Drug use evaluation of transdermal fentanyl in a tertiary hospital

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ABSTRACT

Objectives The primary objective of the study was to assess the rationale of fentanyl patch initiation and continuation for pain. The secondary objectives were to analyse prescribing pattern between disciplines, monitoring criteria and adverse events profile of fentanyl patch in the inpatient wards for a tertiary hospital.

Methods A retrospective case series review was undertaken of patients who received transdermal fentanyl for pain from April to June 2013 at the National University Hospital, Singapore. Relevant data were collected from electronic and physical medical records and audit criteria applied for indication, opioid tolerance, dosage regimen, adverse events and monitoring criteria.

Results 40 patients were prescribed fentanyl patches for pain in the study period. 15 patients (62.5%) had one or more problems during initiation of fentanyl patch. Appropriate use during initiation was low with only 9 (38%) patients meeting all the required criteria. Most of the inappropriate use involved a lack of bridging opioids (58%), wrong opioid conversion dose (42%) and use in opioid-naïve patients (42%). In addition, three cases of inappropriate placement were observed. Monitoring for efficacy and adverse effects generally met audit criteria. There was a low incidence of discontinuation (21%) due to its well-tolerated side effect profile.

Conclusions This study highlighted high incidence of inappropriate initiation of fentanyl patch, and we proposed an in-house guideline to aid physicians in initiating fentanyl patches during admission and to educate nursing staff of the monitoring parameters for efficacy and toxicity.

INTRODUCTION

Fentanyl is a potent opioid analgesic that is available as a transdermal formulation that was initially approved by the US Food and Drug Administration (FDA) in 1995 for the management of chronic, intractable pain in opioid-tolerant patients.^{1 2} The transdermal delivery system is designed to release the drug slowly and consistently over 72 h.^{1 3} Although providing stable fentanyl concentrations with chronic use, initiation of the patch results in an initial delay of 12–24 h before therapeutic analgesic concentrations are achieved. It is available in National University Hospital (NUH) in Singapore in three formulation strengths: 12, 25 and 50 mcg/h. Open comparative studies against sustained-release morphine formulations have suggested equivalent effects for analgesia, measures of quality of life and adverse effects⁴ and a lower frequency of constipation.⁵

The use of the fentanyl patch is not without dangers. In 2006, the Center for Forensic Sciences in

Onondaga County, New York reported eight cases of death due to fentanyl overdose, all of which involved the transdermal formulation.⁶ In 2008, in response to reports from the UK Medicines and Healthcare Products Regulatory Agency, Health Canada and FDA regarding adverse reactions with the use of fentanyl patches, Health Sciences Authority (HSA) published a product safety alert to advise healthcare professionals to be aware of the potential serious and fatal adverse effects associated with the use of fentanyl patches and report suspected adverse events associated with the Pharmacovigilance Branch of HSA.⁷ In 2011, a systematic compilation of case reports of opioid-related problems revealed that fentanyl was the most implicated opioid.⁸ The Institute for Safe Medication Practices (ISMP) also lists this medication as high-risk medication.⁹ Recently in December 2014, ISMP published a case report implicating fentanyl patch as a contributing factor as the cause of opioid-related death in a small community hospital.¹⁰

It is a common practice at the NUH to prescribe fentanyl patches for pain control. In view of potential of harm, delayed initial release profile, a drug use evaluation in NUH was conducted to ensure appropriate medication use and to identify current prescribing trend.

The primary objective of the study was to assess the appropriateness of fentanyl patch initiation and continuation. Secondary objectives were to analyse prescribing pattern between disciplines, monitoring criteria and adverse events profile of fentanyl patch in the inpatient wards in our hospital.

DESIGN

A retrospective descriptive case series of adult inpatients prescribed transdermal fentanyl for pain was undertaken at the NUH, a 1000-bed tertiary teaching hospital in Singapore, from 1 April to 30 June 2013. The arbitrary target sample size set was 50–100 subjects.

The study was approved by the Domain Specific Review Board of National Healthcare Group.

Patient selection (inclusion/exclusion criteria)

Potential study subjects were identified from the computerised pharmacy record system using the search term ‘transdermal fentanyl’ and were included in the review if they were aged >18 years of age and had been prescribed fentanyl patch during an inpatient stay for a documented indication of pain for more than 24 h.

Patients were excluded if they had been prescribed a fentanyl patch for an indication of dyspnoea or had been prescribed fentanyl patch upon discharge due to difficulty of data analysis follow-up.

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Data collection

A specially designed pro forma to record demographic data (race, age and gender), primary treating discipline and fentanyl patch dose was developed and used for data collection. Data were collected from the hospital electronic records, including the computerised patient support system, electronic inpatient medication record, computerised patient record system as well as physical medical records.

The criteria applied for appropriate use of fentanyl were:

Criteria for initiation

1. Use in an opioid-tolerant patient was defined as a patient who received at least one week or more of oral morphine >60 mg/day or equivalent.²
2. Correct dose conversion from other opioids was as per manufacturer's recommendations in the product insert (see [table 1](#)), and was based on 24 h oral morphine equivalence.
3. An appropriate indication for conversion to a transdermal delivery system was defined as relatively well-controlled pain on a short-acting opioid,² or intractable pain requiring continuous opioid administration for an extended period of time.¹ This study defined adequate stable analgesia as an unchanged opioid dose for 72 h prior to the use of fentanyl patch.
4. Adequacy of bridging medication for the period between patch initiation and proven relief from fentanyl patch was defined as a potent opioid (morphine, oxycodone or fentanyl) prescribed on a regular dosing for 8–12 h as bridging pain medication.
5. Appropriate breakthrough analgesia was defined as prescription of a strong opioid (morphine, oxycodone or fentanyl) based on a total daily analgesic dose equivalent to one-sixth of total daily opioid equivalent dose every 4 h given when required.

Criteria for continuation

1. Use in an opioid-tolerant patient and for the appropriate indication of chronic pain and intractable pain.
2. Appropriate breakthrough analgesia was as defined earlier.

Criteria for correct administration

1. Correct site of placement was defined as being placed on non-hairy, non-irritated and non-irradiated skin on a flat surface of the torso, or upper arms.¹

Criteria for efficacy assessment

1. Pain was deemed to have been assessed and recorded if there had been a pain score recorded (based on the visual analog scale numeric rating scale used by nursing staff) at least once during each shift on clinical charts.

Criteria for adverse effects monitoring and prevention

1. Documentation of patient's mental status by nursing staff at least once during each shift on clinical charts to monitor for drowsiness.
2. Documentation of patient's respiratory rate by nursing staff at least once during each shift on clinical charts to monitor

for respiratory depression. Respiratory depression was defined as a breathing rate of less than 10 breaths per minute.¹¹

3. Documentation of any occurrences of nausea/vomiting, constipation. Prescribing laxatives and anti-emetics for pre-emptive treatment of constipation and nausea/vomiting were documented.

Incidence of adverse effects was calculated based on documented occurrences in case notes or clinical evidence found on clinical charts.

The collected data were analysed using Microsoft Excel 2007. Descriptive statistics were generated as percentages. No further statistical analyses were performed as this was a retrospective observational study.

RESULTS

A total of 68 patients from April to June 2013 were identified, and 40 patients who fulfilled the criteria for inclusion were analysed (see [table 2](#)). The reason of exclusion included the use of fentanyl patch for dyspnoea (9), case/scan notes not available (7), inadequate duration (11) and use in a paediatric patient (1) (see [figure 1](#)). The patients were mainly of Chinese race (72.5%) and female (52.5%). The median age of the patients was 65 years (range 32–96). The main primary discipline prescribing fentanyl patch was medical oncology (60%), followed by cardiac (9%), cardiothoracic vascular surgery (7%) and haematology department (7%). The majority of the fentanyl patches prescribed was the 12 mcg/h strength (62%). The length of stay varied from 1 to 30 days with median time of 4.5 days.

Twenty-four patients were newly initiated on fentanyl patch and 16 patients continued their existing fentanyl patch ([figure 1](#)). Among the patients who had initiated fentanyl patch therapy, 14 (58%) patients were opioid tolerant and received

Table 1 Recommended dose conversion from oral morphine to fentanyl patch¹

24 h PO morphine total daily dose (mg)	Recommended fentanyl patch strength (mcg/h)
45–134	12–25
60–134	25
135–224	50

Table 2 Patient profile

	N (%)
Total patient cohort*	40 (100)
Gender	
Male	19 (47.5)
Female	21 (52.5)
Race	
Chinese	29 (72.5)
Malay	6 (15)
Indian	3 (7.5)
Others	2 (5)
Discipline	
Medical oncology	24 (60)
Cardiac	3 (7.5)
Cardiothoracic and vascular surgery	3 (7.5)
Haematology	3 (7.5)
Gastro	2 (5)
Others†	5 (12.5)
Strength of patch ordered (mcg/h)	
6	6 (15)
12	25 (60)
25	5 (12.5)
37	1 (2.5)
50	3 (7.5)

*Minimal—32 years, maximum—96 years, median—65.5 years.

†Other disciplines are rheumatology (1), nephrology (1), general medicine (1), respiratory (1), trauma (1).

Figure 1 Patient flow chart.

the appropriate opioid dose conversion. Seventeen (71%) patients received the therapy for the appropriate indication. The breakthrough dose was prescribed correctly for 17 (71%) patients, while 10 (42%) patients were prescribed with appropriate bridging breakthrough dose (table 3).

Comparatively, 10 (42%) patients were opioid naïve and received fentanyl inappropriately. Seven (29%) patients received fentanyl for inappropriate indications (acute post-operation pain (n=2), acute pain (n=4), acute chest pain (n=1)). Breakthrough doses were either omitted or inappropriately prescribed (eg, tramadol) for 7 (29%) patients, while there were 14 (58%) patients who were not prescribed bridging breakthrough doses of opioid.

Among 16 patients who had continued on fentanyl patch therapy, 16 (100%) patients were opioid tolerant and indications were appropriate. Fifteen (94%) patients were prescribed breakthrough dose of opioid correctly.

Location of the transdermal patch was inappropriate in three instances.

1. Placed over the right leg wound for severe incident pain secondary to calciphylaxis.
2. Placed over the right wrist for acute pain due to arteriovenous fistula complication.
3. Placed over right wrist for acute pain due to steal syndrome from arteriovenous graft creation.

Table 4 Number of problems identified (per patient) during initiation of fentanyl patch

Number of problem(s) during initiation	Number (%)
0	9 (38)
1	4 (17)
2	1 (4)
3	3 (13)
4	2 (8)
5	5 (21)

Number of problems is defined as failure to follow the initiation criteria; use in opioid-naïve patient, incorrect dose conversion, inappropriate indication, lack of bridging opioid on initiation and inappropriate breakthrough analgesia ordered.

Due to inadequate documentation in the case note, appropriateness of patch placement was not assessable for 13 patients.

Overall, there were nine (38%) patients who met the correct initiation criteria. Fifteen (63%) patients had one or more problems with initiation of fentanyl patch, and five (21%) patients had all five problems identified (table 4). It was more commonly observed when prescribed by disciplines other than the oncology and haematology departments.

Pain scores were generally well monitored for 36 (90%) patients even though there were a few instances where the pain scores did not match what was written in the case notes or number of breakthrough doses served.

Drowsiness and respiratory depression due to the fentanyl patch were generally well monitored as they are part of the vital signs documented by the nursing staff every shift. Pre-emptive treatment was ordered by doctors for constipation more frequently than for nausea/vomiting (table 5). Incidence of minor side effects, drowsiness, nausea/vomiting and constipation ranged from 14% to 30% while that of respiratory depression was 3%.

DISCUSSION

To our knowledge, this is the first report examining the use of transdermal fentanyl in an inpatient setting with a focus on drug initiation.

The appropriate use of fentanyl patch during initiation was low with only nine (38%) patients meeting all the required criteria. Most of the inappropriate use involved a lack of bridging opioids (58%), wrong opioid conversion dose (42%) and use in opioid-naïve patients (42%). In addition, three cases of inappropriate placement were observed. The low percentage of patients meeting audit criteria is concerning given fentanyl patch prescription is considered a high-alert medication by ISMP, perhaps

Table 3 Compliance to criteria for fentanyl patches

	Initiation of fentanyl patch (number, %)		Continuation of fentanyl patch (number, %)	
	Meets criteria	Does not meet criteria	Meets criteria	Does not meet criteria
Opioid tolerant	14 (58)	10 (42)	16 (100)	0 (0)
Correct conversion	14 (58)	10 (42)	NA	NA
Correct indication	17 (71)	7 (29)	16 (100)	0 (0)
Appropriate breakthrough pain medication prescribed	17 (71)	7 (29)	15 (94)	1 (6)
Appropriate bridging pain medication prescribed before onset of fentanyl patch	10 (42)	14 (58)	NA	NA

NA, not applicable.

Table 5 Percentage of appropriate monitoring or pre-emptive treatment for side effects and incidence of occurrence of side effects (n=40)

Adverse effect	Appropriate monitoring (%)	Pre-emptive treatment ordered (%)	Incidence (%)
Drowsiness	37 (93)	N/A	24
Respiratory depression	37 (93)	N/A	3
Nausea/vomiting	N/A	16 (40)	14
Constipation	N/A	29 (73)	30

N/A, not applicable.

reflecting non-familiarity with fentanyl patch use. Appropriateness of continuing fentanyl patch in this study was excellent (100%) and this study did not identify any further interventions needed for this subgroup.

In view of the high rate of inappropriate initiation of the fentanyl patch, we propose the use of an in-house guideline to be used by healthcare professionals when a patient is newly initiated on fentanyl patch. The guideline would inform prescribers if the use of fentanyl patch is indicated in their patients, the appropriate dose of fentanyl to use and appropriate breakthrough and bridging pain medications to prescribe concurrently. The guide would remind nursing staff on the correct site of placement of the patch and necessary monitoring parameters for efficacy and toxicity.

Fentanyl patches were prescribed mainly by the oncology team (60%) followed evenly by other disciplines. This was expected as fentanyl patch was proven to be effective in chronic stable cancer pain.⁴ This study is the first to describe current prescribing pattern in an inpatient setting.

Monitoring for efficacy and adverse effects was generally performed well probably reflecting routine monitoring parameters recorded by nurses as vital signs. As nausea/vomiting is a side effect which patients may develop tolerance to, anti-emetics may be unnecessary for patients who were already on the patch. However, pre-emptive laxatives should still be prescribed to prevent constipation, which is a side effect of fentanyl which patients do not develop tolerance to. Our incidence of constipation, 30%, is comparable with another published study (22%–48%).⁵ Other minor side effects reported were drowsiness (24%), nausea/vomiting (14%) and respiratory depression (3%).

We acknowledge the limitations of this study. First, due to the limited sample size of 40 subjects (original target 50–100), meaningful subgroup analysis could not be carried out. Second, more than 50% of the sample did not use a patch for more than 6 days during their admission; the efficacy of chronic pain control within two applications of fentanyl patches could not be assessed. Further longitudinal studies would be necessary to determine the efficacy for chronic pain management. Lastly, being a retrospective study, there could be an underestimation of inappropriate use due to lack of documentation by healthcare professionals in the medical records. However, this retrospective study remains a convenient profiling and understanding of fentanyl use inpatient.

CONCLUSION

This study highlighted the previously undescribed high incidence of inappropriate initiation of fentanyl patch, and we proposed an inhouse guideline to aid physicians in initiating fentanyl patches during admission and to educate nursing staff of the monitoring parameters for efficacy and toxicity. We foresee more research in this area after implementation is in place.

What this paper adds

What is already known on this subject

- ▶ Transdermal fentanyl is a potent opioid and a high-alert medication with high potential of harm.
- ▶ Commonly prescribed for pain control in National University Hospital.
- ▶ No study has evaluated appropriateness use of transdermal fentanyl use in the literature; therefore, a drug use evaluation was conducted.

What this study adds

High incidence of inappropriate initiation of fentanyl patch found and not previously described.

Correction notice This paper has been amended since it was published Online First. The fourth author's surname was spelt incorrectly and this has now been amended.

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Competing interests None declared.

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