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Effect of Propranolol on Antinociceptive and Withdrawal Characteristics of Morphine[1]

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CHIPKIN, R. E., W. L. DEWEY, L. S. HARRIS AND W. LOWENTHAL. *Effect of propranolol on antinociceptive and withdrawal characteristics of morphine.* PHARMAC. BIOCHEM. BEHAV. 3(5) 843–847, 1975. – Propranolol at a dose (10 mg/kg) which did not alter tail-flick latency by itself, did not alter the ED50 of morphine when given 10 min prior to the narcotic. Propranolol at doses of 10 and 25 mg/kg given 10 min prior to naloxone challenge did not significantly alter the frequency of naloxone induced jumping 72 hr after morphine pellet implantation. The ED50 of naloxone in morphine pelleted mice was not altered by treatment with propranolol at 0, 24, and 48 hr after pellet implantation. Naloxone caused hyperactivity in mice when administered 72 hr after morphine pellet implantation. An injection of 25 mg/kg propranolol 10 min prior to naloxone did not block this hyperactivity. In addition, administration of 10 mg/kg of propranolol every 8 hr to rats during withdrawal from morphine failed to alleviate the withdrawal syndrome as evidenced by changes in either body weight or water intake. These data suggest that the beta-adrenergic blocking agent, propranolol, does not alter the antinociceptive activity or lessen the withdrawal syndrome of morphine in rodents.

Propranolol Morphine Withdrawal Beta-antagonist Rodents

WE have previously reported [8] that propranolol, which showed some activity in the mouse tail-flick test at the very high dose of 100 mg/kg, did not alter the effect of morphine in this test when it was given intraperitoneally at 10 mg/kg immediately after morphine. The possible involvement of central β-adrenergic receptors in some of the actions of opiates was later suggested by clinical work [11] and laboratory data [1, 2, 7]. It has been reported that the β-adrenergic blocking agent propranolol was useful in treating a postheroin addict who repeatedly reverted to heroin during previous attempts at withdrawal without propranolol. These results suggested the possible use of propranolol in treating narcotic addiction. In addition, others have reported that another β-adrenergic blocking agent, dichlorisoproterenol (DCI) potentiated the activity of morphine in the mouse tail-flick test and decreased the development of tolerance and physical dependence in mice [1]. The purpose of the present study was to investigate whether propranolol altered either the characteristics of morphine withdrawal or some of the pharmacological activity of morphine in rodents.

METHOD

Animals

Male, albino, Swiss-Webster mice weighing between 16–30 g and male Sprague-Dawley rats weighing between 150–200 g were used in these experiments. Injections in mice were given subcutaneously at a constant volume of 0.1 ml/10 g body weight. Propranolol was given subcutaneously in antinociceptive tests and intraperitoneally in the other experiments.

Procedure

(1) The effect of propranolol on the antinociceptive activity of morphine in mice. Antinociceptive activity was determined in essentially the same manner as previously described [8]. Groups of 6 mice were used and at least 2 groups of animals were used at each dose. Propranolol or saline were given 10 min before morphine; testing took place 20 min afterwards. The percent maximum possible effect (percent MPE) was plotted versus the log dose on probability paper and the ED50 and its 95 percent confidence limits were determined according to appropriate statistical methods [14].

(2) The effect of propranolol on the frequency of naloxone induced jumping in chronic morphinized mice. A 75 mg morphine pellet was implanted subcutaneously in mice under light ether anesthesia as described previously [18]. Groups of mice were injected after 72 hr with either propranolol or saline 10 min before naloxone challenge. The mice, after injection with naloxone, were placed on a

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circular platform 6 in. in dia. and 18 in. off the bench top. The number of mice that jumped in the next 15 min was counted.

(3) The effect of propranolol on the naloxone dose response curve. Morphine pellet implanted mice were challenged at 72 hr with varying doses of naloxone after either saline or propranolol (10 mg/kg) treatment at 0, 24, and 48 hr. The percentage of mice jumping within the next 15 min was determined. The dose response curves with ED50's and 95 percent confidence limits were determined.

(4) The effect of propranolol on locomotor activity in chronic morphinized mice. Mice were implanted with a morphine pellet as described above. Seventy-two hr afterward, 4 groups of 6 mice were injected with either saline, naloxone (3 mg/kg), propranolol (25 mg/kg), or naloxone and propranolol. The mice were immediately placed in a plastic cage which was placed between a light source and photo cell (Autotron®) in such a way that spontaneous locomotor activity was recorded on counters attached to the photo cell. The total number of counts was recorded every 15 min.

(5) The effect of propranolol on the withdrawal syndrome in infused rats. Rats were cannulated intraperitoneally as described [17], and infused with either propranolol, saline, or morphine at a constant rate of 0.0073 ml/min (10 ml/day) for 6 days. Group 1 received saline alone; Group 2 received propranolol alone at a dose of 100 mg/kg/day in addition to injections of propranolol every 8 hr at a dose of 10 mg/kg. Rats receiving morphine continuously were infused on a schedule of 50 mg/kg on Day 1, 100 mg/kg on Day 2, and 200 mg/kg for the remaining 4 days. The morphine group was subdivided into 2 smaller groups. One group received morphine alone and a second group received morphine and upon removal of the narcotic received propranolol (10 mg/kg) every 8 hr for the next 4 days. Body weight and water intake were recorded daily throughout the infusion and for 4 days postinfusion. Changes in body weight and water intake were calculated as a percent relative to the first day of withdrawal [16].

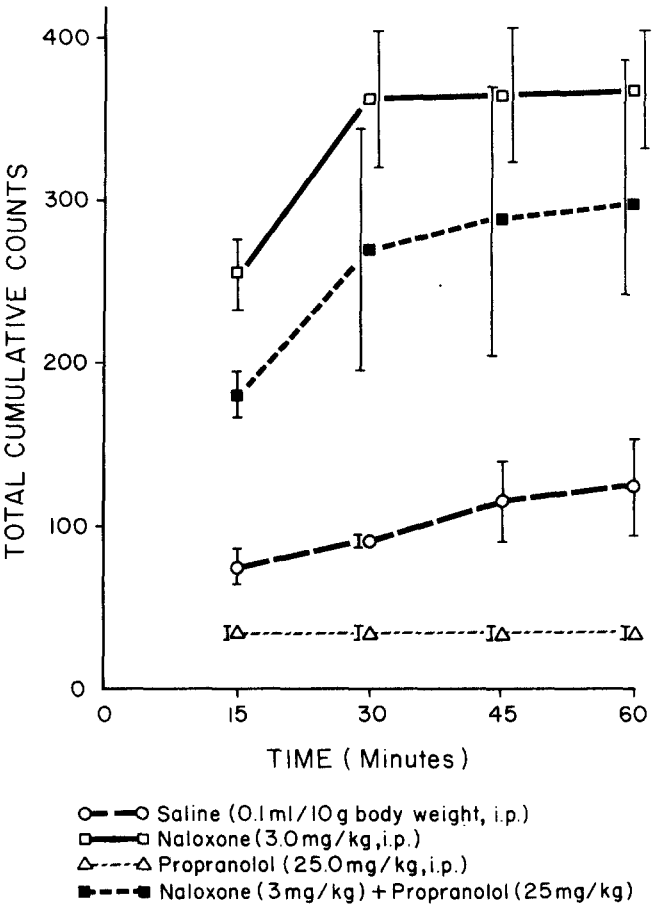

FIG. 1. Effect of naloxone and propranolol alone or in combination on spontaneous locomotor activity in chronic morphinized mice.

RESULTS

(1) The Effect of Propranolol on the Antinociceptive Activity of Morphine in Mice

A dose of propranolol (10 mg/kg) that had no activity itself when tested in the tail-flick test, failed to significantly alter the ED50 of morphine when given 10 min prior to the narcotic. The ED50 for morphine was 9.2 with 95 percent confidence limits of 6.1–13.8 and the ED50 for propranolol plus morphine was 9.8 (7.4–12.9) mg/kg.

(2) The Effect of Propranolol on the Frequency of Naloxone Induced Jumping in Chronic Morphinized Mice

As can be seen in Table 1, doses of naloxone sufficient to induce jumping in 100 percent of the untreated morphinized mice were not effected by a 10 minute prior injection of either 10 or 25 mg/kg or propranolol. Placebo implanted animals failed to jump when injected with propranolol or naloxone.

(3) The Effect of Propranolol on the Naloxone Dose Response Curve

Propranolol when given at a dose of 10 mg/kg at 0, 24, and 48 hr before challenge with naloxone, showed no ability to significantly alter the dose response curve to the antagonist. The ED50 for naloxone was 0.029 mg/kg with 95 percent confidence limits of 0.016–0.051; the ED50 for the propranolol pretreated mice was 0.035 (0.027–0.046) mg/kg.

(4) The Effect of Propranolol on Locomotor Activity in Chronic Morphinized Mice

An injection of naloxone given 72 hr after morphine pellet implantation induced hyperactivity compared to saline treated mice. Propranolol at a dose which by itself caused some hypoactivity in morphinized mice, did not significantly reverse the naloxone induce hyperactivity (Fig. 1).

(5) The Effect of Propranolol on the Withdrawal Syndrome in Infused Rats

The withdrawal syndrome (loss of body weight and decreased water consumption) of rats made dependent by 6 days of morphine infusion was not significantly altered by treatment with 10 mg/kg of propranolol every 8 hr after removal of the morphine (Figs. 2, 3). Propranolol infused at a dose of 100 mg/kg/day along with injections of pro-

TABLE 1

EFFECT OF PRETREATMENT WITH PROPRANOLOL (10 MG/KG AND 25 MG/KG, IP) ON THE JUMPING RESPONSE TO NALOXONE (1 MG/KG AND 10 MG/KG, IP) IN MORPHINE PELLET IMPLANTED MICE. TESTING TOOK PLACE AT 72 HR WITH THE PROPRANOLOL BEING GIVEN TEN MINUTES BEFORE NALOXONE.

		Pellet	
Treatment	N	Morphine (%)	Placebo (%)
Saline (0.1 ml/10 g body wt)	6	0	0
Saline + Saline (0.1 ml/10 g body wt)	6	0	0
Propranolol (10 mg/kg)	6	0	0
Propranolol (25 mg/kg)	6	0	0
Naloxone (1 mg/kg)	6	100	0
Naloxone (10 mg/kg)	6	100	0
Propranolol (10 mg/kg) + Naloxone (1 mg/kg)	6	100	0
Propranolol (25 mg/kg) + Naloxone (1 mg/kg)	6	100	0
Propranolol (10 mg/kg) + Naloxone (10 mg/kg)	6	100	0
Propranolol (25 mg/kg) + Naloxone (10 mg/kg)	6	86.33	0

pranolol every 8 hr throughout the infusion as well as 96 hr postinfusion, did not elicit a withdrawal syndrome.

DISCUSSION

Doses of propranolol at 10 or 25 mg/kg, which in themselves had either no or slight overt behavioral effects, failed to alleviate narcotic withdrawal in mice or rats.

Our initial experiments showed that propranolol fails to change the dose response curve to the antinociceptive actions of morphine. These results are in agreement with other work [4, 6, 9, 10]. Clinically, this is important because it shows that patients being treated with pro-

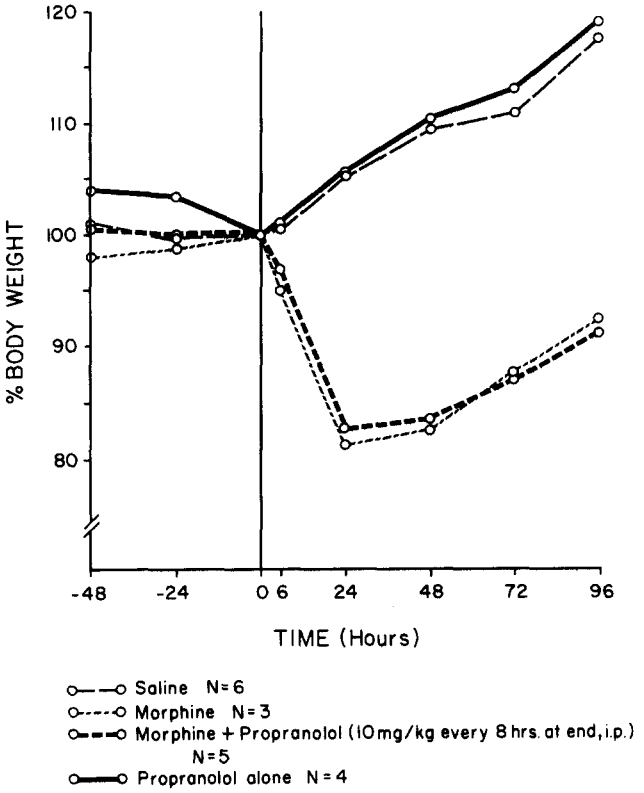

FIG. 2. Effect of propranolol every 8 hr on percent body weight in morphine infused rats.

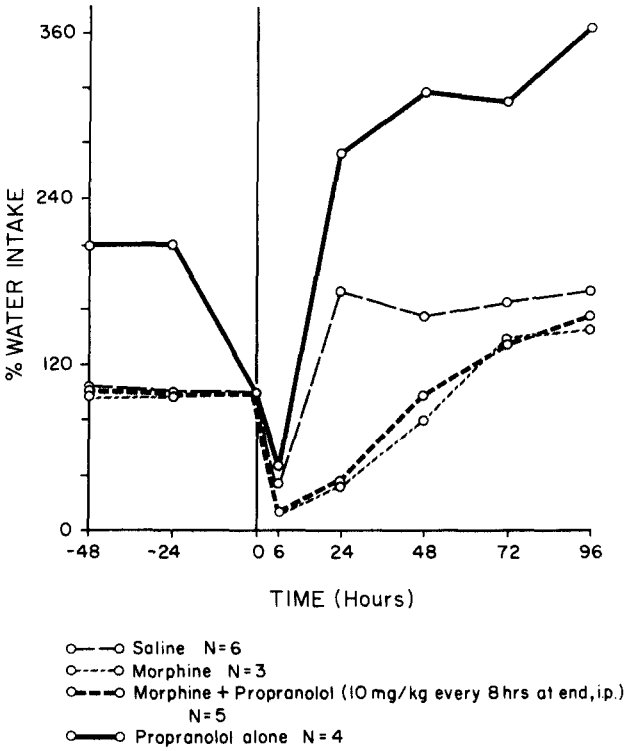

FIG. 3. Effect of propranolol every 8 hr on percent water intake in morphine infused rats.

pranolol should not have to have the dosage of morphine adjusted because of the beta-blocking agent. However, our own results (unpublished data) with concurrent chronic administration of relatively high doses of propranolol and morphine has shown a synergistic lethality, probably due to the decreased cardiac function. Thus, until the dynamics of this interaction can be worked out, caution should be used.

Further, all our data concerning the effect of propranolol on the opiate withdrawal syndrome is in contradiction to the idea that it could be useful in alleviating withdrawal. Propranolol failed to influence either the frequency of jumping in mice challenged with a supramaximal dose of naloxone or the ED50 of the antagonist. Secondly, a dose of naloxone sufficient to cause hyperactivity in chronic morphinized mice was not significantly effected by propranolol. If propranolol were to alleviate the withdrawal syndrome, one would expect to see a reversal of the hyperactivity. Finally, if propranolol were to effectively ameliorate withdrawal, it would alter the pattern of weight loss or water intake upon removal of the opioid in those rats receiving propranolol compared to those animals receiving morphine alone. However, in this case there is clearly no effect seen when propranolol is given every eight hours. (It is unlikely that this could be attributed to effects of propranolol on morphine metabolism [3]). This is in agreement with recently published data on withdrawal in the dog [15], in the rat [5], and in man [12].

However, our work differs from other reported experiments [1, 2, 11]. Perhpas our data differs in one case because we used two different routes of administration, (intracerebral vs. subcutaneous injections) and different drugs (DCI has prominent beta-agonist properties which are not as evident with propranolol). Our data differs from the clinical work (due to obvious species differences) suggesting that propranolol blocks the craving and euphoria induced by opiates. We cannot test the effects of a compound on the craving or euphoria in rodents. Our data concerning the effect of propranolol on the withdrawal syndrome as seen in both the rat infusion data and the mouse naloxone induced jumping data indicate that propranolol does not alleviate withdrawal in rodents. Perhpas what is being seen by the clinicians is not a direct effect upon with withdrawal syndrome due to beta-blockade, but rather a more general anti-anxiety effect. The use of propranolol as an anti-anxiety agent has been previously reported [13] and until this effect can be sufficiently separated from its effects on the physiological characteristics of withdrawal the disparity between these data will remain unresolved.

An intriguing observation during these studies was the effect of propranolol every eight hours on water intake in propranolol infused rats. As can be seen by Fig. 3, these animals have an inordinately high water intake. The reasons for this and the mechanisms underlying this behavior remain to be clarified. Preliminary investigations will begin shortly.

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