The advantages of fentanyl for the treatment of pain: Studies of pharmacological profiles and fentanyl related side effects

Arief Nurrochmad 1), Ozaki Masahiko 2), Minoru Narita 2) dan Tsutomu Suzuki 2)

1) Department of Pharmacology and Clinical Pharmacy, Gadjah Mada University, Sekip Utara Yogyakarta, Indonesia
2) Department of Toxicology, Hoshi University School of Pharmacy and Pharmaceutical Sciences, Ebara 2-4-41, Shinagawa-ku, Tokyo, Japan

Abstract

The understanding of the pharmacological profiles of fentanyl and fentanyl-related side effects seems to be critical for the management for control of pain. Therefore, the present study was designed to investigate the advantages for treatment with fentanyl and the side effects such as emesis and gastrointestinal transit inhibition. The results demonstrated that fentanyl produced a profound antinociception in ferrets and mice than that induced by morphine. These findings are consistent with the experiences in the clinic. Morphine with lower doses than antinociceptive doses, produced a significant increase in gastrointestinal transit inhibition. However, fentanyl produced no gastrointestinal transit inhibition unlike morphine. These findings are consistent with the clinical experiences in the use of fentanyl. The clinical
studies in patients chronic cancer pain showed that transdermal therapeutic delivery system for fentanyl (TTS-fentanyl) produces less side effects such as constipation, nausea and vomiting than that induced by oral morphine. Morphine with lower doses than that used for antinociceptive assay also produced either in the number of retching or vomiting. However, fentanyl failed to produce emetic response in ferrets. These findings indicate that fentanyl produces much less emesis than that induced by morphine. Finally, we conclude that fentanyl produced potent antinociception in ferrets and mice. In addition, fentanyl produced much less side effects including emesis and constipation. These findings may provide evidence for benefit and usefulness of fentanyl for clinical frame on the management of pain treatment.

**Key word**: fentanyl; antinociception; emesis; ferret.

**Introduction**

Morphine has long been “gold standard” for the treatment of moderate to severe cancer pain. However, morphine possesses several side effects such as emesis, constipation and drowsiness, which have provoked the use of “opioid rotation” to alternative opioids. Fentanyl, which is a one series of potent opioids synthetic analgesic, has a high affinity for µ-opioid receptor and exhibits 50-100 times more potent analgesic activity than that of morphine. In the clinic, fentanyl is mainly used as epidural anesthetic and it has been used for the opioid rotation. It is likely that reason for this limited clinical application is related to a poor understanding the functional mechanism of fentanyl-induced analgesic actions and fentanyl-related side effects. It should be noted and some studies in the preclinic and clinic reported that the side effects of fentanyl are less than that of morphine (Ahmedzai and Brooks., 1997; Payne et al., 1998; Megens et al., 1998; Donner et al., 1996).

Opioid rotation is the practice of switching from one opioid to another, in order to improve an unfavorable balance of analgesia and side effects. Opioids are generally the most effective treatment for patients with cancer pain, and pain can be effectively controlled in the most cancer patients with minimal toxicity until their last time. The rationale for opioid rotation is based on interindividual variability in response to different opioids, or intraindividual variability in response to the same opioid over time, which commonly appreciated clinical phenomena in the management of pain (Tarumi, 2002).

Successful pain management with opioids could be achieved by adequate analgesia without excessive side effects. Nausea and vomiting are common and troubling side effects of opioid analgesics in the clinic (Aparasu et al., 1999). The incidence of opioid-induced nausea and vomiting is estimated to be 10% to 40%, and this symptom is ranked as highly distressing by patients (Urie et al., 2000). Opioids induce emesis through a number of mechanism: stimulation of the chemoreceptor trigger zone (CTZ) in the brainstem or through enhanced vestibular sensitivity. Chronic dosing and gradual upward titration of opioid dose may prevent the opioid-induced emesis. The opioid analgesics morphine is widely used to control pain in cancer patients. However, morphine induces severe constipation. It is estimated to occur in 25% to 50% of cancer patients and is the most commonly occurring adverse effect of chronic opioid therapy in patients with advanced cancer (Urie et al., 2000; Fallon and O’Neill., 1997; Fallon and Hanks., 1999). Fentanyl is a potent analgesic and mainly used as epidural anesthetic. The clinical studies in chronic cancer pain showed provide evidence that transdermal therapeutic delivery system fentanyl (TTS-fentanyl) produces less side effects such as constipation, nausea and vomiting than that induced by oral morphine (Ahmedzai and Brooks., 1997; Donner and Zen., 1995; Donner et al., 1996). The basic investigations on the fentanyl-induced side effects such as emesis and constipation may help clinicians to get an alternative opioid with fewer side effects.

The understanding of the pharmacological profiles of fentanyl and fentanyl-related side effects seems to be critical for the management for control of pain. Therefore, the present study was then designed to
investigate the advantages for treatment with fentanyl and the side effects such as emesis and gastrointestinal transit inhibition.

**Methodology**

The present study was conducted in accordance with Guiding Principles for the Care and Use of Laboratory Animals, Hoshi University, as adopted by the Committee on Animal Research of Hoshi University, which is accredited by the Ministry of Education, Culture, Sports, Science and Technology of Japan. Every effort was made to minimize the numbers and any suffering of animal used in the following experiments.

**Animals**

Male ferrets weighing 1-1.5 kg were obtained from Marshall Research Labs (North Rose, NY, USA). Ferrets were individually housed in a room kept at 23±1°C under a 12 hr light/dark cycle (light on 08:00-20:00 hr). They were given a standard cat diet (70-80 g/animal, Oriental Co. Ltd., Chiba, Japan) and allowed free access water. Male ICR mice weighing 20-25 g and male Sprague-Dawley rats weighing 250-300 g were obtained from Tokyo Laboratory Animals Science Co., Ltd, Tokyo, Japan. The animals were housed in a room kept at 23±1°C under a 12 hr light/dark cycle (light on 08:00-20:00 hr). Food and water were available ad libitum.

**Drugs**

The drugs used in the present study were morphine hydrochloride (Sankyo Co., Tokyo, Japan) and fentanyl citrate (Hisamitsu Co.Inc, Tokyo, Japan).

**Experimental procedures**

**Antinociceptive assay (Randal-Selitto test)**

The antinociceptive effects induced by morphine or fentanyl were measured using Randall-Selitto test analgesy-meter (Muromachi Kikai Co., Ltd., Tokyo, Japan). The pressure was directly applied to the tail of the ferret via a negative-shape plunger. The tail withdrawal or vocalization was considered to be a nociceptive response. The pressure force was shown as grams and the cut-off force was set at 354 g. Ferrets were administered subcutaneously (s.c) with morphine or fentanyl, and the measurement of antinociception induced by these drugs were performed every 15 min after the injection. The antinociceptive effect was calculated as a percentage of maximum possible effect (% antinociception) according the following formula: 

\[ \% \text{ antinociception} = \frac{(\text{test threshold} - \text{predrug threshold})}{(354 - \text{predrug threshold})} \times 100. \]

**Antinociceptive assay (Tail-flick test)**

The antinociceptive response produced by fentanyl or morphine were evaluated by recording the tail-flick test (Tail Flick Analgesia Meter Model MK 300B, Muromachi Kikai Co. Ltd., Tokyo, Japan). To prevent tissue damage, we established a 10 sec cut-off time. The tail-flick latency was measured both before and after the challenge with fentanyl or morphine. Antinociceptive response was calculated as a percentage of maximum possible effect (percentage of antinociception) according the following formula: 

\[ \% \text{ antinociception} = \frac{(\text{test latency} - \text{predrug latency})}{(\text{cut off time} - \text{predrug latency})} \times 100. \]

**Evaluation of emetic response**

Before the measurement of emesis induced by morphine or fentanyl, ferrets were acclimatized for 30 min in individual cages. The emetic response was evaluated by counting the number of retching or vomiting for 30 min after the injections of these drugs. Retching was defined as any rhythmic abdominal contraction without expulsion, whereas vomiting was defined as any oral expulsion (solid or liquid) from gastrointestinal tract. An assessment of emesis was made over a 30 min observation following the administration of morphine or fentanyl. The onset time and duration time of action of the retching or vomiting following the drug injection were recorded for each animal. When ferrets did not show an emetic response, the latency was determined by the observation periods.

**Evaluation of gastrointestinal transit**

Gastrointestinal transit was measured according to the method of Kamei et al (1995). Mice were fasted for 12-18 hr before the experiments. Twenty and five min after subcutaneous (s.c) injection of morphine or fentanyl, the suspension of charcoal was administered (p.o) at the volume 0.1 ml/mouse. Twenty min after charcoal administration, the animal was killed by decapitation and its small intestine was removed. The small intestine placed on a ruled template and both the length from the pylorus to the cecum, and the distance traveled by the charcoal was measured. The percentage of gastrointestinal transit was calculated as: 

\[ \frac{(\text{length from the pylorus to the cecum} - \text{distance traveled by the charcoal})}{(\text{length from the pylorus to the cecum})} \times 100. \]

**Statistical analysis**

The data are presented as the mean±S.E.M. The statistical significance of differences between the groups was assessed with a two-way ANOVA,
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followed by Bonferroni/Dunn or Student's t test.
Results and Discussion

Antinociceptive effect of morphine or fentanyl following s.c. injection in the ferrets

Randall-Selitto test

In the present study, we confirmed that either morphine (1.5, 3 and 6 mg/kg, s.c.) or fentanyl (10, 30 and 56 µg/kg, s.c.) produced a dose-dependent antinociception in the ferret using Randall-Selitto test. The maximal antinociceptive response induced by morphine or fentanyl was reached at 30 min and 15 min after the injection, respectively (Fig.1). Ferret has been accepted and usually used as an animal model for the study of nausea and vomiting (Rudd et al., 1994). However, in the present study using Randal-Selitto test, ferrets were also used for antinociceptive assay induced by opioids. The ED₅₀ values for the antinociception induced by morphine or fentanyl were 2.84 (2.48-3.24) mg/kg and 31.67 (26.74-37.42) µg/kg respectively (Fig.2). The ED₅₀ value of antinociception induced by fentanyl was approximately 90 times lower than ED₅₀ value of antinociception induced by morphine (Fig.2). The results demonstrated that fentanyl produced a profound antinociception in ferrets than that induced by morphine.

Antinociceptive effect and gastrointestinal transit inhibition induced by morphine or fentanyl following s.c. injection in mice

Morphine (1, 1.7, 3 and 5.6 mg/kg, s.c.) or fentanyl (10, 17, 30 and 56 µg/kg, s.c.) produced a dose-dependent antinociception in the mouse-tail flick test. The maximal antinociceptive responses induced by morphine or fentanyl was reached at 30 min and 15 min after the injection, respectively. The ED₅₀ values for the antinociception induced by morphine or fentanyl were 2.12 (1.31-3.28) mg/kg and 25.31 (12.76-47.29) µg/kg, respectively (Fig.3). The antinociceptive effect of fentanyl in mice was much potent than that induced by morphine. These findings are consistent with the experiences in the clinic.

The opioid analgesic morphine is widely used to control pain in cancer patients. However, morphine induces severe constipation. Opioids can delay gastric emptying, decrease peristalsis, and slow bowel motility. In the present study, we also confirmed the gastrointestinal transit inhibition induced by morphine in mice. Morphine (0.3, 0.56, 1.7 and 3 mg/kg, s.c) or fentanyl (17, 30, 56 and 100 µg/kg, s.c.) produced dose-dependent inhibition on gastrointestinal transit in mice. Either morphine (3 mg/kg, s.c) or fentanyl (100 µg/kg, s.c) produced the maximal inhibition (100 %). The ED₅₀ values for the gastrointestinal transit inhibition induced by morphine or fentanyl were 0.60 (0.05-1.60) mg/kg, s.c. and 32.71 (19.21-52.04) µg/kg, s.c., respectively (Fig.3). Morphine with lower doses than antinociceptive doses, produced a significant increase in gastrointestinal transit.

![Fig. 1 Antinociceptive effect of morphine (A) or fentanyl (B) following s.c. administration in the ferret using Randall-Selitto test. Antinociception was expressed as a percentage of maximum possible effect (% Antinociception). Each point represents the mean ± S.E.M. of 4-6 ferrets. *p<0.05, **p<0.01, ***p<0.001 vs. saline group]
inhibition. However, fentanyl produced no gastrointestinal transit inhibition unlike morphine. The ED$_{50}$ value for gastrointestinal transit inhibition and ED$_{50}$ value for antinociception induced by fentanyl was equi-

valence (Fig. 3). However, the ED$_{50}$ value for gastrointestinal transit inhibition induced by morphine was approximately 3.5 times lower than ED$_{50}$ value for antinociception by morphine (Fig.3). Other preclinical study can support these data with the low incidence of gastrointestinal adverse effects observed with transdermal fentanyl compared with orally administered morphine (Megens et al., 1998). Inhibition of gastrointestinal transit of systemic opioids on gastrointestinal function is mediated by µ-opioid receptors located in the central nervous system (CNS) as well as by peripheral µ-opioid receptors. The peripheral component of the gastrointestinal transit inhibition induced by opioid agonists depends on the interaction of these agonists mainly at the µ-opioid receptor. The different effect on the gastrointestinal transit inhibition induced by fentanyl and morphine may results from the lipid solubility and CNS penetration rate of fentanyl and morphine (Megens et al., 1998). These findings are consistent with the clinical experiences in the use of fentanyl. The clinical studies in chronic cancer pain showed that transdermal therapeutic delivery system for fentanyl (TTS-fentanyl) produces less side effects such as constipation, nausea and vomiting than that induced by oral morphine

![Fig. 2](image1.png)

**Fig. 2** Dose-response lines of antinociception induced by morphine (s.c.) or fentanyl (s.c) in ferrets using Randall-Selitto test. Antinociception was expressed as a percentage of maximum possible effect (% Antinociception).

![Fig. 3](image2.png)

**Fig. 3** Dose-response lines of antinociception and gastrointestinal transit (GIT) inhibition induced by morphine (A) or fentanyl (B) in mice. Each point represents the mean ± S.E.M. of 5-10 mice. Charcoal was administered (p.o.) 20 min or 5 min after morphine (s.c.) or fentanyl (s.c.) injection, respectively. Gastrointestinal transit was evaluated 20 min after p.o. administration of charcoal.
(Ahmedzai and Brooks, 1997; Donner and Zenz, 1995; Donner et al., 1996; Radbruch et al., 2000).

The emetic response after subcutaneous injection of morphine or fentanyl in the ferrets

Nausea and vomiting are the most distressing adverse effects associated with the use of opioids in cancer patients. Quality of life has shown to be significantly reduced in patients who experience opioid-induced nausea and vomiting. Based on the clinical experiences, we investigated the emetic response induced by opioids in ferrets. Morphine (0.1, 0.3, 0.6, 1.2 and 3 mg/kg, s.c.) induced either the number of retching or vomiting and showed the bell-shaped curve for the expression of retching and vomiting in the ferrets, whereas fentanyl (1, 3, 10, 30 and 56 mg/kg, s.c.) failed to induce either the number of retching or vomiting in the ferrets (Fig.4). The optimal dose of retching and vomiting response induced by morphine were achieved at 0.6 mg/kg, s.c. (Fig.4). The number of retching and vomiting was decreased at 1.2 mg/kg (s.c.) of morphine and completely abolished at 3 mg/kg (s.c.) of morphine. The onset time and duration time of vomiting or retching induced by morphine were achieved with the maximal emetic response at 0.6 mg/kg (s.c.) (Fig.5). This effect was abolished 15 min after the injection (Fig.6). The present study demonstrated that morphine with

![Fig. 4](image-url) The emetic response (vomiting and retching) after morphine (A, B) or fentanyl (C, D) by subcutaneous (s.c.) injection. Each column represents the mean number of vomits or retches ± S.E.M. of 4-6 ferrets. Animals were observed for 30 min after s.c. morphine or fentanyl injection. The fractions represent the number of animals that showed vomits and retches over the number of animals tested in that group.
lower doses than that used for antinociceptive
assay produced either in the number of
retching or vomiting. However, fentanyl failed
to produce emetic response in ferrets. These
findings indicate that fentanyl produces much
less emesis than that induced by morphine.

The bell-shaped curve for emesis was
consistent with previous reports of morphine
in ferrets (Barnes et al., 1991; Thomson et al.,
1992; Marrow et al., 1998). In the present study,
morphine produced a rapid onset and short
duration of emetic response. The maximal
effect of emetic response induced by morphine
was approximately achieved at 6-8 min after
injection. The maximal effect of emetic
response induced by morphine was different
with the antinociceptive effect that was
achieved at 30 min after injection. This finding
indicates the different mechanism and site of
action between emesis and antinociception. In
the clinical experiences, fentanyl could produce
nausea and vomiting, whereas we demonstrated
here that fentanyl failed to produce retching or
vomiting in ferrets. The discrepancy may result
from the different physiology or metabolism
between ferret and human. Other possibility is
the different situation that fentanyl has been
used for cancer patients suffering from severe
pain in the clinic. Patients are also received with
chemotherapy as an anticancer drugs and
radiotherapy. Both treatments also induce
nausea and vomiting in the clinic (Marrow et al.,
1998; Oettle and Riess., 2001; Anonym, 1999).

Fig. 5 The onset time (A) and duration time (B) of retching and vomiting after morphine injection (s.c.) in ferrets. Each column represents the mean number of vomits and retches ± S.E.M. of 4-6 ferrets. Animals were observed for 30 min after s.c. injection of morphine. The fractions represent the number of animals that showed vomits and retches over the number of animals tested in that group.

Fig. 6 Time-course of vomits (A) or retches (B) induced by morphine (0.6 mg/kg, s.c) in the ferrets. Each column represents the mean number of vomits (A) or retches (B) in 2 min interval time ± S.E.M. of 4-6 ferrets. Animals were observed for 30 min after s.c. injection of morphine.
Conclusion
Finally, we conclude that fentanyl produced potent antinociception in ferrets. In addition, fentanyl produced much less side effects including emesis and constipation. These findings may provide evidence for benefit and usefulness of fentanyl for clinical frame on the management of pain treatment.

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