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ORIGINAL REPORT

Rapid Switching Between Transdermal Fentanyl and Methadone in Cancer Patients

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ABSTRACT

Purpose
The aim of this study was to examine the clinical effects of switching from transdermal (TTS) fentanyl to methadone, or vice versa, in patients with a poor response to the previous opioid.

Patients and Methods
A prospective study was carried out on 31 patients who switched from TTS fentanyl to oral methadone, or vice versa, because of poor opioid response. A fixed conversion ratio of fentanyl to methadone of 1:20 was started and assisted by rescue doses of opioids, and then doses were changed according to clinical response. Pain and symptom intensity, expressed as distress score, were recorded before switching doses of the two opioids and after subsequent doses. The number of changes of the daily doses, time to achieve stabilization, and hospital stay were also recorded.

Results
Eighteen patients were switched from TTS fentanyl to methadone, and seven patients were switched from methadone to TTS fentanyl. A significant decrease in pain and symptom intensity, expressed as symptom distress score, was found within 24 hours after switching took place in both directions. Unsuccessful switching occurred in six patients, who were subsequently treated with an alternative therapy.

Conclusion
A rapid switching using an initial fixed ratio of fentanyl to methadone of 1:20 is an effective method to improve the balance between analgesia and adverse effects in cancer patients with poor response to the previous opioid. No relationship between the final opioid dose and the dose of the previous opioid has been found.

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INTRODUCTION

Opioids are the mainstay of moderate to severe cancer pain management. Although morphine is usually considered the preferred drug for the treatment of severe cancer pain because of its wide availability, varied formulations, and well-characterized pharmacologic properties, fentanyl use has been increasing in the last years. Previous experiences have shown that a failure to respond to one opioid does not mean failure to respond to all opioids, and opioid switching may allow better pain control and decrease the intensity of adverse disabling effects.[1-5]

The keystone to the rationale behind opioid substitution is incomplete cross tolerance, although the exact reason why opioid substitution is successful remains unclear. In some patients, poorly responsive pain may arise because of the development of analgesic tolerance to an opioid, whereas tolerance to adverse effects does not develop to the same extent. As a consequence, the escalating dose of any opioid may reach a level at which the adverse effects become predominant. Thus, the benefit of a switch from one opioid to another opioid could depend on cross tolerance to the analgesic effects being less than cross tolerance to the

adverse effects. The disadvantage is that it is impossible to know in advance if the balance between analgesia and adverse effects will be more convenient after opioid substitution. In addition, the dose of the alternative opioid chosen may be uncertain because it will depend on a series of factors, including individual response, pain mechanism, and degree of cross tolerance.[6]

Different modalities and conversion ratios have been reported for switching to methadone. Each approach has a rationale.[2,4,7-9] Methadone is characterized by the risk of accumulation because of its complex pharmacokinetics.[10] Transdermal (TTS) fentanyl prescription is growing among physicians, particularly in some countries. As a consequence, alternative treatments are needed for patients not responding to fentanyl. Methadone may be a useful alternative to improve opioid response. Although equianalgesic conversion ratios between morphine and fentanyl have been established in previous studies, data are lacking about the conversion ratio between fentanyl and methadone, particularly in the setting of a poor opioid response. The aim of this study was to evaluate a protocol of rapid substitution of TTS fentanyl with methadone, or vice versa, using an initial ratio of fentanyl to methadone of 1:20 in patients with a poor opioid response and then modifying the dose according to clinical effects in an intensive setting of palliative care.

PATIENTS AND METHODS

A prospective study was carried out in a sample of consecutive patients admitted in an acute palliative care unit for a period of 1 year. Informed consent and institutional approval were obtained. Thirty-one consecutive advanced cancer patients receiving TTS fentanyl or methadone who were required to switch opioid therapy because of an inconvenient balance between analgesia and adverse effects were included in the study. Patients with a poor analgesic response, despite having their dose doubled in 1 week, were also included.

The following protocol was used. The patients were switched using a fentanyl to methadone ratio of 1:20. The daily dose calculated of methadone was divided into three doses daily, and a further dose of one sixth of the daily dose was provided as needed. Intravenous route was used when the oral tract was unavailable. Fentanyl patches were removed with the first dose of methadone. The same reciprocal ratio (20:1) was used for switching from methadone to fentanyl. Similarly, in patients who were switched from oral methadone to TTS fentanyl, the patch was applied immediately after the last dose of methadone. Rescue doses of oral or intravenous morphine, using the equivalent of one sixth of the daily dose, were provided. The daily dose was changed according to the clinical needs. When the dose calculated was not equivalent to a standard patch, the difference was provided as equivalent doses of continuous intravenous fentanyl.[10] Each day, the sum of all opioids administered was calculated, also taking into account the route of administration of rescue doses. The number of changes in the planned daily doses, the time to reach a stable daily dose (considered as the first of 2 consecutive days requiring no more than two rescue doses), and time to hospital discharge were recorded.

According to department policy, the conversion ratios used among opioids and routes of administration, based on known drug availability for oral, TTS, and intravenous routes of administration,[11-16] were the following: oral morphine 100 = intravenous morphine 33 = TTS fentanyl 1 = intravenous fentanyl 1 = oral methadone 20 = intravenous methadone 16.

Adjuvant drugs that had been previously administered to control symptoms caused by illness or treatment were continued at the same doses during the switching. Nonopioid analgesics were also continued, if previously administered, at the same doses. No patient received anticancer therapy during the course of the study. All patients were strictly monitored with frequent rounds by a team consisting of doctors and nurses experienced in palliative care. Daily doses were changed, according the amount of drugs consumed as rescue doses in the previous day and clinical judgement, to achieve an acceptable analgesia with minimal adverse effects.

The following data were also recorded before switching and after switching until hospital discharge: age; sex; primary cancer and known metastases; pain causes and mechanisms; performance status; preswitching opioid doses; daily opioid consumption, including the planned daily dose and rescue doses; daily opioid doses at time of stabilization; symptoms associated with opioid therapy or commonly present in advanced cancer patients, such as nausea and vomiting, drowsiness, confusion, constipation, dry mouth, and so on, using a scale from 0 to 3 (not at all, slight, a lot, and awful; symptoms were assessed by the patient, and the distress score was calculated from the sum of symptom intensity); pain intensity (measured using the patient's self report on a numerical scale of 0 to 10); and pain syndromes, which were considered on the basis of clinical history, anatomic site of primary tumor and known metastases, physical examination, and investigations when available.

A successful switching was considered when the intensity of pain and/or distress score (the reasons for switching) decreased by at least 33% of the basal value recorded before switching, within a reasonable period of time (commonly 4 to 7 days). Dose stabilization was considered as the planned daily dose requiring no more than two rescue doses. The first of 2 days with a stable dose was considered as time of stabilization. Unsuccessful switching was followed by alternative measures, including intrathecal therapy or a further switching to another opioid, according to department policy.

Statistical Analysis

Frequency analysis was performed with the χ^2 test. The paired Wilcoxon signed rank test was used to compare pain intensity scores and symptom intensity scores in the time periods. The paired samples Student's t test was used to compare opioid mean dose in the time periods. The one-way analysis of variance and Mann-Whitney U statistic test were used for parametric and nonparametric analysis, respectively. All P values were two sided, and $P < .05$ was considered statistically significant.

RESULTS

The characteristics of patients are listed in Table 1. Twenty-four patients were switched from TTS fentanyl to oral

Table 1. Age, Sex, Number of Dose Changes, Time to Achieve a Stable Daily Dose, and Hospital Stay After Switching in the Responsive Patients

Characteristic	Fentanyl to Methadone		Methadone to Fentanyl	
	Mean	SE	Mean	SE
Age, years	54.7	3.9	58.7	5.9
Sex, No.				
Male	7		4	
Female	11		3	
No. of changes of daily dose	3.39	0.31	0.71	0.42
Time to achieve stabilization, days	4.3	0.33	2.0	0.49
Time to discharge after switching, days	5.3	0.71	4.1	0.63

methadone, and seven patients were switched from oral methadone to TTS fentanyl. The reasons for switching from fentanyl to methadone were both adverse effects and poor pain control, despite escalating opioid doses, in 14 patients, poor pain control in four patients, and adverse effects in four patients. The reasons for switching from methadone to fentanyl were both adverse effects and poor pain control in five patients, poor pain control in one patient, and adverse effects in one patient.

The mean preswitching TTS fentanyl daily dose was 4.2 mg/d (equivalent to 420 mg of oral morphine). According to the initial ratio chosen (1:20), this group of patients received an initial daily dose of oral methadone of 84 mg. Of these 24 patients, 20 were receiving TTS fentanyl doses $\geq$ 1.8 mg/d (equivalent to a relatively high dose of oral morphine of approximately 180 mg/d), and four patients were receiving doses less than 1.8 mg/d. Seven patients receiving a mean daily dose of oral methadone of 30.8 mg (equivalent to 154 mg of oral morphine) were switched to a mean initial daily dose of TTS fentanyl of 1.54 mg (Tables 2 and 3). Adjuvant agents used included the following: nonsteroidal anti-inflammatory drugs (n = 17), laxatives (senna, n = 15; lactulose, n = 10), gastroprotectors (n = 15), metoclopramide (n = 10), haloperidol (n = 6), amitriptyline (n = 4), corticosteroids (n = 3), and ondansetron and carbamazepine (n = 2).

Eighteen patients benefited from switching, improving the balance between analgesia and adverse effects, as confirmed by the significant changes in the pain intensity and distress score, even 24 hours after switching took place. At hospital discharge, there was a mean reduction in pain intensity and distress score of more than 33% of basal (preswitching) data. The benefit of switching was observed within 24 to 36 hours (Table 2 and 3). No significant differences between patients who switched because of poor pain control and those who switched because of both poor pain control and adverse effects were observed.

This clinical improvement was observed for both switching directions. In the patients who switched from TTS fentanyl to oral methadone, the mean time to achieve a daily dose stabilization after switching was 4.3 days, whereas the mean time was 2 days in patients who switched from oral methadone to TTS fentanyl; and the number of dose changes required was 3.4 and 0.7 in the two switching directions, respectively. Time to hospital discharge after switching was 5.3 and 4.1 days for the patients who switched from TTS fentanyl to oral methadone and vice versa, respectively.

The mean number of rescue doses in the patients who switched from TTS fentanyl to oral methadone and vice versa during the hospital admission was 1.8 and 2.1 per day, respectively. There were minimal differences (not statistically relevant) between the initial doses calculated and the daily doses at the time of stabilization (15% when switching from fentanyl to methadone, and 30% when switching from methadone to fentanyl; Tables 1 and 2).

In six patients who switched from TTS fentanyl to oral methadone, the treatment was considered unsuccessful.

Table 2. Data of 18 Patients Who Completed the Switch From Fentanyl to Methadone Successfully

Measure	Day 0		Day 1		Day 2		Day 3		Day of Stabilization	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
No. of patients	18		18		18		17		18	
Symptom										
Pain	5.9	5.0 to 6.9	3.3*	2.3 to 4.3	2.7*	2.1 to 3.4	2.6*	1.6 to 3.7	1.8*	1.2 to 2.5
Nausea	0.9	0.3 to 1.5	0.4	0.0 to 0.9	0.3*	0.0 to 0.6	0.3*	0.0 to 0.6	0.3*	0.0 to 0.5
Drowsiness	1.6	1.2 to 1.9	1.1	0.7 to 1.4	1.1	0.8 to 1.3	1.1	0.7 to 1.4	0.8*	0.5 to 1.1
Confusion	0.5	0.1 to 0.9	0.3	0.1 to 0.6	0.1*	0.0 to 0.3	0.3	0.1 to 0.6	0.3	−0.1 to 0.6
Constipation	2.0	1.1 to 2.8	1.6	0.8 to 2.4	1.3	0.7 to 1.9	1.2	0.5 to 1.8	1.1	0.5 to 1.7
Dry mouth	1.2	0.7 to 1.6	0.9	0.6 to 1.3	1.0	0.6 to 1.5	1.0	0.5 to 1.6	0.8	0.4 to 1.1
Distress score	6.5	5.3 to 7.7	4.8*	3.3 to 6.2	3.9*	3.0 to 4.8	3.9*	2.7 to 5.2	3.3*	2.2 to 4.3
Methadone dose, mg/d	84	52 to 115	94	49 to 139	92	50 to 135	89	52 to 126	71	33 to 109

NOTE. See text for symptom scoring.
*$P < .05$ compared with day 0.

Table 3. Data of Seven Patients Who Completed the Switch From Methadone to Fentanyl Successfully

Measure	Day 0		Day 1		Day 2		Day 3		Day of Stabilization	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
No. of patients	7		7		7		5		7	
Symptom										
Pain	5.8	4.1 to 7.6	2.7*	1.0 to 4.4	2.6*	1.2 to 3.9	3.2	2.1 to 4.2	2.6*	1.5 to 3.6
Nausea	1.8	0.7 to 2.9	1.3	0.2 to 2.3	1.4	0.2 to 2.6	1.4	0.3 to 2.5	1.6	0.2 to 2.9
Drowsiness	1.7	1.3 to 2.2	1.3	0.8 to 1.7	1.4	0.9 to 1.9	1.4	0.7 to 2.1	1.1*	0.8 to 1.5
Confusion	1.4	0.9 to 1.9	0.7*	0.2 to 1.2	0.0*	0.0	0.4	−0.3 to 1.1	0.1*	−0.2 to 0.5
Constipation	1.7	0.0 to 3.4	1.4	−0.6 to 3.5	0.7	−0.7 to 2.1	0.4	−0.3 to 1.1	0.9	−0.3 to 1.9
Dry mouth	2.2	1.1 to 3.2	1.7	0.8 to 2.6	2.0	1.2 to 2.7	1.4	0.3 to 2.5	2.1	1.1 to 3.1
Distress score	10.7	7.4 to 14.0	7.1*	3.4 to 10.8	6.1*	3.8 to 8.4	5.4*	3.5 to 7.2	6.1*	3.1 to 9.1
Fentanyl dose, mg/d	1.54	0.49 to 2.6	1.71	0.67 to 2.75	2.15	0.46 to 3.83	3.50	−1.48 to 8.49	2.20	0.46 to 3.94

NOTE. See text for symptom scoring.
*$P < .05$ compared with day 0.

Data regarding these patients are listed in Table 4. These patients received multiple changes in doses to obtain the best balance between analgesia and adverse effects within 4 to 7 days. Three patients underwent a successful intraspinal treatment with a combination of intrathecal morphine and local anesthetics. One patient, who was switched for adverse effects, preferred to go back to fentanyl therapy. In two patients, switching was not able to relieve a global state of suffering (characterized by confusion, drowsiness, and oliguria), which was attributed to a terminal state and required sedation with an intravenous midazolam-morphine combination until death, which occurred on days 15 and 7.

DISCUSSION

The opioid switching between fentanyl and methadone was successful, in both directions, in approximately 80% of patients (25 of 31 patients) using an initial conversion ratio of 1:20 and a stop and go approach (regardless of the dose of the previous opioid) and then modifying the dose of the alternative opioid according to a flexible protocol and depending on the clinical response. This ratio was relatively maintained at time of stabilization, which was achieved within 2 to 4 days, although it required frequent therapeutic interventions during a mean of 4 to 5 days of admission to achieve a timely equilibrium between analgesia and adverse effects. This intensive approach was safe in an intensive setting and allowed for a relatively short time admission.

Data regarding switching from other opioids to fentanyl in unstable patients are lacking, probably because of the unreliable pharmacokinetics of TTS fentanyl. Previous studies performed using a subcutaneous infusion of fentanyl in patients unresponsive to previous opioids suggest similar conversion ratios when using morphine as an intermediate conversion drug.[17] Data on conversion from fentanyl to methadone or vice versa in the raw clinical setting

Table 4. Data of Six Patients Who Switched From Fentanyl to Methadone Unsuccessfully

Measure	Day 0		Day 2		Day 2		Day 3		Last Day*	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
No. of patients	6		6		6		6		6	
Symptom										
Pain	5.8	3.8 to 7.9	4.2	2.9 to 5.4	3.7	1.9 to 5.4	4.0	3.1 to 4.9	3.3	1.1 to 5.6
Nausea	1.5	0.1 to 2.9	1.5	0.1 to 2.9	1.0	−0.3 to 2.3	0.8	−0.4 to 2.1	0.0	0.0
Drowsiness	2.0	2.0	1.5	0.9 to 2.1	1.3	0.5 to 2.2	1.7	1.1 to 2.2	1.7	1.1 to 2.2
Confusion	0.8	0.1 to 1.6	0.5	0.0 to 1.1	0.5	0.0 to 1.1	0.3	−0.2 to 0.9	0.8	0.1 to 1.6
Constipation	0.7	0.1 to 1.2	0.5	−0.3 to 1.4	0.7	−0.6 to 1.9	1.0	0.3 to 1.7	1.7	−0.4 to 3.7
Dry mouth	1.3	0.2 to 2.4	1.2	0.1 to 2.2	1.0	−0.1 to 2.1	0.8	−0.4 to 2.1	1.3	0.5 to 2.2
Distress score	6.8	4.2 to 9.4	5.5	2.9 to 8.1	4.8†	2.2 to 7.4	4.8†	2.5 to 7.2	5.5	3.0 to 7.9
Methadone dose, mg/d	85	−41 to 211	74	19 to 129	81	36 to 126	90	46 to 134	124	−37 to 285

NOTE. See text for symptom scoring.
*Last day corresponds to the day when alternative treatment was started.
†$P < .05$ compared with day 0.

are even more rare in the literature. In a recent experience, a similar initial conversion ratio between TTS fentanyl and oral methadone was used.[18] However, the ratio was used in a different protocol that postponed the administration of methadone from 8 to 24 hours after removing the patch, according to the dose of fentanyl. There are no pharmacokinetic data supporting this approach because elimination curves of fentanyl after removing the patch are similar, independent of the dose. However, methadone has a high distribution volume, and the first doses are unlikely to produce effective plasma concentration because of its body disposition, so the risk of overdose is unlikely, even though fentanyl concentration slowly decays. This is exactly what happens at induction with TTS fentanyl when the last administration of a long-acting opioid (for example, slow-release morphine) is usually administered at the same time as patch application.

In the protocol proposed by Benitez-Rosario et al,[18] patients who are switched for uncontrolled pain, despite receiving high doses of fentanyl, could potentially have an uncovered period of 12 to 24 hours in which their critical conditions are likely to worsen, producing a sort of iatrogenic therapeutic window (ie, a lowering of plasma opioid concentration). Although data on time of stabilization are reported, no data on these crucial first days after switching were provided. The slow decay of fentanyl concentration after removing the patch could correspond in some way to the typical pharmacokinetic delay in increasing blood concentration of methadone during the first 12 to 24 hours. Moreover, methadone doses were changed every 72 hours, and this approach could produce a further delay in achieving the study goal and, thus, prolong the patient's suffering.

The rationale of the approach used in the present study was based on previous experiences, in which a priming dose of methadone was considered necessary to obtain a rapid outcome in an acute clinical setting, such as poor pain control frequently associated with distressing opioid-induced adverse effects, and in which rescue doses were administered according to the clinical need.[7] This approach, which is possible in an intensive setting where patients are strictly monitored, provides a basis to shorten time to achieve stabilization and avoid prolonged distress in patients with high levels of pain or symptom burden, even if that means receiving relatively large doses of opioids after switching. Other modalities have been shown to achieve stabilization within prolonged and, sometimes, unacceptable periods of time.[9]

Some changes have been found between the calculated initial dose and final doses used at time of stabilization, depending on the direction of switching. When switching from fentanyl to methadone, the final doses were approximately 15% lower than the doses calculated when using an initial conversion ratio of fentanyl to methadone of 1:20 (from an initial calculated mean daily dose of 84 mg of oral methadone to a final daily dose of 71 mg), whereas approximately 30% higher final doses of fentanyl were administered when switching from methadone to fentanyl (from an initial daily dose of TTS fentanyl of 1.54 mg to a final dose of 2.20 mg). This means that doses of methadone will be somewhat lower in the first switch direction and fentanyl doses will be higher in the second switch direction compared with the initial ratio chosen (fentanyl to methadone ratios of 1:17 and 1:13, respectively, from an initial ratio of 1:20). This occurred independently of the preswitching opioid dose. A similar observation was reported in a previous study, where the final ratio between fentanyl and methadone was less than 1:20 (1:17).[18] Despite being more complicated, presumably this approach allowed for rapid symptom control, as inferred by the early improvement immediately observed in the first days after switching and by the quick stabilization time, which was reached within a mean of 4 days.

A lower number of patients were switched from methadone to fentanyl. This reflects the higher number of patients receiving TTS fentanyl, which is the opioid more frequently used in Italy, compared with oral methadone. Patients who switched to fentanyl required fewer changes in daily doses, and time of stabilization was shorter. This observation can be explained by the type of drug delivery, which does not allow frequent changes. The simultaneous administration of intravenous fentanyl allowed us to change the size of the patch when the doses required were consistent in the range of the new patch dose. In contrast to other studies, which reported a complex switching from methadone to other opioids,[19] switching to fentanyl was equally effective.

Because, in some patients, it is often necessary to use more than one route of administration during switching (for example, in the presence of nausea and vomiting for methadone) or to support a slow route (such as the TTS route), it is important to manage conversion ratios between different routes of administration, other than among opioids. Conversion ratios used in this study were based on pharmacokinetic data concerning opioid availability with different routes. In a previous study, a conversion ratio of 0.6 mg/d of intravenous fentanyl to 2.4 mg/d of methadone (1:4) was used when substituting intravenous methadone for intravenous fentanyl to calculate the initial dose of methadone in advanced cancer patients with uncontrolled pain and central adverse effects, such as drowsiness and confusion.[20] Given that the TTS to intravenous ratio for fentanyl is equal to 1 (see Kornick et al[21]) and the intravenous to oral ratio for methadone is 0.8, according to oral methadone availability (although a ratio of 0.5 has often been used),[11,22] the large differences reported in conversion ratios between the two routes (TTS fentanyl to oral methadone ratio of 1:20 *v* intravenous fentanyl to intravenous

methadone ratio of 1:4) can be explained by the need to strongly increase the opioid dose in specific clinical circumstances of uncontrolled pain.

No differences were found when considering the reasons for switching. However, this could be attributed to the low number of patients presenting different indications (ie, both poor pain control and adverse effects, poor pain control, or adverse effects). Other limitations of this study reflect those limitations that are well known in palliative care research that is performed in patients in critical conditions that can be difficult to control in a complex context, such as patients with poor pain relief and/or severe adverse effects, which require extreme efforts to improve the balance between analgesia and adverse effect as early as possible. Thus, this data should be considered as preliminary and needs to be confirmed by larger experience. The approach used in this study requires expertise and strict surveillance in an acute setting, where symptom monitoring and continuous evaluation is the basis to maintain a high level of safety while providing timely symptom control. It is possible that this approach cannot be extended to other settings. However, the approach to these kinds of patients with relevant clinical problems requires high-level facilities.

In conclusion, when switching between fentanyl and methadone, the use of an initial ratio of 1:20, when stopping the first drug and initiating the second one, resulted in a clinical improvement in approximately 80% of patients, independently of the dose and direction of switching. Nevertheless, patients should be carefully monitored on an individual basis for possible unexpected responses until they achieve a clinical stabilization.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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