Comparative Analgesic, Behavioral, and Dependence Properties of Morphine and *O*-(4-Methoxylphenylcarbamoyl)-3-diethylaminopropiophenone Oxime Hydrochloride

NATHAN WATZMAN * **and JOSEPH P. BUCKLEY** ‡x

Received July 9, 1979, from the *Research Laboratories, Department of Pharmacology, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA 15261.* Accepted for publication August 30, 1979. *Present address: Health Resources Administration, Department of Health, Education, and Welfare, Hyattsville, MD 20782. ‡Present address: College of Pharmacy, University of Houston, Houston, TX 77004.

Abstract □ The analgesic activity of *O*-(4-methoxylphenylcarbamoyl)-3-diethylaminopropiophenone oxime hydrochloride was investigated in Swiss–Webster mice using an electroshock technique in which the pain threshold was the minimum voltage producing tonic extension of the hindlimbs in response to an electroshock delivered to the feet. The analgesic potency of *O*-(4-methoxylphenylcarbamoyl)-3-diethylaminopropiophenone oxime hydrochloride was equal to, or greater than, that of morphine. Neither nalorphine nor withdrawal produced visible behavioral effects in rats treated with *O*-(4-methoxylphenylcarbamoyl)-3-diethylaminopropiophenone oxime hydrochloride for 21 days, suggesting that the physical dependency liability of the compound may be less than that of morphine.

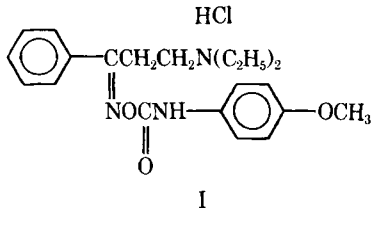
Keyphrases □ Morphine sulfate—comparative effects with *O*-(4-methoxylphenylcarbamoyl)-3-diethylaminopropiophenone oxime hydrochloride in rodents, pain threshold, physical dependency, tolerance, analgesic, withdrawal syndrome □ *O*-(4-Methoxylphenylcarbamoyl)-3-diethylaminopropiophenone oxime hydrochloride—analgesic, behavioral, and dependence properties, compared to morphine sulfate □ Analgesics—morphine sulfate, *O*-(4-methoxylphenylcarbamoyl)-3-diethylaminopropiophenone oxime hydrochloride, comparative studies in rodents

The clinical use of morphine has been limited by its undesirable capacity to induce tolerance and physical and psychogenic dependence. The synthesis of meperidine[1] (1) gave impetus to the search for new chemical molecules possessing the same pharmacological properties as morphine without the undesirable characteristics. Compounds such as methadone[2], unlike morphine in chemical structure, have been reported to possess the same or greater analgesic effects as morphine (2); unfortunately, they also possess the undesirable ability to produce the same three adaptive processes.

The present study investigated the analgesic activity of *O* - (4-methoxylphenylcarbamoyl)-3-diethylaminopropiophenone oxime hydrochloride (I) in rodents.

EXPERIMENTAL

Pain sensitivity was determined in 48 male albino mice[3] utilizing a modified flinch jump method (3). The aluminum test chamber contained four (10.2 × 10.2 × 10.2-cm) compartments with a grid floor designed so that 2-sec shocks of increasing intensity were delivered to the feet every 8 sec; timers and a grid scrambler[4] with a 1.5-megaohm resistor were used. Beginning with 143 v (0.1 mamp), the current was increased progressively until the pain threshold was reached or a maximum of 385 v (0.25 mamp) was applied without the pain response. The threshold was designed as the minimum voltage that produced tonic extension of the hindlimbs and jumping in response to three successive shocks applied at each voltage level. Four of the eight groups (six animals each) received placebo (0.9% saline, 0.1 ml/10 g body weight) or one of three doses of morphine sulfate (2, 5, or 10 mg/kg sc) 30 min before testing; the four other groups received placebo treatment or one of three doses of I identical to morphine.



I

To observe the chronic effects of the two test compounds as well as to monitor the morphine tolerance behavior, male Sprague–Dawley rats were administered the test compounds for 3 weeks in doses regarded as sufficient to produce addiction. Both compounds were administered subcutaneously according to the following dose schedule: 5, 10, and 20 mg/kg twice daily during the 1st, 2nd, and 3rd weeks, respectively. When 20 mg of I/kg was administered on the 15th day (Day 1 of the 3rd week), convulsions and death occurred in three of six animals. A similar morphine sulfate dose did not produce any marked changes.

Based on preliminary trials, 18 male Sprague–Dawley rats were divided into three equal treatment groups. Each group received, subcutaneously, I, morphine sulfate, or normal saline twice daily for 21 consecutive days according to the following morphine dosage schedule utilized by Gunne (4). For I, the initial dose (2.5 mg/kg/injection) was doubled every 7th day so that the dose level for each of the 3 weeks was 2.5, 5.0, and 10

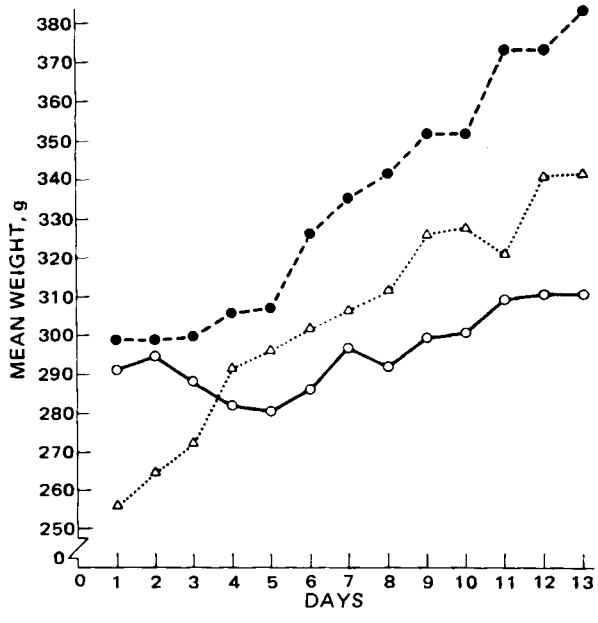


Figure 1—*Comparative effects of morphine sulfate and I on the weight gain of rats. Key:* ●, *saline;* △, *I; and* ○, *morphine sulfate.*

[1] Demerol, Winthrop Laboratories, New York, N.Y.
[2] Dolophine, Eli Lilly & Co., Indianapolis, Ind.
[3] Swiss–Webster, Hilltop Caviary, Scottdale, Pa.
[4] Lehigh Valley Electronics, Fogelsville, Pa.

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Table I—Comparative Effects of Subcutaneously Administered Morphine Sulfate and I on the Pain Threshold of Mice

Mouse	Volts Delivered							
	Group I, Saline	Group II, Morphine, 2 mg/kg	Group III, Morphine, 5 mg/kg	Group IV, Morphine, 10 mg/kg	Group V, Saline	Group VI, I, 2 mg/kg	Group VII, I, 5 mg/kg	Group VIII, I, 10 mg/kg
1	231	242	330	385[a]	220	231	308	385[a]
2	220	231	341	330	220	297	319	374
3	220	319	319	374	231	308	330	385
4	220	286	319	319	242	242	352	385[a]
5	187	297	319	165	187	220	374	374
6	242	297	275	385	187	275	253	385[a]
	1320	1672	1903	1958[a]	1287	1573	1936	2288[a]
$\bar{X}$	220	279	317	326[a]	214	262	323	381[a]

[a] Maximum voltage tested; threshold not achieved.

mg/kg/injection, respectively. For morphine sulfate, the initial dose (20 mg/kg/injection) was tripled every 7th day so that the dose level for each of the 3 weeks was 20, 60, and 180 mg/kg/injection, respectively.

One animal died from the initial morphine dose. On the 22nd day (Day 1 of drug withdrawal), half of the animals of each group (two of the morphine-treated animals) were administered a single 10-mg/kg sc dose of the narcotic antagonist nalorphine[5] to precipitate withdrawal symptoms. The other half of the groups (three animals each) received no drugs. All animals were observed for 1 week in their individual observation cages and home cages.

RESULTS

Table I shows the response threshold to electrical shock for each of the 48 mice and the average threshold for each drug dosage. The thresholds for the two saline control groups were similar, and the effects of the compounds did not differ statistically in thresholds produced at the two lowest doses (2 and 5 mg/kg). However, I produced a greater increase in pain threshold than did morphine at the highest dose level (10 mg/kg). Three of six animals receiving the highest dose of I did not reach the response criteria, whereas only one of six animals treated with the same dose of morphine failed to reach the criteria.

The early stages of chronic morphine administration initially produced hyperactivity and headbobbing, with the head carried close to the ground. After 10 min, the hyperactivity was replaced by a cataleptic-like state in which the animals remained in peculiar postures with a fixed stare. By the 16th day (Day 2 of 180-mg/kg dose), the animals were sedated but their bodies were stiff when handled, indicating an increase in muscular tone and stimulation of the spinal cord. Water and food intake decreased with time, and the animals became increasingly more difficult to handle. They were hyperactive only immediately after injection, jumping onto the back of the cage and over each other, and then they assumed trance-like postures similar to the description by Gunne (4). No behavioral effects were noted at any I dose level. Manifestations of central nervous system depression (ataxia, *etc.*) as well as autonomic effects were reported (5) in rhesus monkeys chronically administered I for 40 days.

Figure 1 shows the weight gains for each drug group. Compound I-treated animals and the saline controls had similar weight gains, and their fur appeared normal throughout the study. However, the weight gain of the morphine-treated animals was far below that of the other two groups, and their fur was off-white or brownish. On the last weighing day (19th day), the mean weights ± *SE* for the saline-, I-, and morphine-treated groups were 383 ± 11.9, 341 ± 11.1, and 310 ± 5,1 g, respectively. These data were statistically different ($p < 0.05$) by the Student t test. There were no visible physical effects among the saline control animals.

A single nalorphine injection to the morphine-treated rats on the 1st withdrawal day produced extreme sedation, ptosis, and increased defecation with diarrhea, reflecting the expected precipitation of the withdrawal syndrome (6). These symptoms, except the diarrhea, disappeared by Day 5 of withdrawal. Withdrawn morphine-treated animals (no nalorphine) also showed sedation, ptosis, and diarrhea and they returned to normal by Day 5 of withdrawal. Compound I- and saline-treated animals were not affected visibly by nalorphine, and I did not demonstrate withdrawal-like symptoms. Compound I partially suppressed morphine abstinence in morphine-dependent rhesus monkeys, reflecting some morphine antagonist properties of its own (7).

[5] Nalline, Merck Sharp & Dohme, West Point, Pa.

DISCUSSION

Data from the pain threshold study indicate that I has analgesic potency equal to or greater than morphine. Although the compounds did not differ in the pain thresholds produced at the two lowest doses, I induced a greater threshold increase at the highest dose (10 mg/kg). The differences in potency between the two compounds would have been greater had the trials continued beyond the maximum experimental voltage (385 v) and every animal reached criteria. Three of the six I-treated animals did not reach criteria compared to only one of the six in the morphine group.

The basic behavior elicited by chronic morphine administration to rats was an initial hyperactivity followed by a cataleptic-like immobile state with fixed stare. As the program progressed, the initial hyperactivity increased and the animals became more difficult to handle. The major effects of morphine withdrawal and nalorphine in morphine-treated rats were sedation, ptosis, and increased defecation with diarrhea. No such behavioral effects were produced by chronic I administration.

There were no qualitative differences between the morphine–nalorphine-treated animals and the morphine-withdrawn animals, except that diarrhea persisted longer in the former group. Thus, nalorphine apparently precipitated withdrawal-like symptoms. Neither nalorphine-administered I animals nor withdrawal from I produced any visible behavioral effects. The marked difference between the doses of I and morphine sulfate should not negate the results since, within experimental design limits, the animals did not develop a tolerance to the experimental compounds. Therefore, the data suggest that I does not produce the same autonomic and behavioral effects as morphine, nor do I-treated animals display the same syndrome of effects when withdrawn from the drug.

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