Characterization of Tolerance in Children during Fentanyl Continuous Infusions

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Abstract

Tolerance is a complication of fentanyl continuous infusions (CINs) in critically ill children, but the incidence and time of onset are lacking. The primary objective was to identify the incidence of tolerance. Secondary objectives were to determine the onset time and compare risk factors between children with tolerance versus no tolerance and between children with early (< 24 hours) versus late tolerance. Children aged 0 to 17 years, receiving fentanyl CIN > 3 days from May 1, 2012 to June 30, 2013 were included. Tolerance was defined as a doubling of the fentanyl CIN dose. Descriptive and inferential statistics were performed. A logistic regression model was used to assess the relationship between the development of tolerance and independent variables. A total of 59 CINs were included. Tolerance occurred in 46 CINs (78%), with median time to tolerance of 26 hours (range: 1–160 hours). Early tolerance was identified in 21 CINs (45.7%). Patients with tolerance had higher peak CIN doses ($p < 0.001$), final CIN doses ($p = 0.031$), and cumulative exposure ($p = 0.017$). No significant differences were noted between those with early versus late tolerance. The regression model noted factors associated with the odds of development of tolerance were lower initial fentanyl dose ($p = 0.007$; odds ratio [OR]: 0.011, 95% confidence interval [CI]: 0.0004–0.29) and higher cumulative exposure ($p = 0.009$; OR: 1.01, 95% CI: 1.001–1.01). Tolerance developed in 78% of children, and half developed it within 24 hours. Lower initial opioid dose and higher cumulative exposure were independently associated with tolerance.

Keywords

- ▶ fentanyl
- ▶ opioid
- ▶ continuous infusion
- ▶ tolerance
- ▶ critically ill
- ▶ child

Introduction

Sedation and analgesia are essential components in the care of critically ill children who are mechanically ventilated. Opioid continuous infusions (CINs) are commonly utilized as the backbone of sedation/analgesia regimens in the pediatric intensive care unit (PICU). However, long-term exposure to opioid infu-

sions may result in complications such as the development of tolerance during the CIN and subsequent development of symptoms of withdrawal when the CIN is tapered or discontinued.¹

Opioid tolerance occurs through desensitization of opioid receptors and unopposed nociceptive signaling.¹ Clinically, patients with tolerance may require an escalation in opioid dose to maintain the desired level of sedation and analgesia,

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resulting in an increased cumulative opioid exposure.¹ Currently, no diagnostic tools or biomarkers are available to identify opioid tolerance. In a recent study, Anand et al assessed the development of tolerance in mechanically ventilated PICU patients receiving fentanyl or morphine CIN.² They defined tolerance as a doubling of the total daily opioid dose. By this definition, tolerance occurred in 16% of the total sample by day 7 and 20% by day 14. In a subgroup analysis of patients receiving opioid infusions at least 96 hours, tolerance was even more pronounced, occurring in 28 and 35% of patients by day 7 and 14, respectively. Factors associated with the development of tolerance included duration of infusion ≥ 7 days, admission for a nonsurgical diagnosis, lower initial opioid dose, and concomitant benzodiazepine CINs.

The appropriateness of the definition for tolerance that Anand et al used has some potential limitations. The context-sensitive half-life of fentanyl is approximately 21 hours in critically ill children when administered as a CIN.³ Therefore, tolerance would be unlikely to develop before the 3rd day of CIN therapy; it would be more likely that a doubling of dose before the 3rd day of therapy would be secondary to inappropriate selection of initial dose resulting in inadequate analgesia. There is a further need to elucidate the onset time of tolerance and characteristics associated with the development of tolerance in critically ill children to determine the clinical utility of this definition. The objectives of this study were to characterize the development of tolerance and compare risk factors between patients with and without tolerance as well as patients who developed “early” versus “late” tolerance following initiation of fentanyl CIN.

Methods

Study Design and Participants

This retrospective, descriptive, institutional review board-approved study was conducted in a tertiary care academic hospital licensed for 230 beds, including 25 PICU beds. PICU patients who received a fentanyl CIN of at least 3 days between May 1, 2012 and June 30, 2013 were included if they were > 37 weeks postconceptual age and < 18 years of age at initiation of fentanyl CIN. Children receiving fentanyl CIN < 3 days were excluded from the analysis as the context-sensitive half-life of fentanyl is 21 hours, so it would be unlikely they would develop a tolerance before steady-state is achieved.^{1,3} Each of the fentanyl CIN regimens were included for patients receiving more than one course of therapy during the study period, provided at least 2 weeks elapsed between scheduled opioid regimens. In these cases, each CIN was counted as a distinct regimen. Patients were excluded if they: (1) were exposed to scheduled opioids within 2 weeks before fentanyl infusion, (2) had a history of drug abuse or alcohol dependence, (3) were being treated for neonatal abstinence syndrome (NAS), (4) were initiated on fentanyl CIN while admitted to the neonatal intensive care unit (NICU), (5) were receiving palliative care, (6) received initial therapy with continuous infusion of another opioid agent, or (7) had incomplete medical records.

Data Collection

Demographic data were collected, including age, weight, sex, previous PICU admissions (i.e., defined as a PICU admission within the previous year), and diagnosis upon admission (surgical or medical). Body mass index (BMI) (patients ≥ 2 years of age) and weight-for-length percentile (patients < 2 years of age) were also collected as appropriate to evaluate the impact that these may have had considering sedatives and analgesics are lipophilic medications. Based on these categories, patients were classified into “low-normal weight” (i.e., weight-for-length < 98 th percentile or BMI < 85 th percentile) and “high weight” (i.e., weight-for-length ≥ 98 th percentile or BMI ≥ 85 th percentile). Fentanyl infusion rates ($\mu\text{g/kg/h}$) were recorded including the initial rate, peak rate, and final rate. The final rate was defined as the fentanyl dose immediately before discontinuation. For calculation of the fentanyl cumulative exposure, an attempt was made to include all bolus doses administered throughout the CIN. The concomitant sedative CINs and neuromuscular blocking agent regimens were also collected. Sedative and analgesic dose changes were made at the discretion of the provider to achieve an individually tailored, daily goal sedation score as assessed by the State Behavioral Scale (SBS).⁴ Tolerance was defined as a doubling of the fentanyl infusion rate ($\mu\text{g/kg/h}$). “Early tolerance” was defined as a doubling of the initial CIN rate < 24 hours following fentanyl CIN initiation. “Late tolerance” was defined as a doubling of the initial CIN rate occurring ≥ 24 hours following fentanyl CIN initiation. The cumulative exposure (mg/kg) of any additional sedative agents was also recorded.

The primary objective of this study was to identify the incidence of tolerance in critically ill patients receiving fentanyl CIN. Several secondary objectives were also assessed and included evaluation of the time to onset of tolerance. In addition, a comparison of characteristics of children with and without tolerance, as well as children with early versus late development of tolerance was performed.

Statistical Analyses

Descriptive and inferential statistics were performed. Nominal data were assessed using chi-square or Fischer exact tests of association as appropriate. Continuous data were analyzed via Wilcoxon–Mann–Whitney tests given the nonnormal distribution of the data. A multivariate logistic regression analysis was performed to assess the dependent variable (development of tolerance) with several independent risk factors (i.e., age, weight category, diagnosis, initial fentanyl CIN rate, final fentanyl CIN rate, and cumulative fentanyl exposure). Data management and analyses were conducted using Stata v13.1 (StataCorp, College Station, Texas, United States) with the a priori α set at $p \leq 0.05$.

Results

A total of 245 separate fentanyl CINs were administered during the study period. Of these, 186 were excluded from analysis. Infusions were excluded for the following reasons: fentanyl CIN < 3 days ($n = 154$), scheduled opioids within

2 weeks of fentanyl initiation ($n = 10$), incomplete medical records ($n = 13$), fentanyl initiation during NICU admission or for NAS ($n = 3$), initial therapy with another opioid CIN ($n = 1$), and other ($n = 5$). A total of 59 CINs met the inclusion criteria, representing 56 patients. Two patients received more than one fentanyl CIN during the study period. One patient received two separate CINs, while the other received three separate CINs. Each CIN occurred during a different hospital admission, and neither patient received scheduled opioids for at least 2 weeks between regimens.

Baseline characteristics of patients receiving fentanyl CINs are described in ►Table 1. The majority (61%) were males with a median age of 0.65 years. Overall, 43 (72.9) fentanyl CINs were initiated in children admitted for a medical diagnosis. Twelve (20.3%) patients receiving a fentanyl CIN were classified as “high weight.” Approximately one-third of fentanyl CINs were in children with a previous PICU admission.

Table 1 Characteristics of patients receiving fentanyl continuous infusions ($n = 59$)

Variable	Median (IQR) or number (%)
Age (y)	0.65 (0.18–3.6)
Males	36 (61.0)
Height (cm)	66 (53.5–95.6)
Weight (kg)	6.47 (4.55–14.5)
Weight-for-length percentile classifications ^a	
Low ($\leq$ 2nd percentile)	6 (16.2)
Normal (2.1–97.9th percentile)	26 (70.3)
High ($\geq$ 98th percentile)	5 (13.5)
BMI and BMI percentile ^b	
BMI (kg/m^2)	16.8 (14.7–18.8)
BMI percentile ^c	52 (10–93)
BMI classifications ^{a,b}	
Underweight ($<$ 5th percentile)	4 (19.0)
Normal weight (5.0–84.9th percentile)	10 (47.6)
Overweight (85.0–94.9th percentile)	2 (9.5)
Obese ($\geq$ 95th percentile)	5 (23.8)
Diagnoses	
Medical	43 (72.9)
Surgical	16 (27.1)
Previous PICU admits	
Yes	17 (28.8)
Number of previous admits	2 (1–5)

Abbreviations: BMI, body mass index; IQR, interquartile range; PICU, pediatric intensive care unit.

^a $N = 37$.

^b $N = 21$; height unavailable for one patient so BMI and BMI percentile unavailable.

^cBMI percentile for height, sex, and age.

Table 2 Fentanyl CIN dosage regimens ($n = 59$)

Variable	Median (IQR) or number (%)
Fentanyl infusion rate ($\mu\text{g}/\text{kg}/\text{h}$)	
Initial rate	1 (1.0–2.0)
Peak rate	3 (2.0–5.4)
Final rate	1 (1.0–2.8)
Fentanyl CIN duration (h)	156 (91.0–267.5)
Fentanyl cumulative exposure	
μg	4,074.0 (1,148.0–8,528.4)
$\mu\text{g}/\text{kg}$	395.2 (194.9–1,012.5)

Abbreviations: CIN, continuous infusion; IQR, interquartile range.

Fentanyl Regimens

►Table 2 describes the fentanyl CIN regimens received by study patients. There was a wide variability in fentanyl regimens and in cumulative fentanyl exposure among patients. The median initial fentanyl infusion rate was 1 $\mu\text{g}/\text{kg}/\text{h}$ with a maximum infusion rate of 3 $\mu\text{g}/\text{kg}/\text{h}$. The median cumulative fentanyl exposure was 4,074 μg (395.2 $\mu\text{g}/\text{kg}$), which includes any fentanyl boluses received during the continuous infusion, and the median duration of fentanyl CINs was 6.5 days. The median final rate, or the infusion rate just before fentanyl discontinuation, was also 1 $\mu\text{g}/\text{kg}/\text{h}$ (range: 0.5–12). However, it should be noted that eight patients were transitioned to hydromorphone ($n = 7$) or morphine ($n = 1$), rather than continuing fentanyl for the duration of sedation and analgesia. Additionally, two patients expired, and three patients were transferred to another institution while receiving fentanyl CINs. Without these 13 CINs, the final fentanyl rate ranged from 0.5 to 4 $\mu\text{g}/\text{kg}/\text{h}$.

Additional Sedatives and Neuromuscular Blockers

Additional sedative CINs were administered during 55 (93.2%) of the fentanyl CIN regimens (►Table 3). The most common sedatives were midazolam (51 infusions, 86.4%) and

Table 3 Sedatives and neuromuscular blockers

Variable	Median (IQR) or number (%)
NMBs	
Paralyzed with NMBs	22 (37.3)
Day of fentanyl that NMBs initiated	2.5 (1–13)
Duration of NMB (h)	78 (5–235)
Sedative CINs received	
Midazolam	51 (86.4)
Dexmedetomidine	26 (44.1)
Ketamine	5 (8.5)
Propofol	4 (6.8)
Pentobarbital	1 (1.7)

(Continued)

Table 3 (Continued)

Variable	Median (IQR) or number (%)
Sedative CINs combinations ^a	
Midazolam alone	25 (42.4)
Dexmedetomidine alone	17 (28.8)
Midazolam + dexmedetomidine	4 (6.8)
Midazolam + ketamine	1 (1.7)
Midazolam + propofol	1 (1.7)
Midazolam + pentobarbital	3 (5.1)
Midazolam + dexmedetomidine + ketamine	1 (1.7)
Midazolam + dexmedetomidine + propofol	2 (3.4)
Midazolam + dexmedetomidine + ketamine + propofol	1 (1.7)
Midazolam CIN regimen	
Cumulative exposure (mg)	162.5 (55.7–342.0)
Cumulative exposure (mg/kg)	13.7 (6.5–39.2)
Peak rate (mg/kg/h)	0.1 (0.01–0.28)
Day of fentanyl initiated	1 (1.0–1.0)
Duration (h)	132 (80.0–220.5)
Dexmedetomidine CIN regimen	
Cumulative exposure (μg)	256.7 (51.2–759.2)
Cumulative exposure (μg/kg)	46.9 (3.5–86.3)
Peak rate (μg/kg/h)	0.8 (0.63–0.88)
Day of fentanyl initiated	5 (2.0–8.8)
Duration (h)	59.5 (6.5–133.5)
Ketamine CIN regimen	
Cumulative exposure (mg)	1,108.1 (201.5–1,933.1)
Cumulative exposure (mg/kg)	47.4 (18.7–63.6)
Peak rate (mg/kg/h)	0.9 (0.6–1.2)
Day of fentanyl initiated	5 (4.0–5.0)
Duration (h)	98 (46.0–100.0)
Propofol CIN regimen	
Cumulative exposure (mg)	503.3 (197.4–828.5)
Cumulative exposure (mg/kg)	51.4 (24.9–71.5)
Peak rate (μg/kg/min)	62.5 (43.8–81.3)
Day of fentanyl initiated	6 (5.5–6.3)
Duration (h)	11.3 (8.8–13.5)
Pentobarbital CIN regimen	
Cumulative exposure (mg)	22,459.5
Cumulative exposure (mg/kg)	270.9
Peak rate (mg/kg/h)	1.5
Day of fentanyl initiated	1
Duration (h)	249

Abbreviations: CIN, continuous infusion; IQR, interquartile range; NMBs, neuromuscular blockers.

^aN = 55; four patients did not receive sedative CINs in addition to fentanyl.

dexmedetomidine (26 infusions, 44.1%). At least two additional sedative CINs were required during nine (15.3%) fentanyl CIN regimens, while three or more sedative CINs were required with four (6.8%) fentanyl CINs. These combinations and sedative infusion regimens are described in ►Table 3. Propofol was initiated near the end of four fentanyl CINs to facilitate extubation. Additionally, neuromuscular blocker CINs were utilized during 22 (37.3%) fentanyl CIN regimens.

Development of Tolerance

A total of 46 (78%) regimens, representing 44 patients, met the definition of tolerance. One patient developed tolerance during two separate admissions, while another patient developed tolerance during two of three distinct fentanyl CINs. The median time to the first doubling of the fentanyl infusion rate was 26 hours (range: 1–160). Of those who developed tolerance, the median number of times that CIN rates were doubled was 1 (range: 1–4). Characteristics of patients who developed tolerance and those who did not are described in ►Table 4. There were significant differences in the peak infusion rate, final rate, number of rate increases, and cumulative exposure between groups. There was also a numerical, but not statistical, difference in the number of patients with a medical diagnosis who developed tolerance. Similarly, there was a numerical, but not statistical, difference in the initial infusion rate in patients who developed tolerance versus those who did not.

Early versus Late Tolerance

A subgroup analysis was performed on those fentanyl CIN regimens meeting the definition of tolerance in the first 24 hours of infusion ($n = 22$, 47.8%) compared with those developing tolerance after 24 hours. Characteristics of the early and late tolerance groups are described in ►Table 5. Time to development of tolerance was significantly different between groups, with a median time to doubling of fentanyl CIN infusion rate of 3 hours (range: 1–22) in the early tolerance group versus 50.5 hours (range: 25–160) in the late tolerance group ($p < 0.01$). There was also a statistically significant difference in previous PICU admissions between groups (50 vs. 12.5%, $p = 0.01$). There were no other differences between the early and late tolerance groups.

Regression Analysis

A logistic regression analysis was conducted to evaluate the effect of various factors on the development of tolerance. Factors significantly associated with the development of tolerance were decreased initial fentanyl infusion rate ($p = 0.007$; odds ratio [OR]: 0.011, 95% confidence interval [CI]: 0.004–0.29) and increased cumulative fentanyl exposure ($p = 0.009$; OR: 1.01, 95% CI: 1.001–1.01). Age, weight category, diagnosis, and final fentanyl infusion rate were not significantly associated with the development of tolerance.

Discussion

This is the first study to focus specifically on the development of opioid tolerance with fentanyl CINs in critically ill children

Table 4 Comparison of patients with tolerance versus no tolerance

Variable	Tolerance (n = 46)	No tolerance (n = 13)	p Value
	Median (IQR) or number (%)		
Age (y)	0.91 (0.23–3.56)	0.24 (0.11–3.57)	0.197 ^a
Male	27 (58.7)	9 (69.2)	0.362 ^b
Weight category ^c			0.459 ^b
Low-normal weight ^d	35 (76.1)	11 (84.6)	
High weight ^e	10 (21.7)	2 (15.4)	
Diagnoses			0.08 ^b
Medical	36 (78.3)	7 (53.8)	
Surgical	10 (21.7)	6 (46.2)	
Previous PICU admission	14 (30.4)	3 (23.1)	0.235 ^f
Fentanyl rate (μg/kg/h)			
Initial rate	1 (1.0–2.0)	2 (1.0–2.0)	0.063 ^a
Peak rate	4 (2.6–6.0)	2 (1.0–3.0)	< 0.001 ^a
End rate	1.45 (1.0–3.0)	1 (1.0)	0.031 ^a
Rate increases (n)	3 (2.0–4.8)	0 (0–1.0)	< 0.001 ^a
Infusion duration (h)	176.5 (99.5–278.3)	121 (80.0–237.0)	0.246 ^a
Cumulative exposure			
μg	5,144.9 (2,154.7–9,442.8)	3,113.5 (578.4–3,228.5)	0.009 ^a
μg/kg	460.3 (262.5–1,187.7)	187.1 (165.3–238.3)	0.017 ^a
Sedative CIN			
Midazolam	40 (87.0)	11 (84.6)	0.569 ^b
Dexmedetomidine	22 (47.8)	4 (30.8)	0.22 ^b
Ketamine	5 (10.9)	0 (0.0)	0.214 ^b

Abbreviations: BMI, body mass index; CIN, continuous infusion; IQR, interquartile range; PICU, pediatric intensive care unit.

^aWilcoxon–Mann–Whitney test.

^bFisher exact test.

^cN = 58; height unavailable for one patient.

^dLow-normal weight was defined as a weight-for-length <98th percentile or BMI <85th percentile.

^eHigh weight was defined as a weight-for-length ≥98th percentile or overweight/obese based on BMI ≥85th percentile.

^fChi-square test of independence.

not receiving extracorporeal membrane oxygenation (ECMO). In this study we noted 78% of fentanyl CINs administered for > 3 days of duration resulted in the development of tolerance. We chose to include children who received fentanyl CINs for ≥ 72 hours. Because the context-sensitive half-life of fentanyl administered by CIN is 21 hours in children, it is unlikely that tolerance would develop before achievement of steady state concentrations < 72 hours after initiation of CINs.³ Surprisingly, though, tolerance occurred in 48% of infusions within 24 hours of initiation based on our definition. These infusions may in fact represent inadequate initial dosing rather than tolerance.

Three previous studies have investigated the occurrence of tolerance with fentanyl CINs in pediatric patients. Two of these studies investigated tolerance in neonates receiving fentanyl CINs for sedation and analgesia during ECMO.^{5,6} These studies report both a need for increasing fentanyl infusion rates and increasing fentanyl plasma concentrations

to maintain effective sedation and analgesia. In addition, a cumulative fentanyl exposure of > 1.6 mg/kg and the duration of exposure > 5 days were significantly associated with the development of tolerance.⁵ However, pharmacokinetic (PK) parameters of fentanyl may be altered in patients undergoing ECMO due to adherence of fentanyl to the membrane oxygenator and ECMO circuit, limiting application of these results to children not receiving ECMO.

A third study by Anand et al investigated the prevalence of tolerance in mechanically ventilated children receiving fentanyl and morphine CINs.² This study described tolerance in 35% of the children receiving fentanyl or morphine CINs for ≥ 96 hours, which is less than the 78% reported in our study. Several factors may have contributed to the high rate of tolerance in our study. A total of 36% of the patients in the Anand et al study received morphine, rather than fentanyl infusions. This aligns with previous evidence that fentanyl is associated with greater development of tolerance.^{1,2} They

Table 5 Comparison of patients with early tolerance versus late tolerance

Variable	Early tolerance (n = 22)	Late tolerance (n = 24)	p Value
	Median (IQR) or number (%)		
Age (y)	1.10 (0.54–6.8)	0.37 (0.125–2.45)	0.09 ^a
Male	12 (54.5)	15 (62.5)	0.58 ^b
Weight category ^c			0.73 ^d
Low-normal weight ^e	18 (81.8)	17 (70.8)	
High weight ^f	4 (18.2)	6 (25.0)	
Diagnoses			
Medical	16 (72.7)	20 (83.3)	0.48 ^d
Surgical	6 (27.3)	4 (16.7)	
Previous PICU admits	11 (50.0)	3 (12.5)	0.01 ^a
Fentanyl rate (µg/kg/h)			
Initial rate	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.62 ^a
Peak rate	4.0 (3.0–5.0)	4.0 (2.0–8.3)	0.97 ^a
End rate	1.6 (1.0–3.0)	1.5 (1.0–3.0)	0.94 ^a
Rate increases (n)	3 (2.0–5.5)	3 (1.8–4.3)	0.73 ^a
Infusion duration (h)	130.0 (94.5–223.8)	205.0 (125.0–279.8)	0.36 ^a
Cumulative exposure			
µg	6,809.9 (3,664.5–9,791.1)	4,032.9 (1,912.6–8,774.4)	0.37 ^b
µg/kg	456.7 (290.5–1,156.8)	564.3 (247.1–1,177.0)	0.94 ^b
Sedative CIN			
Midazolam	19 (85.7)	21 (87.5)	1.00 ^d
Dexmedetomidine	12 (54.5)	10 (41.7)	0.38 ^b
Ketamine	3 (13.6)	2 (8.3)	0.66 ^d

Abbreviations: BMI, body mass index; CIN, continuous infusion; IQR, interquartile range; PICU, pediatric intensive care unit.

^aWilcoxon–Mann–Whitney test.

^bChi-square test of independence.

^cN = 45; height unavailable for one patient.

^dFisher exact test.

^eLow-normal weight was defined as a weight-for-length < 98th percentile or BMI < 85th percentile.

^fHigh weight was defined as a weight-for-length ≥ 98th percentile or overweight/obese based on BMI ≥ 85th percentile.

also found that children receiving a higher initial fentanyl dose of 1 µg/kg/h had reduced odds for developing tolerance (adjusted OR: 0.96, 95% CI: 0.95–0.98).² In our study, it is possible that we had a higher number of children who developed tolerance because they were initiated on a lower median initial dose than those who did not develop tolerance, 1 versus 2 µg/kg/h (►Table 4).

Another factor that may have contributed to differences between our study and the Anand et al study was the definition of tolerance. The authors of the Anand et al study defined tolerance as a doubling of the daily fentanyl dose after 7 and 14 days of therapy.² We utilized a similar, though slightly different, definition of tolerance, which was doubling of the fentanyl infusion rate. It should be noted that there is no widely accepted clinical definition of tolerance in practice. Additionally, there are no biochemical markers for detecting tolerance. Our definition of tolerance may have led to increased identifi-

cation of tolerance among children who required rapid increases in their fentanyl infusion rate during the first 24 hours of therapy when comparing the results to Anand et al. Unlike the definition of tolerance by Anand et al, which allowed for the inclusion of fentanyl boluses in the total daily dose, we did not include PRN fentanyl boluses in our definition of tolerance. It is our belief that including fentanyl boluses in the definition could lead to difficulties in capturing a true estimate of tolerance. For example, many critically ill children receive PRN sedatives and analgesics for procedures (e.g., chest tube placement, dressing changes). Including all of these additional boluses would likely overestimate the patients' opioid requirements, since these boluses would not be provided in response to decreasing opioid response, but for increased pain or agitation due to their disease or for procedures.

Previous studies have identified potential risk factors for opioid tolerance. Anand et al employed a multivariate logistic

regression and found that children receiving midazolam continuous infusions and those who had a history of a PICU admit within the previous year before admission were more likely to develop opioid tolerance based on their definition.² Approximately 86% of the patients receiving a fentanyl CIN also received a midazolam CIN in our study. Additionally, 28.8% were admitted to the PICU more than one time during the previous year, though we did not find a statistically significant difference between children who developed tolerance versus no tolerance based on PICU admission status (► **Table 4**). Nonpostoperative (vs. postoperative) status has also been identified as a factor significantly associated with development of tolerance ($p < 0.001$).² The previous study by Anand et al enrolled a 1:1 ratio of nonpostoperative to postoperative patients.² Our patient population, however, included a higher ratio of nonpostoperative patients (nearly 3:1). It is possible that all of these factors may have predisposed our patients to a higher likelihood of tolerance.

Another patient characteristic that may impact the likelihood the impact of tolerance is extremes of weight. In our study, we attempted to identify the number of children who had a “high weight” classification. Studies in adults have noted alterations of PK including higher volume of distribution (Vd) for lipophilic medications and increased glomerular filtration rates.⁷ With the higher Vd, children may require a higher initial loading dose for lipophilic agents such as fentanyl to alleviate pain and achieve the targeted sedation goal.⁸ In our study, we noted a higher percentage of children with a “high weight” classification who developed tolerance versus those who did not, 10 versus 2; this difference was not statistically significant, but this could have been a result of inadequate power (► **Table 4**). It is possible that we noted more children in the “high weight” category who developed tolerance because they had an inadequate initial dose relative to their altered volume of distribution. If these patients then received rapid escalations in their fentanyl CINs, they could be at risk for oversedation over time as a result of the longer elimination half-life, since adipose tissue serves as a depot for lipophilic medications.⁸

Decisions about dose adjustments for sedatives and analgesics in this study were made by the discretion of the providers. At the time of this study, our institution did not utilize sedation holidays or nursing-driven sedation protocols. Rather, dose adjustments were made to achieve a daily goal SBS score selected individually for each patient. One study by Gupta et al utilized a sedation holiday versus standard of care approach in 102 children receiving mechanical ventilation > 48 hours with the primary objective being a comparison of mechanical ventilator days and ICU length of stay.⁹ They found statistically significant differences in primary objectives, but they did not specifically assess whether this intervention decreased the incidence of opioid and/or sedation tolerance. Four studies have investigated the use of a nursing-driven sedation protocol on the impact of various outcomes in PICUs with varying results on the impact of sedative/analgesic cumulative exposure.^{10–13} The largest study to date by Curley et al prospectively evaluated 1,225 children receiving a nursing-driven protocol versus 1,224

children receiving sedation as according to the standard of care.¹³ They did not note a statistically significant difference in the opioid and/or benzodiazepine exposure. It is reasonable to assume that utilization of a nursing-driven protocol or sedation holiday may decrease sedative/analgesic cumulative exposure, but it is not clear whether these interventions would prevent or delay the development of opioid tolerance.

There are several limitations with this study. The major limitation revolves around the lack of a consistent definition of opioid tolerance with CINs in the literature. Given the limitations of the different definitions of opioid tolerance, it is imperative that we develop a better definition that incorporates PK and pharmacodynamic (PD) parameters. Without appropriate understanding of PK/PD, it is impossible to determine whether changes in dosing requirements are due to tolerance or to other factors such as inadequate initial dosing or increased analgesic requirements. Future prospective studies should focus on consideration of quantitative dose–exposure–response relationships to detect the development of tolerance using serum fentanyl concentrations and the measurement of PD response with goal sedation using a validated sedation scoring tool in children.

Another limitation is that as this was a retrospective study, it was difficult to identify whether increases in the fentanyl infusion rates were secondary to the development of opioid tolerance or for procedural related requirements. Finally, this study was performed at a single center, and there was wide variability noted in the adjuvant sedative CIN regimens used. As discussed previously, the majority of patients received midazolam CINs. Benzodiazepines have been associated with an increased risk of tolerance while the use of ketamine has been suggested to decrease opioid tolerance.^{1,2} Only 5% of fentanyl CINs were administered with ketamine CINs. There is limited data on the influence of other sedative agents such as dexmedetomidine on the development of opioid tolerance. Likewise, there are no current data comparing various combinations of sedative and opioid CINs regimens, so it is difficult for us to determine if the variability of adjuvant sedative CINs affected our results.

Tolerance is a frequent complication of prolonged opioid exposure in critically ill children who receive fentanyl CINs for sedation and analgesia. Based on the study definition, tolerance occurred in 78% of the children, and half developed it within 24 hours. Lower initial opioid rate and higher cumulative exposure were independently associated with tolerance. Future PK and PD studies should be utilized to further refine the definition of tolerance and to develop guidelines for initial CIN doses to reduce incidence of tolerance development.

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Presentations

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Note

At the time of data collection and article preparation, Dr. Ibach was a PGY2 resident at the College of Pharmacy, University of Oklahoma.

Conflict of Interest

Jamie L. Miller is on the Speakers' Bureau for Chiesa, Cary, NC, United States. The authors have declared no other potential conflict of interest.

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