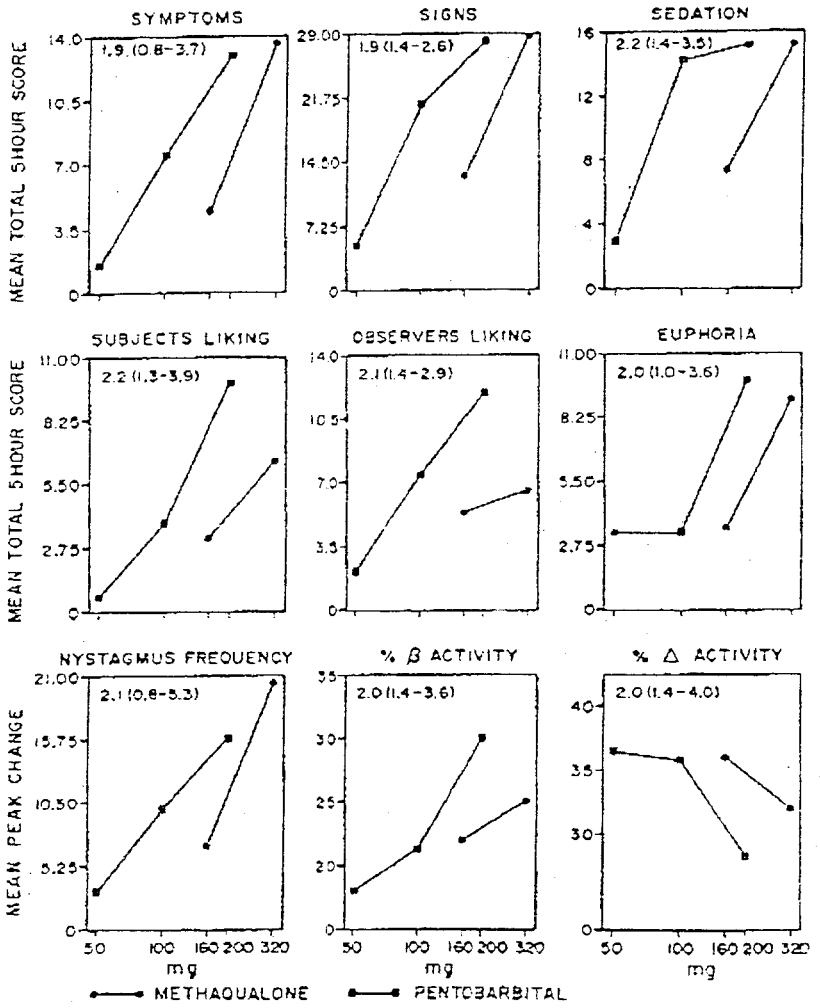

Fig. 11. Dose response curves for the comparison of orally administered methaqualone, pentobarbital, and placebo (Methaqualone Study II). Numbers in upper left hand corner of each graph represent mg of methaqualone equivalent to 1 mg pentobarbital and 95% confidence limits.

These studies indicate that acutely administered methaqualone is capable of producing a profile of typical pentobarbital-like effects in man.

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