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Brief Report

Optimizing the Dosing Regimen During Rotation From Subcutaneous to Transdermal Administration of Fentanyl

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Abstract

Context. Subcutaneous (SC) administration of fentanyl allows for rapid dose titration to treat urgent cancer-related pain. After establishing the optimal fentanyl dose, patients typically rotate towards transdermal (TD) fentanyl patches. Continuing the SC fentanyl up to 12h after application of the patch led to elevated fentanyl concentrations and fentanyl-related toxicities. Based on these findings, and simulations using a pharmacokinetic (PK) model, SC fentanyl administration was discontinued immediately following the application of the patch.

Objectives. To validate the fentanyl rotation schedule by assessing the PK equivalence in fentanyl exposure before and after rotation.

Methods. PK samples and clinical data were prospectively collected from 12 hours prior to rotation until 12 hours after rotation in patients with cancer-related pain undergoing fentanyl rotation.

Results. Between December 2021 and September 2023, 29 evaluable patients were enrolled in the study. The 90% confidence interval (CI) of the geometric mean ratio between the post- over pre-rotation area under the curve (AUC) fell within the prespecified 0.8−1.25 equivalence interval (90% CI 1.05−1.16). Patient-reported intensity of both nausea ($P = 0.047$) and transpiration ($P = 0.034$) decreased post-rotation. Pain intensity and other adverse events did not differ significantly pre and post-rotation. One patient needed adjustment of opioid therapy 40 hours after rotation due to fentanyl-related toxicities.

Conclusion. The updated rotation scheme, implying a 1:1 dose conversion and discontinuation of SC fentanyl directly after rotation, resulted in equivalent fentanyl exposure pre and post-rotation. Moreover, the dosing regimen showed to be safe and efficacious during rotation. The new dosing regimen when rotating from SC to TD fentanyl can be effectively and safely implemented in routine palliative care. J Pain Symptom Manage 2024;68:e491−e499.

Key Words

Fentanyl, subcutaneous, pharmacokinetics, rotation

Key Message

In this prospective trial we validated a new dosing regimen when rotating from subcutaneous to transdermal administration of fentanyl in patients with cancer-related pain. This novel dosing regimen leads to equivalent fentanyl exposure, similar patient-reported pain scores, and less patient-reported side effects during rotation as compared to the former scheme.

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Introduction

Fentanyl is a potent opioid pain medication commonly used to treat moderate to severe cancer-related pain. Due to its chemical properties (low molecular weight and high lipophility) fentanyl is suitable for transdermal administration. This method of administration is easy to use and patient friendly. It is especially beneficial in patients in whom the enteral route cannot be used. Moreover, due to its hepatic metabolism and minimal renal excretion, fentanyl is the opioid of first choice in patients with renal failure.[1] Furthermore, fentanyl causes less constipation compared to other opioids.[2,3] These characteristics make fentanyl a frequently used option for effectively managing cancer-related pain in various patient populations.

When patients are admitted to the hospital with inadequately controlled cancer-related pain, rapid titration of opioid plasma levels is essential to quickly reach adequate pain control. This is typically achieved using parenterally administered opioids and, in many cases, subcutaneously administered fentanyl is the preferred option, based on the advantages depicted above, although its use is off-label. It has been demonstrated that SC administration of fentanyl is safe and equally effective compared to IV administration.[4] Moreover, SC administration is more patient-friendly and avoids complications as it does not require vascular access.[5]

Once an adequate dose is found during dose titration and pain control is achieved, patients are eligible for rotation to TD fentanyl patches before hospital discharge. Previously, a rotation scheme validated for the rotation from IV to TD fentanyl was used for rotating from the SC to TD administration route of fentanyl.[6,7] In this previously used dosing regimen, SC fentanyl administration was continued, following the application of the fentanyl patch, at 100% of the pre-rotation rate for six hours. After this, the SC fentanyl dose was reduced to 50% of the original dose for an additional 6 hours. However, in an observational study focusing on the SC to TD rotation a significant increase in plasma fentanyl concentrations was observed when using this tapered dosing regimen.[5] Consequently, 65% of patients experienced an increase in fentanyl-related toxicities, including respiratory depression. In total, 21% of all patients experienced fentanyl-related toxicity after rotation, necessitating treatment adjustments. In this study, a population pharmacokinetic (popPK) model was developed which was used to simulate alternative SC to TD rotation dosing regimens. A new dosing regimen, where the continuous infusion is discontinued directly after the application of the patch (Fig. 1), was readily implemented in clinical practice. The new dosing regimen should result in more stable fentanyl exposures post-rotation and consequently a stable clinical condition of the patient after rotation.

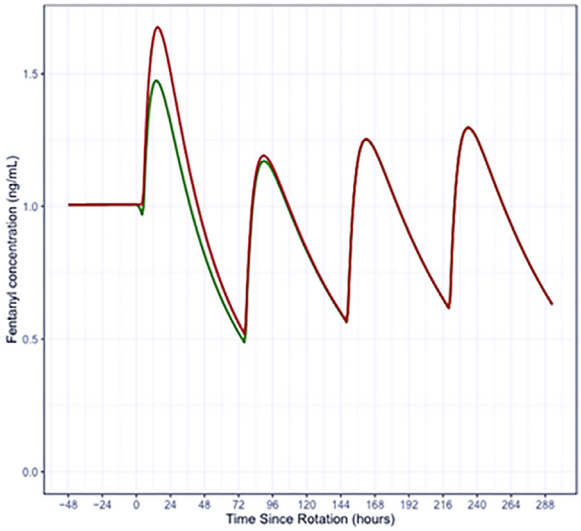

Fig. 1. Expected model-informed fentanyl plasma concentrations after the original tapered dosing schedule (red line) in which SC fentanyl is continued at 100% for 6 hours whereafter the SC dose is subsequently continued for an additional 6 hours (until 12 hours after rotation). The green line depicts the presently used dosing regimen in which the SC fentanyl administration is discontinued directly after application of the patch.

Here, we aim to validate the novel fentanyl rotation dosing regimen by measuring the fentanyl exposure before and after rotation and assessing equivalence.

Methods

Study Design and Patient Eligibility

In this observational single-center cohort study hospitalized patients treated with SC fentanyl for moderate to severe cancer-related pain were asked to participate. Patients were usually treated with continuous SC administration combined with a patient-controlled analgesia mechanism to counter breakthrough pain, allowing patients to self-administer an SC fentanyl bolus every hour. The dose of the bolus usually mirrors the fentanyl dose given per hour. These boluses were used to evaluate pain control, adequate pain control is usually determined by acceptable patient-reported pain scores and the use of ≤5 additional boluses each day. If patients needed ≥8 additional boluses, the continuous infusion dose was mostly increased.

Eligible participants were aged 18 years or older and were able to give written informed consent. Additionally, patients needed to have been treated with SC fentanyl for at least 36 hours prior to rotation to ensure steady-state fentanyl plasma concentrations. The rotation had to be initiated by the physician which meant that pain control should be adequate. Patients concomitantly using strong CYP3A4 inhibitors or inducers were

not eligible for inclusion. To be evaluable, a 1:1 dose conversion ratio from SC to TD fentanyl should be used. The study was approved by the medical ethics review board of the Erasmus Medical Center (MEC 21-0581) and was conducted in accordance with the Declaration of Helsinki. The trial was registered in the Dutch Trial Register (NL54225, https://onderzoekmetmensen.nl/nl/trial/54225).

Data collection times were at 12 and 0.5 hours before rotation, and four-, eight-, and 12-hours post-rotation. At these time points a plasma sample was obtained and patients were asked to assess the average pain intensity in the previous 4 hours on a Numeric Rating Scale (NRS) and fentanyl-related adverse events (constipation, hallucinations, confusion, transpiration, respiratory depression, drowsiness, and myoclonia) on a four-point Likert scale. Medication to counter breakthrough pain, which was mostly additional SC fentanyl boluses, was switched to oral nonfentanyl opioids, such as short-acting oxycodone, before the first PK sample obtainment, 12 hours before rotation. The use of breakthrough pain medications was documented throughout the 24-hour study period. Patients were followed until discharge to follow up on fentanyl dose changes.

Blood samples for PK analysis were collected in lithium heparinized tubes. Samples were centrifuged at 2000 g for 10 minutes and plasma was stored at −70°C until analysis at the Laboratory of Translational Pharmacology (Erasmus MC Cancer Institute). Fentanyl plasma concentrations were assessed using a validated UPLC-MS/MS method.[5]

Pharmacokinetic Analysis

The primary objective of the study was to assess equivalence in fentanyl exposure during the 12 hours following rotation compared to the 12 hours before rotation. The systemic fentanyl exposure, quantified as the area under the curve (AUC) was obtained by coding an AUC compartment in the previously developed popPK model.[5,8] However, to ensure accurate estimation of fentanyl exposure, first the model needed to be validated. Validation of the model was conducted through a prediction-corrected visual predictive check (VPC); a standard method for assessing the performance of popPK models.[9]

A popPK model is able to extrapolate to timepoints where a PK sample could not be obtained in clinical practice. This is particularly useful in situations where a patient was discharged early (<12 hours post-rotation) or when the rotation was unplanned within 12 hours prior to the event. In the latter case patients might have received SC fentanyl for breakthrough pain during the study period. Using the acquired PK data, the model was used to extrapolate to scenarios where these boluses were not administered, thus allowing these patients to be included in the study analysis.

Statistical Analysis

The primary objective of the study was to assess equivalence in fentanyl exposure before and after rotation, quantified as the area under the curve (AUC). The sample size analysis was performed using simulations of 1000 patients with the popPK model. These showed that the expected ratio in fentanyl exposure pre over post-rotation was 1.04. When also considering a standard deviation of 0.32 on a log scale, in fentanyl AUC during steady-state subcutaneous fentanyl treatment, and obtaining 90% power and using a two-sided alpha of 5%, a sample size of 27 evaluable patients was required to evaluate the hypothesis.

The comparison between fentanyl exposure 12 hours pre-rotation and 12 hours post-rotation was performed using a paired t-test on log transformed AUCs. The exponentiation of the observed difference and the 90% confidence interval (CI) bounds obtained from the paired t-test provided the geometric mean ratio and its corresponding CI. To establish equivalence, the 90% CI should entirely fall within the bio-equivalence boundaries (80%−125%).[10] As a secondary endpoint, the fentanyl concentration obtained at 0.5 hours prior to rotation and at the T_{max} (12 hours post-rotation) were compared using the geometric mean and its corresponding 90% CI.

Additional secondary clinical endpoints involved assessing changes in the intensity of patient-reported pain and adverse effects (AE) during rotation using a Wilcoxon signed-rank and descriptive statistics. The median and interquartile range (IQR) were calculated separately for pre and post-rotation pain and AE intensity. Additionally, the frequency of administration of breakthrough pain medication pre and post-rotation was reported and analyzed through descriptive analysis.

Results

Patients

In total, 43 patients were enrolled of whom 29 were evaluable. Patients were unevaluable due to issues with blood sampling (n = 5), noncompliance related to any of the study procedures (n = 5), or the rotation towards TD fentanyl did not occur (n = 4). Two evaluable patients participated in the study twice with the rotation from SC to TD fentanyl occurring during different hospital admissions. The demographic and clinical characteristics of the evaluable patients are summarized in Table 1.

Pharmacokinetic Analysis

PK samples 12 hours prior to the rotation were not obtained in eight rotations. One patient was discharged prior to the 12 hours post-rotation sampling time. All other PK samples were obtained for all patients. In

Table 1
Patient Characteristics

Characteristics N = 29	n / median (range)
Age (yrs)	64 (25–82)
Sex	
Male	19
Female	10
Body Mass Index (kg/m^2)	26 (18–39)
Primary tumor localization	
Urinary tract (including the kidney)	4
Melanoma	4
Prostate	3
Soft tissue sarcoma/GIST	3
Other	15
Unknown	1
Median fentanyl dose μg/h	75 (12–200)
Concomitant CYP3A4 influencing medication use	
Dexamethasone	5
None	24

GIST = gastro-intestinal stromal tumor.

total, 14 patients received an SC rescue within the 12 hours before rotation. Of these patients, nine received one rescue in this period which was administered >6 hours prior to rotation. The VPC showed adequate descriptive performance of the existing popPK model (Fig. S1).

The systemic fentanyl exposures pre and post-rotation were equivalent, as determined by the geometric mean ratio (1.10, 90% CI 1.05–1.16), that fell completely within the predefined range for bioequivalence (*i.e.,* 0.80–1.25) (Fig. 2).

A dose-normalized course of fentanyl concentrations during rotations is depicted in Fig. 3. When comparing maximum pre- and post-rotation observed fentanyl plasma concentrations, the pre-rotation peak (1.48 ng/mL) was lower compared to the post-rotation peak (1.97 ng/mL). The geometric mean ratio for maximum concentrations post- over pre-rotation was 1.19 (90% CI 0.94–1.50). The post-rotation fentanyl concentration divided by the pre-rotation fentanyl rotation ranged from 0.66 to 4.53.

Clinical Efficacy

Pain intensity data was incomplete for two patients resulting in 29 rotations evaluable for efficacy. Patient-reported pain intensity did not differ pre and post-rotation (P = 0.688). Nonetheless, the median (IQR) pain intensity decreased from four (3–5) pre-rotation to three (3–4) post-rotation (Table S1). The use of additional opioid medications to counter breakthrough pain was similar before and after rotation (median of 1 used both pre and post-rotation). Three patients were dose-increased due to pain increase 20–72 hours after rotation. None of these patients showed remarkably lower fentanyl concentrations up to 12 hours post-rotation.

Safety and Tolerability

Out of the 31 rotations, safety data was missing for one patient, resulting in 30 evaluable rotations for this topic. Intensity of toxicities was scored lower post-rotation for nausea (P = 0.047) and transpiration

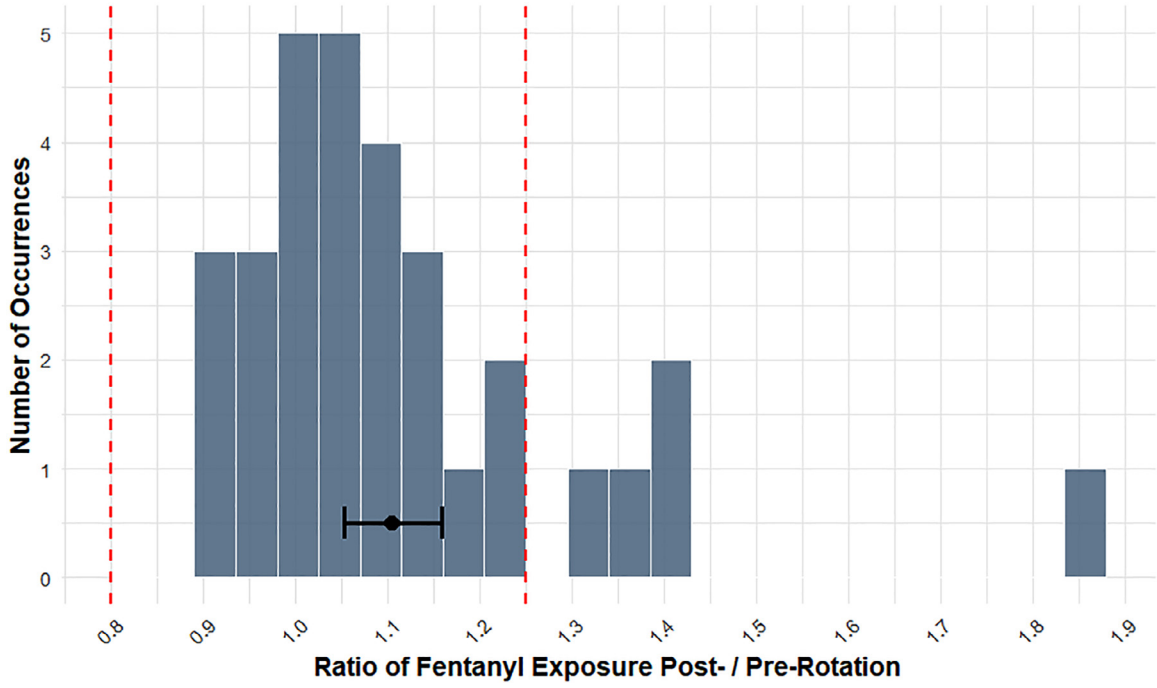

Fig. 2. The ratio of post- over pre-rotation fentanyl exposure. *The black point represents the geometric mean ratio and its corresponding 90% confidence interval. The dashed red lines indicate the equivalence interval.*

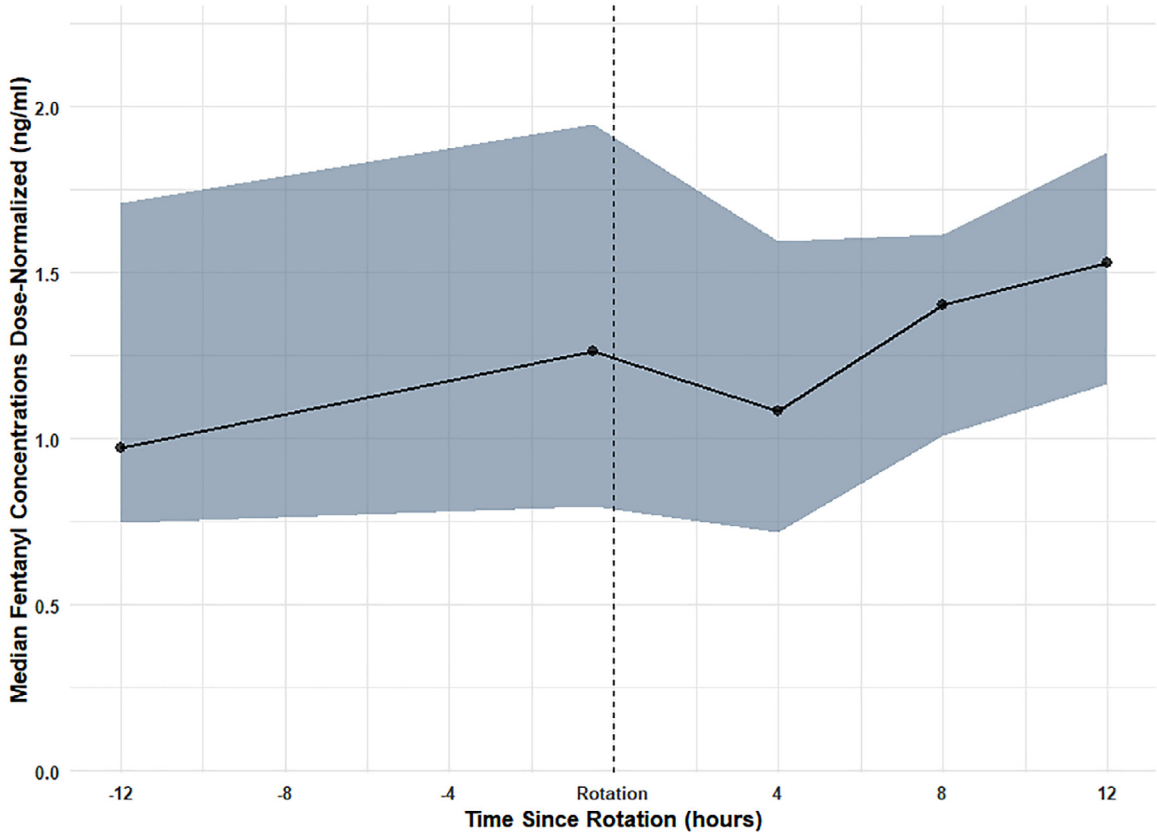

Fig. 3. Dose-normalized (50 μg/h) median observed fentanyl plasma concentrations over time. *The solid dark line represents the median observed fentanyl concentration, and the blue area depicts the 25th to 75th percentile interval. The dashed vertical line represents the time of rotation.*

(P = 0.034) (Table S2). Other toxicities did not show a significant difference pre and post-rotation. In total, 57% of patients experienced an increase in severity of any of the toxicities compared to pre-rotation. A dose reduction was necessary for one patient, 40 hours post-rotation, due to severe drowsiness and vomiting. In this patient, fentanyl plasma concentrations increased from 2.30 ng/mL at rotation to 4.52 ng/mL 12 hours post-rotation and the toxicity was therefore most probable fentanyl induced. No clinically significant decrease in respiratory rate was observed in any of the patients throughout the study duration.

Discussion

This prospective study in patients with cancer-related pain in need of dose titration with SC fentanyl due to inadequate pain treatment, validates the currently used fentanyl rotation dosing regimen. Discontinuing the SC fentanyl administration directly after application of the patch and using a 1:1 dose conversion leads to equivalent fentanyl exposure pre and post-rotation and results in effective and safe treatment. This dosing regimen can be safely implemented in the standard of care.

The prior two-step tapered dosing schedule was shown to be safe and effective when rotating from IV to TD fentanyl.[6,7] However, due to the slow absorption from the SC compartment, the use of this schedule resulted in high fentanyl plasma concentration and its associated adverse effects. When comparing the clinical effects of the prior SC to TD rotation dosing regimen with the current, updated version, the proportion of patients with an increase in the intensity of side effects dropped slightly from 64% to 57% during the current dosing regimen.[5] Importantly, one of the patients (3%) needed opioid treatment reduction, whereas in the previous dosing regimen opioid treatment reductions were necessary in 21% of patients. When also considering the similar patient-reported NRS pain intensity pre and post-rotation, the current dosing schedule stabilizes patient-reported efficacy and safety. Nonetheless, a peak in fentanyl plasma concentrations is still observed twelve hours post-rotation. This is a characteristic of the diffusion from the fentanyl patch into the subcutaneous tissue and is therefore unavoidable.[11] Additionally, the popPK model showed substantial uptake from the subcutaneous compartment to up to 96 hours after cessation of SC fentanyl administration. The prolonged uptake of fentanyl from the SC

compartment in combination with the pharmacokinetics of transdermally administered fentanyl will unavoidably result in increased peak concentrations in the first hours after rotation. This can only be countered by cessating the subcutaneous continuous administration prior to rotation with the risk of reaching low fentanyl plasma concentrations and therefore undertreatment.

Although the use of SC administered fentanyl is off-label, it is a feasible administration route with proven efficacy and some advantages over the intravenous route.[12-17] Extensive experience is apparent in routine hospice care. In the United States, 73% of all hospices utilized the SC administration route, primarily for palliative pain management.[18] Due to the slower absorption, SC administered fentanyl pharmacokinetics do not show high maximum concentrations or low trough concentrations. This should lead to low rates of respiratory depression, as this is mostly caused by rapid fluctuations in opioid exposure.[19] As fentanyl shows fast diffusion into the central nervous system, and therefore fast effect, the occurrence of toxicity should be related to the maximum concentrations.[20] These are especially high for IV treatment and are lower for SC treatment which should therefore lead to less toxicity.

The limitations of the current study are primarily of logistical nature. Obtaining a PK sample and patient-reported pain and toxicity intensities 12 hours before rotation was not possible in 26% of the patients. This was due to the unpredictability of time needed to achieve adequate pain control. However, this issue was adequately addressed by using a popPK model that could extrapolate fentanyl plasma concentrations towards moments in which no plasma sample was obtained, based on collected PK data. Additionally, peak concentrations might extend beyond the initial 12-hour post-rotation period as we did not observe a drop in fentanyl plasma concentrations during the study period. Most patients were discharged from the hospital 12 hours post-rotation. We did not deem it ethical to retain patients in the hospital for additional plasma PK samples. Nonetheless, both the observations and the model predictions showed that the increase in fentanyl plasma concentrations flattened eight hours after rotation, indicating that the peak in fentanyl exposure is not expected to rise significantly further after 12 hours post-rotation.

Future research should focus on elucidating the factors causing inter-individual variability in fentanyl PK. Especially the inter-individual variability in the uptake rate and bioavailability of TD fentanyl patches is poorly understood. A fast uptake rate results in high post-rotation fentanyl plasma concentrations, causing toxicity, whereas a low uptake rate of the patch might result in lower clinical efficacy and in some cases, this might cause the need for fentanyl dose increases after rotation. The differences in uptake rate could not be explained by patient characteristics in this cohort. Conversely, some patients also showed. The bioavailability of fentanyl administered through TD patches shows a broad interindividual range from 18% to 100%.[21] This variation might be explained by differences in genetic factors or by different skin characteristics.[22,23] Understanding factors affecting the bioavailability and uptake rate of TD fentanyl may lead to personalized dosing regimens during rotations and informed modifications of the dose conversion ratio when needed. In addition, understanding what causes variability in SC fentanyl uptake rate could be used to faster attain adequate pain control. A study is now performed that investigates whether giving loading boluses after starting a new dose of continuous SC fentanyl administration will result in faster attainment of steady-state pharmacokinetics (euclinicaltrials.eu: 2023-507355-30).

The validated dosing regimen in which SC fentanyl administration is discontinued directly after application of the patch provides a standardized method for transitioning from fentanyl SC to TD fentanyl administration. Clinicians can confidently implement this approach using a 1:1 dose conversion ratio in practice as it ensures equivalent fentanyl exposure. Both the patient reported intensity nausea and transpiration decreased post-rotation. Patient-reported pain remained stable pre and post-rotation. Additionally, implementation of the new dosing regimen resulted in less toxicity-related treatment adjustments.

Disclosures and Acknowledgments

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Supplementary Material

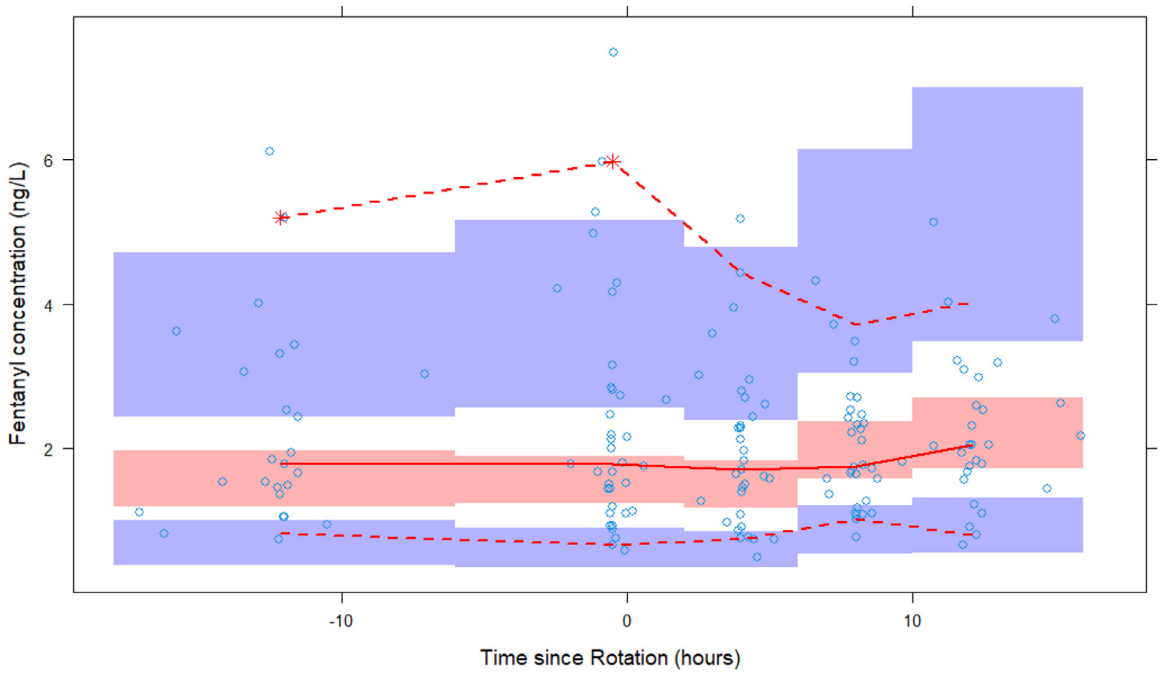

Fig. S1. Prediction-corrected visual predictive check of the original model. Fentanyl concentrations are dose-normalized (50 μg/h). The solid red line represents the median measured concentrations, and the dashed red line represents the corresponding confidence interval. The red area indicates the 95% confidence interval of the median predicted concentration, and the grey areas represent the 95% confidence intervals of the 2.5th and 97.5th percentile. The blue dots represent individual patients.

Table S1
Patient Reported Pain Intensity During Rotation

Time points	Pre-rotation (%)				Post-rotation (%)					
	−12h n = 21 (%)		−0.5h n = 26 (%)		4h n = 27 (%)		8h n = 26 (%)		12h n = 29 (%)	
NRS										
0	1	(5)	3	(12)	1	(4)	1	(4)	4	(14)
1	1	(5)	2	(8)	1	(4)	2	(8)	1	(3)
2	1	(5)	1	(4)	3	(11)	3	(12)	3	(10)
3	5	(24)	4	(15)	5	(19)	9	(35)	7	(24)
4	5	(24)	6	(23)	8	(23)	5	(19)	7	(24)
5	2	(10)	6	(23)	2	(7)	2	(8)	3	(10)
6	3	(14)	3	(12)	4	(15)	1	(4)	2	(7)
7	1	(5)	1	(4)	2	(7)	2	(8)	2	(7)
8	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
9	2	(10)	0	(0)	1	(4)	0	(0)	0	(0)
10	0	(0)	0	(0)	0	(0)	1	(4)	0	(0)

NRS = numeric rating scale.

Table S2
Percentages of the Intensity of Patient-Reported Toxicities During Rotation

Time points	Pre-rotation				Post-rotation						*P*-Value[a]
	−12h n = 21 (%)		−0.5h n = 28 (%)		4h n = 28 (%)		8h n = 27 (%)		12h n = 29 (%)		
Nausea											0.047
1	12	(57)	18	(64)	21	(75)	21	(78)	25	(86)	
2	8	(38)	7	(25)	6	(21)	3	(11)	3	(10)	
3	0	(0)	3	(11)	1	(4)	2	(7)	1	(3)	
4	1	(5)	0	(0)	0	(0)	1	(4)	0	(0)	
Vomiting											0.13
1	19	(90)	22	(79)	26	(93)	25	(93)	27	(93)	
2	2	(10)	5	(18)	2	(7)	1	(4)	2	(7)	
3	0	(0)	1	(4)	0	(0)	1	(4)	0	(0)	
4	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	
Myoclonia											0.25
1	11	(52)	17	(61)	18	(64)	18	(67)	19	(66)	
2	8	(38)	9	(32)	9	(32)	9	(33)	9	(31)	
3	2	(10)	2	(7)	1	(4)	0	(0)	1	(3)	
4	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	
Constipation											0.53
1	11	(52)	15	(54)	18	(64)	18	(67)	17	(59)	
2	5	(24)	10	(36)	5	(18)	5	(19)	8	(28)	
3	5	(24)	3	(11)	3	(11)	2	(7)	3	(10)	
4	0	(0)	0	(0)	2	(7)	2	(7)	1	(3)	
Dry mouth											0.51
1	3	(14)	7	(25)	8	(29)	8	(30)	7	(24)	
2	10	(48)	11	(39)	11	(39)	10	(37)	10	(34)	
3	7	(33)	10	(36)	6	(21)	7	(	8	(28)	
4	1	(5)	0	(0)	3	(11)	2	(7)	4	(14)	
Confusion											0.17
1	15	(75)	24	(86)	21	(75)	21	(78)	21	(72)	
2	5	(25)	4	(14)	6	(21)	5	(19)	7	(24)	
3	0	(0)	0	(0)	1	(4)	1	(4)	0	(0)	
4	0	(0)	0	(0)	0	(0)	0	(0)	1	(3)	
Hallucinations											0.92
1	19	(90)	26	(93)	25	(89)	27	(100)	27	(93)	
2	2	(10)	2	(7)	3	(11)	0	(0)	2	(7)	
3	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	
4	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	
Drowsiness											0.95
1	6	(29)	8	(29)	7	(25)	7	(26)	11	(38)	
2	13	(62)	18	(64)	18	(64)	16	(59)	16	(55)	
3	2	(10)	2	(7)	2	(7)	3	(11)	2	(7)	
4	0	(0)	0	(0)	1	(4)	1	(4)	0	(0)	
Transpiration											0.034
1	13	(62)	21	(75)	21	(75)	21	(78)	25	(86)	
2	4	(19)	5	(18)	5	(18)	5	(19)	3	(10)	
3	2	(10)	1	(4)	2	(7)	1	(4)	1	(3)	
4	2	(10)	1	(4)	0	(0)	0	(0)	0	(0)	

[a] *P*-Value: Wilcoxon signed-rank test comparing the median patient reported intensity pre and postrotation.