Journal of Pharmacological Sciences 130 (2016) 8–14

HOSTED BY

Contents lists available at ScienceDirect

Journal of Pharmacological Sciences

journal homepage: www.elsevier.com/locate/jphs

Full paper

Nalfurafine hydrochloride, a selective κ opioid receptor agonist, has no reinforcing effect on intravenous self-administration in rhesus monkeys

Kaoru Nakao [a, *], Mikito Hirakata [a], Yohei Miyamoto [a], Mie Kainoh [a], Yoshio Wakasa [b], Tomoji Yanagita [c]

[a] Pharmaceutical Research Laboratories, Toray Industries, Inc., 10-1, Tebiro 6-chome, Kamakura, Kanagawa 248-8555, Japan
[b] Marketing Department, Ina Research Inc., 2148-188 Nishiminowa, Ina-shi, Nagano 399-4501, Japan
[c] Scientific Advisor, Ina Research Inc., 2148-188 Nishiminowa, Ina-shi, Nagano 399-4501, Japan

ARTICLE INFO

Article history:
Received 15 June 2015
Received in revised form
20 November 2015
Accepted 24 November 2015
Available online 2 December 2015

Keywords:
Nalfurafine hydrochloride
TRK-820
κ opioid receptor
Self-administration
Monkey

ABSTRACT

Nalfurafine hydrochloride [(*E*)-*N*-[17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6β-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide monohydrochloride; nalfurafine] is used in Japan as an antipruritic for the treatment of intractable pruritus in patients undergoing hemodialysis or with chronic liver disease. It is a potent and selective agonist at the κ opioid receptor, but also has weak and partial agonist activity at μ opioid receptors. Opioids, especially those acting at μ receptors, carry a risk of abuse. This is an important factor in the consideration of therapeutic risk vs. benefit in clinical use and the potential for misuse as a public health problem. It is therefore necessary to carefully evaluate the reinforcing effects of nalfurafine. To this end, we investigated intravenous self-administration of nalfurafine in rhesus monkeys. The number of self-administration of nalfurafine at doses of 0.0625, 0.125 and 0.25 μg/kg/infusion was not higher than that of saline in rhesus monkeys that frequently self-administered pentazocine (0.25 mg/kg/infusion). These results indicate that nalfurafine has no reinforcing effect in rhesus monkeys in the intravenous self-administration paradigm.

1. Introduction

The selective κ opioid receptor agonist nalfurafine hydrochloride [(*E*)-*N*-[17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6β-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide monohydrochloride; nalfurafine] is a well-tolerated and effective treatment for intractable pruritus in hemodialysis patients (1–4). It was approved for clinical use in January 2009 by the Japanese Ministry of Health, Labour and Welfare (1,3). Receptor binding and functional studies of recombinant human and rat opioid receptors have shown nalfurafine to be a more potent and selective agonist at κ receptors than μ and δ opioid receptors (3,5). Opioids, such as morphine, carry a risk of abuse mediated by their activation of μ receptors (6). However, unlike μ receptor agonists, which play a major role in reward and place preference conditioning in animals, selective κ agonists generally lack a reinforcing effect (7), and are considered not to have the potential to become drugs of abuse in humans. Although nalfurafine is a selective κ agonist, forskolin-stimulated cAMP accumulation studies have shown that the drug also possesses weak partial agonist activity at μ receptors (3). Its potential risk of abuse must therefore be carefully evaluated. No evidence was found of psychological or physical dependence on nalfurafine in a clinical study in Japanese hemodialysis patients with severe pruritus (2). However, animal studies of abuse liability have the advantages of using a wider range of doses and including a positive control drug. Nalfurafine does not induce conditioned place preference in mice (8) or rats (9), indicating that the drug does not produce a rewarding effect; however, no studies of nalfurafine self-administration in rats or monkeys have been reported to date, despite the usefulness of such studies in evaluating potential abuse liability in humans (7,10–13). Therefore, the present study was designed to investigate the reinforcing effect of nalfurafine using intravenous self-administration in rhesus monkeys.

* Corresponding author. Tel.: +81 467 32 2111; fax: +81 467 32 8465.
E-mail address: Kaoru_Nakao@nts.toray.co.jp (K. Nakao).
Peer review under responsibility of Japanese Pharmacological Society.

http://dx.doi.org/10.1016/j.jphs.2015.11.008

2. Materials and methods

2.1. Animals

Six male and four female adult rhesus monkeys (*Macaca mulatta*) were used. The animals were drug-free for 6–18 months and weighed 3.9–6.7 kg. The monkeys were housed individually at 22–28 °C, 40–80% humidity, and under a 12-hour light/dark cycle (lights on at 7:00 a.m.). The monkeys received approximately 100 g of solid feed (PS, Oriental Yeast Co., Ltd., Tokyo, Japan) once a day in Experiment 1, and about 120 g in Experiment 2. Additionally, half a banana was occasionally given to each monkey in both experiments. The monkeys were allowed free access to drinking water. All experiments were conducted in accordance with the principles specified by the Institutional Animal Care and Use Committee of Ina Research Inc.

2.2. Experiment 1: gross behavioral observation after a single intravenous dose

Six monkeys (three male, three female) were used in a series of experiments comprising three trials conducted at 1-week intervals (Table 1). In each trial, the general condition of the animals was observed prior to drug administration. Animals were assessed for the following signs, in accordance with the observation criteria of the test facility: salivation, retching, vomiting, continuous movement, hypoactivity, crouching, prone posture, aggression towards the observer, reactivity to the observer, reaction towards the observer by grimacing (a sign of fear), eye closing, pupil dilation or contraction, slow movement, and ataxia. The animals' general condition was also observed after drug administration at 0, 15 and 30 min, and 1, 2, 3, 4 and 5 h. Where changes in general condition persisted for 5 h, those animals were assessed again 24 h after administration. Food consumption was observed on the day of administration and the following day, and any changes were recorded. The diameter of each pupil was estimated by eye; a change in diameter of approximately 2 mm or more compared with the pre-administration diameter was recorded as dilation or contraction.

2.3. Experiment 2: intravenous self-administration

Four monkeys (three male, one female) that had previously self-administered pentobarbital sodium and/or cocaine intravenously were used in a series of self-administration experiments. In each animal, a silicon catheter (outer diameter: 2 mm; inner diameter: 1 mm) was implanted into the jugular or femoral vein under pentobarbital anesthesia and connected to an automatic drug infusion apparatus. A red light approximately 5 cm above the self-administration lever was illuminated when drug solution was available, and turned off during infusion. Table 2 shows the schedule for Experiment 2. In the first study period, the self-administration solution was saline (0.25 mL/kg/infusion). For each monkey, when self-administration did not exceed 10 infusions/day for 7 consecutive days, the monkey was allowed to self-administer pentazocine freely (0.25 mg/kg/infusion). When pentazocine self-administration reached 35 infusions/day or more for 3 consecutive days, it was replaced with 5% mannitol solution (0.125 mL/kg/infusion), until self-administration decreased to 10 infusions/day or fewer for 7 consecutive days. Monkeys were then allowed free access to nalfurafine self-administration (0.0625, 0.125 or 0.25 μg/kg/infusion) for 2 weeks at each dose, after which all monkeys received scheduled intravenous infusions of nalfurafine (0.25 μg/kg/infusion) at 6-hour intervals for 2 weeks. During this repeated infusion period, the monkeys were still allowed free access to self-administered nalfurafine at the same unit dose. When self-administration occurred, scheduled intravenous infusion of nalfurafine was postponed by 6 h from the self-administered infusion. After a 2-week period of scheduled infusions, self-administration of nalfurafine (0.25 μg/kg/infusion) was observed for an additional 2 weeks. In the final study period, nalfurafine was replaced with 5% mannitol (0.25 mL/kg/infusion) for 1 week of self-administration. During the pentazocine and nalfurafine study periods, raisins were attached to the self-administration lever when self-administration fell to three infusions/day or fewer for 3 consecutive days, to encourage pressing of the lever and maintenance of self-administration behavior; these data were excluded from the analysis, and the self-administration periods were subsequently extended by the number of days that were excluded. Animals were assessed for hypoactivity and slow movement between 9:00 and 10:00 during each study period.

Table 1
Administration schedules for gross behavioral observation of rhesus monkeys.

Animal ID No. (Sex)	Dose of nalfurafine (μg/kg)		
	1st trial	2nd trial	3rd trial
#1333 (male)	0[a]	0.5	–[b]
#1376 (female)	1.0	0[a]	0.25
#1381 (female)	–[b]	0.5	0[a]
#1400 (male)	0[a]	2.0	0.25
#1410 (male)	–[b]	2.0	–[b]
#1405 (female)	1.0	0[a]	0[a]

[a] Administration of 5% mannitol solution.
[b] No assignment in corresponding trial.

2.4. Administration

In Experiment 1, each animal was seated on a chair designed for a monkey and the test solution was administered intravenously into the forelimb. The injection volume and rate were 0.25 mL/kg and 1 mL/23 s, respectively. In Experiment 2, the monkeys self-administered the solution intravenously (14) by pressing the lever of the self-administration apparatus. Drug or control solution was infused through a catheter inserted into the vein under a fixed ratio schedule in which every lever press resulted in an infusion (FR1). Infusion volume and rate were 0.125 or 0.25 mL/kg and 1 mL/23 s, respectively. There was no limit to the number of infusions that could be received. Daily self-administration was recorded for 24 h (9:00–9:00 a.m.). On the days in which the test solution was replaced, observations were interrupted for 1 h (9:00–10:00 a.m.).

2.5. Drugs

Nalfurafine hydrochloride (Toray Industries, Inc., Tokyo, Japan) was dissolved in 5% mannitol solution to ensure stability of the drug. Pentazocine (in ampoules of 30 mg/mL; Sosegon® Inj. 30 mg, Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan) was diluted with saline.

2.6. Statistical analysis

No statistical analyses were performed in Experiment 1. For data obtained in Experiment 2, means and standard errors were calculated for the number of infusions self-administered by each animal per day, for each solution. A repeated measures analysis of variance (ANOVA), in which the error terms were assumed to be correlated within an animal, was used to estimate the mean number of self-administered infusions per day for study periods 1–9, and to test the period effects of study periods 2–9 vs. study period 1. The