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Novel pharmacology of anesthetic agents in neonates and pediatrics

Bita Malekianzadeh MD, Pediatric Anesthesiologist, TUMS

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About the Speaker



- Bita Malekianzadeh, MD
- Pediatric Anesthesiologist
- Children’s Medical Center, Tehran University of Medical Sciences
- Research and clinical focus: Pediatric anesthesia, Cellular and molecular anesthesia, Regional anesthesia

Outline

1. Background and problem
2. Review of current evidence
3. Main findings
4. Clinical application
5. Conclusion and questions

The pharmacological management of anesthetic agents in pediatric patients



Adequate depth of anesthesia and appropriate analgesia during surgery, while ensuring a calm and complication free emergence

- Respiratory : apnea, decreased respiratory drive
- Cardiovascular: hypotension, bradycardia,
- CNS: seizure, emergence agitation
- Metabolic: hyperkalemia, hypoglycemia
- Neuromuscular: prolonged muscular block
- Thermoregulation: hypothermia, MH
- Allergic reactions
- Prolonged effects: neuroapoptosis

Remember
Pharmacokinetics & Pharmacodynamics

- **Pharmacokinetics**: How the *patient/body affects* the drug or how drug concentrations in the body change over time
  - Altered by immature kidney or liver function
  - Altered by protein binding
  - Altered by body composition (fat/muscle/total body fluid/ volume of distribution)

- **Pharmacodynamics**: How the *drug affects* the patient/body
  Sensitivity in small children

Drug distribution in neonates

Remember

Acidic drugs bind mostly to **albumin,** e.g diazepam or barbiturates

Basic drugs bind to globulins, lipoproteins, and **plasma alpha-1-acid glycoproteins,** e.g. lidocaine or alfentanil

Drug distribution in neonates

- Neonates have **reduced total protein & albumin** levels – result: ***increase*** levels & effect from "unbound" medications
- Neonates have **reduced clearance** of drugs from decreased renal/hepatic clearance – result: ***increase*** medication levels
- Neonates have **increased volume of distribution** of drugs (increase in total body water) – result: ***decrease*** medication levels

Body composition

Preterm & term infants have larger % body water than older children

-Result - overall, **increased loading dose**

-larger distribution volumes for water-soluble drugs & smaller for lipophilic drugs

Preterm and term infants have less muscle & fat

-Less area for redistribution = **prolonged peak blood concentrations**

-Example: opioids with prolonged sedation/respiratory depression

Metabolism

- Reduced function & blood flow to liver in infants

- Drugs dependent on **liver** glucuronidation:
  - Morphine, acetaminophen, dexmedetomidine,
- Different enzyme system mature at different rates.
- Glomerular filtration & tubular function fully **mature by 12 to 24 months of age**

  -Aminoglycoside & cephalosporin antibiotics have prolonged duration of action in neonates

- Extrahepatic
  - **Nonspecific esterases** in tissues & erythrocytes are **mature at birth**
  - No change in remifentanil and succinylcholine clearance

- Basic pharmacokinetic–pharmacodynamic studies in otherwise healthy children are necessary before studying those children who have greater vulnerability : neonates, infants, or critically ill children
- These vulnerable populations require specialized dosing to account for their distinct pharmacokinetics and heightened sensitivity to anesthetic agents.

Important pharmacological rule

- A simple weight-based dose does not always predict drug exposure
- Age, body composition, maturation, disease and organ failure must also be considered



Weight- based versus Effect- based dosing

- Weight- based dosing: establish an initial dose, standardized and reproducible, does not account for individual sensitivity, Examples: propofol induction, antibiotics, local anesthetics
- Effect-based dosing: dose adjusted according to clinical response, achieve the desirable clinical effect, individualized treatment, requires appropriate monitoring, Examples: propofol maintenance, opioids and neuromuscular blockers

Neither weight-based dosing alone nor effect-based dosing alone is appropriate for every anesthetic drug



ONE IMPORTANT POINT

We should not simply reduce anesthetic drug doses to prevent adverse effects

Underdosing can cause: inadequate anesthesia, awareness, movement and physiological stress

The goal: lowest effective individually titrated drug exposure that provides safe and adequate anesthesia

Precise dosing

The requirement for adequate and readily controlled depth of anesthesia and the foremost importance of patient safety have shifted the anesthetic drug development paradigm.

The recent trend towards a ‘soft drug’ design, defined by rapid onset of action and recovery, increased therapeutic index and predictable metabolism to inactive metabolites



- Total intravenous anesthesia (TIVA) reduces emergence delirium, postoperative nausea and vomiting, and perioperative respiratory adverse events while supporting neurophysiologic monitoring.
- Universal target-controlled infusion (TCI) models and PK-EEG strategies improve dosing accuracy and safety, particularly in neonates and infants.
- Processed EEG (pEEG) indices such as BIS are unreliable in infants, especially under 1 year of age, up to 70% of adequately anesthetized infants exhibit falsely elevated BIS values during sevoflurane anesthesia or TIVA, often prompting unnecessary propofol escalation

Review > Curr Opin Anaesthesiol. 2026 Jun 1;39(3):304-316.
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Update on total intravenous anesthesia in children

Vinícius Caldeira Quintão [1 2 3], Ricardo Vieira Carlos [2 3], Britta S von Ungern-Sternberg [4 5 6 7]
Affiliations + expand
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Abstract

Purpose of review: To summarize recent evidence in pediatric total intravenous anesthesia (TIVA), highlighting advances in pharmacokinetics-pharmacodynamics, target-controlled infusion (TCI), electroencephalography (EEG)-guided titration, emerging agents, safety, and sustainability, and to provide clinicians with an updated, practical framework for pediatric TIVA practice.

Recent findings: Recent evidence highlights major advances in pediatric TIVA, including clearer developmental pharmacokinetic-pharmacodynamic patterns, refined propofol-remifentanil dosing, and growing use of dexmedetomidine. Remimazolam shows promise but currently has limited pediatric evidence. Universal TCI models improve dosing accuracy across ages, while EEG-guided and combined pharmacokinetics-EEG strategies enhance safety in infants. TIVA reduces emergence delirium, postoperative nausea and vomiting, and perioperative respiratory adverse events; supports neurophysiologic monitoring; and yields substantially lower environmental greenhouse gas emissions than inhalation anesthesia.

Summary: Pediatric TIVA is moving toward greater precision, safety, and sustainability. Moderate effect-site targets, opioid titration, and early down-titration remain central, particularly in neonates. Propofol infusion syndrome is exceedingly rare, and organ-protective effects of TIVA are reported in major surgery. Despite clinical and environmental advantages, adoption varies globally due to limited training, variable pump availability, and regulatory barriers. Expanding structured education and pediatric-specific TCI tools is essential for broader implementation.

Keywords: drug dose– response relationship; intravenous anesthesia; pediatric anesthesia; perioperative complications; perioperative outcomes; sustainable development.

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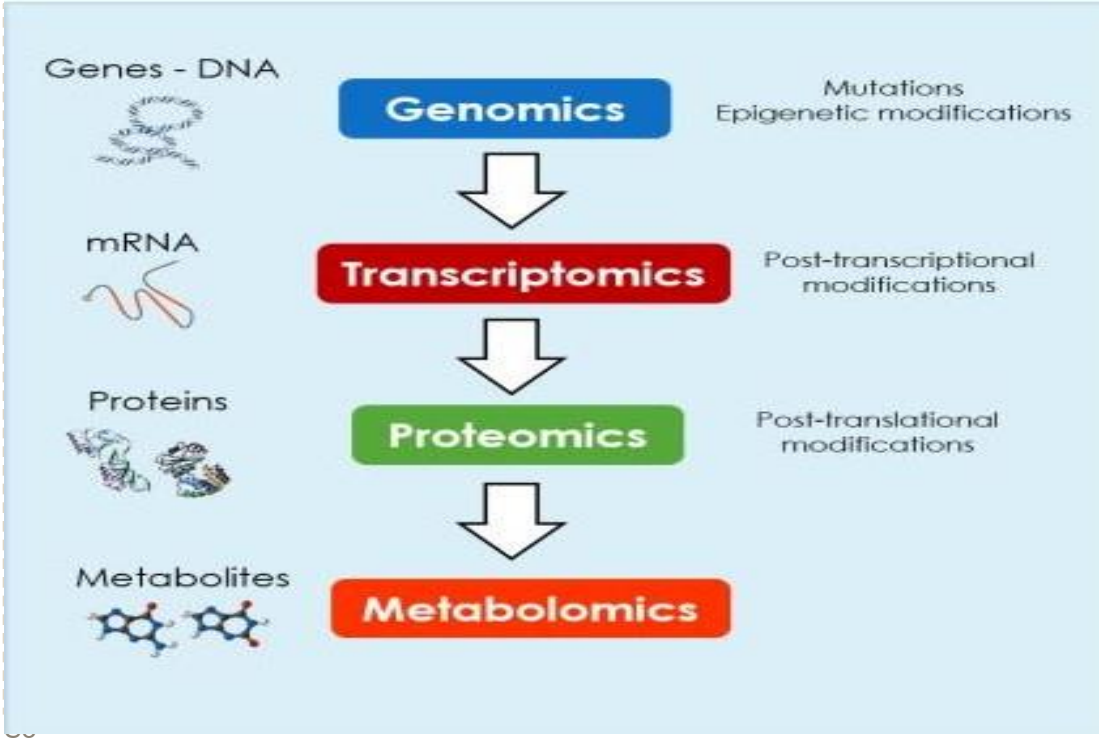
omics

Our knowledge of pharmacogenetics related to anesthetic agents is expanding. Widespread acceptance of personalized medicine is on the horizon.

We will learn how to overcome challenges to integration and produce actionable clinical pharmacogenetic guidelines for anesthetic drugs.



These **omics levels** are **highly interconnected**, forming a complex network of biological regulation and response.

omics

Pharmacogenetics – use of patients' genetic information to guide drug therapy, is emerging as a major component of personalized medicine and targeted interventions. Completion of the human genome project has allowed for an increasing number of drug–gene pairs to be characterized. Over 300 drugs now contain pharmacogenetic information on their labels and nearly 100 drugs have dosing guidelines based on pharmacogenetics. Pharmacogenetics in anesthesia and pain medicine is a growing field with an expanding body of actionable evidence

Gene	Drug(s)
BCHE	Succinylcholine, mivacurium
RYR1	Sevoflurane, isoflurane, desflurane
CACNA1S	Volatile anesthetics
CYP3A5	Midazolam
CYP2D6	Codeine, tramadol
CYP2D6	Ondansetron

Practical approach

- Family history
- Previous anesthetic surgery
- Genetic testing
- Medication selection
- Monitoring

Anesthetic neurotoxicity
What has changed in 2026

- Clinical studies provide substantial reassurance that a single, relatively brief exposure to general anesthesia in otherwise healthy young children is not associated with clinically meaningful impairment in general intelligence;
- Anesthetic drug neurotoxicity is an important and evolving topic in pediatric anesthesia particularly in neonates, infants and children younger than 3 years.

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Paediatric anaesthesia and the developing brain

Assist Prof Jean-Philippe Salaün, MD PhD [a,b,c] · Peter Frykholm, MD PhD [d,*] · Prof Nicolas Poirel, PhD [e,f,*] · Prof Sulpicio Soriano, MD [g,*] · Mary Ellen McCann, MD MPH [g,*] · Britta S von Ungern-Sternberg, MD PhD [h,i,j,k] · et al. Show more

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Show Outline

Summary

Concerns persist regarding the potential long-term effects of general anaesthesia on brain development in children. This narrative review summarises recent preclinical and clinical evidence (2019–25) and updates consensus messages. Preclinical studies show that commonly used anaesthetic agents can interfere with neurodevelopmental processes during vulnerable developmental periods. Clinical evidence is less clear. Randomised trials indicate that a single, short exposure in infancy is not associated with measurable impairment in cognitive outcomes, whereas observational studies report mixed findings. Several large population-based studies consistently identified a small, increased risk of attention-deficit hyperactivity disorder following early exposure to general anaesthesia. Emerging evidence also suggests modifications in visual development and processing, including preferential processing of global visual information, although these findings remain preliminary. Interpretation is limited by confounding related to surgery, comorbidity, and environmental factors. Communication with families should emphasise acknowledgment of parental concerns, individualised anaesthetic care, physiological stability, and that necessary procedures should not be delayed because of theoretical neurodevelopmental risks.

novel general and local anesthetics should be designed with anesthesia-induced developmental neurotoxicity in mind.

REMIMAZOLAM: A NOVEL ULTRA-SHORTACTING BENZODIAZEPINE

- Superior hemodynamic stability
- Reduced emergence delirium compared to standard agents
- It is not a universal replacement for established anesthetics
- Its use in specific clinical scenarios, particularly for preventing post-sevoflurane emergence delirium and in hemodynamically unstable patients.
- Absence of infant and long-term neurodevelopmental safety data necessitates continued research before widespread adoption.

ETOMIDATE ANALOGS: A QUEST FOR CARDIOVASCULAR AND ADRENAL SAFEGUARD

- A different line of research developed ET-26 hydrochloride (ET-26HCl), another etomidate analog currently approved for clinical trials in China. Early research showed that ET-26HCl preserved the rapid onset and hemodynamic stability of parent compound etomidate with very little adrenocortical suppression, which was comparable to that of CPMM. The hemodynamic and adrenal stability together with superior myocardial performance following ET-26HCl administration
- Two of the etomidate analogues, CPMM and ET-26HCl, are currently being investigated as intravenous anesthetics with less adrenocortical suppression while maintaining hemodynamic stability.
- Non of these investigational analogues can currently be recommended as a routine replacement in pediatric anesthesia.

QUATERNARY LIDOCAINE DERIVATIVES: NOVEL DEVELOPMENTS IN REGIONAL ANESTHESIA

In contrast to the recent trends in general anesthetic development where the focus is on quick ‘on’ and ‘off’ effects and rapid metabolism, which allows for greater anesthesia control and easier titration, recent advances in the development of local anesthetics have focused on increasing the duration of action while keeping the systemic adverse effects to a minimum.

XENON: AN ANESTHETIC-SPARING AGENT

Xenon production is especially costly; the favorable cardiovascular profile and potential neuroprotective properties could mean that the use of xenon as an adjuvant anesthetic might increase in the upcoming years.

Further human studies are needed; the technical feasibility of xenon anesthesia and substantial preclinical evidence might bring this almost forgotten anesthetic back in the operating rooms.

Cipepofol (ciprofol)

- Less injection pain
- Improved hemodynamic stability
- Rapid onset
- Rapid recovery

Green anesthesia

- The practice of delivering safe and high-quality anesthetic care
- Minimizing the environmental impact of anesthesia drugs
- TIVA, low flow anesthesia, regional anesthesia

Opioid sparing and Opioid free strategy

Key Message

The right drug,

at the right dose,

for the right child,

at the right developmental stage

Future

- Genomic pharmacology in practice
- Novel drugs: ciprofol, etomidate analogues,..
- Equipment improvement: Pediatric TCI , EEG,..



Take-Home Messages

1

One dose does not fit all, move to individualized dosing

2

Consider both Weight-based and effect -based dosing

3

Novel anesthetic agents and drug delivery strategies may improve hemodynamic stability, faster recovery, better analgesia and fewer adverse effects

References

1.Useinovic N, Jevtovic-Todorovic V. Novel anesthetics in pediatric practice: is it time? Curr Opin Anaesthesiol. 2022 Aug 1;35(4):425-435. doi: 10.1097/ACO.0000000000001156. Epub 2022 Jul 5. PMID: 35787582; PMCID.

2.PMacfarlane AJR, Gitman M, Bornstein KJ, et al. Updates in our understanding of local anaesthetic systemic toxicity: a narrative review. Anaesthesia 2021; 76(Suppl 1):27–39MC10104442.

3. Packiasabapathy S, Rangasamy V, Horn N, Hendrickson M, Renschler J, Sadhasivam S. Personalized pediatric anesthesia and pain management: problem-based review. Pharmacogenomics. 2020 Jan;21(1):55-73. doi: 10.2217/pgs-2019-0108. PMID: 31849281; PMCID: PMC7132778.

4.Quintão VC et al. Update on total intravenous anesthesia in children. Curr Opin Anesthesiol. 2026;39:304–316

5. Smitht's Anesthesia for infants and children,10 ed, 2022

6. Zhang Y, Chen Q, Wang L, Zeng Q, Cui H, Guo S, Xiang F, Mo Y. Remimazolam in pediatric anesthesia: a systematic review for clinical decision-making. Front Pediatr. 2025 Sep 23;13:1662752. doi: 10.3389/fped.2025.1662752. PMID: 41064632; PMCID: PMC12500429.

7.Satoshi Kimura, Moritoki Egi, Remimazolam in pediatric sedation and anesthesia: current perspectives and clinical considerations, *Journal of Intensive Care* *2026 April 15*

8. Personalized Medicine in Anesthesia, Pain and Perioperative Medicine, 2020

9.A Practice of Anesthesia for infants and Children, 7th edition, 2024

Thank You for Your Attention

bmalekianzadeh@sina.tums.ac.ir