Dependence Studies of New Compounds in the Rhesus Monkey, Rat and Mouse (1989)

M. D. Aceto, E. R. Bowman, L. S. Harris and E. L. May

The identities of the test compounds were unknown to us when they were originally submitted except for NIH 10616 (Flumazenil). Dr. Arthur Jacobson, Laboratory of Medicinal Chemistry, NIADDK, NIH, supplied all the compounds except caffeine. This study was done under the auspices of the Committee on Problems of Drug Dependence, Inc.

For the most part, the procedures described by Seevers and his colleagues (1936, 1963) and Deneau (1956) regarding the facilities and training of the monkeys were used and a brief description follows. The monkeys were injected with 3.0 mg/kg s.c. of morphine sulfate every 6 hr for at least 90 days before being used. This dose regimen was reported by Seevers and Deneau (1963) to produce maximal physical dependence.

Modified procedures for the precipitated withdrawal (PPt-W) and single-dose suppression (SDS) tests were reported by Aceto and co-workers (1977 and 1978). The PPt-W test was initiated by the injection of a test drug 2 1/2 hr after an injection of morphine and the animals were observed for signs of withdrawal. The SDS test was started approximately 15 hr after the last dose of morphine at which time the animals were showing withdrawal signs. The onset and duration of action of the test drug were noted. In both tests, a vehicle control and an appropriate positive control (naloxone hydrochloride, 0.05 mg/kg or morphine sulfate, 3.0 mg/kg) along with 2 or 3 different treatments (doses) of a test compound were randomly allocated to the 4 or 5 monkeys of a group. Usually, 3 or 4 groups per compound were used. All drugs were given subcutaneously (1 ml/kg) and the vehicle was water except where indicated. The observer was "blind" with regard to the treatment given. A minimal 2-week washout and recuperation period between tests was allowed. In the primary physical dependence (PPD) tests, the animals of a group received the drug every 4-6 hr for 30-50 days. They were placed in abrupt withdrawal and challenged with naloxone periodically, then observed for signs of physical dependence. All potency estimates are rough approximations only.

The rat-infusion method was reported by Teiger (1974) and certain modifications are indicated as follows. Semi-restrained, male, Sprague-Dawley rats were medicated with a drug by continuous infusion through indwelling intraperitoneal cannulas for 6 days. Rats were anesthetized after which each was fitted with a specially prepared cannula which was passed subcutaneously from the nape of the neck to the lateral side of the lower abdomen and then inserted into the peritoneal cavity. The cannula was anchored at both ends with silk sutures and attached to a

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low-through swivel mechanism which allowed the animal to move about in the cage and eat and drink normally. The swivel was connected to a syringe which was attached to a syringe pump. The animals received 7-10 ml of solution every 24 hr.

In the substitution for morphine (SM) test, the animals first received morphine (50 mg/kg/24 hr on the first day, 100 mg/kg/24 hr on the second day, and 200 mg/kg/24 hr from days 3-6). Then, a test drug was substituted for 2 days. The morphine controls received an infusion of water. The animals were observed for changes in body weight and for behavioral-withdrawal signs for 1/2 hr at 24, 48, 72 and/or 96 hr after stopping the infusion of morphine.

In the primary physical dependence (PPD) study, the rats received test compound for 6 days and then were placed in abrupt withdrawal and observed as above. Occasionally, a drug was given with morphine.

Three mouse tests were used in our laboratory to provide a preliminary estimate of the potency and profile of activity of each test compound. The tests were the tail-flick agonist (TF) and the morphine antagonist (TF vs M) tests and the phenylquinone (PPQ) test (Dewey et al., 1970; Dewey and Harris, 1971). Reference-standard data for these tests are shown in Table 1. In addition, Dr. Jacobson occasionally provided us with estimated starting doses. These doses were based on results obtained from the mouse-hot plate (HP) (Eddy and Leimbach, 1953; Jacobson and May, 1965; Atwell and Jacobson, 1978) and Nilsen (N) (Perrine et al., 1972) tests from his laboratory. Reference data for these tests are shown in Table 2.

Table 1

Comparative Data-ED50, mg/kg s.c. (95% C.L.) of Selected Standards in 3 Mouse Agonist-Antagonist Tests

Drug	Tail-Flick Test	Tail-Flick Antagonist Test	Phenylquinone Test
Pentazocine	15% at 10.0	18 (12-26)	1.7 (1.0-2.5)
Cyclazocine	17% at 1.0[a]	0.03 (0.020-0.78)	0.01(0.005-0.03)
Nalorphine·HCl	None at 10.0	2.6 (0.7-10.0)	0.6 (0.03-1.44)
Naloxone·HCl	None at 10.0	0.04 (0.01-0.09)	No Activity
Naltrexone·HCl	None at 10.0	0.007 (.002-0.02)	No Activity
Morphine Sulfate	5.8(5.7-5.9)	-----	0.23(0.20-0.25)

[a]Mice were ataxic at 3.0 and 10.0 mg/kg but there was no further increase in reaction time.

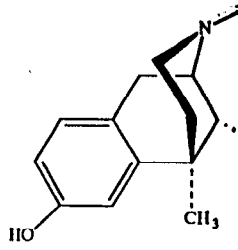
Table 2

Comparative Data (ED50 mg/kg) [95% C.L.] from the Hot Plate and Nilsen Assays

	Hot Plate s.c./p.o.	Nilsen s.c./p.o.
Morphine Sulfate	0.98 (0.83-1.1) 6.3 (4.7-8.3)	1.3 (1.0-1.7) 8.3 (6.0-11.4)
Codeine Phosphate	6.8 (4.5-10.2) 13.5 (9.7-18.7)	7.4 (4.9-11.0) 14.7 (9.2-23.3)
Levorphanol Tartrate	0.2 (0.1-0.3) -	0.2 (0.16-0.3) 2.5 (1.7-3.7)
Meperidine·HCl	5.3 (4.0-7.1) -	- -
(-)-Metazocine·HBr	0.6 (0.5-0.9) 10.6 (8.0-14.1)	0.5 (0.3-0.7) 26.0 (21.0-33.0)
Dihydromorphinone·HCl	0.19 (0.15-0.25) 0.9 (0.7-1.2)	0.2 (0.15-0.3) 1.8 (1.5-2.1)
Nalorphine·HCl	9.9 (5.7-2.1) -	23.0 (16.2-32.7) -
Cyclazocine Pentazocine	1.5 (1.1-2.1) 9.3 (6.7-12.8) -	0.1(0.07-0.16) 6.5 (4.4-8.8) -
Chlorpromazine·HCl	1.1 (0.9-1.5) -	- -

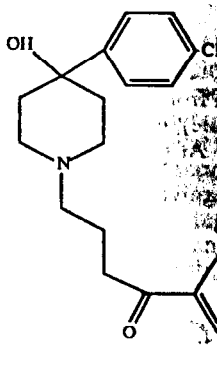
No dose response for naloxone and naltrexone.
Phenobarbital, amobarbital, oxazepam, flurazepam, meprobamate and mescaline are inactive on the hot plate test.

NIH 7912 (±)-N-



A. Special Study: AD
(1.9 - 9.5)
B. Special Study: AD
(1.9 - 9.8)
C. Special Study: AD
0.9 (0.3 - 2.2)

NIH 8032, Haloperidol



MONKEY DATA
(SDS)

This study was initiated
N-butyrophenone-prod
were found to have opi
by the observation, in
monkey, when medicate
his handler. The doses
neuroleptic signs were

As can be seen in the f
highest dose, more ret

lected Standards in 3

Phenylquinone Test

1.7 (1.0-2.5)
0.01(0.005-0.03)
0.6 (0.03-1.44)
No Activity
No Activity
0.23(0.20-0.25)

no further increase in

Hot Plate and Nilsen

Nilsen s.c./p.o.

1.3 (1.0-1.7)
8.3 (6.0-11.4)
7.4 (4.9-11.0)
14.7 (9.2-23.3)
0.2 (0.16-0.3)
2.5 (1.7-3.7)
-
-
0.5 (0.3-0.7)
26.0 (21.0-33.0)
0.2 (0.15-0.3)
1.8[1] (1.5-2.1)
23.0 (16.2-32.7)
-
0.1(0.07-0.16)
6.5 (4.4-8.8)
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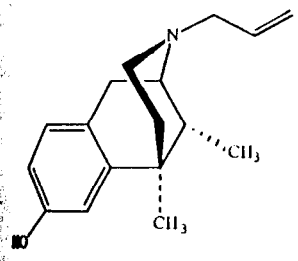
NIH 7912 (±)-N-allylnormetazocine, (±)-SKF 10,047, (±)-NANM

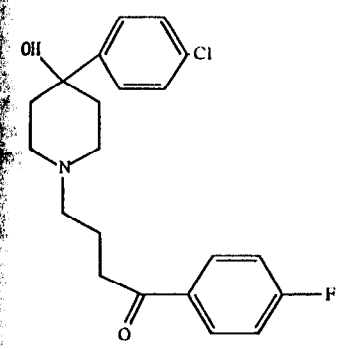


MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M. - 1.9 (0.7 - 6.0)
3) PPQ - 10.4 (5.3 - 20.3)
4) HP - Inactive to 50.0
5) N - Inactive to 50.0

A. Special Study: AD50 of NIH 7912 vs ED80 of morphine in PPQ Test = 3.3 (1.9 - 9.5)
B. Special Study: AD50 of naloxone vs ED80 of NIH 7912 in PPQ Test = 3.4 (1.9 - 9.8)
C. Special Study: AD50 of yohimbine vs ED80 of NIH 7912 in PPQ Test = 0.9 (0.3 - 2.2)

NIH 8032, Haloperidol



MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

1) TF - 14.6 (10.9 - 19.5)[a]
2) TF vs. M. - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 0.011 (0.002 - 0.048)

Rodent data reported previously.

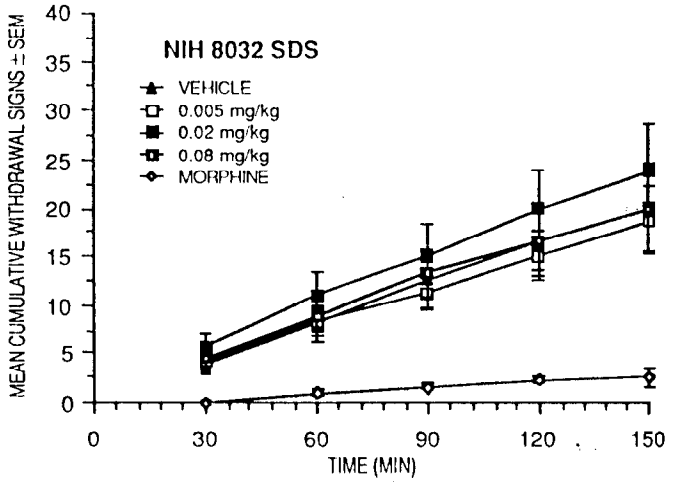
[a]Very erratic results. Naloxone produced 65% antagonism vs the ED60 of haloperidol.

MONKEY DATA
(SDS)

This study was initiated to provide comparative data for the evaluation of certain N-butyrophenone-prodine compounds (NIH 10494 and NIH 10495), which were found to have opioid/neuroleptic properties. This study was also prompted by the observation, in a previous study, that a normally docile male rhesus monkey, when medicated with haloperidol, became unusually aggressive towards his handler. The doses selected in this study were not in the range where severe neuroleptic signs were observed.

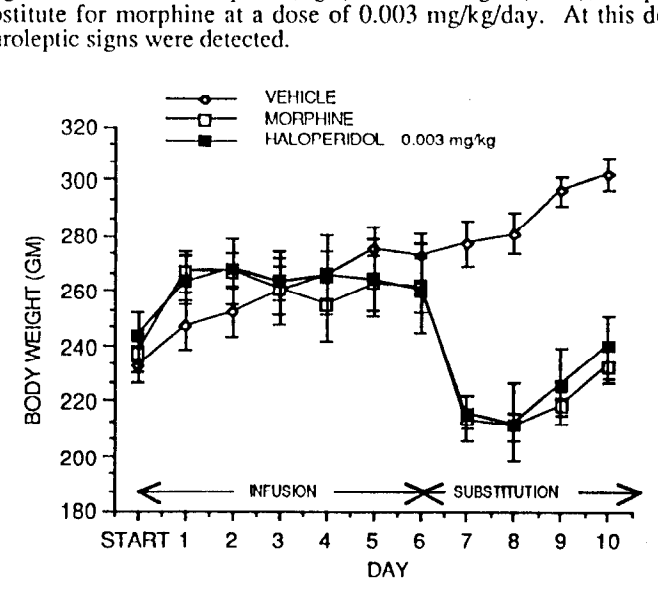
As can be seen in the fig., haloperidol did not substitute for morphine. At the highest dose, more retching and tremors were observed than with the vehicle

controls. In addition, some of these animals appeared slower and subdued. At the two lower doses, more restlessness and retching were noticed than in the controls. In this dose range, none of the animals exhibited aggressive behavior.



RAT INFUSION

A) Substitution for morphine (R-SM) As can be seen from the data on body weight and water consumption (figs.) and overt signs (table), haloperidol did not substitute for morphine at a dose of 0.003 mg/kg/day. At this dose, no overt neuroleptic signs were detected.



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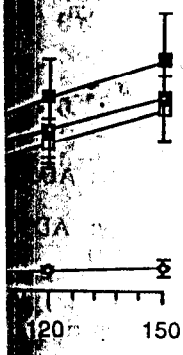

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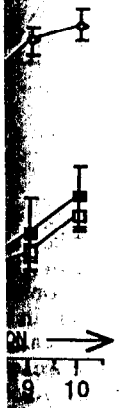
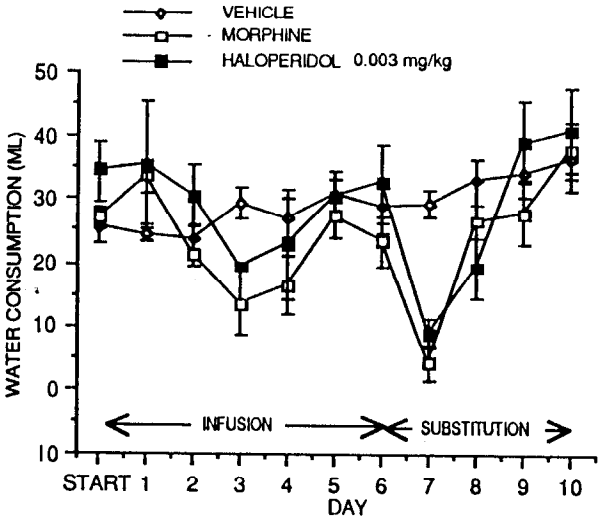
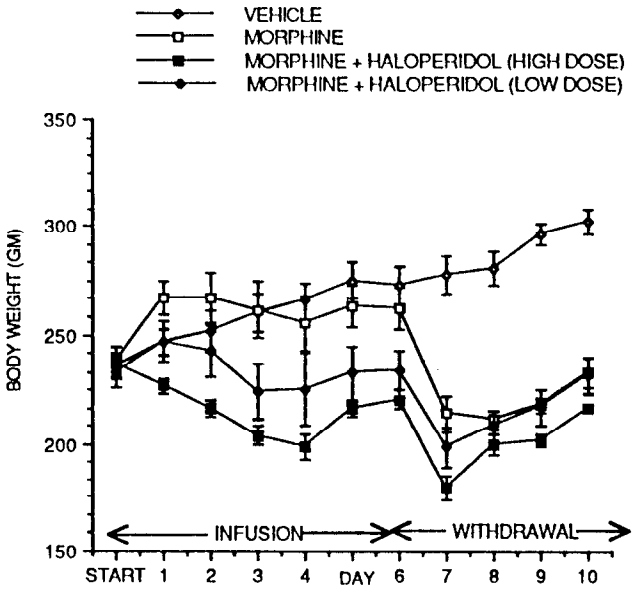




B) Special Morphine Plus Haloperidol Primary Physical Dependence Study (SR-PPD) When morphine plus haloperidol, at 2 dose levels, and morphine were given and then abruptly withdrawn after 6 days, the withdrawal syndromes were qualitatively similar to each other. Quantitatively, at 24 hrs, the animals receiving haloperidol and morphine showed more weight loss and overt withdrawal signs than those receiving morphine only or vehicle. This was in spite of the fact that the animals receiving the combination of drugs showed severe disturbances such as weight loss, changes in water consumption and neuroleptic behavioral signs during the administration of drugs.



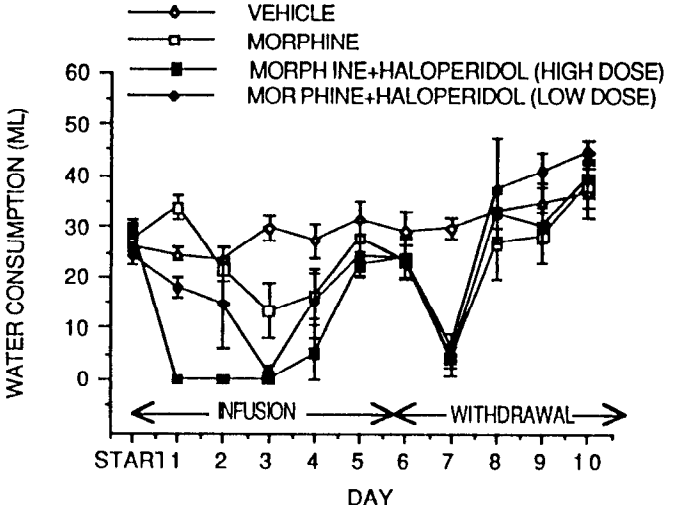


Table. Evaluation o

Rat Infusion Studies
and morphine simul

Vehicle Infusion[b]
N=4

Morphine Infusion[d]
Vehicle Substitution
N=3

Morphine Infusion[d]
Haloperidol Substitu
N=3

Morphine plus Halo
Infusion[d,f], Vehicle
(high-dose regimen)
N=3

Morphine plus Halo
Infusion, Vehicle St
(low-dose regimen)
N=3

[a]Mean number of o
observation period
squealing, hypers
chewing.
[b]Vehicle volume w
[c]Statistically signifi
treated group. Oi
[d]Morphine S04 infu
days 3-6.
[e]Haloperidol infusi
0.01 mg/kg days
[f]Haloperidol infusi
[g]Haloperidol infusi
3-6 (low dose).

Table. Evaluation of overt withdrawal signs observed in the infusion studies.

Rat Infusion Studies: Haloperidol substitution for morphine and haloperidol and morphine simultaneously.

	Overt Withdrawal Signs				
	24hr	48hr	72hr	90hr	120hr
Vehicle Infusion[b] N=4	0.0	0.6	0.3±3	1.5±1.5	0.0
Morphine Infusion[d] Vehicle Substitution N=3	9.0±3.5[c]	9.0±2.3[c]	6.3±3.9	2.0±1.2	1.0±0.7
Morphine Infusion[d] Haloperidol Substitution[e] N=3	7.7±3.2[c]	11.0±5.9[v]	3.7±2.2	1.3±0.9	1.7±1.7
Morphine plus Haloperidol Infusion[d,f], Vehicle Substitution (high-dose regimen) N=3	12.7±4.3[c]	8.0±3.8[c]	4.3±2.4[c]	2.0±1.5	1.0±0.6
Morphine plus Haloperidol[d,g] Infusion, Vehicle Substitution (low-dose regimen) N=3	16.0±4.5[c]	7.3±1.6[c]	5.3±1.6[c]	2.3±0.5	0.3±0.3

[a]Mean number of opioid-like withdrawal signs ± S.E.M. noted in a 1/2 hr observation period at specified intervals. Signs are hypersensitivity, squealing, hypersensitivity, aggression, wet-dog shakes, rubbing and chewing.

[b]Vehicle volume was 8 ml/24 hr days 1-10.

[c]Statistically significant differences (p = 0.05 or less) between Vehicle only and treated group. One-tailed test (Mann-Whitney test).

[d]Morphine SO_4 infusion - 50 mg/kg day 1, 100 mg/kg day 2, and 200 mg/kg days 3-6.

[e]Haloperidol infusion 3.0 mg/kg day 1, 1.5 mg/kg day 2, 0.5 mg/kg day 3, 0.01 mg/kg days 3-6 (high dose)

[f]Haloperidol infusion - 0.03 mg/kg on days 7 and 8, Vehicle on days 9 and 10

[g]Haloperidol infusion 0.5 mg/kg day 1, 0.15 mg/kg day 2, 0.003 mg/kg days 3-6 (low dose).

NIH 8773 (-)-N-allylnormetazocine, (-)-SKF 10,047, (-)-NANM

MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

See NIH 7912

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M. - 0.2 (0.1 - 0.6) 7.1
3) PPQ - 1.3 (0.4 - 5.0) 10.3[a,b,c]
4) HP -
5) N - Inactive to 50.0

A. Special Study: AD_{50} of naloxone vs ED_{80} of NIH 8773 in PPQ Test = 0.13 (0.05 - 0.3)
B. Special Study: AD_{50} of NIH 8773 vs ED_{80} of morphine in PPQ Test = 1.2 (0.6 - 2.3)
C. Special Study: AD_{50} of yohimbine vs ED_{80} of NIH 8773 in PPQ Test = 0.2 (0.1 - 0.3)

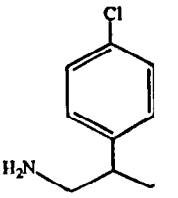
NIH 8775 (+)-N-allylnormetazocine, (+)-SKF 10,047, (+)-NANM

MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

See NIH 7912

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs M. - 13.2 (6.6 - 26.2) 30.0
3) Inactive to 40.0
4) HP - Inactive to 50.0
5) N - Inactive to 20.0

NIH 9512



MONKEY DA
(PPt-W)

NIH 9512 was
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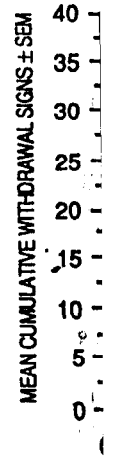
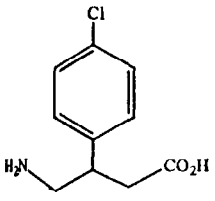


NIH 9512 Baclofen, Lioresal



MOUSE DATA-ED OR AD50
(95% C.L.) (mg/kg or % change)

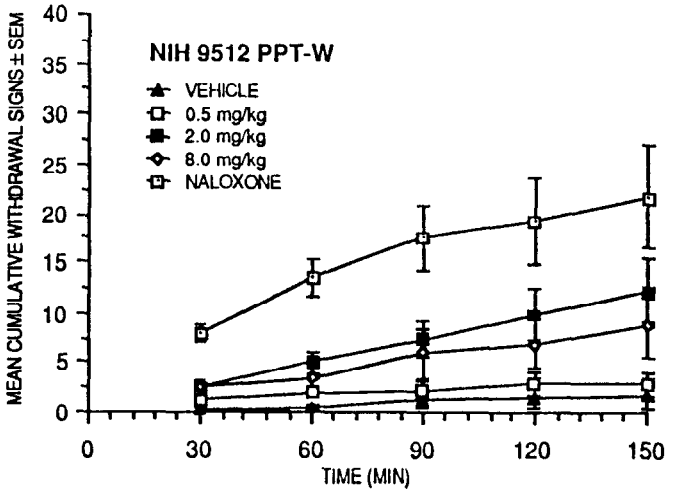
1) TF - 0% at 1.0, 45% at 3.0, 64% at 10.0 and 3% at 30.0
2) TF vs. Morphine - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 1.2 (0.4 - 3.1)
4) HP - 2.1 (1.5 - 2.7)
5) N - Inactive to 20.0

[a]Previously reported as very active [AD50 - 0.06 (0.02 -0.17)] in NIDA Monograph 27, 1979.

MONKEY DATA
(PPt-W)

NIH 9512 was studied in the single-dose suppression (SDS) test in monkeys (NIDA Monograph 27, 1979). It did not substitute for morphine. In order to fully investigate possible antagonist properties, a precipitated withdrawal test was conducted.

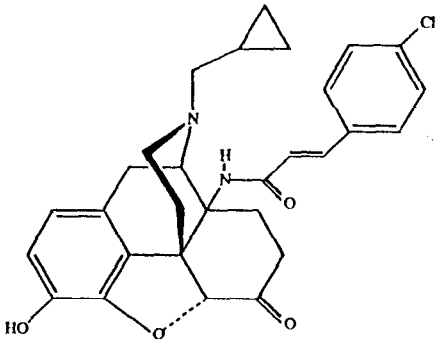
In non-withdrawn, morphine-dependent monkeys, this compound increased the incidence of certain withdrawal signs designated fighting, avoids contact, vocalizing and in one monkey, at the high dose, retching, vomiting and coughing. In addition, at 2.0 mg/kg, 2 monkeys vocalized when their abdomens were palpated and had rigid abdominal muscles. Thus, although the compound increased the incidence of certain withdrawal signs, it did not precipitate a full withdrawal syndrome. The vehicle was H_3PO_4 and H_20.



Conclusion

This compound does not show antagonist activity either in the mouse antinociception vs morphine assay or morphine-dependent monkeys.

NIH 10443 14β-(*p*-Chlorocinnamoylamino)-7,8-dihydro-N-cyclopropylmethyl-normorphinone mesylate



MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

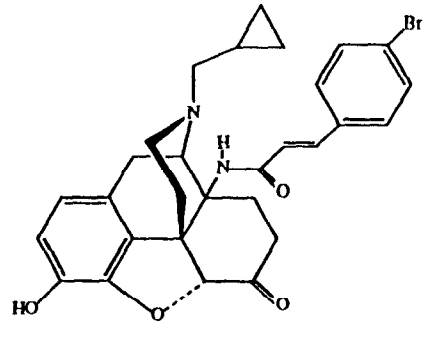
1) TF - Inactive at 1.0, 10.0 and 30.0[a]
2) TF vs. M. - 0.12 (0.07 - 0.23)[a]
3) PPQ - 23% at 3.0, 34% at 10.0, 69% at 30.0 and 54% at 10.0[a]
4) HP - Inactive to 20.0

[a]Reported previously in NIDA Monograph 81, 1987

Special Duration Study: Morphine antagonism of NIH 10443 ED_{200}

Pretreatment Time (hr)	% Antagonism
24	76
48	19
72	18

NIH 10445 14β-(*p*-Bromocinnamoylamino)-7,8-dihydro-N-cyclopropyl-methylnormorphinone mesylate



MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

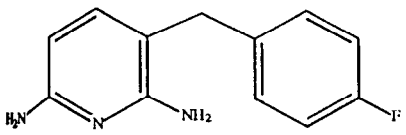
1) TF - Inactive at 1.0, 10.0 and 30.0[a]
2) TF vs. M. - 0.8 (0.6 - 1.0)[a]
3) PPQ - 7.1 (3.1 - 16.4)[a]
4) HP - Inactive to 20.0[a]

[a]Reported previously in NIDA Monograph 81, 1987

Special Duration Study: Morphine antagonism of NIH 10445 ED_{200}

Pretreatment Time (hr)	% Antagonism
24	80
48	57
72	36
96	29
120	1

NIH 10446 2,6-Diamino-3-*p*-fluorobenzylpyridine

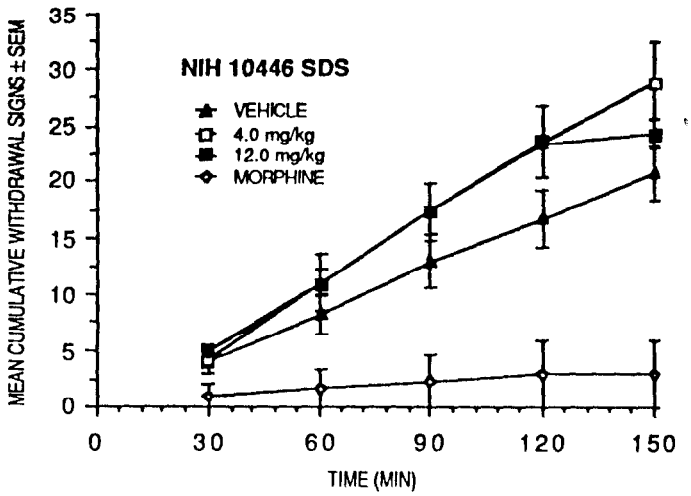


MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

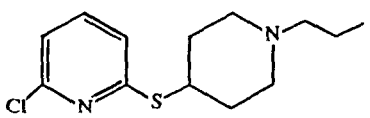
1) TF - 3% at 0.1, 20% at 1.0, 6% at 1.00 and 0% at 30.0
2) TF vs. M. - 22% at 1.0, 0% at 10.0 and 0% at 3.0
3) PPQ - 0.96 (0.31 - 2.98)
4) HP - Inactive at 5.0 and 20.0

MONKEY DATA
(SDS)

In the dose range of 4.0 - 12.0 mg/kg, NIH 10446 did not substitute for morphine. The drug may have exacerbated withdrawal (see fig.). One animal receiving 4.0 mg/kg showed myoclonic jerks.



NIH 10447, MCV 4517 2-Chloro-6-(4-N-*n*-propylpiperidino)thiopyridine hydrochloride



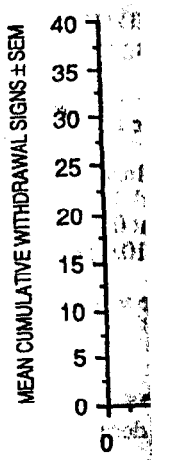
MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M. - 27% at 1.0, 47% at 10.0 and 16% at 30.0
3) PPQ - 2.6 (0.5 - 12.7)
4) HP - Inactive to 20.0

MONKEY DATA

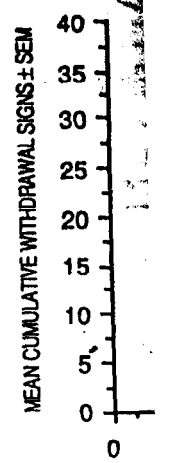
A. (SDS)

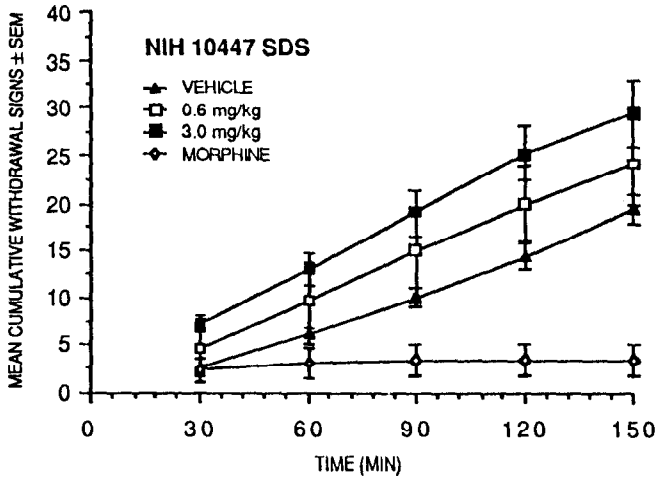
NIH 10447 does not substitute for morphine. The drug seemed to exacerbate withdrawal (Fig. 2); however, this may be a reflection of the fact that the vehicle controls showed an unusually weak abrupt-withdrawal syndrome.



B. (PPt-W)

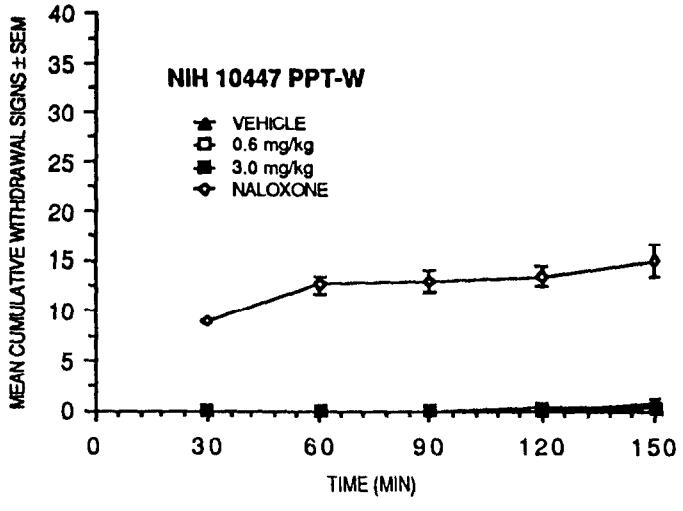
As shown in the
morphine-addicte
drowsy and move
highest dose was



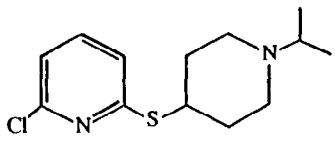


B. (PPt-W)

As shown in the figure, NIH 10447 was inactive in precipitating withdrawal in morphine-addicted monkeys. Two animals receiving the highest dose were very drowsy and moved about slowly one hour after drug was given. Another, at the highest dose was not as aggressive as usual.



NIH 10448, MCV 4518 2-Chloro-6-(4-N-isopropylpiperidino)thiopyridine oxalate

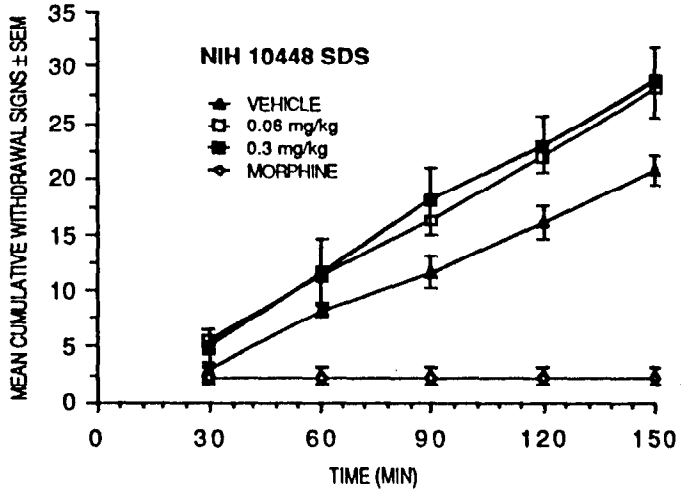


MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

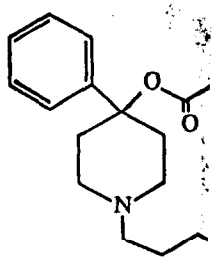
1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M. - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 37% at 0.1, 40% at 1.0, 54% at 10.0 and 84% at 30.0
4) HP - Inactive to 20.0

MONKEY DATA
(SDS)

This compound does not substitute for morphine (see fig.). The drug may have exacerbated withdrawal although the effect does not seem to be dose related.



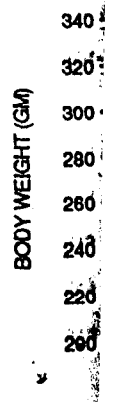
NIH 10495, MCV
pionyloxy piperidi



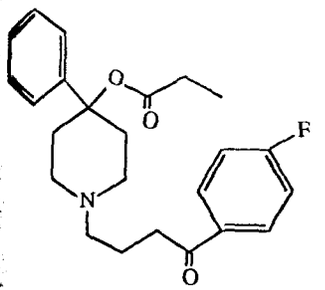
RAT INFUSION

A. (SDS)

As shown in the
partly substituted
table), the drug ne
delayed onset o
behavioral withd
reemerged on d
substituted.



NIH 10495, MCV 4560 N-3-(*p*-Fluorobenzoyl)propyl-4-phenyl-4-propionyloxy piperidine hydrochloride



MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

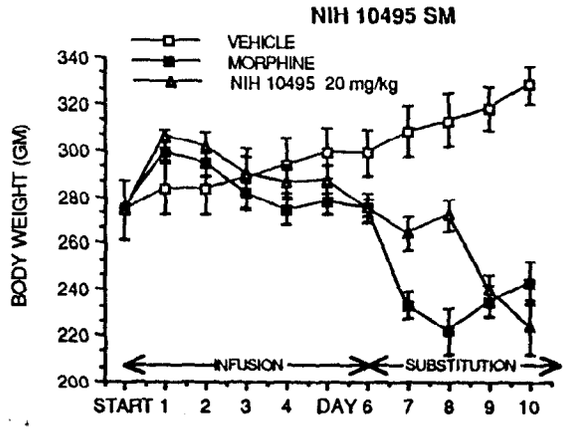
1) TF - 0.3 (0.1 - 1.1)
2) TF vs. M. - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 0.07 (0.02 - 0.18)
4) HP - 0.32 (0.25 - 0.42)

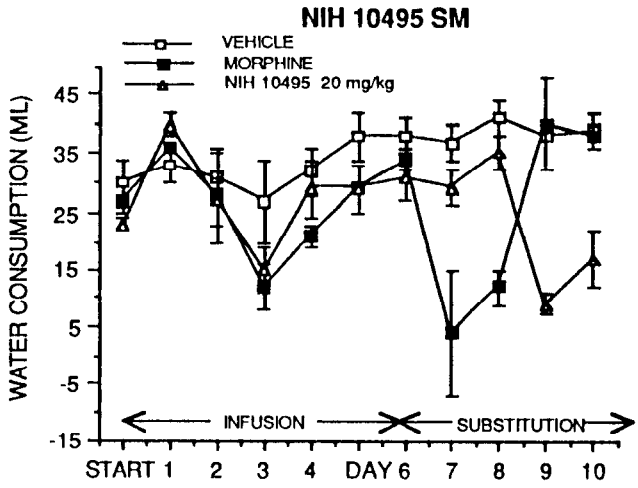
Rodent and monkey data reported in NIDA Monograph 90, 1988.

RAT INFUSION

A. (SDS)

As shown in the figs. (body weight loss and water consumption), NIH 10495 partly substituted for morphine at 20.0 mg/kg. Regarding behavioral signs (see table), the drug nearly substituted for morphine. It is possible that the drug has a delayed onset of action since body weight loss, water consumption and behavioral withdrawal were less on days 8 than day 7. Withdrawal signs reemerged on days 9 and 10 after the drug was withdrawn and vehicle substituted.



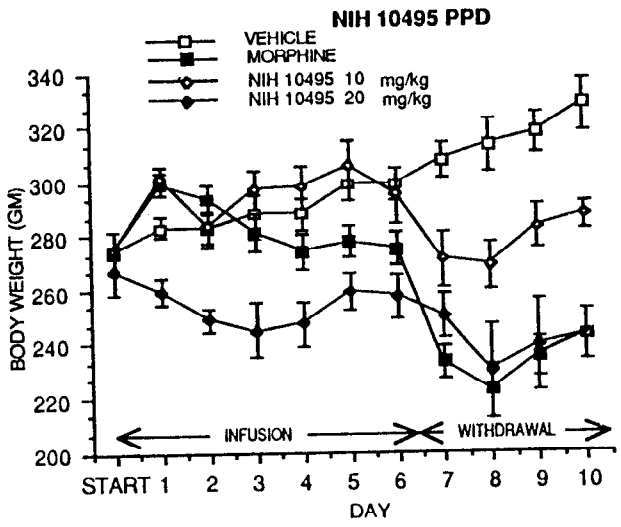


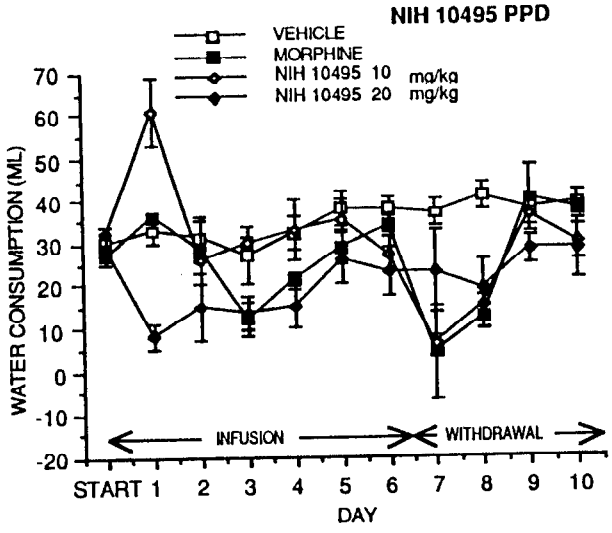
Rat Infusion - Cont'd

B. (PPD)

NIH 10495 produced a dose-related fall in body weight and drop in H_20 consumption (see figs.) and dose-related increases in withdrawal signs (see table) when withdrawn after 6 days of continuous infusion. During the first day of infusion, the drug produced unusual changes in the H_20 consumption, the low dose increased and the high dose decreased consumption dramatically. Whether or not this is a spurious happening is uncertain.

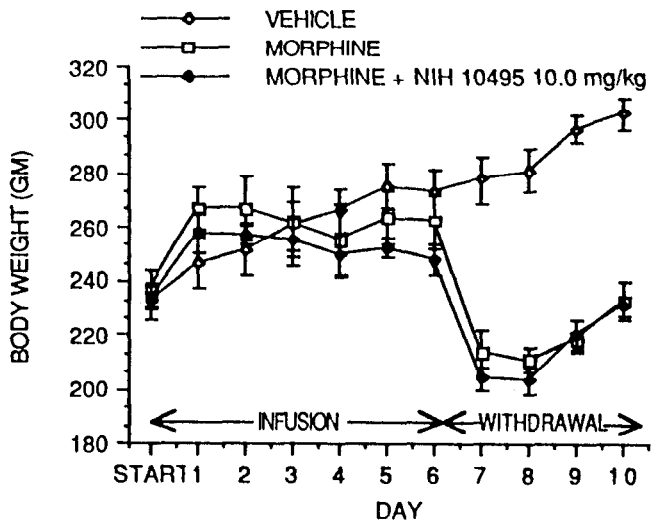
In any case, a physical dependence syndrome, similar to morphine's, develops with this agent.


NIH 10495 PPD
VEHICLE
MORPHINE
NIH 10495 10 mg/kg
NIH 10495 20 mg/kg
BODY WEIGHT (GM)
340
320
300
280
260
240
220
200
INFUSION
WITHDRAWAL
START 1 2 3 4 5 6 7 8 9 10
DAY


NIH 10495 PPD
VEHICLE
MORPHINE
NIH 10495 10 mg/kg
NIH 10495 20 mg/kg
WATER CONSUMPTION (ML)
70
60
50
40
30
20
10
0
-10
-20
INFUSION
WITHDRAWAL
START 1 2 3 4 5 6 7 8 9 10
DAY

C. Special Study: Morphine + NIH 10495 R-PPD

The withdrawal syndrome resulting from the abrupt withdrawal of a solution containing morphine and NIH 10495 was qualitatively and quantitatively similar to that produced by the morphine controls (see figs. and table).



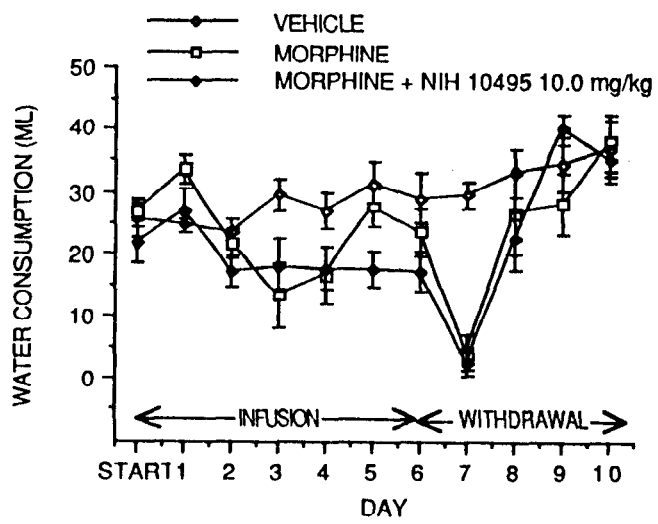


Table: Primary Physical Dependence (PPD) and Substitution for Morphine Studies (SM) with NIH 10495 in Continuously-Infused Rats

Treatment	Hr in Withdrawal 24	48	72	96
	Mean Number of Withdrawal Signs [a,b]			
1. Vehicle Controls[c]	0.5	1.5	0	1.3
2. Morphine Controls[d]	14.2[b]	20.0[b]	9.0[b]	2.0
3. NIH 10495-PPD[e] (high dose)	9.3[b]	9.3[b]	8.0	3.7
4. NIH 10495-PPD[f] (low dose)	12.5	6.5	5.3	2.3
5. NIH 10495-SDS[g] (high dose)	3.8	0.8	12.8[b]	8.0[b]

[a]Hypersensitivity, squeaking, aggression, wet-dog shakes, rubbing and chewing;

[b]One-tailed test Mann-Whitney U test, $p < 0.05$, probability value vs. water controls;

[c]8 ml/24 hr. N=4;

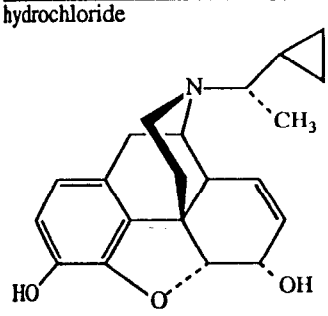
[d]Dose regimen of morphine SO_4, 50 mg/kg on day 1, 100 mg/kg on day 2, 200 mg/kg on days 3-6. N=5;

[e]Dose regimen of NIH 10495, 20 mg/kg/day on days 1-6; then H_20 as above during withdrawal. N=3;

[f]Dose regimen of NIH 10495 10.0 mg/kg on days 1-6; then, H_20 as above during withdrawal. N=4;

[g]Morphine SO_4 Infusion, days 1-6 as above then, NIH 10495 on days 7 and 8, 20 mg/kg, and H_20 as above on days 9 and 10. N=5 on days 7 and 8; and 4 on days 9 and 10.

NIH 10497, MCV 4558 N-[(1R)-1-Cyclopropyl]ethylnormorphine hydrochloride

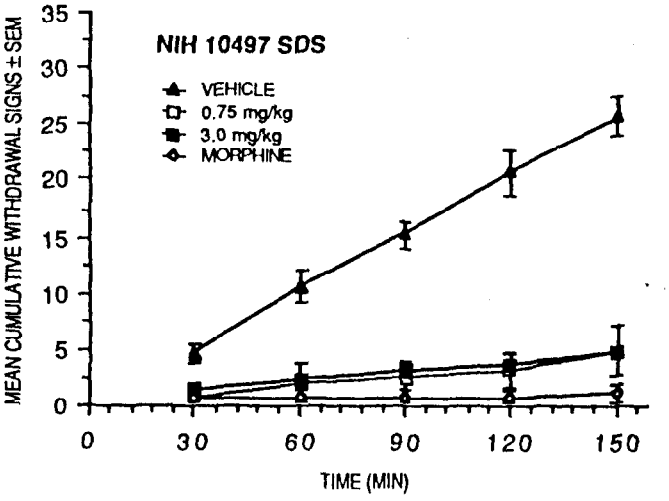


MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

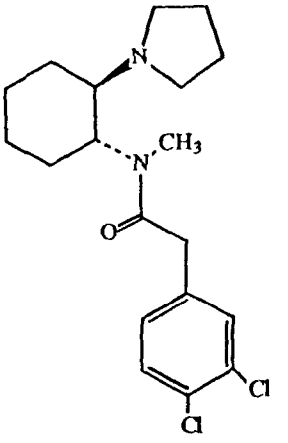
1) TF - 2.0 (0.6 - 6.6)
2) TF vs. M. - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 0.03 (0.01 - 0.2)

MONKEY DATA
(SDS)

NIH 10497 substituted completely for morphine. The drug acted promptly and its duration of action was about 2 hr. (see fig.). In addition, this drug is slightly less potent than morphine. Many drug-related side effects were seen including body sag, jaw sag, slowing, staring, and salivation. The incidence of drowsiness was more than that observed in morphine-treated controls.



NIH 10532, MCV 4581 (+)-*trans*-3,4-Dichloro-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl-1] benzeneacetamide *d*-tartrate, ((+)-U 50,488 *d*-tartrate)



MOUSE DATA-ED OR AD50
(95% C.L.) (mg/kg or % change)

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M. - 0% at 1.0, 2% at 10.0 and 21% at 30.0
3) PPQ - 6.5 (2.0 - 20.9)[a]
4) HP - Inactive at 20.0

Reported previously in NIDA Monograph 90, 1988.

[a]Special Study: Naloxone vs NIH 10532 ED_{80} in PPQ test

Naloxone Dose mg/kg sc	% Antagonism
40.0	67%
20.0	64%
10.0	29%
1.0	14%

Conclusion: Very high doses of naloxone only partially antagonize the antinociceptive activity of NIH 10532 in the PPQ test.

NIH 10533, MCV 4582 (-)-*trans*-3,4-Dichloro-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl-1] benzeneacetamide *l*-tartrate, ((-)-U 50,488 *l*-tartrate)

See NIH 10532

MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

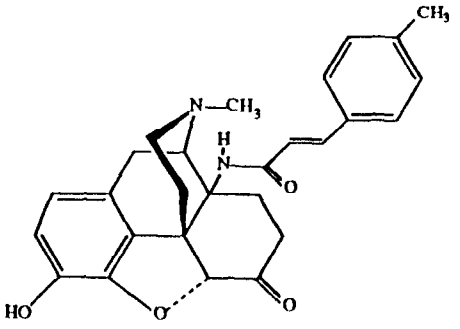
1) TF - 2.5 (1.0 - 6.0)[a]
2) TF vs. M. - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 0.2 (0.08 - 0.54)[b]
4) HP - 8.9 (6.0 - 13.2)

Rodent data reported previously in NIDA Monograph 90, 1988.

a. Special Study: Naloxone vs NIH 10533 ED_{80} in TF test = 0.7 (0.2 - 3.2)

b. Special Study: Naloxone vs NIH 10553 ED_{80} in PPQ test = 1.0 (0.3 - 2.9)

NIH 10544 mesylate — 14β-(*p*-Methylcinnamoylamino)-7,8-dihydromorphinone

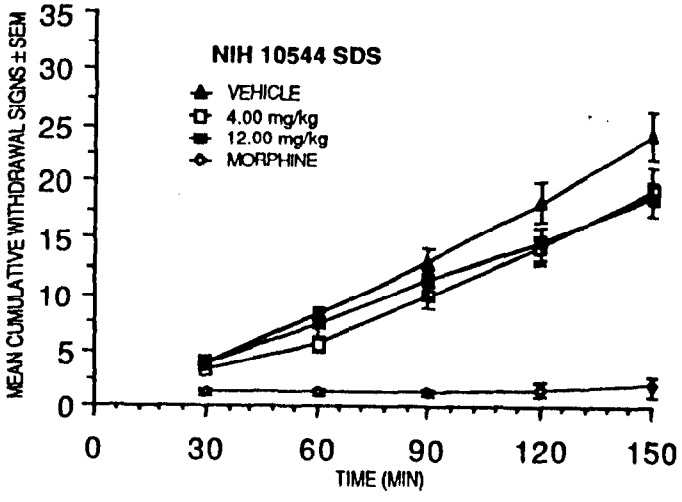


MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

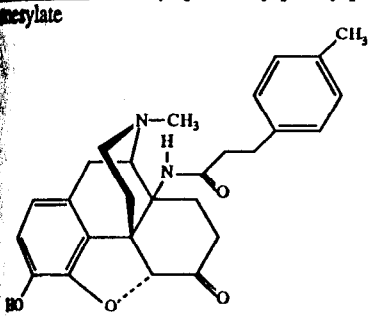
1) TF - 11% at 1.0 and 10.0 and 14% at 30.0
2) TF vs. M. - 0.6 (0.2 - 1.4)
3) PPQ - 17% at 0.1, 57% at 1.0, 57% at 3.0, 63% at 10.0, 51% at 30.0 and 69% at 60.0
4) HP - Inactive at 2.0 and 10.0

MONKEY DATA
(SDS)

As shown in the accompanying graph, NIH 10544, at doses of 4 and 12 mg/kg neither substituted for morphine nor exacerbated withdrawal.



NIH 10545 14β-(*p*-Methylphenylpropionylamino)-7,8-dihydromorphinone mesylate

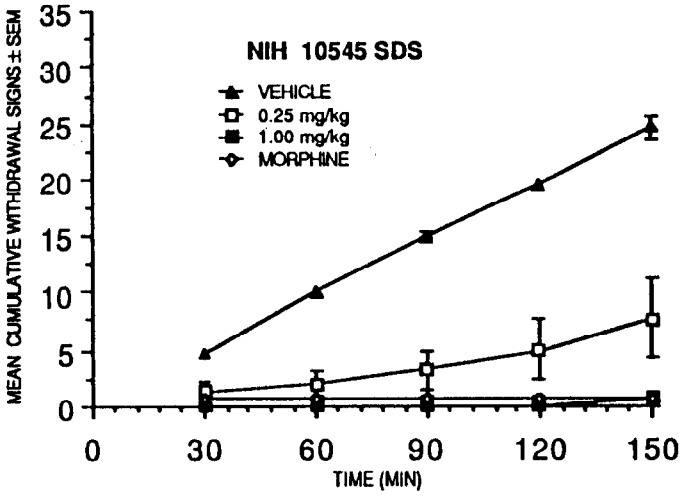


MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

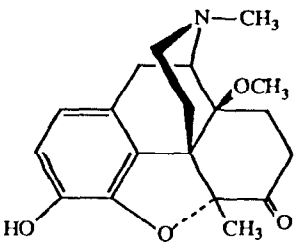
1) TF - 0.5 (0.2 - 1.5)
2) TF vs. M - 0% at 1.0 and 10.0 and 17% at 30.0
3) PPQ - 0.09 (0.03 - 0.24)
4) HP - Inactive at 2.0 and 10.0

MONKEY DATA
(SDS)

A dose-related suppression of abstinence signs in morphine-dependent and withdrawn monkeys was observed. At 1.0 mg/kg, the drug substituted completely for morphine. Onset of action was prompt offset of action was at least that of morphine (> 140 min). NIH 10454 is estimated to be 3 to 5 x more potent than morphine.



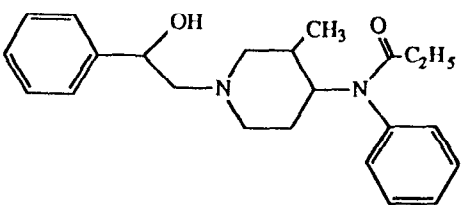
NIH 10549 14β-Methoxy-5-methyl-7,8-dihydromorphinone hydrobromide



MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

1) TF - 0.02 (0.007 - 0.05)
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 0.003 (0.001 - 0.006)

NIH 10551 (±)-*cis*-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenylpropanamide hydrochloride



MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

1) TF - 0.0002 (0.0001 - 0.0005)
2) TF vs. M. - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 0.00013 (0.00006 - 0.0003)
4) HP - < 0.0002

Rodent data reported previously in NIDA Monograph 90, 1988.

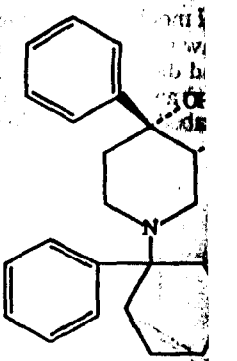
A. Special Study: Naloxone vs NIH 10551 ED_{80} in PPQ test AD50 = 3.7 (1.3 - 10.7)

B. Special Study: Naloxone vs ED80 of NIH 10551 in TF = 0.06 (0.03 - 0.1)

MONKEY DATA
(*SDS*)

Estimated potency in SDS test was 25,000 x morphine. SDS results reported previously in NIDA Monograph 90, 1988.

NIH 10553 (+)-
piperidine hydrochlo

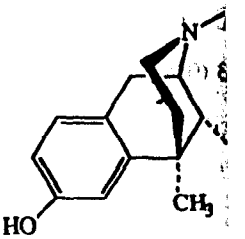


[b]Special Study: Nal
- 0.12)

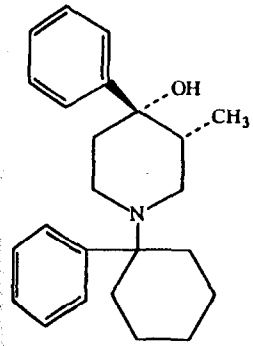
NIH 10554 (-)-4
piperidine hydrochlo

See NIH 10553

NIH 10556 (+)-
hydrochloride



NIH 10553 (+)-4-Hydroxy-3-methyl-4-phenyl-1-(1-phenylcyclohexyl)-piperidine hydrochloride



MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

1) TF - 8.7 (4.1 - 18.3)[a]
2) TF vs. M. - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 0.7 (0.3 - 2.1)[a,b]
4) HP - 16% at 20.0

Vehicle-5% Tween 80 in H_2O

[a]Rodent data reported previously in NIDA Monograph 90, 1988.

[b]Special Study: Naloxone vs NIH 10553 ED_{80} in PPQ test. AD_{50} = 0.06 (0.03 - 0.12)

NIH 10554 (-)-4-Hydroxy-3-methyl-4-phenyl-1-(1-phenylcyclohexyl)-piperidine hydrochloride

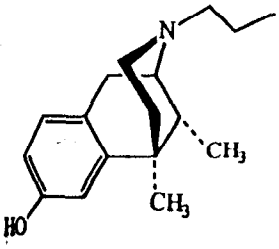
MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

See NIH 10553

1) TF - 0% at 1.0, 14% at 10.0 and 34% at 30.0[a]
2) TF vs. M. - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 2.5 (0.8 - 7.3)[a]
4) HP - Inactive to 20 mg/kg

[a]Vehicle 4% Tween80 in H_2O

NIH 10556 (+)-5,9α-Dimethyl-2'-hydroxy-2-propyl-6,7-benzomorphan hydrochloride



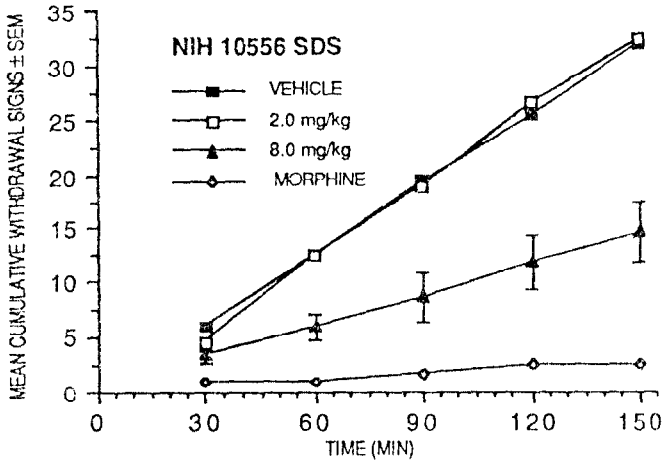
MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

1) TF - Inactive at 1.0, 3.0, 10.0 and 30.0[a]
2) TF vs. M. - 0% at 1.0, 6% at 10.0 and 20% at 30.0
3) PPQ - Inactive at 1.0, 10.0 and 30.0
4) HP - Inactive to 20 mg/kg

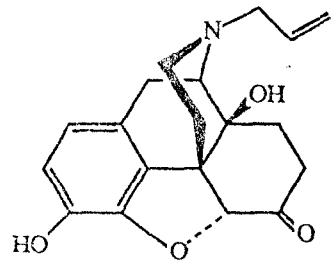
[a]slight ataxia

MONKEY DATA
(SDS)

At the highest dose (8.0 mg/kg), severe ataxia was noted in all monkeys receiving NIH 10556. In addition, one monkey vomited, developed jaw sag and appeared stuporous. However, as shown in the graph, this compound did not substitute completely for morphine. Most of the suppression of withdrawal signs at 8.0 mg/kg may be attributed to dimunition of response following abdominal palpation and to a decrease in restlessness.



NIH 10562, NIH 7890 Naloxone hydrochloride



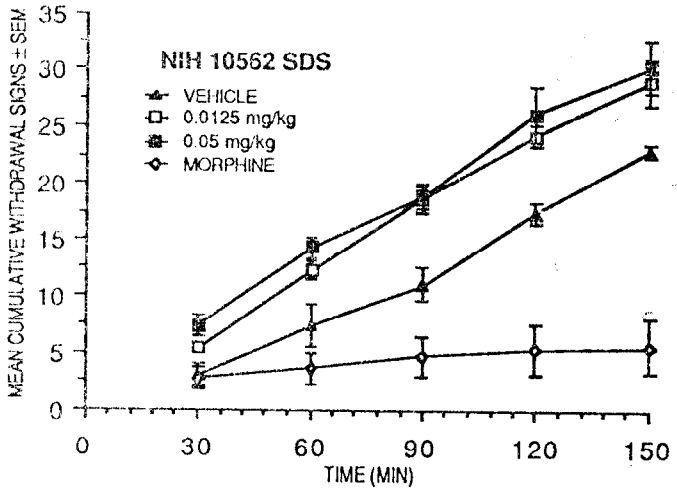
MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M. - 0.03 (0.01 - 0.1)
3) PPQ - 1.3 (0.2 - 6.8)

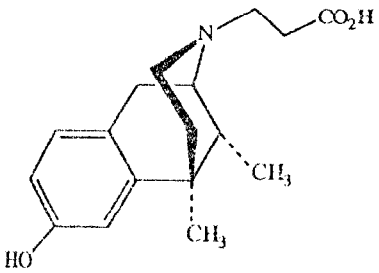
MONKEY DATA
(SDS)

As shown in the fig., NIH 10562, at 0.05 and 0.0125 mg/kg, exacerbated withdrawal. Onset of action was prompt and offset was greater than 150 min. It

should be noted that antagonists are much more potent and have a longer duration of action in withdrawn, morphine-dependent monkeys.



NIH 10564 (±)-2-(2-Carboxyethyl)-5,9α-dimethyl-2'-hydroxy-6,7-benzomorphan hydrochloride



MOUSE DATA-ED OR AD50 (95% C.L.) (mg/kg or % change)

1) TF - Inactive at 1.0, 10.0 and 30.0[a]
2) TF vs. M. - Inactive at 0.1, 1.0, 3.0, 10.0 and 30.0
3) PPQ - 1.4 (0.3 - 6.4)[a]

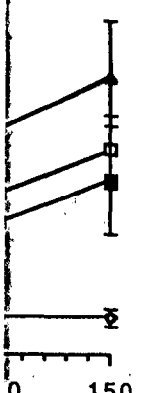
[a]Repeated: 16% at 0.3, 34% at 1.0, 61% at 5.0, 50% at 10.0 and 47% at 30.0

7-benzomorphan

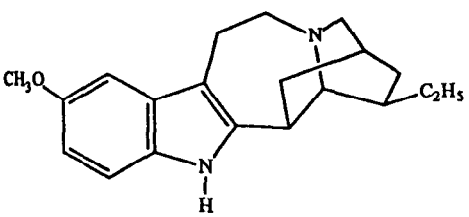
TA-ED OR AD50
(mg/kg or %

active at 1.0, 10.0
0
M. - Inactive at 1.0
0
23% at 0.1, 29% at
% at 1.0, 14% at
% at 10.0 and 43%

animals also appeared
e monkeys at the high
when their abdomens
ug did not substitute



NIH 10567 Ibogaine hydrochloride



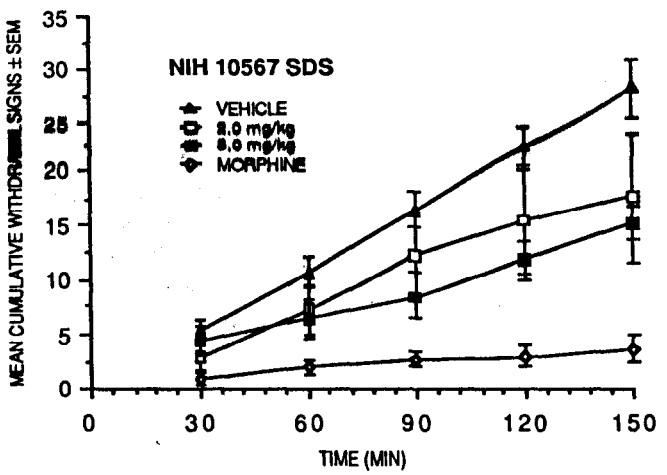
MOUSE DATA-ED OR AD50
(95% C.L.) (mg/kg or %
change)

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M. - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 9.7 (2.8 - 34.0)
4) HP - Inactive to 20.0

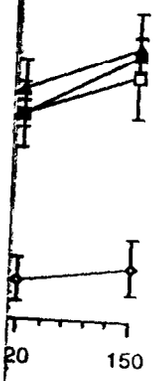
Vehicle - 2% Tween80 in H_2O

MONKEY DATA
(SDS)

As shown in the fig, NIH 10567 reduced the total number of withdrawal signs but did not substitute completely for morphine. Some of the monkeys, especially at the highest dose had relaxed abdominal muscles and did not vocalize when palpated. Partial substitution does not necessarily imply opioid activity. Severe tremors were noted at the highest dose.



ubstituted for morphine
highest dose, frequent



20 150

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