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ARTICLE

Physiologically based modeling reveals different risk of respiratory depression after fentanyl overdose between adults and children

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Abstract

Despite a rapid increase in pediatric mortality rate from prescription and illicit opioids, there is limited research on the dose-dependent impact of opioids on respiratory depression in children, the leading cause of opioid-associated death. In this article, we extend a previously developed translational model to cover pediatric populations by incorporating age-dependent pharmacokinetic, pharmacodynamic, and physiological changes compared to adults. Our model reproduced previous perioperative clinical findings that adults and children have similar risk of respiratory depression at the same plasma fentanyl concentration when specific endpoints (minute ventilation, CO_2 tension in the blood) were used. However, our model points to a potential caveat that, in a perioperative setting, routine use of mechanical ventilation and supplemental oxygen maintained the blood and tissue oxygen partial pressures in patients and prevented the use of oxygen-related endpoints to evaluate the consequences of respiratory depression. In a community setting when such oxygenation procedures are not immediately available, our model suggests that the higher oxygen demand and reduced cerebrovascular reactivity could make children more susceptible to severe hypoxemia and brain hypoxia, even with the same plasma fentanyl concentration as adults. Our work indicates that when developing intervention strategies to protect children from opioid overdose in a community setting, these pediatric-specific factors may need to be considered.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Based on some perioperative clinical studies, adults and children have similar risk of respiratory depression at the same plasma fentanyl concentration.

Shilpa Chakravartula and Bradlee Thrasher contributed equally to this work.

The opinions expressed in this manuscript are those of the authors and should not be interpreted as the position of the U.S. Food and Drug Administration.

WHAT QUESTION DID THIS STUDY ADDRESS?

Can these perioperative observations be translated to a community setting?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study incorporates known age-dependent PK/PD and physiological changes into a published and validated translational model. The model suggests that previous observations in perioperative settings may be confounded by the routine use of mechanical ventilation and supplemental oxygen. Under community settings, where these oxygenation procedures are not immediately available, there is a higher risk of developing hypoxemia and brain hypoxia due to opioid-induced respiratory depression in children compared to adults.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This work calls for a pediatric-specific intervention and prevention strategy to protect children from accidental overdose of prescription or illicit opioids.

INTRODUCTION

Opioid overdose has become a serious public health issue impacting all segments of US society, including the pediatric population. Between 1999 and 2016, the national pediatric mortality rate from prescription and illicit opioids increased nearly threefold.[1] However, while the opioid epidemic's impact on adolescents and adults has received substantial attention, its impact on young children has received less consideration.[2] In line with this, there is only sparse evidence concerning the exposure-response relationship between opioids and respiratory depression in children,[3] which is the primary cause of death in opioid overdose.[4]

In 2019, the Society for Pediatric Anesthesia published a set of recommendations for the use of opioids in children during the perioperative period.[3] On the topic of the respiratory depressant effects of opioids in children versus adults, the recommendations cited some clinical studies[5,6] suggesting that children (older than 3 months of age) are not at an increased risk of opioid-induced respiratory depression when compared to adults at the same plasma opioid concentration. It is unclear if such recommendations based on perioperative clinical studies can be translated to other scenarios, such as accidental opioid poisoning in children at home or in a community setting.

It is important to note that children are not simply smaller versions of adults. Their bodies are physiologically different and still developing, which can affect their ability to handle physical stressors such as opioid-induced respiratory depression. For example, children's metabolism, especially the oxygen consumption rate in the brain, is much faster than adults'.[7,8] Together with the fact that brain metabolism accounts for a higher percentage (up to 65%) of the total body resting metabolic rate in children than in adults,[8] this creates a much higher oxygen demand in children to support growth and development in addition to daily activities. On the contrary, compared to adults, children may have a diminished capability of regulating cerebral blood flow (CBF) to maintain the oxygen supply in response to changes in blood gas partial pressures such as hypercapnia,[9] which commonly occurs during opioid-induced respiratory depression. This suggests that the respiratory depressant effects of opioids can pose a greater risk to children. In this work, we extended a physiologically based translational model previously developed based on adults' data[10] to cover children of age 2–12 years old by incorporating published age-dependent changes in fentanyl pharmacokinetics (PK), physiology of respiration and blood flow regulation, and metabolism.

METHODS

For fentanyl pharmacokinetics (PK) in pediatrics, we used our previously developed adult fentanyl PK model[10] as a base and allometrically scaled the plasma compartment clearance and volume of distribution parameters using age-dependent differences in body sizes. The scaling for the clearance is defined as $P_i = P^*(W_i/W)^{0.75}$, where P_i and W_i are the age-based PK parameter values and weight for an i-year-old child (the subscript i varies from 2 to 12), P represents PK parameter values for an adult.[11] The weight W for an adult is assumed to be 70 kg. For the central volume of distribution, we followed Okada et al.[12] to scale it with the fat-free mass (FFM): $P_i = P^*(\mathrm{FFM}_i/\mathrm{FFM})$. Typical pediatric FFM values for each age (FFM_i) were obtained by translating median body weight and BMI from CDC growth charts[13] to FFM values[14] and averaging male and female values for each age. Adult FFM

is assumed to be 56.1 kg.[14] Typical FFM and body weight values for each age can be found in Table S1.

To capture the pediatric physiological changes in comparison to adults, related physiological parameters corresponding to brain and body weight, lung, brain and other tissue volume, brain, and other tissues blood flow, and cardiac output are chosen based on literature values (see Supplemental Methods—Physiological Component in Appendix S1). Further parameter estimation was conducted for brain and other tissues' gas (oxygen and carbon dioxide) metabolic rate, and some parameters in respiratory physiology (baseline of CBF and other tissue blood flow, wakefulness drive, central drive, neural firing frequency of peripheral chemoreceptors, parameters relating to the amplitude of the CBF response to O_2 and CO_2, rate constant for CBF response to O_2 and CO_2) so that both the steady-state variables such as minute ventilation, partial pressure of arterial oxygen and carbon dioxide, and the dynamic changes of cerebral blood flow to hypercapnia, lie within the range observed in clinical studies (see Table S4).

To simulate perioperative fentanyl usage and compare the data to clinical observations,[5] we first ran our model under normal conditions for 30 min to reach a steady state. Starting with the steady state, we simulated a 2-h surgery period with mechanical ventilation maintaining end-tidal PCO_2 at 32.5 mmHg, followed by a 30-min weaning period. Fentanyl was administered via continuous intravenous (IV) infusion throughout the first 1.5 h of the surgery period. The fentanyl dose was chosen so that the plasma concentration is 2 ng/mL (dose 28.0 μg/kg for 3-year-olds and 18.3 μg/kg for adults) or 4 ng/mL (dose 56.0 μg/kg for 3-year-olds and 36.5 μg/kg for adults) at the end of the simulated weaning period (30 min after surgery). During the weaning period, the patient was slowly taken off the mechanical ventilation while spontaneous breathing returned. We simulated this period by 15 min with the mechanical ventilation volume reduced to half, followed by 15 min with the mechanical ventilation volume set to 0.

To simulate fentanyl overdose in a non-perioperative situation (without mechanical ventilation and supplemental oxygen), a high dose (23.2 μg/kg for adults and 21.5 μg/kg for children) of fentanyl IV push (90 s) was simulated on a virtual subject representing an adult and a 10-year-old child, respectively. The values of various variables, including fentanyl plasma concentration, minute ventilation, and oxygen partial pressures in the brain and arterial blood, were calculated and output every 0.1 s during the simulated time course. Only the first 100 s post fentanyl injection were used to compare the physiological responses between adults and children, because beyond that severe hypoxia and hypercapnia may induce significant pharmacokinetic changes for fentanyl,[10] making it difficult to assess the physiological changes under the same exposure of fentanyl.

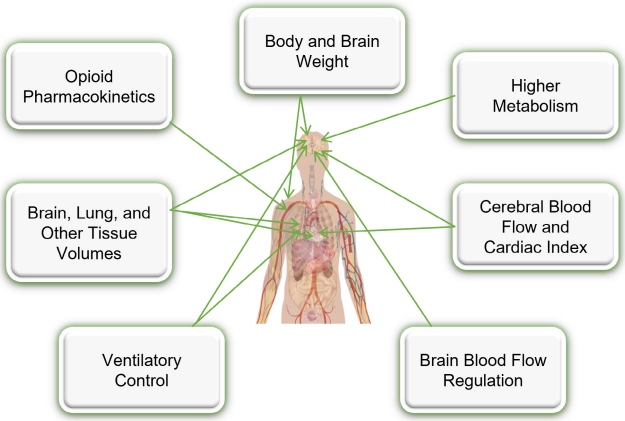

FIGURE 1 Physiological and pharmacological differences between adults and children. Key differences between adults and children that may have an implication on the response to opioid overdose.

RESULTS

Overall strategy in modeling the differences between adults and children

Figure 1 shows the key differences between adults and children that were incorporated into our model. In addition to fentanyl pharmacokinetic (PK) differences, children have smaller body and brain weight, smaller brain, lung, and other tissue volumes, higher cerebral blood flow, and cardiac index,[15] as well as higher metabolic rate in the brain.[8] Their cerebrovascular reactivity (capability of brain blood flow regulation) may be reduced.[9] When incorporating these reported physiological differences, we also found it necessary to adjust some ventilatory control parameters (e.g., the set point of peripheral and central chemoreflex drive) so that the steady-state physiological variables like minute ventilation can match clinically observed values (see Table S4).

Differences between adults and children in fentanyl pharmacokinetics

As can be seen from Figure 2, after fentanyl intravenous (IV) infusion (over 2 min) with age-specific dosing, our model was able to reproduce the plasma fentanyl profiles

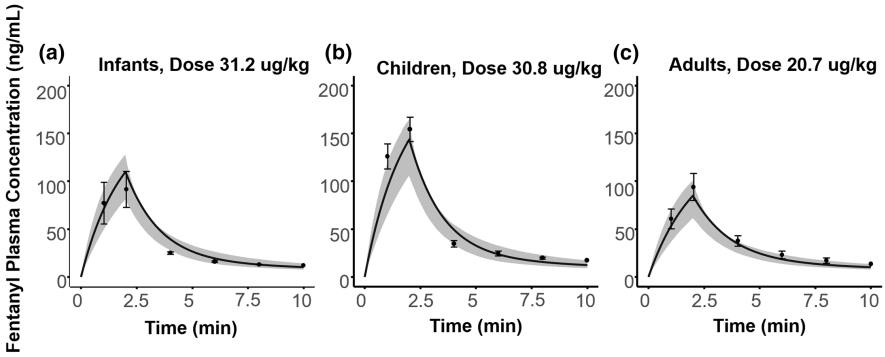

FIGURE 2 Fentanyl plasma concentrations against time. The fentanyl pharmacokinetic (PK) simulation is the black line (typical patient) and gray band (population simulation), while Singleton et al. clinical data of fentanyl bolus intravenous (IV) injection are shown as dots (mean) and error bars (standard deviation). (a) Infants, mean age 6 months, dose 31.2 μg/kg, (b) Children, mean age 2.7 years, dose 30.8 μg/kg, and (c) Adults, mean age 33 years, weight is assumed to be 70 kg, dose 20.7 μg/kg. Because Singleton et al. did not give total body weight (TBW) or fat-free mass (FFM) values for their cohort, we fitted these values to the mean data of Singleton et al. by allowing these weight values to vary plus or minus 10% of the typical values. The procedure to calculate typical values can be found in Section 2. Of note for infants (6 months), CDC growth charts do not provide BMI values, so we used WHO growth chart BMI values to calculate typical FFM values for 6 months old. This resulted in an estimated mean TBW values of 7.4 kg (infants) and 14.9 kg (children), and estimated mean FFM values of 6.5 kg (infants) and 9.7 kg (children), respectively. *X* axis: time (in minutes) since the IV injection. *Y* axis: fentanyl plasma concentration.

for adults, children (mean age 2.7 years), and infants (mean age 6 months), as reported in a clinical study.[16] This was achieved by allometrically scaling the volume of distribution by fat-free mass (FFM), and clearance by total body weight (see Section 2 for details).[12]

Differences between adults and children in metabolism

To understand the pharmacodynamic (PD) effect of fentanyl on children, first, we investigated physiological differences between children and adults under normal circumstances (with no exposure to fentanyl). Figure 3a,b highlight the developmental changes of the brain metabolism by age. During early childhood, the brain undergoes rapid growth and development that demands higher energy consumption,[8] resulting in a rapid increase in brain metabolism in the first few years of life, peaking at around 5 years of age, followed by a gradual decline as the brain reaches maturity (Figure 3a). The Relative Metabolic Rate (RMR), an indicator of the brain metabolism relative to the whole-body energy expenditure, has a similar time course (Figure 3b). The metabolic rate parameters in our model were adjusted for each age to capture this age-dependent developmental pattern (Figure 3a,b). Other tissue metabolic rates are calculated from the RMR and brain metabolism. The brain and other tissue metabolic rates for each age can be found in Table S2.

Differences between adults and children in respiratory physiology and blood flow regulation

The developmental changes in model compartment volumes (brains, lungs, and other tissues), baseline brain blood flow, and cardiac output, as well as other physiological variables, are adjusted to reflect the age-dependent changes clinically observed[15,17–20] (see Supplemental Methods—Physiological Component in Appendix S1 for details). Figure 3c shows that the age-dependent value of minute ventilation volumes simulated at a steady state from our model lies within the clinical range.

Other than these steady-state physiological variables, children and adults can differ in dynamic responses to physiological and pathophysiological stimuli. Specifically, it has been shown that, while the cerebral blood flow (CBF) increases in both adults and children in response to hypercapnia, children may have a weaker response.[9] This information is incorporated into the model (see Supplemental Methods—Physiological Component in Appendix S1 and Figure S2 for details). As shown in Figure 3d, our pediatric model recapitulated the slower increase rate and lower increase amplitude of CBF in children versus adults, while breathing in a hypercapnic gas mixture. As hypercapnia-induced CBF increase is an important compensation mechanism to deliver more oxygen to the brain during opioid overdose, this suggests children may have less capacity to protect their brains from hypoxia.[21,22]

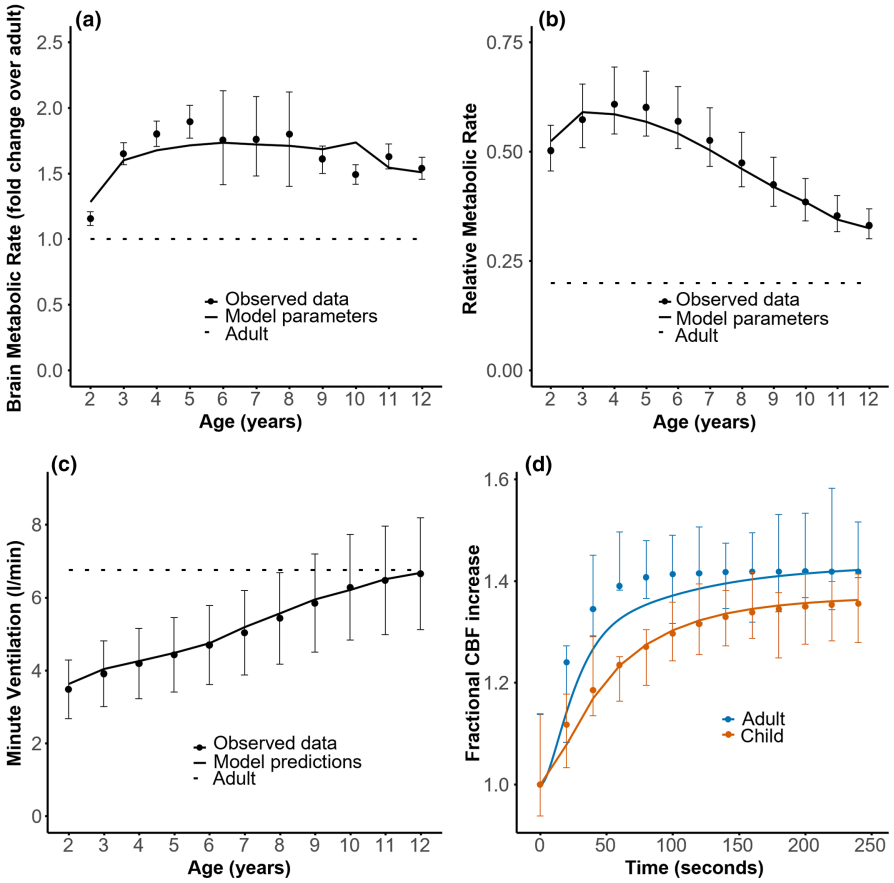

FIGURE 3 Developmental changes of various physiological variables. (a) The rate of brain oxygen metabolism (fold change over adult value) by age. (b) The ratio of brain metabolism relative to whole body (relative metabolic rate) by age. In humans, this was measured as the ratio between daily glucose uptake by brain and that by whole body, on a per-gram basis. In simulation, this was calculated as the ratio between the oxygen consumption rate of brain and that of whole body. In panels (a) and (b), the solid lines represent model parameters and the dots and error bars depict the mean and range of measured values from Kuzawa et al.[8] The horizontal dashed lines represent adult parameters as a reference. (c) Minute ventilation by age. The clinical data of the respiration rate and tidal volume taken from refs [9,18,19] is used to compute the minute ventilation at each pediatric age. The mean adult minute ventilation volume is depicted as horizontal dashed lines for comparison. (d) Fractional cerebral blood flow increases versus time in response to a hypercapnic stimulus. The simulation results are compared with data from Tallon et al.[9] where the mean age of children is 9.9 years. In panels (c) and (d), the solid lines represent model simulation. The dots and error bars depict the mean and range of measured values from published clinical data described above.

Adults and children have similar degree of respiratory depression and hypercapnia with similar plasma fentanyl concentrations

As one of the few studies to evaluate whether children are more sensitive than adults to fentanyl on the PD level, Hertzka et al.[5] measured the risk of respiratory depression after perioperative use of fentanyl. They discovered that, as long as the plasma concentrations of fentanyl are similar, the severity of respiratory depression, measured as the increase in arterial carbon dioxide partial pressure ($PaCO_2$) and the irregularity in respiration patterns, were similar between adults and children.

To check the clinical relevance of our pediatric models, we used the models to simulate the clinical procedures in Hertzka et al. From Figure 4, we see that our model reproduced these patterns. When fentanyl plasma concentrations are increased from 2 to 4 ng/mL, children (3-year-olds) and adults have a similar degree of increase of $PaCO_2$, suggesting that children have a similar risk of developing hypercapnia (which is one measure of respiratory depression) as that of adults when the plasma fentanyl concentrations are the same. Although, we note that in perioperative studies such as Hertzka et al., the patient's tissue and blood oxygen partial pressure are usually maintained at a constant level by mechanical ventilation or supplemental oxygen.

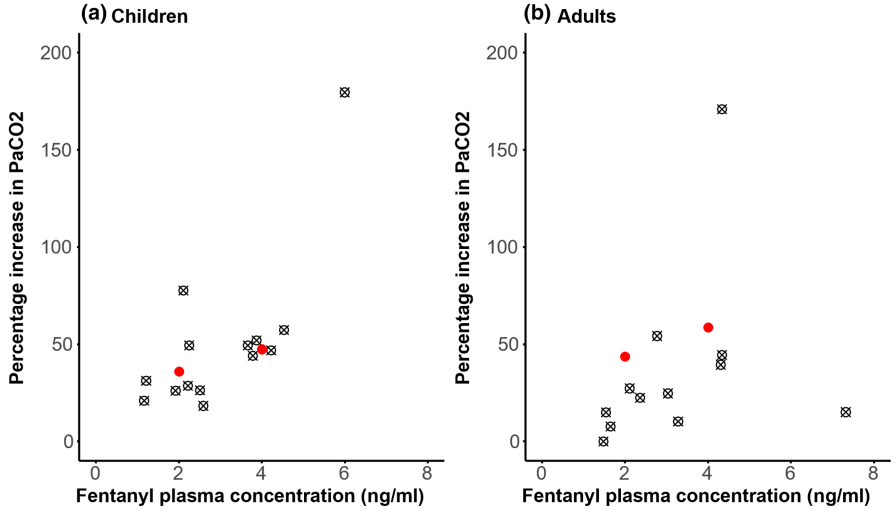

FIGURE 4 Change in arterial carbon dioxide partial pressure ($PaCO_2$) over baseline after perioperative exposure to fentanyl is plotted against fentanyl plasma concentration and compared with clinical data from Hertzka.[5] (a) Children (3 years old), (b) Adults. Red dots represent simulation values for an average virtual subject and circles with cross represent the clinical data from individual patients. *X* axis: fentanyl plasma concentration at the end of the weaning period. *Y* axis: $PaCO_2$ (percentage above baseline) at the time when fentanyl plasma concentration was measured. Note that for both simulation and clinical data, children's percentage increase in $PaCO_2$ is not higher than adults' at the same fentanyl plasma concentration. Of note, Hertzka et al. also reported data for infants (1–12 months of age). However, currently, our model was not expanded to cover children younger than 2 years old (see Section 4) so no simulation was compared to infants' data.

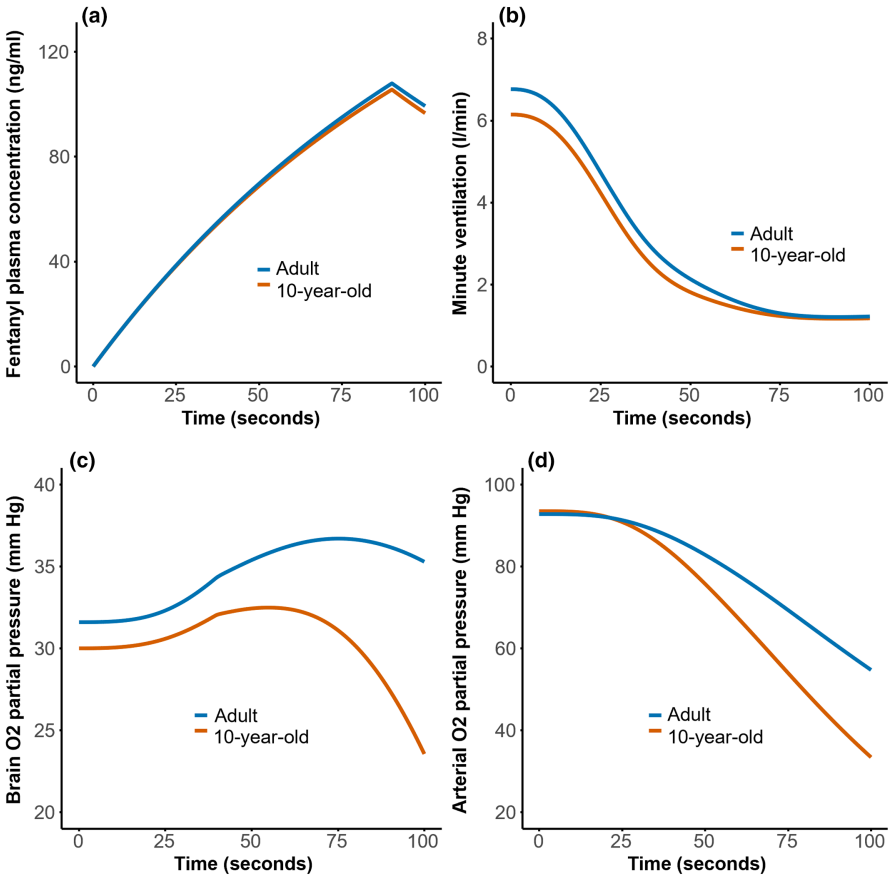

FIGURE 5 Simulated effects of fentanyl overdose after an IV push of fentanyl (dose 23.2 μg/kg for adults and 21.5 μg/kg for children) in children versus adults. In panel (a) fentanyl plasma concentration (ng/mL), (b) Minute ventilation (L/min), (c) Brain oxygen partial pressure (mmHg), and (d) Arterial oxygen partial pressure (mmHg) are plotted against time since fentanyl IV injection. The blue curves correspond to adults and the red curves correspond to children (10 year old). Note that for plasma concentrations (a) and minute ventilation (b), children have similar values compared to adults. However, for brain oxygen partial pressure (c) and arterial oxygen partial pressure (d), children's value declines much faster than adults'.

Children may have more severe hypoxemia and hypoxia than adults with similar plasma fentanyl concentrations

Next, we ran a simulation with fentanyl overdose in children and adults without mechanical ventilation or supplemental oxygen. We chose an age of 10 years old in our simulation because this is the age where we have more complete clinical data, including the crucial data for dynamic response to hypercapnia (Figure 3). In Figure 5, we see the trajectory of fentanyl plasma concentration and physiological variables minute ventilation, brain oxygen partial pressure (PBO_2), and arterial oxygen partial pressure (PaO_2) after an IV injection of fentanyl (23.2 μg/kg for adults and 21.5 μg/kg for children). The adult dose was chosen as such because for a 70 kg adult, this amounts to 1.625 mg fentanyl IV, which was estimated as the median of the fatal fentanyl overdose cases in the community setting.[10] The child dose was set so that the plasma fentanyl concentration was similar to that of an adult throughout the simulation. We see that for the same degree of fentanyl exposure (Figure 5a), the minute ventilation volume is depressed to a similar level between children and adults (Figure 5b). In contrast, physiological variables related to oxygen partial pressures, such as PBO_2 (Figure 5c) and PaO_2 (Figure 5d) drop much faster in children than adults. This suggests that children may have a higher risk of developing hypoxemia and hypoxia than adults, even if the plasma fentanyl concentrations are the same.

To probe into the role various physiological parameters played in causing the increased severity of hypoxemia and brain hypoxia in children, we performed a sensitivity analysis by applying a small change (15%) to each parameter individually prior to simulating fentanyl overdose (see Supplemental Sensitivity Analysis in Appendix S1). The severity of hypoxemia and brain hypoxia was measured by the percentage decrease from baseline at the end of the simulation for PaO_2 and PBO_2, respectively. The impact of the two oxygen-related mechanisms, oxygen demand, and cerebrovascular reactivity is depicted in Figure 6. A 15% reduction in oxygen demand had a significant impact on reducing the severity of hypoxemia in children. For the severity of brain hypoxia, a 15% reduction in oxygen demand, or a 15% increase in cerebrovascular reactivity, had a significant impact. This is consistent with the role these two mechanisms play in maintaining tissue and blood oxygen partial pressures.

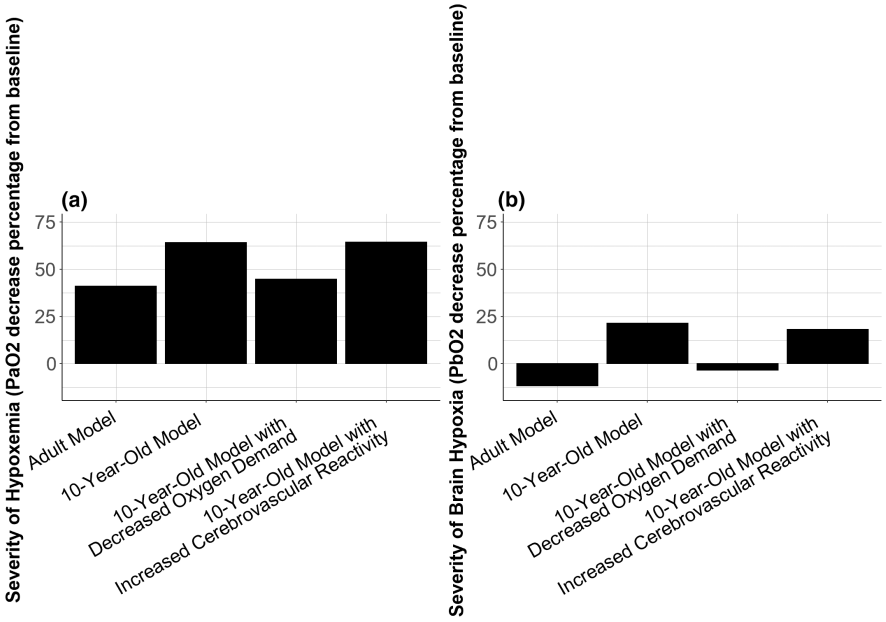

FIGURE 6 Sensitivity analysis of the impact of oxygen demand and cerebrovascular reactivity on the severity of hypoxemia and brain hypoxia. (a) *Y* axis: severity of hypoxemia, defined as PaO_2 decrease percentage from the baseline, 100 s after fentanyl intravenous push at a dose of 23.2 μg/kg for adults and 21.5 μg/kg for children. *X* axis: the four models with different parameters. The adult model and the 10-year-old model are the first two bars. For the 3rd bar, the 10-year-old model's oxygen metabolic rate in the brain was reduced by 15%. For the 4th bar, the 10-year-old model's cerebral blood flow (CBF) reactivity amplitude and rate were both increased by 15%. (b) The same as A, but *Y* axis is the severity of brain hypoxia, defined as PBO_2 decrease percentage from the baseline at 100 s after fentanyl intravenous bolus injection. For the adult model, the severity of brain hypoxia is negative because its PBO_2 was actually increased, instead of decreased, at 100 s after fentanyl injection, due to the body's compensation mechanism (high cerebrovascular reactivity in adults) (see Supplemental Methods – Figure S3 for more details).

DISCUSSION

In this work, we extended a previously published translational model[10] to cover pediatric subjects in order to investigate potential differences between children and adults in response to fentanyl overdose. We considered both pharmacokinetic (PK) and pharmacodynamic (PD) factors that could drive an age-dependent fentanyl overdose response.

On the PK side, when exposed to the same dose of fentanyl through the same dosing route, children usually have a higher plasma concentration, as shown in studies involving transdermal fentanyl patches.[23] This is reflected in the model through children having smaller plasma compartment clearance and volume of distribution, and therefore higher C_{max} (maximum plasma concentration), than adults. On the contrary, in clinical practice, pediatric fentanyl doses are adjusted according to their body weight, which would result in a total fentanyl dose smaller than, but plasma fentanyl concentrations similar to, what adults would get.[16] Based on these considerations, in subsequent investigations, we focused on the PD difference, and asked the question: would children and adults have the same degree of respiratory depression at the same plasma fentanyl concentration?

Given the complex physiological feedback loops (e.g., chemoreflex, blood flow regulation) governing the oxygen and carbon dioxide partial pressures in the tissues and blood,[24,25] it is conceivable that the relationship between the plasma fentanyl concentration and its PD effects (respiratory depression, hypoxia, hypercapnia, etc.) may depend on the underlying physiology, which undergoes significant changes throughout development. Indeed, the brain oxygen demand of children can be twice that of adults, despite the smaller size of brain tissues.[7] When incorporating children's metabolism levels reported in the literature,[8] our model shows that children have a lower baseline PBO_2 than adults, even without fentanyl or any other ventilation suppressors (Figure 5, time 0). Due to technical aspects of PBO_2 monitoring (e.g., spatial heterogeneity), normal PBO_2 levels in a healthy human brain have not been established.[26] The simulated baseline PBO_2 level in children and adults in our model (~30 mmHg) is within the range of normal values reported in some studies,[26] but on the lower end of the range (30–48 mmHg) reported in other studies.[27] One possible explanation is that the model intends to simulate PBO_2 under normal conditions, while the reported PBO_2 values were mostly measured in patients under general anesthesia. Animal studies suggested the procedure of general anesthesia could by itself increase PBO_2 values, with or without supplemental oxygen.[28]

Under normal conditions, the high demand for oxygen is met through developmental changes in other parts of physiology, for example, cerebral vasodilation in children.[29] However, if children's cerebral blood vessels are already in a dilated state under normal conditions, the capability of further increasing the blood flow (called cerebrovascular reserve[9]) is likely reduced in children compared to adults.[29] This can be illustrated by the smaller amplitude and slower increasing rate of cerebral blood flow (CBF) in response to a hypercapnic stimulus in children compared to adults (Figure 3d). Of note in the corresponding clinical study,[9] the amplitude of CBF increase was nominally lower (3.71 in children vs. 4.12% $mmHg^{-1}$ in adults) but did not reach statistical significance ($p = 0.098$). It is unclear if this is due to the relatively small sample size ($n = 20$). We had fit the pediatric model to the nominal values so that in our model children have a slightly lower CBF increase amplitude compared to adults in response to hypercapnia.

In line with these physiological differences between adults and children, our model demonstrated that, even with the same fentanyl plasma concentrations and similar degree of minute ventilation depression, children's oxygen partial pressure in the blood and brain tissues drop much faster than adults (Figure 5). We argue that this does not contradict with the Society for Pediatric Anesthesia recommendations that children (older than 3 months) and adults have similar risk of respiratory depression at the same plasma opioid concentration.[3] Those recommendations were based on, and would apply to, perioperative patients where mechanical ventilation and supplemental oxygen can be used to maintain adequate oxygenation in the blood and tissues. This maintenance limits the usefulness of oxygen-related endpoints like hypoxemia and brain hypoxia. Consequently, respiratory depression is monitored through respiratory patterns and $PaCO_2$. When simulating such perioperative conditions (Figure 4), our model recapitulated the clinical observations that the minute ventilation and $PaCO_2$ changes are similar between children and adults, as long as the fentanyl plasma concentration is the same. The more severe hypoxemia and brain hypoxia in children compared to adults could happen in accidental exposure situations at home or in the community, where mechanical ventilation and supplemental oxygen are not immediately available.

There are some limitations in our pediatric model. First, the lower age limit is 2 years old. Fentanyl (the main type of opioid investigated in this study) is predominantly metabolized in the liver by the cytochrome P450 enzyme CYP3A4,[30,31] the expression of which may differ from adults in the first 2–3 years of life.[32,33] In addition, we found that the reported physiological values (e.g., brain metabolism, blood flow) for those under 2 years old would result in unexpected ventilation patterns when simulating fentanyl injection in this age group (data not shown). More work is needed to extend our pediatric model to younger children.

Second, while we considered many physiological changes in children, the relationship between the fraction of fentanyl-bound opioid receptors and the decreased ventilatory drive was assumed to be the same as in adults. To estimate such a relationship in children, clinical studies will need to be conducted on pediatric subjects with enough fentanyl dosing to cause respiratory depression, which is ethically difficult. In contrast, the fact that our current pediatric model was able to predict fentanyl-mediated dose-dependent PaO_2 increase in perioperative pediatric patients (Figure 4) suggests it is reasonable to make such an assumption.

Lastly, although one of the original goals of this study was to evaluate dosing strategies of opioid antagonists like naloxone for pediatric subjects of accidental opioid overdose in a community setting, our current model is inadequate for this goal due to the lack of a pediatric PK model to capture the differences in plasma naloxone profiles between adults and children after administration of naloxone products. This is because we were unable to find readily usable clinical PK data on naloxone products in pediatric patients in the literature. The only study with such published time profiles[34] used mucosal atomizing devices to intranasally deliver a generic naloxone formulation, with a concentration (0.4 mg/mL) significantly lower than other intranasal naloxone products intended for community use,[35,36] using a dosing strategy with repeat nasal delivery that last as long as 2 min, and a sparse PK sampling strategy (the earliest time point is 5 min after the end of administration). These design factors limited the generalizability of the published data to evaluate the PK and PD of pediatric naloxone products in a community setting. We plan to incorporate pediatric naloxone PK into our model when such data becomes available.

In conclusion, our model represents the first attempt to systematically integrate age-dependent changes in fentanyl PK and respiration physiology into a quantitative framework to study the differential responses between children and adults, as well as among different age groups of children (2–12 years old), after fentanyl overdose. Our model reproduced previous clinical observations and supported the Society for Pediatric Anesthesia recommendations, that in a perioperative setting children and adults have similar risk of respiratory depression at the same plasma fentanyl concentration. However, our model also pointed out a possibility that in a community setting, without immediate ventilation support, children may have a higher risk of hypoxia and hypoxemia, even with the same plasma fentanyl concentration as adults. More work is warranted to evaluate the intervention strategies in a community setting to reduce the mortality rate of children due to fentanyl overdose.

AUTHOR CONTRIBUTIONS

S.C., B.T., J.M., A.C., X.H., A.D., J.F., D.S., and Z.L. wrote the manuscript; Z.L. designed the research; S.C. and B.T. performed the research; Z.L., S.C., and B.T. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interest for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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