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Dosing for Fentanyl Infusion in Obese Children: Just Because It's What We Have Always Done Doesn't Mean It Is Right

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ABBREVIATIONS BMI, body mass index; PBPK, physiologically based pharmacokinetic model; PICU, pediatric intensive care unit

KEYWORDS child; dosing; fentanyl; obesity; pharmacokinetics

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It is estimated that nearly 19% of admissions to children's hospitals involve obese children.¹ Some of these children will be admitted to the pediatric intensive care unit (PICU), where they may be initiated on sedatives and analgesic medications. Many of these medications, including midazolam, propofol, and fentanyl, are lipid soluble at physiological pH. These highly lipophilic drugs widely distribute to organs and tissues, including adipose tissues; hence, they could have altered drug disposition characteristics in obese individuals.^{2,3}

Harskamp-van Ginkel et al⁴ performed a systematic review of pharmacokinetic studies conducted between 1970 and 2012 in obese children. Pharmacokinetic studies were available for only 21 drugs; fentanyl was not among these agents. Fentanyl is favored for its fast onset and short half-life when used in boluses. However, its half-life when administered as a continuous infusion increases by approximately one-fold for every hour increase in the duration of infusion due to a greater extent of drug distributed to adipose tissue and slow redistribution into plasma for elimination.⁵ Two retrospective studies compared surrogate pharmacodynamic markers, including number of dosage changes per day and time to reach goal sedation, in obese and non-obese children receiving fentanyl infusions in the PICU.^{6,7} Findings from these studies allude to potential differences in these pharmacodynamic outcomes that could reflect pharmacokinetic alterations in obese children, but this is difficult to confirm without pharmacokinetic data.

Though there are no pharmacokinetic data for fentanyl infusions in obese children, previous studies evaluating pharmacokinetics of some lipophilic medications have noted larger volumes of distribution and accelerated clearance in obese patients versus non-obese patients.⁸ Therefore, based on this higher volume of distribution, obese children may require a higher initial dose or loading dose to achieve analgesia

and sedation, considering the 3-compartment model of fentanyl. Once distribution to the adipose tissue in the third compartment has reached equilibrium, a lower maintenance infusion may be needed to prevent oversedation. Undesirable outcomes, such as respiratory depression, prolonged use of mechanical ventilation, and longer PICU stays, could follow in cases of oversedation.⁹

Dosing for fentanyl infusions is generally weight-based in children. This approach is problematic for obese patients because clinicians must choose the correct weight to use. Various weight adjustments, including ideal body weight [i.e., (50th percentile body mass index for age and gender) × (height (m²))], and adjusted body weight [i.e., (ideal body weight) + (pre-specified cofactor) × (total body weight – ideal body weight)], have been proposed for obese children. For lipophilic drugs such as fentanyl, some have proposed to use total body weight for loading doses and ideal body weight for maintenance doses. Shibutani et al¹⁰ conducted a pharmacokinetic study of fentanyl infusions in adults and developed a non-linear model that demonstrated lower weight-normalized clearance with increasing body weight and possible accumulation if total body weight was used. As a result of the potential risk for accumulation based on total body weight, Ross et al¹¹ recommended an adjusted body weight, with a cofactor of 0.25, for fentanyl dosing in obese children.

The use of fixed cofactor adjustment may not take into consideration the other pharmacokinetic variations that are noted in children versus adults. To illustrate this point, we utilized deidentified data from 4 females between the ages of 4 and 9 (Group 1) weighing approximately 30 kg, and another 4 females between the ages of 12 and 15 (Group 2) weighing approximately 44 kg who were admitted to our institution. Each age group included 3 obese patients and 1 non-obese patient (Table). For these patients, we calculated the total body

Table. Comparison of Demographics and Fentanyl Infusion Dosing in Eight Female Pediatric Patients

Characteristics	Group 1				Group 2			
	Obese			Non-Obese	Obese			Non-Obese
	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8
Age, yr	4	5	7	9	11	12	13	15
Weight, kg	30.2	29.8	29.9	30	44	43.6	43.6	44.1
Height, cm	124.1	124.5	123.5	142	134.6	127	121.9	159
BMI, kg/m ²	19.6	19.2	19.6	14.9	24.3	27.0	29.3	17.4
BMI percentile	98.7	96.6	95.5	16.4	95.6	98.2	97.6	11.3
Fentanyl infusion dose,* mcg/hr:								
Total body weight-based	30	30	30	30	44	44	44	44
Ideal body weight-based [†]	19	24	23	—	31	28	28	—
Adjusted body weight-based [‡]	25	25	25	—	34	32	32	—

BMI, body mass index; Pt, patient

* The dose was calculated based on 1 mcg/kg/hr using different dosing weights; the values were rounded to the nearest 10th.

[†] Ideal body weight = [(50th percentile BMI for age) × (height in m²)].

[‡] Adjusted body weight = [(Ideal body weight) + 0.25 × (total body weight – ideal body weight)].

weight, ideal body weight, and adjusted body weight. We used these weights to calculate a dose based on 1 mcg/kg/hr of these different dosing weights. As noted in the Table, the use of the cofactor of 0.25 to calculate adjusted body weight resulted in fentanyl doses of 25 mcg/hr for all patients in Group 1, and doses ranging from 32 to 34 mcg/hr for patients in Group 2. The adjusted body weight is largely affected by height; hence, this dosing weight assumes larger doses are required for taller patients. Although adjusted body weight incorporated the 50th percentile of body mass index specific for the age and gender, the influence of age and gender on dosing weight were relatively small.

We also used data from published studies to compare the relationship to total body weight and clearance in adults and children receiving fentanyl infusions. Adult clearance data were obtained from Shibutani et al.¹⁰ Clearance data for children were extracted from a study by Katz et al.¹² evaluating the pharmacokinetic data of fentanyl infusions in 19 children. As this study did not report patient weights, we used the weight of the 50th percentile for their age to approximate their clearance and weight relationship. Using the nonlinear clearance and weight relationship model from Shibutani et al.,¹⁰ we included total body weight from the pediatric patients from the study by Katz et al.¹² and plotted these data together (Figure). A commonly used allometric model and an extrapolation model based on Clark's rule were compared with the adult non-linear model. The allometric and Clark's rule models are described as the following equation:

$$CL_{\text{Children}} = CL_{\text{Adult}} \times (\text{Weight}/\text{Weight}_{\text{Adult}})^{\gamma}$$

where $\text{Weight}_{\text{Adult}}$ was assumed to be 70 kg, and the γ -exponent is 0.75 for the allometric model and 1 for Clark's rule.

All 3 models were overlaid with the adult clearance values from Shibutani et al.¹⁰ and the pediatric clearance

values from Katz et al.¹² The Figure shows that the adult non-linear model well described the adult population, but not the pediatric population. The adult non-linear model was not developed to be extrapolated to children, and lower limit of the range of body weight is 22 kg. In contrast, the allometric model better predicted pediatric clearance, but did not perform well in adults at body weights >100 kg. Allometry was a better fit in children than adults, because it takes into account the relationship of body size and physiology.

These results are supported by findings of Liu et al.,¹³ who examined the predictability of pediatric drug clearance using the allometric scaling approach. They reported that the deviation of predicted clearance were within two-fold of actual clearance for 46 drugs and within 50% for 31 drugs. Clark's rule did not provide a good fit for adults and children and has fallen out of favor in determination of dosing.

Although the allometric model is a reasonable approach for weight-based dosing selection in pediatrics, the effect of age and obesity on pharmacokinetics should not be ignored. If the dosing regimen were designed solely based on the weight and clearance relationship, then all 4 patients in Group 1 would receive a fentanyl infusion dose of 30 mcg/hr, and the patients in Group 2 would receive an infusion dose of 44 mcg/hr, regardless of their age and other characteristics (Table). Studies have shown that fentanyl clearance varies with age in children.^{12,14} Due to the heterogeneity in pharmacokinetic parameters across the continuum of age in children and the effects of obesity on these age-specific pharmacokinetic parameters and fentanyl pharmacokinetics, future studies of fentanyl pharmacokinetics in obese children require stratification into separate age groups in order to examine the weight and age effects.

Because of these complexities, it may be more appro-

Figure. Comparison of 3 models (adult nonlinear,¹⁰ allometry, and Clark's Rule model) that describe the relationship of total body weight and clearance overlaid with adult¹⁰ and pediatric¹² clearance values.

appropriate to utilize more sophisticated approaches, such as a population physiologically based pharmacokinetic (PBPK) model that incorporates interindividual variability and physiologic data. Mula et al¹⁵ recommended the use of either a “bottom up” or a “top down” approach to improve pediatric clinical study design. The “bottom up” approach utilizes a PBPK and simulation technique to predict drug disposition (i.e., absorption, distribution, metabolism, and excretion) in obese children. The “top down” approach employs population pharmacokinetic modeling and simulation based on clinical data to investigate the population pharmacokinetic parameters and the source of variability (i.e., age, weight, renal function) for individual patients.

In conclusion, pharmacokinetic studies of obese children receiving fentanyl infusion are needed. A more sophisticated approach, including population PBPK modeling, can be used to account for age-related and obesity-related effects on fentanyl pharmacokinetics. Until further research is conducted, clinicians should continue to utilize pharmacodynamic targets, such as sedation and pain scores, to guide dosing of fentanyl infusions in obese children. Clinicians should be mindful that, due to the higher volume of distribution, obese children may initially require a higher mcg/kg dose than non-obese children, but ultimately require a lower maintenance mcg/kg dose once fentanyl distributes to deep or slowly equilibrating tissues.

ARTICLE INFORMATION

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