Original Article

Comparison of the Analgesic and Intestinal Effects of Fentanyl and Morphine in Rats

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Abstract
Clinical studies report a low incidence of intestinal side effects with transdermally administered fentanyl (TTS-fentanyl) in comparison with oral morphine. To support these clinical data, analgesic and intestinal effects of both opioids were compared in rats. After subcutaneous injection, analgesia in the tail withdrawal reaction test was obtained at a peak effect dose of 0.032 mg/kg with fentanyl and 8.0 mg/kg with morphine. This analgesic dose exceeded the ED_{50} for inhibition of castor oil–induced diarrhea only slightly (1.1 ×) in the case of fentanyl (0.028 mg/kg) but markedly (36 ×) in the case of morphine (0.22 mg/kg). To reverse completely the antidiarrheal effect of equivalent analgesic doses of the opioids (their ED_{50}s for analgesia lasting 2 hours), much more naloxone was required in the case of morphine (5.4 mg/kg) than in the case of fentanyl (0.19 mg/kg). After oral administration, the difference between both opioids was less pronounced. Analgesia was obtained at 0.85 mg/kg with fentanyl and 32 mg/kg with morphine. This analgesic dose only slightly (1.7 ×) exceeded the antidiarrheal dose in the case of fentanyl (0.49 mg/kg) but significantly (6.2 ×) in the case of morphine (5.2 mg/kg). To reverse completely the antidiarrheal effect of equivalent analgesic oral doses of the opioids (their ED_{50}s for analgesia lasting 2 hours), more naloxone was required in the case of morphine (11 mg/kg) than in the case of fentanyl (2.0 mg/kg). Rapid penetration of fentanyl into the brain is thought to be responsible for the small dissociation between the analgesic and intestinal effect of this lipophilic opioid. The present data provide preclinical evidence to support the relatively low incidence of intestinal side effects observed clinically with the use of TTS-fentanyl in comparison with orally administered morphine. J Pain Symptom Manage 1998;15:253–258. © *U.S. Cancer Pain Relief Committee, 1998.*

Key Words
Fentanyl, fentanyl-TTS, morphine, analgesia, side effects, in vivo, rats

Introduction

Fentanyl is a potent opioid analgesic that is used in general anesthesia.[1–4] Recently, the therapeutic application of fentanyl in pain management was broadened by the development of a transdermal therapeutic delivery system (TTS-fentanyl).[5,6] Clinical studies[6–8] in chronic cancer pain report TTS-fentanyl to have considerably fewer gastrointestinal side effects, such as nausea, vomiting, and constipation, than other opioid treatments, such as oral morphine. This reduced side effect liability could significantly enhance the quality of life of the patients.

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The present study compares the analgesic and intestinal activity of fentanyl and morphine in rats, both after subcutaneous (s.c.) and after oral (p.o) administration. The opioid analgesic activity was measured in the tail withdrawal reaction test.[1,9] The intestinal activity of the opioids was evaluated in the castor oil diarrhea test.[9] A second series of experiments evaluated the amount of the opioid antagonist naloxone required to reverse completely the antidiarrheal effect of equivalent analgesic doses of fentanyl and morphine. The required amount of naloxone is thought to reflect the intensity of the intestinal effect.

Materials and Methods

Animals

Wistar rats (Janssen Research Foundation) were transferred to the air-conditioned laboratories the day before the experiment and housed in individual cages under standard laboratory conditions (21 ± 2°C; 65 ± 15% relative humidity; light–dark cycle set at 12 hr). They were fasted overnight, but tap water remained available ad libitum except during the test period. All studies were controlled by the institutional animal care and use committee and performed in compliance with national laws and regulations consistent with the Declaration of Helsinki.

Pharmacological Tests

Castor oil diarrhea test in rats. Castor oil (1 mL, p.o.)–induced diarrhea was assessed by visual inspection at several time intervals after castor oil challenge in female rats (200–240 g).[9,10] Absence of diarrhea at 2 hr after the castor oil challenge (which occurred in only 1.8% of the historical control population; $n = 2500$) was used as an all-or-none criterion for determining the ED_{50} of the test compound for inhibition of castor oil–induced diarrhea. Test compound or solvent was given either s.c. simultaneously with the castor oil challenge or p.o. at 1 hr before the castor oil challenge (in order to allow more time for absorption of the opioids before the castor oil challenge and to avoid interaction of the orally administered opioids and the castor oil within the stomach).

Tail withdrawal reaction test in rats. Tail withdrawal reaction time after immersion of the distal 5-cm part of the tail into hot water (55°C) was recorded electronically in male rats (200–220 g) at regular time intervals up to 8 hr after administration of test compound or solvent. The criterion selected for drug-induced blockade of the tail withdrawal response was >10 s (cut-off time; observed in only 0.2% of the control animals; $n = 500$).

Statistics

Doses in the active dose range were given to at least five animals each, tested in separate experimental sessions including solvent-treated control animals. All-or-none criteria, based on the distribution of the results obtained in a large number of solvent-treated animals, were used to calculate ED_{50}-values and 95% confidence limits according to Finney's iterative method.[11] The criteria selected for drug-induced effects are mentioned in the test descriptions just provided.

Experimental Set-Up

In the first experiment, the analgesic activity of the opioids was studied as a function of time after either s.c. or p.o. administration. The analgesic activity was compared with the doses required for inhibition of castor oil–induced diarrhea. In a second experiment, the dose of the opioid antagonist naloxone (given 1 hr before castor oil challenge) required to reverse completely the antidiarrheal effect of equivalent analgesic doses of fentanyl and morphine (the ED_{50}s of the opioids for analgesic activity lasting 2 hours in the tail withdrawal reaction test) was determined. The opioids were tested via both the s.c. and the p.o. route of administration.

Results

Subcutaneous Route of Administration

Figure 1 shows the analgesic activity of fentanyl and morphine in the tail withdrawal reaction time as a function of time after s.c. injection. For each compound, the horizontal bar indicates the ED_{50} (and 95% confidence limits) for inhibition of castor oil-induced diarrhea. The peak effect dose for analgesia was 0.032 mg/kg for fentanyl (at 0.6 h after injection) and 8.0 mg/kg for morphine (at 1 h after injection) (Figure 1; Table 1). The analgesic dose exceeded the antidiarrheal dose only slightly (1.1 ×) in the case of fentanyl (0.028 mg/kg)

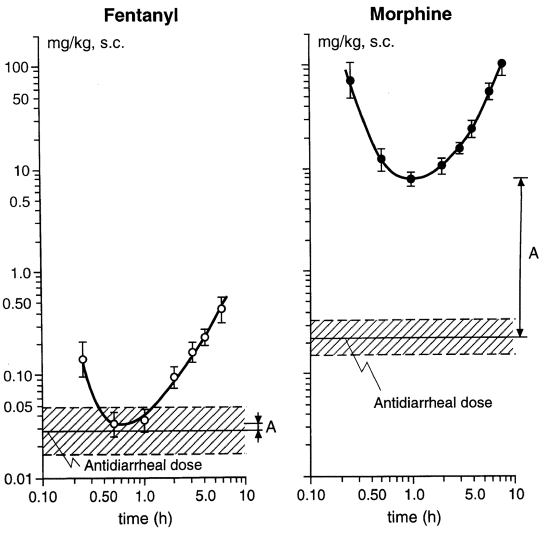

Fig. 1. ED_{50}s (and 95% confidence limits) of fentanyl (left) and morphine (right) for analgesic activity in the tail withdrawal reaction test as a function of time after subcutaneous administration. The *horizontal bars* indicate the ED_{50}s (and 95% confidence limits) of the compounds for inhibition of castor oil–induced diarrhea. The dissociation between both effects is indicated by the *line with the symbol "A"*. For further details, see the text and Table 1.

but markedly (36 ×) in the case of morphine (0.22 mg/kg) (Figure 1 and Table 1: index A). To reverse completely the antidiarrheal effect of equivalent analgesic doses of the opioids (their ED_{50} for analgesia lasting 2 hours [0.090 mg/kg for fentanyl; 10 mg/kg for morphine]), a considerably larger amount of naloxone was required in the case of morphine (5.4 mg/kg) than in the case of fentanyl (0.19 mg/kg) (Table 2).

Oral Route of Administration

After p.o. administration, the difference between both compounds was less pronounced. The peak effect dose for analgesia was 0.85 mg/kg for fentanyl (0.5 hr after administration) and 32 mg/kg for morphine (1–2 hr after administration) (Figure 2; Table 1). Like after s.c. injection, the analgesic dose only slightly (1.7 ×) exceeded the antidiarrheal dose of fentanyl (0.49 mg/kg) but significantly (6.2 ×) in the case of morphine (5.2 mg/kg) (Figure 2, Table 1; index A). To reverse completely the antidiarrheal effect of equivalent analgesic doses of both opioids (their ED_{50} for analgesia lasting 2 hours [1.6 mg/kg for fentanyl; 34 mg/kg for morphine]), a larger amount of naloxone was required in the case of morphine (11 mg/kg) than in the case of fentanyl (2.0 mg/kg) (Table 2).

Discussion

It is well known that opioids have both antidiarrheal and analgesic properties that are mediated via peripheral and central opioid receptors. A wide variation in the dissociation between the central analgesic and the peripheral antidiarrheal effects has been observed among the available opioids.[9] Opioids with a wide dissociation margin between both effects, such as diphenoxylate, loperamide, and loperamide oxide, have been developed as specific antidiarrheals without central side effects.[9,10] It seems evident that the opposite, that is, a small dissociation between analgesic and constipating effects, might be required to minimize the gastrointestinal side effect liability of opioids that are used as analgesics.

Table 1
Comparison of the Analgesic Doses of Morphine and Fentanyl in the Tail Withdrawal Reaction Test and Their Antidiarrheal Doses in the Castor Oil–Diarrhea Test [a]

	Analgesic dose [b] (ED_{50}; mg/kg)	Antidiarrheal dose (ED_{50} and 95% CI; mg/kg)		Dissociation factor (A)
Subcutaneous route				
Fentanyl	0.032	0.028	(0.016, 0.048)	1.1
Morphine	8.0	0.22	(0.15, 0.33)	36
Oral route				
Fentanyl	0.85	0.49	(0.30, 0.79)	1.7
Morphine	32	5.2	(4.0, 6.7)	6.2

[a] For further details, see the text and Figures 1 and 2.
[b] ED_{50} at time of peak effect (graphically estimated from Figures 1 and 2).
CI, confidence interval.

Table 2
Dose–Response Relations for the Ability of Naloxone to Reverse the Antidiarrheal Effect of Equivalent Analgesic Doses of Fentanyl and Morphine

	Fraction of animals displaying diarrhea at the indicated dose			
	Subcutaneous route		Oral route	
Naloxone dose (mg/kg, s.c.)	Fentanyl (0.090 mg/kg)	Morphine (10 mg/kg)	Fentanyl (1.6 mg/kg)	Morphine (34 mg/kg)
0	0/11	0/8	0/8	0/11
0.02	0/5			
0.04	2/5			
0.08	0/5			
0.16	2/5			
0.31	2/5			
0.63	5/5	0/5	0/5	
1.25		0/5	1/5	
2.5		1/5	4/5	0/5
5.0		2/5	4/5	1/5
10		4/5	5/5	1/5
20				5/5
ED_{50} (mg/kg):	0.19	5.4	2.0	11
LL (mg/kg):	0.11	3.3	1.3	7.2
UL (mg/kg):	0.33	8.7	3.3	16

ED_{50}, median effective dose; LL, lower limit; UL, upper limit.

The present results indicate that the dissociation between the analgesic and intestinal effects is much smaller in the case of s.c. administered fentanyl than in the case of morphine or orally administered fentanyl. At analgesic doses of fentanyl, therefore, a minimum stimulation of intestinal opioid receptors might be expected. This is confirmed by the small amount of the opioid antagonist naloxone that is required to reverse the antidiarrheal effect of a subcutaneous dose of fentanyl that produces analgesia lasting 2 hours.

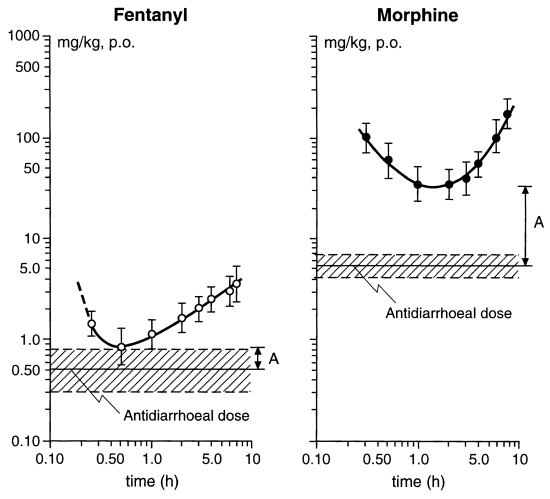

Fig. 2. ED_{50}s (and 95% confidence limits) of fentanyl (left) and morphine (right) for analgesic activity in the tail withdrawal reaction test as a function of time after oral administration. The *horizontal bars* indicate the ED_{50}s (and 95% confidence limits) of the compounds for inhibition of castor oil–induced diarrhea. The dissociation between both effects is indicated by the *line with the symbol "A"*. For further details, see the text and Table 1.

Fentanyl is very lipophilic and passes the bloodbrain barrier very rapidly, as evidenced by a rapid onset and short duration of action. In contrast, morphine has low lipid solubility, penetrates the brain less rapidly, and is slower in onset of analgesic action.[12–15] This difference in lipophilicity and in central nervous system (CNS) penetration rate also underlies the difference between both drugs in ''gut-selectivity,'' that is, the dissociation between central analgesic and peripheral gastrointestinal effects that has already been reported previously.[2,9,16,17] Owing to its high lipophilicity, fentanyl enters the brain to produce analgesia at doses that are only slightly higher than required for its intestinal action. This is particularly evident after parenteral administration, which avoids the first-pass metabolism in the liver that occurs after oral administration. In the case of morphine, on the other hand, the brain penetration required for the analgesic effect is obtained only at doses that are much higher than those required for the intestinal effects. At analgesic doses of morphine, therefore, excessive stimulation of peripheral opioid receptors and appearance of the corresponding side effects might be expected.

The transdermal drug delivery system (TTS-fentanyl) takes maximum advantage of the pharmacological properties of fentanyl. The device can produce a plasma concentration of fentanyl within the therapeutic window and may provide continuous analgesia while minimizing gastrointestinal side effects. In the case of oral morphine administration, on the other hand, prolonged duration of action obtained by increasing dose levels will result in higher peak plasma levels and a corresponding increased incidence of side effects. This difference is clearly demonstrated by the present results in rats. With s.c. fentanyl, analgesia is already obtained at the dose of 0.032 mg/kg, that is, just above the antidiarrheal dose (1.1 ×). With a transdermal system, this therapeutic concentration can be delivered over a prolonged period, providing continuous analgesia with a minimum of intestinal effects. With oral morphine, analgesia is obtained at a peak effect dose of 32 mg/kg, which is several times the antidiarrheal dose (6.2 ×). Using this formulation of oral morphine, a higher dose of about 100 mg/kg would be required to extend analgesia to 8 hours; this dose exceeds the antidiarrheal dose by a factor as high as 19 (see Figure 2).

It should be stressed that the present data result from a single multidose study that uses the s.c. and p.o. oral routes of administration. Nevertheless, we think that the s.c. route closely mimics the transdermal system, which continuously delivers small amounts of fentanyl to the subcutaneous space. A continuous level of analgesia with a minimum stimulation of intestinal opioid receptors and a corresponding minimum of intestinal side effects should be feasible with such a transdermal device. In any case, the present animal results might at least indicate that faster brain penetration with fentanyl might be an important factor to explain the lower intestinal side effect liability of TTS-fentanyl as compared with oral morphine.

References

1. Janssen PAJ, Niemegeers CJE, Dony JGH. The inhibitory effect of fentanyl and other morphine-like analgesics on the warm water induced tail withdrawal reflex in rats. Arzneimittelforschung 1963;13:502–507.

2. Gardocki JF, Yelnosky J. A study of some of the pharmacologic actions of fentanyl citrate. Toxicol Appl Pharmacol 1964;6:48–62.

3. Andrews CJH, Prys-Roberts C. Fentanyl: a review. Clin Anaesth 1983;1:97–122.

4. Janssen PAJ. Potent, new analgesics, tailor-made for different purposes. Acta Anaesthesiol Scand 1982;26:262–268.

5. Sandler A. Transdermal fentanyl: acute analgesic clinical studies. J Pain Symptom Manage 1992;7: S27–S35.

6. Ahmedzai S, Allan E, Fallon M, et al. The TTS-fentanyl multicentre study group: transdermal fentanyl in cancer pain. J Drug Dev 1994;6:93–97.

7. Donner B, Zenz M. Transdermal fentanyl: a new step on the therapeutic ladder. Anticancer Drugs 1995;6:39–43.

8. Donner B, Zenz M, Tryba M, Strumpf M. Direct conversion from oral morphine to transdermal fentanyl: a multicenter study in patients with cancer pain. Pain 1996;64:527–534.

9. Niemegeers C, Lenaerts F, Awouters F. Preclinical animal studies of modern antidiarrheals. In: Van Bever W, Lal H, eds. Synthetic antidiarrheal drugs, vol 7. New York/Basel: Marcel Dekker, Inc., 1976: 65–203.

10. Niemegeers CJE, Awouters, F, Lenaerts FM, Artois KSK, Vermeire J. Antidiarrheal specificity and safety of the N-oxide of loperamide (R 58 425) in rats. Drug Dev Res 1986;8:279–286.

11. Finney DJ. Maximum likelihood estimation. In: Probit analysis, vol 4, 3rd edition. London: Cambridge University Press, 1980:50–80.

12. Herz A, Albus K, Metys J, Schubert P, Teschemacher HJ. On the central sites for the antinociceptive action of morphine and fentanyl. Neuropharmacology 1970;98:539–551.

13. Von Cube B, Teschemacher HJ, Herz A, Hess R. Permeation morphinartig wirksamer Substanzen an den Ort der antinociceptiven Wirkung im Gehirn in Abhängigkeit von ihrer Lipoidlöslichkeit nach intravenoser und nach intraventrikulärer Applikation. Naunyn Schmiedebergs Arch Pharmakol Exp Pathol 1970;265:455–473.

14. Herz A, Teschemacher H-J. Activities and sites of antinociceptive action of morphine-like analgesics and kinetics of distribution following intravenous, intracerebral and intraventricular application. Adv Drug Res 1971;6:79–119.

15. Soudijn W, Van Wijngaarden I, Janssen PAJ. Biotransformation of neuroleptanalgesics. Int Anesthesiol Clin 1974;12:145–155.

16. Megens AAHP, Canters LLJ, Awouters FHL, Niemegeers CJE. Is in vivo dissociation between the antipropulsive and antidiarrheal properties of opioids in rats related to gut selectivity? Arch Int Pharmacodyn 1989;298:220–229.

17. Megens AAHP, Canters LJ, Awouters FHL, Niemegeers CJE. Normalization of small intestinal propulsion with loperamide-like antidiarrheals in rats. Eur J Pharmacol 1990;17:357–364.