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Effects of a Novel Fentanyl Derivative on Drug Discrimination and Learning in Rhesus Monkeys

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GERAK, L. R., J. M. MOERSCHBAECHER, J. R. BAGLEY, L. L. BROCKUNIER AND C. P. FRANCE. *Effects of a novel fentanyl derivative on drug discrimination and learning in rhesus monkeys.* PHARMACOL BIOCHEM BEHAV **64**(2) 367–371, 1999.—Three monkeys discriminated 1.78 mg/kg of mirfentanil while responding under a fixed-ratio 5 schedule of stimulus-shock termination. Two mirfentanil derivatives, OHM3295 and OHM10579, substituted for mirfentanil in all subjects. However, other drugs produced variable effects among monkeys; for example, μ and κ opioid agonists and clonidine substituted for mirfentanil on some occasions in two monkeys. Cocaine, amphetamine, and ketamine did not substitute in any subject. Opioid antagonists did not attenuate the effects of mirfentanil. In monkeys responding under a repeated acquisition and performance procedure, errors increased only during the acquisition phase at doses of mirfentanil that decreased response rates. Thus, unlike fentanyl, the discriminative stimulus effects of mirfentanil do not appear to be mediated exclusively through opioid receptors. Finally, mirfentanil does not appear to disrupt complex behavioral processes. © 1999 Elsevier Science Inc.

Mirfentanil Fentanyl derivative Discriminative stimulus effects Rhesus monkey

FENTANYL and its derivatives are used clinically as anesthetics and analgesics. The synthesis of mirfentanil (1) led to the discovery of a novel pharmacology within this chemical class. Like the parent compound fentanyl, under some conditions, mirfentanil had μ-agonist effects (2,3). However, under other conditions, mirfentanil differed from fentanyl in that it had μ-antagonist effects (3). Collectively, these results indicated that mirfentanil was a low-efficacy μ-agonist. Under still other conditions, mirfentanil had effects that were not mediated by opioid receptors (3). This unusual pharmacology of mirfentanil could reflect a better therapeutic profile compared to typical opioid analgesics, perhaps by relieving pain without adverse effects commonly associated with opioids (e.g., ventilatory depression).

In an effort to further characterize both the opioid and nonopioid components of mirfentanil, monkeys were trained to discriminate mirfentanil from saline. Although the opioid component of mirfentanil has been evaluated in other drug discrimination procedures (2,3), the nonopioid actions of mirfentanil have not been characterized. Two approaches were used to characterize the discriminative stimulus effects of mirfentanil: substitution studies were conducted with μ- and κ-agonists as well as nonopioids; and the opioid antagonist naltrexone was studied in combination with mirfentanil.

The effects of mirfentanil on complex behavioral processes were determined using a repeated acquisition and performance procedure in monkeys. Given the possible clinical utility of a drug with nonopioid antinociceptive effects, it is important to determine potential adverse effects of mirfentanil.

METHOD

Drug Discrimination

Three rhesus monkeys discriminated 1.78 mg/kg of mirfentanil under a fixed ratio (FR) 5 schedule of stimulus-shock termination. The training dose of mirfentanil was the largest dose that did not decrease mean response rate to <80% of control. Initially, sessions comprised a single, 25-min cycle. The first 15 min of the cycle were a time-out period, during which responses had no programmed consequence, and the last 10 min were a response period, during which stimulus lights were illuminated and shock was scheduled to be delivered every 15 s. Monkeys could extinguish stimulus lights and postpone the shock schedule for 30 s by emitting five consecutive responses

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on the lever designated correct by an injection administered during the first minute of the time out.

Stimulus control was considered adequate when ⩾80% of the total responses occurred on the correct level and when <5 responses were emitted on the incorrect lever prior to the first reinforcer. After monkeys satisfied these criteria (five consecutive or six of seven sessions), the procedure was changed to multiple cycles with sessions comprising several 15-min cycles: 10-min time out and 5-min response period.

Tests sessions were identical to training sessions except that responding on either level postponed shock and increasing doses of drugs were administered during each cycle. Drugs were given up to the dose that produced ⩾80% responding on the mirfentanil-appropriate lever, decreased response rates sufficiently to result in the delivery of shock, or up to the largest dose that could be safety administered (e.g., amphetamine). Various μ- and κ-agonists, including other fentanyl derivatives, as well as several nonopioids were tested for their ability to substitute for mirfentanil. Antagonism studies were conducted by administering a single dose of antagonist on the first cycle and cumulative doses of mirfentanil, or drugs that substituted for mirfentanil (e.g., fentanyl), on subsequent cycles.

Repeated Acquisition and Performance

Three monkeys responded under a multiple schedule of repeated acquisition and performance of conditional discriminations; monkeys received food pellets after completing a two-member chain (8). Sessions began with the acquisition component, which alternated with the performance component after 20 food presentations or 15 min, whichever occurred first; components were separated by 5-s time-out periods. Within each component of the multiple schedule, monkeys could respond on the left or right key, with the correct key designated by stimuli displayed on the center key (i.e., a combination of four different colors and four different geometric shapes). When the first member of the two-member chain was completed with a correct response, the chain advanced to the second member with a different combination of stimuli presented on the center key. A correct response in the second member resulted in the delivery of a banana-flavored pellet; incorrect responses in either member of the chain resulted in a 5-s time out. During the acquisition component, subjects acquired a different chain of conditional discriminations for each experimental session and, during the performance component, subjects responded under the same

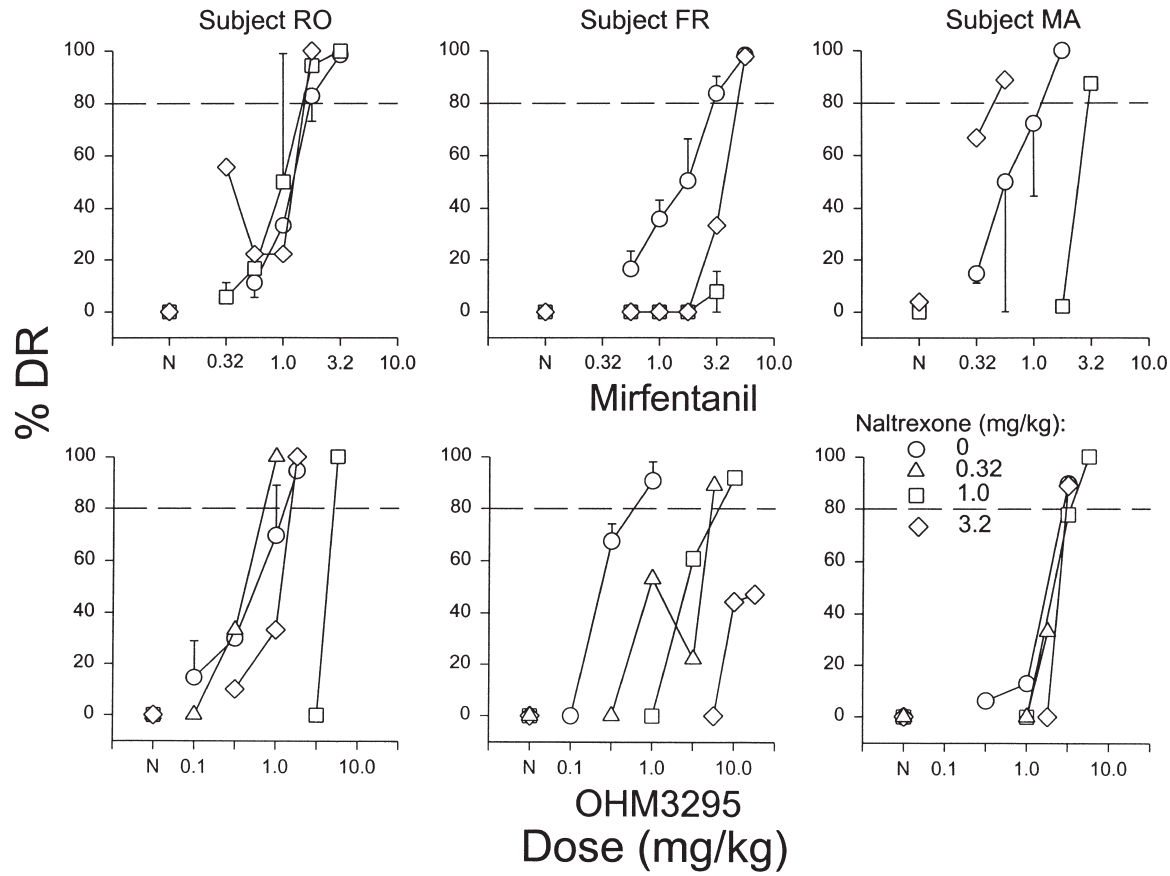

FIG. 1. Discriminative stimulus effects of mirfentanil (upper panels) and OHM3295 (lower panels), studied alone and in combination with 0.32, 1.0, or 3.2 mg/kg of naltrexone, in three monkeys discriminating 1.78 mg/kg of mirfentanil from saline. Each panel represents effects in a single subject. The mirfentanil dose–effect curves were determined at least twice in each subject. Abscissae: dose of mirfentanil (upper panels) or OHM3295 (lower panels) in mg/kg body weight; points above *N* represent the effects of naltrexone administered alone. Ordinates: mean percentage of total responding that occurred on the mirfentanil-appropriate lever ± 1 SEM (% DR).

chain of conditional discriminations for all experimental session. Sessions ended after 200 food presentations or 90 min, whichever occurred first. Mirfentanil and naltrexone were administered 15 and 35 min, respectively, prior to sessions.

RESULTS

Drug Discrimination

Under the single-cycle procedure, stimulus control between 1.78 mg/kg of mirfentanil and saline was established after 172 to 190 training sessions; when the procedure was changed to multiple cycles, an additional 5 to 25 training sessions were required to reestablish stimulus control. There was a dose-related generalization to mirfentanil in all three subjects; however, the dose required to produce ⩾80% mirfentanil-appropriate responding varied among tests (circles, upper panels, Fig. 1).

Only two drugs, the mirfentanil derivatives OHM3295 and OHM10579, substituted for mirfentanil in all three subjects (Table 1). The nonopioids cocaine, amphetamine and ketamine did not substitute for mirfentanil in any subject. The remaining drugs substituted in some monkeys. For example, in subject RO, all of the opioid agonists and clonidine substituted for mirfentanil on at least one occasion. In subject MA, clonidine as well as the opioid agonists butorphanol, fentanyl and spiradoline substituted for mirfentanil, whereas in subject FR, none of these compounds substituted. Moreover, the mirfentanil derivative OHM3463 substituted in two of the three monkeys.

Naltrexone differentially affected the discriminative stimulus effects of mirfentanil and other drugs among subjects. Naltrexone appeared to shift the mirfentanil (upper panels, Fig. 1) and OHM3295 (lower panels, Fig. 1) dose–effect curves to the right in two monkeys, although these effects were not clearly related to the dose of naltrexone. Naltrexone also antagonized OHM3463, a mirfentanil derivative that substituted for mirfentanil in two monkeys (data not shown). In subject RO, both fentanyl and spiradoline substituted for mirfentanil (Table 1), and naltrexone antagonized the discriminative stimulus effects of each of these agonists (data not shown), with a dose of 1.0 mg/kg producing a 200-fold shift to the right in the fentanyl dose–effect curve and a 10-fold shift to the right in the spiradoline dose–effect curve.

Repeated Acquisition and Performance

Mirfentanil did not markedly increase errors in either component of the repeated acquisition and performance schedule up to doses that decreased response rates to <50% of control. During the acquisition component, response rates were decreased to <50% of control at a dose of 1.78 mg/kg of mirfentanil in two monkeys, whereas a slightly larger dose (3.2 mg/kg) was required to decrease response rates in the third monkey. Naltrexone did not modify the accuracy of responding, nor did it antagonize the rate-decreasing effects of mirfentanil in either component (data not shown).

DISCUSSION

Mirfentanil is a fentanyl derivative that has been shown to have an unusual pharmacology: low-efficacy μ-agonist actions and nonopioid (e.g., antinociceptive) effects (3). In light of this unusual pharmacological profile, it is possible that mirfentanil might be a better therapeutic than morphine, depending on the mechanism of action of the nonopioid component and its profile of adverse effects. The current study extended previous reports by attempting to examine the nonopioid component of mirfentanil using a drug discrimination procedure and by assessing potential adverse effects using a repeated acquisition and performance procedure. Results from these studies support the view that the pharmacological profile of mirfentanil is novel.

One goal of the current study was to establish stimulus con-

TABLE 1

SUBSTITUTION STUDIES IN THREE RHESUS MONKEYS DISCRIMINATING 1.78 mg/kg OF MIRFENTANIL

	RO	FR	MA	No. Substitute/*n*
μ Agonists				
Morphine	100*/89.8† (17.8)‡/(17.8)	0/1.9 (17.8)/(1.78/17.8)	8.2 (5.6/17.8)	1/3§
Methadone	100/11.1 (3.2)/(1.0/10.0)	2.1 (5.6)	2.2 (10.0)	1/3
Nalbuphine	91.1/0 (0.56)/(3.2)	1.9 (1.0/3.2)	11.1 (3.2/5.6)	1/3
Butorphanol	100/83.3 (1.0)/(3.2)	23.7 (1.0)	100 (3.2)	2/3
Fentanyl	12.7/100 (0.01/0.1)/(0.0178)	0/2.0 (0.056)/(0.032/0.056)	100/0 (0.01)/(0.056)	2/3
κ Agonists				
Enadoline	0/87.5 (0.001/0.00178)/(0.0056)	0/8.8 (0.01)/(0.0056)	22.8 (0.01)	1/3
Spiradoline	100/88.9 (0.056)/(0.1)	2.2 (0.1)	77.8/88.9 (0.056)/(0.032)	2/3
Nonopioids				
Amphetamine	0/0 (1.0)/(1.0)	0 (1.0)	0 (1.0)	0/3
Cocaine	0/0 (3.2)/(3.2)	0 (3.2)	15.2 (3.2)	0/3
Ketamine	0/11.1 (5.6)/(3.2/5.6)	8.9/12.5 (1.78/3.2)/(3.2)	28.6 (1.0/5.6)	0/3
Clonidine	0/100 (0.1)/(0.1)	11.1 (0.32/3.2)	97.9 (0.032)	2/3
Mirfentanil Derivatives				
OHM3463	100 (1.0)	10.2 (1.0)	100 (1.0)	2/3
OHM3295	88.9/88.9 (1.0)(1.78)	83.3/98.0 (1.0)/(1.0)	89.6/95.7 (3.2)/(0.32)	3/3
OHM10579	100 (3.2)	83.3 (3.2)	88.9 (1.0/3.2)	3/3

*Largest percentage of responding on the mirfentanil-appropriate lever during the first determination of the dose–effect curve.

†Largest percentage of responding on the mirfentanil-appropriate lever during the second determination of the dose–effect curve.

‡The dose that produced the largest percentage of responding on the mirfentanil-appropriate lever followed by the largest dose studied during that determination of the dose–effect curve; if the same dose produce both effects, it is only listed once.

§The number of monkeys in which the drug substituted for mirfentanil on at least one occasion over the number of monkeys in which that drug was studied.

trol with mirfentanil and determine whether its discriminative stimulus effects were mediated by a nonopioid mechanism. That the opioid antagonist naltrexone did not reliably antagonize mirfentanil suggests that there is a nonopioid component to the mirfentanil discriminative stimulus. Unfortunately, the varied substitution pattern for mirfentanil among monkeys precluded conclusive determination of the mechanism of action of mirfentanil. Although drugs that are pharmacologically similar to mirfentanil substituted in all subjects, other drugs substituted in only some monkeys. Even among individual monkeys in which other drugs substituted for mirfentanil, its mechanism of action could not be determined because drugs from several pharmacological classes produced mirfentanil-lever responding (e.g., subject RO, Table 1). Therefore, despite the fact that there appeared to be a nonopioid component to the discriminative stimulus effects of mirfentanil in all subjects, the specific mechanism of these effects was not determined.

Some drugs that substituted for mirfentanil were studied in combination with naltrexone to determine whether the effects of those drugs were mediated by opioid receptors. OHM3295 is structurally and pharmacologically similar to mirfentanil with both an opioid and a nonopioid component (1,2), and it produced mirfentanil-lever responding in all subjects. The effects of naltrexone on the discriminative stimulus effects of OHM3295 varied among subjects from no antagonism in one subject to a 10-fold shift to the right in the mirfentanil dose–effect curve following administration of 1.0 mg/kg of naltrexone in the other two monkeys. This dose of naltrexone produces a 30-fold shift to the right in the alfentanil (μ-opioid agonist) dose–effect curve (5); however, the involvement of an opioid component in the discriminative stimulus effects of OHM3295 cannot be confirmed because of the variability of the data among subjects as well as the lack of dose dependency for naltrexone.

Other drugs that substituted for mirfentanil clearly produced discriminative stimulus effects through opioid receptors, as evidenced by antagonism studies conducted with naltrexone in the subject RO. Naltrexone antagonized the discriminative stimulus effects of fentanyl and spiradoline, and the magnitude of these shifts strongly suggests that the discriminative stimulus effects of fentanyl were mediated by μ-receptors and the effects of spiradoline by κ-receptors [e.g., (5)]. Another fentanyl derivative, OHM3463, is structurally related to mirfentanil and has a pharmacological profile more similar to fentanyl than to mirfentanil (3); like fentanyl, OHM3463 substituted for mirfentanil in fewer monkeys than OHM3295, and its discriminative stimulus effects were antagonized by naltrexone in those monkeys in which it substituted for mirfentanil. Thus, the mechanisms of action differed among drugs that substituted for mirfentanil, and these data further support the notion that, in subject RO, the mirfentanil discriminative stimulus is nonselective.

Mirfentanil functioned as a reliable discriminative stimulus throughout the course of these studies (1.5 years). Despite the need for a comparatively large number of training sessions to establish stimulus control [e.g., see (6,7)], the mirfentanil discriminative stimulus did not appear to change over time. In those subjects (RO and MA) in which the mirfentanil discriminative stimulus appeared to be nonselective, it remained nonselective throughout the experiment; in contrast, the mirfentanil discriminative stimulus appeared to be selective in subject FR throughout the experiment, with only OHM3295 and OHM10579 substituting for mirfentanil. Thus, although the mirfentanil discriminative stimulus appears to be multifaceted with different monkeys attending to different features of the stimulus, its effects were consistent for a subject throughout the experiment.

In addition to nonopioid discriminative stimulus effects, it also appears as though the rate-decreasing effects of mirfentanil are not mediated by opioid receptors. Naltrexone did not antagonize the rate-decreasing effects of mirfentanil in monkeys responding under the stimulus-shock termination procedure (drug discrimination) or in monkeys responding to receive food (repeated acquisition and performance). This nonopioid mechanism for the rate-decreasing effects of mirfentanil is consistent with results in pigeons (4).

There are a number of adverse effects that can occur during the clinical use of opioids, including ventilatory depression as well as the development of tolerance and dependence. Although evaluation of these effects in rhesus monkeys or pigeons has indicated that mirfentanil does not differ from other low-efficacy μ-opioid agonists (3,4), it is still unclear whether there are conditions under which the nonopioid component of mirfentanil might modify effects produced by the opioid component. Therefore, a possible adverse effect (i.e., disruption of complex behavior) was assessed in the current study using a repeated acquisition and performance procedure; errors increased only during the repeated acquisition component of the multiple schedule and only at doses of mirfentanil that decreased response rates, indicating that mirfentanil has little effect on complex behavior. In previous studies, similar results were obtained with other low-efficacy μ-opioid agonists [e.g., (9)]. Collectively, these data suggest that mirfentanil is no more disruptive than typical opioid analgesics. Overall, results of the current study further support the safety of mirfentanil for use as an analgesic in humans, particularly outside of the clinic.

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