Review article

UDC: 615.212.015:616-053.2
doi: 10.5633/amm.2023.0108

INFLUENCE OF PATIENT-RELATED FACTORS ON FENTANYL PHARMACOKINETICS IN CHILDREN

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Fentanyl is commonly used in a hospital setting for achieving sedation and analgesia in children. The aim of this review was to clarify the pharmacokinetic aspects of the intravenous fentanyl use in children.

In general, drug pharmacokinetics is altered in children at all levels, but there is a significant variability between children of different age, as well. After intravenous drug administration, the difficulties related to oral route and gastrointestinal absorption are avoided. Changes in drug distribution, metabolism and elimination are due to differences in the volume of extracellular and total body water compartments, organ perfusion, acid-base balance, membrane permeability and cardiac, liver and kidney function. Nevertheless, the greatest impact is attributed to the body size.

Children are the most vulnerable population. Therefore, it is of extreme importance to dose fentanyl safely, but efficiently as well. Common weight-based dosing strategy may not always be the optimal, due to numerous covariates of the fentanyl pharmacokinetics. In a certain clinical setting, beside hidden factors such as genetics, age and gestational age, obesity and potential drug interactions are the first to be taken into account. *Acta Medica Medianae 2023;62(1):56-61.*

Key words: *fentanyl, pharmacokinetic, children*

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Introduction

The importance of pain management lies in the fact that it is one of the most common acute symptoms and, therefore, one of the most common complaints. Primarily, it protects the organism from further damage, but this cannot be related to all types of pain. On the other hand, irrespectively on the type of pain, it affects the patient's quality of life. Managing pain in children is of the same importance, even though, historically, it was thought that the nervous system in neonates was not developed enough to sense pain. When the opiophobia is added into concern, for long, opioid analgesics were avoided in the pediatric population.

Nociceptive circuits are not like other sensory networks, dependant on external stimulation, so infants born even before 35 weeks of gestation have nervous system functional enough to sense pain stimuli (1). Nevertheless, it undergoes postnatal maturation, both peripherally and centrally. Therefore, its functionality greatly depends on the child's age. These changes also involve the endogenous opioid system. In adults, pain perception becomes modulated by mu-opioid receptors (MOR) activation, unlike in the younger age, so this type of signaling is stronger in children. Opioidergic stimulation, by endogenous or exogenous MOR agonists, has an important role in neuronal migration, differentiation and maturation (2). It is supposed that this process includes the development of supraspinal control over the spinal activity. The reaction of neonates to pain greatly differs form the one in the adults, and is described as either exaggerated or inappropriate, due to high activity of excitatory and low activity of the inhibitory neurons in the dorsal horns. The MOR is expressed in neonates both superficially and in deeper laminas of the dorsal horns. The later ones disappear with

age. These differences cause the age-dependent variability in sensitivity and selectivity of the opioid pharmacological actions (3, 4). Increased sensitivity may be explained by the expression of MOR in both A and C-fibres nociceptors, while they are, with age, confined to solely C-fibres (5).

Fentanyl is commonly used in a hospital setting for achieving sedation and analgesia in children. There is a wide range of fentanyl formulations, including parenteral, transmucosal and transdermal preparations. In the pediatric population, especially in the intensive care units, the preferred route of administration is parenteral (6). Therefore, the aim of this review is to clarify the pharmacokinetic aspects of the intravenous fentanyl use in children.

Fentanyl pharmacokinetics

As a relatively new opioid analgesic, introduced in 1963, the main difference from the previously used opioids was its lipophilicity. Greater lipophilicity provided faster absorption and greater distribution into brain tissue, leading to quicker and stronger effects, more than 100 times greater in comparison to morphine. It is primarily a MOR agonist, while it has lower affinity for kappa- and delta-opioid receptors. The half-life of the distribution into the central nervous system is 5 – 6 min, predominantly via passive diffusion enabled by its physical characteristics, but also by active transport. Primary distribution involves highly vascularized tissues, while during redistribution it may accumulate in muscle and adipose tissue, causing long elimination half-life (estimated at 3 – 8h). As a consequence of these pharmacokinetic properties, its pharmacological effects depend on the way of administration, bolus injection or continuous infusion (6, 7). Prolonged continuous infusion of fentanyl increases the context-sensitive half-time (8). Only 20% of fentanyl dose is available to distribution into tissues, due to high affinity for binding to plasma proteins. It is metabolized in liver by CYP3A4/5, therefore the inducers/inhibitors of this izoenzyme may affect the drug concentrations. Fentanyl metabolites are mostly excreted renally (6, 7).

Factors influencing fentanyl pharmacokinetics in children

In general, drug pharmacokinetics is altered in children at all levels, but there is a significant variability between children of different age, as well. After intravenous drug administration, the difficulties related to oral route and gastrointestinal absorption are avoided. Changes in drug distribution, metabolism and elimination are due to differences in the volume of extracellular and total body water compartments, organ perfusion, acid-base balance, membrane permeability and cardiac, liver and kidney function (9). Nevertheless, the greatest impact is attributed to the body size (10). The importance of elucidating factors affecting fentanyl pharmacokinetics in children lies in its relatively narrow therapeutic window. Concentrations inducing mild analgesia are estimated at 0.6 ng/ml, while 1.2-3 ng/ml concentrations are associated with substantial analgesia (11).

Both the volume of distribution (Vd) and fentanyl clearance decrease with age. Previous studies reported a wide range of Vd and clearance values in different age group. They are not all comparable due to different clinical settings and ways of drug administration, but their values gradually decreased with age in all the studies (12 – 18). The volume of distribution decreases form around 6 l/kg in neonates and infants to 2 - 4 l/kg in children above the age of 12. The clearance of fentanyl approaches the adult level after the age of 13 (12). Age-dependency is explained by higher metabolic elimination (larger liver volume and more intense blood flow through liver), but also by age-related differences in liver enzymes activity and fentanyl binding to proteins (8, 12). In preterm neonates, Vd was found to be higher than in at-term neonates, which is attributed to differences in body water/fat ratio and albuminemia (8). Clearance is lower in preterm neonates, increasing gradually after birth until it stabilizes after 10 – 15 days, emphasizing the importance of gestational age for the maturation of enzymatic activity (19).

Fentanyl is a highly lipophilic drug. Due to its distribution into adipose tissue, weight based dosing may be problematic and cause overdosage. Obesity is associated with higher Vd and lower weight-normalized clearance of fentanyl, but higher overall clearance. With similar weight-adjusted doses, higher concentrations were achieved in obese, but it took longer time to achieve steady state due to longer drug half-life. The differences between obese and non-obese are more prominent in older children. In these cases, the dosing strategy, without weight adjustments, resulted in similar steady state concentrations, but still with prolonged time to achieve maximum in the obese. The clearance increase is less than proportional to the body weight, due to non-weight-dependent clearance mechanisms (protein binding, intrinsic clearance). For lipophilic drugs such as fentanyl, some have proposed to use total body weight for loading doses and ideal body weight for maintenance doses. Therefore, the obese children would need lower doses adjusted for weight (12, 20). The same weight-based fentanyl dosing may not be optimal for each age—in an twice older infant with the same weight, equal dosing would lead to more than twice lower fentanyl concentration (10).

In adults, factors affecting liver function were confirmed to impact achieved fentanyl concentrations since CYP3A4/5 mediated metabolism is the primary route of fentanyl elimination (18). In children, this has not be confirmed due to low number of cases, but there were individual case reports or small studies describing the potential impact (8). It is assumed

that half of the adult's level of enzyme activity is reached at the age of 6-12 months (10). Increased intraabdominal pressure, present after abdominal surgery, decreases liver perfusion, and, therefore, diminishes drug clearance. Known CYP3A4 inhibitors, such as azole antifungal drugs, may increase fentanyl levels and risk of toxicity (18). The interactions confirmed in children leading to increased fentanyl metabolism include CYP3A4/5 inducers fosphenytoin and phenobarbital, often used in critically ill children (11). Genetic factors are described as a cause of interindividual variability in fentanyl metabolism, in children as well. Intermediate and poor metabolism, in carriers of CYP3A5*3 and CYP3A5*6 alleles (heterozygous and homozygous, respectively), were associated with significant decrease in fentanyl clearance (21). Other possible SNPs, confirmed in adult patients, include CYP2D6*9, CYP2D6*29 and CYP3A4*1B (22). Decreased fentanyl metabolism and increased availability may also be present in patients with decreased liver function, the state characterized by hypoalbuminemia, as well.

The relevance of albuminemia is questionable. Even though fentanyl has high affinity for albumin, not many studies have confirmed the influence of hypoalbuminemia, such as in burn patients. In children, neither liver nor renal failure were associated with changes in fentanyl pharmacokinetics (8).

Genetic and ontogenetic factors have strong impact on fentanyl pharmacokinetics, as previously described CYP3A4 polymorphisms. Fentanyl is a substrate of P-glycoprotein. This efflux transporter is involved in limiting the distribution of morphine and other opioids, besides fentanyl, to brain (9). The efflux via P-glycoprotein expressed at blood-brain barrier is lower in newborns leading to higher drug concentrations in the brain tissue and an increased sensitivity to opioids. This may last for 3 – 6 months, when the density of P-glycoprotein increases to the adult level (2, 23). Genetic variability of ABCB1 gens (rs1045642 AA genotype) was associated with lower fentanyl dose needed, due to low activity of the transporter (24).

Critically ill children

Pharmacokinetic analysis in critically ill children on mechanical ventilation has shown age-dependant variability in Vd, clearance and elimination half-life, similar to the other studies, but with greater interindividual variability (16). There is still a large percentage of unexplained variability in pharmacokinetic factors. In adult critically ill patients, the highest influence was in the following factors: liver disease, congestive heart failure and weight (11). The rate of fentanyl liver extraction has not been studied. On the other hand, commonly used drugs in critically ill children, such as anticonvulsive drugs phenobarbital, phenytoin, and its prodrug fosphenytoin, induce fentanyl metabolism in the liver, by inducing the transcription of CYP3A4/5 genes. The effect of co-administration of these drugs and metabolism induction is the most prominent after the end of fentanyl infusion, decreasing the half-life up to 30% and accelerating the drug clearance from the central nervous system. These facts imply the need of higher doses or infusion rates in patients administered CYP3A4/5 inducers, but extremely cautiously because of the high interindividual variability in fentanyl pharmacokinetics. At some instances, the achievement of lower steady-state concentrations may be even beneficial, when only moderate analgesia is needed, because of the lower risk of depressant adverse effects. On the contrary, depressant fentanyl effect is desirable in patients with severe lung disease or ventilator asynchrony, if used to facilitate mechanical ventilation (11). We can assume numerous other factors that may affect fentanyl pharmacokinetics in these circumstances, but up today, there are no valid evidence. They might include other inducers and inhibitors of CYP3A4/5 enzyme, other drug interactions involving drug transporters and plasma proteins, pharmacogenomics, vasopressor use, hepatic disease and intraabdominal pressure (11).

During cardiovascular procedures involving extracorporeal circulation, numerous factors change the pharmacokinetics of intravenous fentanyl. Hemodilution increases Vd, affects protein binding and increases elimination half-life. Liver function, both enzyme activity and perfusion, is decreased due to hypothermia and changes in Vd (25). Fentanyl may also be sequestrated in lungs. Besides, drug molecules may bind to extracorporeal circuit components diminishing fentanyl availability, even up to 60 – 90% (8, 26, 27). It is supposed that the membrane oxygenator is the primary point of the drug binding, while the siliconized tubes have lesser importance. The proportion of the drug sequestered is a lot higher in children, compared to only 10% in the adults, due to higher circulation rate (26).

Drug pharmacokinetics changes greatly in patients with burns. There is a substantial increase in the volume of intra and extracellular fluid due to increased capillary permeability, but because of the fluid administration as well. Consequently, interstitial edema occurs, and the drug abundantly diffuses into the extracellular compartment, especially in the burned area (28). Within hours after the injury, the volume of the interstitial fluid is doubled. This increase lasts for 36 – 48h until the unburnt tissues have been affected by proinflammatory mediators. Systemic consequences of the burn injury are seen in all patients with more than 25% of body surface affected (29). One week after the burn injury, and during the following month, fentanyl Vd is increased with lower plasma concentrations achieved, which is partially influenced by the increased clearance and increased cardiac output (22, 28). The hypermetabolic state in burn patients is associated with decreased systemic vascular resistance, increased cardiac output, and therefore, the increased blood flow through the elimination organs and increased clearance by almost 50%. On the other hand, liver function is often impaired after

major burns (28). This may explain smaller impact of fentanyl clearance on its plasma concentration. Decreased albuminemia in this second phase leads to an increase in free drug concentrations enabling it to be easily distributed and eliminated (29). This clinical situation increases the risk of pharmacokinetic interactions with fentanyl, since there is a great need for the antimicrobial treatment, especially with drugs that are expected to induce or inhibit fentanyl metabolism. All these pharmacokinetic changes have not been confirmed in pediatric population with burn injuries, but previous studies have shown great variability in the pharmacokinetic parameters. The impact of all the proposed factors is yet to be determined (18).

Conclusion

Children are the most vulnerable population. Therefore, it is of extreme importance to dose fentanyl safely, but efficiently as well.

Due to the ethical problems, as well as to the great intragroup variability, previous studies are not consistent in estimating the pharmacokinetic parameters, as well as in determining the significance of the factors influencing fentanyl pharmacokinetics. Common weight-based dosing strategy may not always be the optimal, due to numerous covariates of the fentanyl pharmacokinetics. In a certain clinical setting, beside hidden factors such as genetics, age and gestational age, obesity and potential drug interactions are the first to be taken into account.

Acknowledgement

The work resulted from a project led by Prof. Dr. Goran Marjanović, approved by the Ethics Committee, entitled: "The influence of immunomodulatory and pharmacokinetic properties of fentanyl and alfentanil on the variability of the therapeutic response in the postoperative period in pediatric patients".

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Pregledni rad **UDC: 615.212.015:616-053.2**
doi: 10.5633/amm.2023.0108

FARMAKOKINETIKA INTRAVENSKE PRIMENE FENTANILA KOD DECE

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Fentanil se obično koristi intrahospitalno za postizanje sedacije i analgezije kod dece. Cilj ovog pregleda jeste razjašnjenje farmakokinetičke aspekte intravenske upotrebe fentanila kod dece.

Generalno, farmakokinetika leka je promenjena kod dece na svim nivoima, ali postoji značajna varijabilnost i između dece različitog uzrasta. Nakon intravenske primene leka, izbegavaju se poteškoće u vezi sa oralnim unosom i gastrointestinalnom apsorpcijom. Promene u distribuciji leka, metabolizmu i eliminaciji su posledica razlika u zapremini ekstracelularnog i ukupnog telesnog vodenog odeljka, perfuziji organa, acido-baznoj ravnoteži, permeabilnosti membrane i funkciji srca, jetre i bubrega. Ipak, najveći uticaj pripisuje se veličini tela.

Deca su najugroženija populacija, pa je zbog toga od izuzetnog značaja da se fentanil dozira bezbedno, ali i efikasno. Uobičajena strategija doziranja zasnovana na težini možda nije uvek optimalna, zbog brojnih kovarijata farmakokinetike fentanila. U određenom kliničkom okruženju, pored skrivenih faktora, kao što su genetika, starost i gestacijsko doba, gojaznost i potencijalne interakcije sa lekovima, prvo se uzimaju u obzir. *Acta Medica Medianae 2023;62(1): 56-61.*

Ključne reči: *fentanil, farmakokinetika, deca*