Clinical Note

Intravenous Fentanyl for Cancer Pain: A "Fast Titration" Protocol for the Emergency Room

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Abstract
Patients with cancer sometimes are admitted to the emergency room due to severe pain. Despite the fact that morphine's hydrophilicity can delay its peak effects after intravenous administration up to 30 minutes, it is still the most commonly used opioid during cancer pain emergencies. Fentanyl is a synthetic, lipophilic opioid, more potent than morphine, and achieves peak effects after intravenous administration in 5 minutes. According to our observations, intravenous fentanyl could be safely used in the emergency room to treat patients who need fast titration of an opioid to control their pain. In our study, fentanyl was employed in a four-step protocol to treat patients admitted to our palliative care emergency room due to severe pain, regardless of the previous use of morphine at home. Titration with intravenous fentanyl was successfully employed in 18/18 (100%) patients, with an average time for pain control at about 11 minutes, and without relevant adverse effects. We conclude that intravenous fentanyl could be safely used for severe cancer pain when rapid titration is being considered. J Pain Symptom Manage 2003;26:876–881.

Key Words
Severe cancer pain, emergency room, intravenous fentanyl, titration

Introduction

Pain imposes suffering in the population with cancer. Despite the correct use of the World Health Organization's (WHO) guidelines,[1] cancer pain patients still seek the emergency room due to severe pain. In these situations, intravenous morphine is usually employed for titration. A protocol for rapid morphine titration has been suggested by Hagen et al.[2] These emergency room admissions may be due to breakthrough pain, neuropathic syndromes, pathologic fractures, infection, hemorrhage, and perforated viscus.[3] Tolerance, and the accumulation of morphine metabolites, can shift the dose-response curve for analgesia[4] and potentially lead to pain severe enough to warrant an emergency room visit.

To our knowledge, intravenous fentanyl has not been reported as a drug for fast titration during cancer pain emergencies. The aim of this study was to evaluate the use of intravenous fentanyl as an alternative to morphine for fast pain control in patients who were admitted to our palliative care center's emergency room due to severe pain.

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Methods

Patients with severe cancer pain admitted to our palliative care center's emergency room between April 2001 and June 2002 were eligible for the study. The inclusion criteria, which were adapted from Hagen et al.,[2] were: age between 18 and 80, concurrent morphine therapy for at least 2 weeks, and severe pain at initial assessment. Patients were asked to rate their degree of pain using a verbal scale of 0–10 (score 0 indicates no pain, and score 10 indicates worst pain possible). Severe pain was defined as pain intensity score 7 or greater, which was sustained for at least 6 hours and was increasing over the course of several hours to days. Patients with pure neuropathic syndromes, allodynia, or known tumor spreading to peripheral or central nervous structures were excluded from the protocol. Patients with breakthrough pain, as defined by Portenoy and Hagen,[5] (pain of 5 or greater, which occurs transiently, lasts minutes to hours, and is superimposed on a baseline level of pain rated as 5 or less) were also excluded from the protocol.

A detailed pain history had been taken before the protocol started, and only patients who were not eligible for any urgent image evaluation or surgical procedure, were included into the study. All patients were evaluated by at least one of the authors. Before entry into the study, written informed consent was obtained from the patients.

Intravenous fentanyl was administered as a bolus dose, over 10 seconds, in a four-step protocol (Fig. 1). Patients on oral morphine therapy were first converted to equivalent intravenous morphine, using a 3:1 ratio, and then to intravenous fentanyl. The conversion ratio used for intravenous morphine to fentanyl was 1:100.[6] During Steps 1 and 2, the intravenous fentanyl bolus doses corresponded to 10% of the total intravenous morphine daily dose taken in the previous 24 hours. Each step consisted of bolus doses, administered at five-minute intervals. An increase in 50% of the previous fentanyl bolus dose was performed in Step 3, and if necessary, we repeated the Step 3 bolus dose at Step 4.

For example, if a patient had been using 300 mg of oral morphine a day, we first converted this to 100 mg of intravenous morphine, and then to 100 micrograms of intravenous fentanyl (10% of the total morphine consumption in the last 24 hours). Steps 1 and 2 would consist of bolus doses of 100 micrograms of intravenous fentanyl, and Steps 3 and 4 would consist of a bolus dose of 150 micrograms of intravenous fentanyl.

The target point was pain intensity score less than 4. If significant side effects or the target point had occurred, the protocol was interrupted. Vital signs were monitored during the protocol, and 6 hours afterwards. Significant side effects were defined as vomiting, a decrease in respiratory rate below 8, hypotension, and bradycardia (frequency below 30% basal rate), thoracic rigidity, hallucinations or drowsiness. In these cases, the protocol had to be interrupted and naloxone 0.1mg could be administered, at a 2-minute interval, until reversal of side effects.

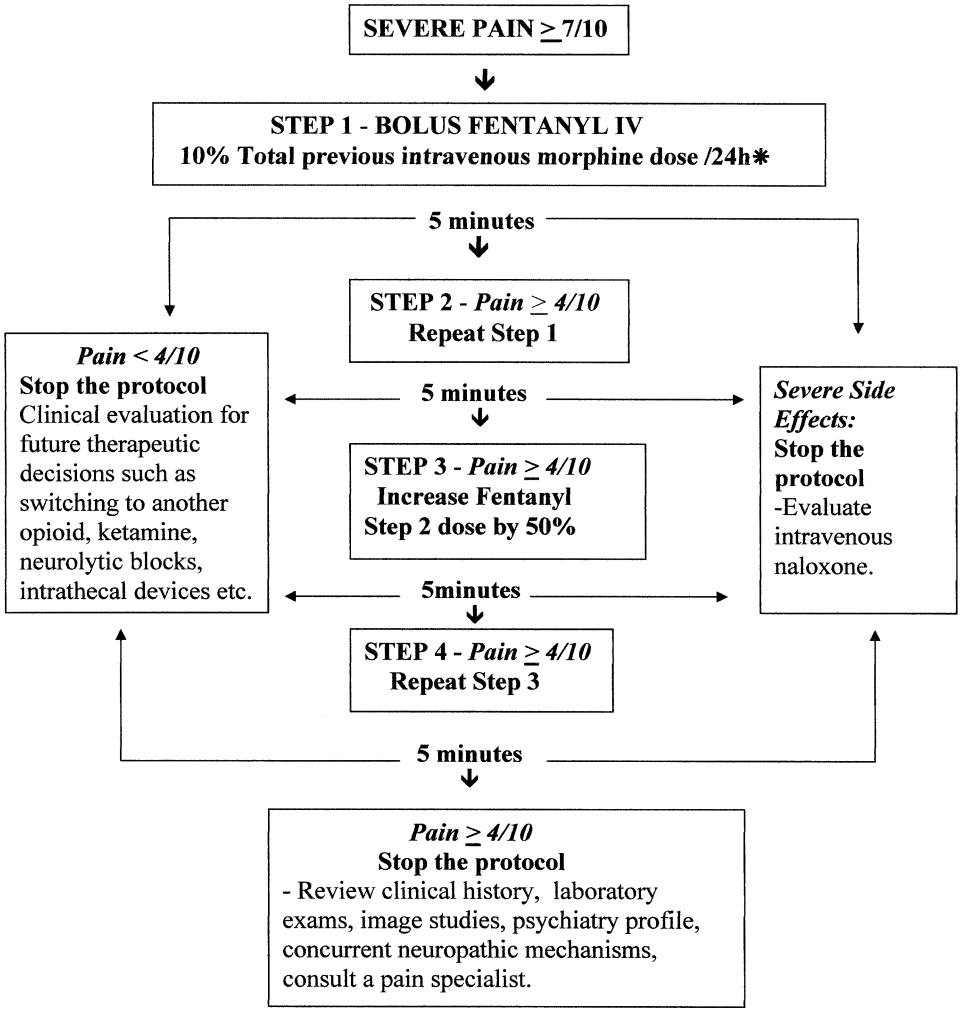
Results

Initially, we included in our study 20 patients who were admitted to our emergency room due to severe pain. Table 1 reports demographics, tumor, pain syndrome, total oral morphine dose used in the previous 24 hours, fentanyl total dose employed, and the time for pain control. Two patients were excluded from the study. Although not identified at admission, these two patients had CT scan evidence of tumor spreading into adjacent nervous structures.

All patients had their pain controlled during the protocol. The average age was 51 (range 34–74). The average time required for pain control was 11 minutes (range 5–25). The average oral morphine daily consumption was 276 mg (range 180–600), and the mean dose of intravenous fentanyl required for pain control was 214 micrograms (range 60–525). Side effects requiring protocol interruption were not observed, but slight somnolence occurred in 5 patients. The protocol was not intended to predict future doses of opioids, and the maintenance regimen after the protocol was based mainly on clinical judgment.

Discussion

Patients with cancer admitted into the emergency room complaining about pain must be closely evaluated. Concomitant acute conditions such as pathologic fractures, obstructed or



***Convert oral morphine to intravenous morphine using a ratio 3:1, and then to fentanyl using a ratio 1:100.**

Fig. 1. Four-step fentanyl protocol for the emergency room.

perforated viscus, vascular emergencies, and spinal cord compression, should be corrected as soon as possible. Tolerance, metabolic disturbances, and tumor spreading to adjacent structures also produce pain, and an increase in the opioid dose, rotation strategy, or another route of opioid administration[7] are some of the proposed types of treatment.

Regardless of the cause, severe pain occurs, and a prompt approach is needed. In these circumstances, morphine is usually employed.[8,9] Morphine administered orally is not adequate for fast pain control, and although the intravenous route can be effective, morphine hydrophilicity can delay its peak effects. Morphine crosses this blood-brain barrier relatively slowly, and although its onset can be observed within 5 minutes, peak effects may be delayed for 10 minutes or longer.[6,10] For these reasons, titration with morphine in the emergency setting should respect intervals between doses of over 30 minutes. Although Mercadante et al. have showed that titration with morphine can be safely done with a two-minute interval between additional doses (pain control was achieved in around 9 minutes[11]), the delay to peak effect may undermine efforts to replicate this fast titration method. Patients with neuropathic and incidental pain syndromes were included in the Mercadante et al. study, and the majority of

Table 1
Patient Demographics, Diagnosis, Pain Syndrome, Oral Morphine Consumption, Total Fentanyl Dose, and Time for Pain Control

Patient	Age	Sex	Tumor	Syndrome	Total Oral Morphine/24h	Fentanyl Dose	Time (Minute)
1	49	male	pharynx	mixed	180mg	300μg	20
2	53	female	cervix	visceral	180mg	210μg	15
3	51	female	cervix	visceral	180mg	120μg	10
4	58	male	parotid	mixed	600mg	200μg	5
5	72	male	lung	visceral	600mg	200μg	5
6	68	male	penis	somatic	300mg	200μg	10
7	37	female	cervix	visceral	180mg	300μg	20
8	45	male	mouth	somatic	210mg	140μg	10
9	59	female	cervix	visceral	180mg	120μg	10
10	64	male	gastric	visceral	300mg	200μg	10
11	70	male	lung	visceral	300mg	350μg	15
12	48	male	mouth	somatic	300mg	100μg	5
13	34	female	rectum	somatic	180mg	60μg	5
14	38	female	cervix	neuropathic	600mg	1000μg	excluded
15	40	female	neck	somatic	180mg	120μg	10
16	74	female	breast	somatic	180mg	60μg	5
17	36	male	gastric	mixed	180mg	300μg	20
18	37	male	gastric	mixed	300mg	350μg	15
19	35	female	cervix	visceral	450mg	525μg	15
20	45	female	cervix	neuropathic	300mg	500μg	excluded

patients were on Step 2 of the WHO analgesic ladder. When an intravenous morphine titration is performed in patients who are already using high doses of this opioid, up to 215 minutes may be required for pain control.[2] The use of more lipophilic drugs such as fentanyl would result in a faster titration than with morphine, as peak plasma levels could be obtained in five minutes.

Fentanyl is a synthetic opioid related to the phenylpiperidines. It is 7000 times more lipophilic,[12] and 75 to 200 times more potent, than morphine. It is highly protein bound in both the plasma (67%) and the brain (90%), and it has a high affinity for fat. As a result, prolonged exposure may result in accumulation in fat tissues.[13] The drug has entered palliative care as a useful strong opioid, and has substituted for morphine in some cases. Transdermal fentanyl has been frequently used in cancer pain patients as a part of the rotation strategy, or as an alternative route for opioid administration.[14]

Recently, transmucosal oral fentanyl has emerged as an attractive option for breakthrough pain,[15] and the subcutaneous route for fentanyl also has shown to be effective in palliative care patients.[16,17] Opioid administration by such parenteral routes yields a shorter time to peak analgesic effect when compared to oral or transdermal routes.[18,19]

Anesthesiologists are used to administering intravenous fentanyl, but some palliative care physicians are not so familiar with this route of administration. We have shown in this study that fentanyl can be used safely in the emergency room for cancer pain, as a part of a "fast titration" protocol. The equianalgesic conversion ratio between opioids is mainly based on relative potency charts derived from single dose studies, case reports, and case series.[20–22] During this study, intravenous fentanyl was applied in a nonlinear titration protocol, based on previous morphine consumption in the last 24 hours. There is some evidence that during the switching process, the equianalgesic dose ratio between opioids is dependent on previous opioid dose,[23] and a geometrical upward titration could increase the risk of adverse side effects during a protocol for fast pain control.

Beyond very fast pain control, fentanyl does not release histamine and affords hemodynamic stability. Rapid administration of high doses of intravenous fentanyl may result in chest wall rigidity, and severe ventilatory difficulty, especially during induction of anesthesia. In our study, all patients remained conscious and responsive and thoracic rigidity was not observed. This finding has been reported by Streisand et al.,[24] who found no thoracic rigidity despite high fentanyl doses in patients who remained awake and responsive. Monitoring for

chest wall rigidity is advisable, and a ventilation mask and oxygen should be promptly available in these cases.

This study has two important limitations. First, we excluded patients with breakthrough pain, predominant neuropathic syndromes, and surgical patients. These patients represent a significant number of admissions in the emergency room. Although the two excluded patients had CT scan evidence of tumor spreading into nervous structures, an exclusion criterion for the protocol, we did not perform CT scan in all patients. However, a careful review of the medical records, including pain characteristics, previous imaging studies, and the disease natural history, did not suggest a mainly neuropathic syndrome in the patients enrolled for the study. Although not identified initially, the two excluded patients had had a history of previous admission in another emergency room due to severe pain, and episodes of breakthrough pain at rest were reported by the family during a detailed interview with the pain management team. These two patients were refractory to the fentanyl protocol, and subsequently intrathecal catheters were placed in both for pain control. Neuropathic and breakthrough pain syndromes do not mean resistance to opioids, but the complexity of both syndromes makes titration an unpredictable process. In our view, once the protocol was based on prior morphine consumption, excluding neuropathic and breakthrough pain patients would be advisable. There is some evidence that opioid doses for breakthrough pain are not related to the baseline analgesic regimen.[25] Previous protocols had not taken into account morphine baseline consumption, and had selected arbitrarily morphine doses.[2,8,11] Patients admitted with severe pain, unrelated to the tumor, such as a perforated viscus or a vascular emergency, were also excluded from the study because of the possibility that the baseline morphine dose would yield an inaccurate estimate of the fentanyl dose.

Second, the follow-up after the titration was carried on by several physicians, with variable levels of pain management training. This fact resulted in different approaches, such as increasing the previous morphine dose (9 patients), immediate switching of the opioid (3 patients), switching to another route of opioid administration (5 patients), and ketamine infusions (5 patients). Due to fentanyl's pharmacologic properties, we recommend reassessing continuously and starting the proposed maintenance treatment as soon as possible. However, due to its pharmacokinetics, the conversion to transdermal fentanyl may be complex and many days could be required.[26] Future studies with intravenous fentanyl or other highly lipophilic opioids should evaluate the drug redistribution time, because if no adequate treatment is started, pain recurrence will be a potential problem.

The emergency physician faces several issues during the treatment of the terminally ill patients.[27] In the palliative care setting, the emergency room is sometimes chaotic. Bleeding, dyspnea, vomiting, and of course severe pain, frequently compose the scenario. Very fast pain control facilitates the physical examination and the medical interview, which constitute the key point to choose the correct treatment.[28] Furthermore, the "fast titration" protocol can result in a better utilization of the human resources at the emergency room. This is particularly important for many poor countries, where the local conditions and the resources available are limited, and sometimes the attending physician is alone to solve many problems at the same time.

In summary, fentanyl is a lipophilic opioid, with a higher affinity for mu receptors than morphine. These preliminary results confirm that patients with severe cancer pain who are admitted into the emergency room could have their pain controlled very fast and safely with an intravenous fentanyl titration. Correct identification of the underlying pain mechanisms and continuous reassessment are the cornerstones for choosing the best maintenance analgesic treatment.

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