Chapter 7
Pediatric Personalized Anesthesia

Bita Malekianzadeh

Introduction

Neonatal and pediatric anesthesia is an important issue. Because this group of population is in growth and developmental stages, they are prone to perioperative complications. Millions of pediatric surgeries are annually performed worldwide. In the USA, 6 million children undergo surgery each year, among them, 1.5 million are infants. Different drugs are used in daily practice by pediatric anesthesiologists. The safety margin of these drugs is very narrow and anesthetic agents can produce various responses in different children. Combining anesthesia agents to achieve ideal anesthesia with minimal complication is still considered a challenge in pediatric patients. Traditional approaches do not always lead to an ideal clinical response. Another important aspect in pediatric anesthesia is the issue of potential effects of anesthetic drugs on developing brain; the FDA has announced some warnings about neuroapoptosis in children younger than 3 years old and fetus of pregnant women during their third trimester who undergo repeated or prolong general anesthesia or sedation.

Personalized medicine has created a revolution in the practice of anesthesia and perioperative care especially regarding its paramount role in pediatric patients. Recent advantages in omics science have opened a new horizon in pediatric medicine (Ama et al. 2010; Galinkin et al. 2010; Chidambaran et al. 2012; Andropoulos and Greene 2017).

In this chapter, the basic and current understanding of pharmacogenomics, epigenomics, proteomics, metabolomics, and interactomics relevant in perioperative practice for infants and children are discussed.

Some aspects of this question will be addressed: why the similar patients have very different perioperative responses and complications?

B. Malekianzadeh (✉)
Anesthesiology Department, Children's Medical Center,
Tehran University of Medical Sciences, Tehran, Iran

A. Dabbagh (ed.), *Personalized Medicine in Anesthesia, Pain and Perioperative Medicine*, https://doi.org/10.1007/978-3-030-53525-4_7

Nowadays, it is believed that each child is unique, and he/she should benefit from the best perioperative care.

Preoperative Care

The Goal of Providing Preoperative Anesthetic Care

Newborn infants, babies, and children are special population groups that should be given special attention during the pre-operative visits. Proper evaluation and preparation in this group of patients before surgery are of significant importance. One of the purposes of visiting patients before the surgery is to identify factors, which may increase the risk of anesthesia and by administering the interventions, this risk can be lowered. The second purpose is to establish a relationship between the anesthesia specialist and the patient and his parents, which can help to relieve the patient's stress before the surgery, which can, in turn, improve the outcome. The condition of the patient and his/her family should be optimized (Serafini et al. 2014; Basel and Bajic 2018).

Monitoring

Traditional Approach

Throughout the pre-operative care, a number of laboratory tests are requested according to the patients' conditions and clinical examinations, and anesthesia plan should be prepared for each patient. Pre-operative evaluation starts with examining patients' history. For this purpose, patient and his family were interviewed and any current disease and his past medical history were recorded. Issues such as cholinesterase deficiency, malignant hyperthermia, and other side effects of anesthesia in the patient and his family are scrutinized. Also, the patient and his family's smoking history, record, medicine use, and detailed account of their allergies are important. In the review of system and physical examination, pre-maturity, BPD, airway problems, cardiovascular, pulmonary, musculoskeletal, gastrointestinal, kidney, hematology, oncology, metabolic, and endocrine were evaluated and the patient's circumstances according to his underlying disease, and optimized and the necessary paraclinical tests are requested.

It seems that conducting laboratory tests on a regular basis before the operation cannot significantly affect patients' outcome; and the tests selected based on the patients' history, circumstances, and operation type can have a more positive effect.

Routine hemoglobin for most elective operations have no indications and it is usually measured in patients who are quite expected to bleeding during the

operation, patients with hemoglobinopathy, pre-term neonates, and infants under 5–6 months. Coagulation tests including counting the number of platelets, INR (international normalized ratio), PTT (partial thrombin time) are not recommended for patients who have no coagulopathy, as it cannot be an accurate criterion in identifying the patients at the risk of bleeding. These tests can be employed before major reconstruction operations, patients with bleeding history, or for tonsillectomy at some centers (Bamedi et al. 2017; Bogusaite et al. 2018; Nelson et al. 2018; Zhong et al. 2018).

Current risk stratification, which can be determined based on the history and patient examination comorbidities, and the operation circumstances account for only a small part of the issues involved perioperative (Bilkey et al. 2019).

Personalized Medicine Approach

Adverse drug reaction (ADR) in children due to their pharmacokinetic and pharmacodynamic complexity during development, is an important issue. Genetic differences among people can determine the susceptibility to perioperative events. Genetic is equal to 20–95% of individual differences in response to the medicines. Personalized pre-operative evaluation should be started before the operation. Regarding, this is quite novel about children and new-born babies. As the human genome project completed, it is hypothesized that the treatment can be administered according to precise molecular changes. Although genomic discoveries have affected different areas of medicine such as cardiovascular, neurologic system, metabolic diseases, and cancer, it has not been paid attention in the anesthesia field (Nashibi et al. 2016; Mottaghi et al. 2017; Safari et al. 2017). It seems that it is the ripe time for all the pediatric patients to have gene sequence as a standard preoperative workup just similar to the other experiments as follows: hemoglobin, electrolytes, etc. Every person undergoes this experiment once in his lifetime, and its results can be used forever. In the future, the specific functions of pharmacologic can be determined using one blood sample; and accordingly, the right decisions can be made on drug prescription and proper dosage. The process of taking care of patients and the clinical outcome will improve the use of this approach (Gabriel et al. 2017; Iravani et al. 2017; Bilkey et al. 2019; Sezari and Dabbagh 2019).

Point of care test (POCT) includes the tests performed near the patient and frequently at the bedside. So far, perioperative POCT has included the following: arterial blood gas monitoring, chemistry, the co-oximetry panel, parathyroid hormone assay, and coagulation testing such as thromboelastometry (ROTEM), thromboelastography (TEG) (Rhee and Kahn 2010; Shaw 2016; Arboleda and Garner 2017).

This technology is developing in recent years, and it has been used by some companies to analyze genetic polymorphism that can affect drug metabolism. The practical example is CYP2D19 analysis, which activates clopidogrel. CYP2D19 different alleles impair the enzyme's ability to metabolize the drug and lead to side effects (Roberts et al. 2012; Naderi et al. 2016).

POCT (Point of Care Testing) is so helpful for the anesthesiologist to make a perioperative quick decision due to the rapid preparation of results. However, there may be some concerns about its accuracy. POCT is performed by the clinical staff, not by trained laboratory personal, but if it is done with controlled quality, it can be very practical (Shaw 2016).

PG screening can be directly transferred to EHR (electronic health record). By studying and examining the Electronic Health Record, anesthesia specialist can prescribe the drugs with respect to the patients' pharmacologic and can also employ preoperative pharmacogenomic in the daily practice (Gabriel et al. 2017; Iravani et al. 2017; Bilkey et al. 2019; Rahmatizadeh et al. 2020).

The reasons for patients readmission to the GOLDILOKs (genomic and ontogeny-linked dose individualization and clinical optimization for kids) clinic from 2010 to 2016 has been studied, respectively. In addition to other causes, ADRs (adverse drug reactions) and inappropriate response to medication was important referral cases. Most patients were Caucasian men. In these patients, pharmacogenetics was widely used as a treatment guide. The patients were evaluated by multidisciplinary pediatric personalized medicine. However, pharmacogenetic tests are not the only means of precision treatment in children; and the identification of many pharmacodynamics errors such as drugs interfere with the receptor, is not available (Sandritter et al. 2019).

Single nucleotide polymorphism (SNP) is a substitution of a single nucleotide that occurs at a specific position in the genome. SNPs are the most genetic variations among individuals and can cause susceptibility of individual differences to certain diseases such as thalassemia, sickle cell anemia, and cystic fibrosis. A polymorphism can affect the drug action at any organ of the body. Polymorphism can be in the form of SNP, as a substitution of a single nucleotide base pair on an entire chromosome to multiple inherited linked base pair changes (a haplotype). A single nucleotide polymorphism can alter the absorption, metabolism, drug transport, or receptor site; and has a profound effect on the drug action. The function of some perianesthetic drugs is altered by gene polymorphism (Table 7.1) (Shenfield 2004; Galinkin et al. 2010; Dabbagh and Rajaei 2013).

Premedication

The Traditional Drugs

Benzodiazepines: midazolam is a benzodiazepine with rapid onset; however, it has short effects. It is frequently used in pediatric anesthesia as oral premedication. Through binding GABA in CNS, midazolam has sedative, anti-stress, amnesia, and hypnotic effects. Children show quite different reactions to midazolam. It is quite likely that it serves as a stress-reliever; however, it has not proven to be effective in another patient or even side effects such as paradoxical reactions may be observed (Shin et al. 2013b; Pacifici 2014).

Table 7.1 Clinically relevant gene polymorphism of perioperative anesthetic drugs

Drug	Gene	Effect of polymorphism
Midazolam	CYP3A4 CYP3A5	Clearance reduction
Dexmedetomidine	CYP2A6 ADR2C	Lower efficacy
Propofol	UGT1A9 5HT2A	Higher induction dose Shorter onset time
Ketamine	CYP2B6	Decreased metabolism
Inhalation agents	CYP2E1	No significant clinical effect
N2O	MTHFR	Homocysteine elevation
Fentanyl	CYP3A4	Variation in drug response
Local anesthetics	SCN5A	LA resistance
Succinylcholine Mivacurium	Bche	Clearance reduction
Rocuronium	SLCO1B1 ABCB1	Prolonged recovery time
NSAIDS	CYP2C9 CYP2C8	Metabolism reduction
Ondansetron Granisetron	CYP2D6 multicopy	Rapid metabolism

Midazolam is metabolized into its active metabolite, and 1-hydroxymidazolam in the liver by CYP3A4 and CYP3A5 enzymes. These enzymes are not very active in the first weeks of life and the metabolism rate of midazolam is lower in infants compared to older children and adults. The meta-analysis of seven clinical trials showed that environmental factors exert a stronger influence on midazolam deposition compared to CYP3A4/5 (Miao et al. 2009).

However, other studies have shown that CYP3A can affect the pharmacokinetics of midazolam. The effect of genetic polymorphism of CYP3A on midazolam pharmacokinetics was studied in Asian patients suffering from cancer. The results showed that clearance of midazolam for CYP3A*5 with (1*/1* or 1*/3*) expressories were 22% lower than CYP3A5 *3 expression and homozygotes (CYP3A5 1*/1* is the normal genetic status of the enzyme) (Seng et al. 2014). Shin et al. reported that the clearance of intravenous midazolam is reliably dependent on CYP3A5 *3 (Miao et al. 2009).

The impact of CYP3A5 *3 on clearance of midazolam in basal, induced and inhibited conditions were examined. CYP3A5 genotype had no significant effect on midazolam pharmacology under the basal and induced conditions. However, under inhibited conditions created by using Itraconazole in this study, participants carrying CYP3A5 *1 were less likely to undergo clearance changes. People carrying CYP3A5 3*/3* experienced a more significant drop in systematic clearance compared with 1*/1* (Yu et al. 2004).

CYP3A4 is the main CYP in the liver and intestine of human beings and can play a key role in the metabolism of many drugs. This enzyme has many variations in the

public. A new allele, CYP3A4* 22rs with a frequency of 5–7 % in the Caucasian population is accompanied by a drop in CYP3A4 expression and the enzyme activity, and affects statin, tacrolimus, and cyclosporine metabolism. CYP3A4* 22 results in a drop in midazolam metabolism in patients suffering from cancer.

In people carrying CYP3A4* 22, 20.7% lower than CYP3A4 1*/1* and for CYP3A5 *3 and CYP3A4 *22, there is a 38.7% drop in the rate of metabolism of midazolam. In children with CYP3A5 *3 and CYP3A4* 22, a drop in the metabolism of midazolam and its longer-lasting effect was observed (Elens et al. 2013).

Oral lorazepam and temazepam are useful sedatives in older children. Diazepam does not have a clinical application for this purpose, because of its prolonged duration of action (Ronaghi et al. 2016; Chennou et al. 2019; Dave 2019).

Ketamine: ketamine is an NMDA receptor antagonist, used for pediatric premedication. It is an effective sedative and analgesic but isn't amnestic. Ketamine can also cause nausea and vomiting, psychological disturbance and prolonged recovery. Its intramuscular injection used as premedication in uncooperative and combative children (Yuen and Bailey 2018).

There are individual differences, especially regarding the effects of ketamine analgesia. Ketamine is metabolized to its active metabolite, norketamine, through CYP2B6 and CYP2A4 in the liver. CYP2B6 is the major isoform that metabolizes ketamine. The CYP2B6 coding gene is highly polymorphic. The CYP2B6*6 is the most common CYP2B6 gene allelic variant that decreases ketamine clearance and explains the many differences in steady-state ketamine concentration. In chronic pain patients who treated with ketamine, this allele has been associated with a marked decrease of ketamine clearance and an increase in its complications (Li et al. 2015; Cook-Sather et al. 2016; Dinis-Oliveira 2017).

Opioids: the use of opioids is uncommon as premedication in healthy children. Dysphoria, nausea and vomiting, pruritis and respiratory complications should be considered. Oral transmucosal fentanyl citrate has a rapid onset and it is effective as midazolam, however, preoperative opioids use is limited to children with pain. The OMICS approach for opioids will be discussed later, in the analgesia section (Chatrath et al. 2018).

The newer clinical agents: Alpha-2-Adrenoreceptor agonists: dexmedetomidine is employed for creating light sedation and analgesia. It is a highly selective α2 agonist that has been paid lots of attention by children pediatric anesthesiologists as it maintains breathing and causes no apnea. Clonidine is an older alpha2 agonist with a longer duration of action. Hypotension and bradycardia may occur, however, its incidence in the preoperative setting is low (Dabbagh 2011; Moghadam et al. 2012; Jabbary Moghaddam et al. 2013; Su et al. 2016; Afshari 2019).

There are significant differences in sedation caused by dexmedetomidine among people, which is associated with genetic differences. The metabolism of dexmedetomidine is mainly dealt with CYP2A6, α2 adrenoreceptor (ADRA2C, ADR2B, and ADR2A), and UGT (UGT1A4, and UGT2B10). The variance of ADRA2C1291 is related to a longer onset time effect and lower efficacy of dexmedetomidine (Le et al. 2011; Dahmani et al. 2014; Holliday et al. 2014; Andropoulos 2018; Zhou et al. 2018a).

Preoperative Risk Stratification

Over the past decades, different models have been developed to improve pediatric perioperative mortality and morbidity prediction, especially in noncardiac surgeries. Risk stratification scores are estimated by considering the patient's comorbidity and intrinsic risk factors of surgery. The patient's age, prematurity, presence of at least one of the comorbidities (respiratory disease, congenital heart disease, renal insufficiency, neurologic disease, hematologic disease) and urgent surgery are the main items for this purpose; however, the risk assessment tools have a limited mortality and morbidity prediction (Valencia et al. 2019; Nasr et al. 2016).

Omics can be potentially used for individual ***perioperative risk stratification*** in many patients. MicroRNAs are small, non-coding RNAs that regulate gene expression in a specific way. Their function as post transcription regulators is to interfere with target mRNA. Binding of microRNA to protein coding transcripts can prevent the translation of mRNA into a functional protein. In fact, miRNAs mainly act as negative regulators. MiRNAs are involved in all physiological processes including differentiate, proliferation, metabolism, homeostasis, apoptosis, and inflammation. Many of these processes are important in anesthesia and critical care (Zeng et al. 2014; Neudecker et al. 2016).

The role of miRNA transcription in personalized medicine has been considered increasingly much more crucial. Patterns of miRNA emergence suggest new diagnoses, as well as new therapies to target miRNA. Different drug approaches addressing miRNAs are being evaluated in the treatment of various diseases. In pre-operative field, miRNA can be used as preoperative biomarkers to stratify the risks and complications during and following surgery and specific organ damage. Using this risk indicator can help optimizing the anesthesia and operation conditions, and prevent acute organ damage and severe inflammatory responses. MiRNAs can be employed in the daily practice of anesthesia and critical care for different patients (Twaroski et al. 2014). The role of miRNA in neuroprotection has been studied in various studies and it can be of significant importance in the field of infants and children anesthesia (Huang et al. 2014).

Shortly after the discovery of miRNA in 1993, its profile studies revealed the association between miRNA expression and various diseases in humans. Various studies have shown that miRNA plays a critical role in human cardiovascular disorders including myocardial infarction, fibrosis, and heart failure. The role of miR-155 in the development of atherosclerosis is well known. MiRNA-208a is an important regulator and modulator of cardiac stress response, and plays a specific role in regulating myocardial function. Accordingly, its genetic deletion showed a decrease in hypertrophy and fibrosis in response to cardiac stress in mice (van Rooij et al. 2007; Aghajani et al. 2017). MiRNA-208a up regulation leads to increase in incidence of βMHC (myosin heavy chain), and increases the risk of arrhythmia and fibrosis; therefore, it is a strong predictor of cardiac death and heart failure (Callis et al. 2009; Satoh et al. 2010).

LNA (Locked nucleic acid) is a pharmacological inhibitor of miRNA 208a that has been tested in vivo and specifically targets this miRNA (Montgomery et al. 2011). Reduced expression of miR-208a increases the resistance to high-fat obesity and can be used in the treatment of metabolic syndrome. The MiRNA-208a inhibitor can increase the level of mediator complex subunit 13 (Med13), which is involved in regulating energy expenditure and various cardiac balance genes (Grueter et al. 2012).

In children with arrhythmia, paroxysmal or persistent tachycardia are common, and can result in heart remodeling and heart failure. MiRNA1 can be a good predictor of supraventricular tachycardia in children. Patients with SVT have lower level of miRNA1. MiRNA-133 can more accurately predict ventricular single-cardiomyocytes, and this biomarker shows higher levels in VT. In animal models, miRNA1 is elevated in acute MI and is associated with ischemia-induced arrhythmias. Arterial pulmonary hypertension leads to right heart failure. More than 30 circulatory miRNAs are associated with the development of pulmonary hypertension, and the levels of some of them are consistent with the pulmonary vascular resistance index (Zhou et al. 2018a).

Congenital heart diseases encompasses a wide range of heart disease in infants and children. Different types of congenital heart diseases such as VSD, ASD, TOF, and PDA account for more than 40% of perinatal deaths, and recent evidence has shown the significance of miRNA in CHD. Specific miRNAs are required for fetal heart development and their dysregulation can lead to cardiovascular structural abnormalities. For example, the role of miRNA1-1 and miRNA181 in VSD and specific expression changes of more than 61 miRNAs in the TOF, have been demonstrated (Smith et al. 2015; Sucharov et al. 2015). Increased blood levels of miRNA1 have been shown in congenital heart disease, as predictive of short-term outcome after surgery. MiRNA1 is a new biomarker that can be measured during perioperative period and improves the care taking of CHD (Stoica et al. 2019).

Since ***pulmonary complications*** are the most common postoperative complication in non-cardiac thoracic surgery patients; the risk of these complications has been determined in different ways. MiRNA21, a biomarker of vital role and biological function, has been seen as an early predictor of pulmonary complications such as ARDS in these patients. High levels of miRNA1 are associated with extra-pulmonary complications and death within 1 year (Liu et al. 2016).

Recent studies have shown the important role of miRNA in mediating and modulating the effects of various drugs. CYP3A4 is involved in the metabolism of more than 50% of common prescription drugs, and individuals' response to the drugs is significantly dependent on the level of CYP3A4. Studies on liver biopsy specimens have shown the correlations among four miRNAs and the reciprocal translational efficacy of CYP3A4. MiR577, miR1, micRNA532-3p, and micRNA627 are considered as miRNAs that lead to individual differences in response to CYP3A4 metabolized drugs in the general population (Wei et al. 2014).

The role of proteomics in personalized pediatric anesthesia: the product of the translation of the genes are proteins. There are several millions of unique proteins and the expression of all proteins in a cell, tissue or organism is essential for cell-specific function.

In terms of the physiology and pathophysiology of different cells and tissues, there are different proteomes. In fact, in some cases, the product of initial translation undergoes some types of modification and post-translation modification, which involves a wide range of irreversible reactions. This can be affected by age, environmental conditions, and diseases. Different types of proteins are found in biological or clinical specimens. Protein biomarkers can be measured by new methods including two-dimensional gel electrophoresis or protein microarray chips (Piazza et al. 2013; Atkins and Johansson 2006). These biomarkers should be detected in body fluids such as plasma, CSF, blood, urine, serum, and saliva.

Proteomic analysis allows the proteins of each individual to act as biomarkers playing a critical role in the study of diseases diagnosis processes and also from a prognostic point of view. It contributes to understanding the mechanism of the action of many drugs in anesthesiology and is of significant importance in clinical practice, risk stratification, and response to treatment. It is also widely used in ICU and chronic pain for diagnostic and prognostic cases. New diagnostic tests can be even suggested using proteomic analysis, which constitutes an important component of personalized therapeutics (Giudice and Petsalaki 2019).

Studies in this area on children are not widely available in adults. However, in recent years, several studies of protein risk stratification in children, especially in acute kidney injury after cardiac surgery, have shown that serum creatinine is a delayed marker for acute kidney injury. Preoperative timing is essential in these patients. Preoperative measurement of urinary biomarkers complement factor 8 (CFB) and histidine rich glycoprotein (HRG), significantly improved the risk stratification in these patients (Merchant et al. 2018). Pre-operative IL8 level and post-operative TNFα can be used as a predictor of AKI following cardiac surgery in children over 2 years old. The best method for risk stratification is evaluating the patient and using laboratory data, respectively (Park et al. 2016; de Fontnouvelle et al. 2017).

The Apolipoprotein E (APOE) genotype is associated with brain post-ischemic and brain trauma recovery. APOE gene sits on chromosome 19 and the APOE protein play an important role in neuronal repair. The APOE protein contains lipoproteins and the major lipid transporters in the CNS, and it is known as a key factor in the mobilization, redistribution of cholesterol, and phospholipid remodeling of neuronal membranes. There are three isoforms of APOE (E2, E3, and E4), which are encoded by three alleles (ε_2, ε_3, ε_4). APOEε_2 allele is associated with worsening early neurological outcome after infant cardiac surgery (Gaynor et al. 2014).

Intra-operative Pediatric Care

Anesthesia Induction, Traditional and Personalized Approach

Clinical response to anesthetic agents during induction and maintenance of anesthesia in similar children at the same dose is not identical. In traditional method, the type and dosage of anesthetic drugs are adjusted according to the patient's condition e.g. the patient's weight and comorbidities. Omics is considered in personalized medicine for anesthetized patients, especially in the case of narcotics, which is a great variation in the response of individuals (Kaymak et al. 2008).

Inhalation Induction

Sevoflurane is the most commonly used inhaled anesthetic for induction of pediatric patients; both in infants and children. Sevoflurane is a safe anesthetic agent with relatively low side effects. It has become a popular induction drug, due to ease of administration, rapid onset, less airway irritation and hemodynamic stability. However, the prevalence of emergence agitation with sevoflurane induction is higher than the other anesthetic agents.

Sevoflurane is metabolized by microsomal CYP2E1 in the liver and kidneys. Halogenated inhalation agents reduce hepatic blood flow and sevoflurane anesthesia can cause a mild disorder in hepatocellular integrity.

Glutathione s-transferase (GST) is a liver marker that is elevated in sevoflurane administration, as a cytosolic liver enzyme, and it might enable earlier detection of liver injury. GSTP1 genetic polymorphism has a significant effect on GST serum levels and GSTA1 is associated with an increase of concentration of GST, 24 hours after the end of anesthesia. However, no subsequent studies were performed to select the dose of sevoflurane (Mikstacki et al. 2016; Kaymak et al. 2008; Caplan and Felberg 2017).

Intravenous Induction

Propofol is an intravenous anesthetic with benefits of rapid onset and offset, lower incidence of nausea and vomiting and emergence agitation. It activates the GABA inhibitory neurotransmitters. The usual induction dose is 1–3 mg/kg, depends on the patients age (Chidambaran et al. 2015; van Hoff et al. 2015; Kim et al. 2019). Propofol causes systolic, mean and diastolic blood pressure reduction. There is a substantial individual susceptibility to propofol. Its etiology can be related to genetic polymorphism. A mutation in the 5HT2A gene (rs6313) is along with individual susceptibility to propofol. In carries of the minor allele (G) of 5HT2A rs6313, propofol requirement is lower and the onset time is shorter. Dominant mutations in GABA A1 rs2279020, GABAA2 rs11503014, and CHRM2 rs1824024 are along

with propofol cardiovascular effects (Zhong et al. 2017). On the other hand, it has been showed that UGT1A9-1887-TG variant heterozygotes need larger dose of propofol (Khan et al. 2014). The effect of intraoperative different anesthetics on miRNA expression and proteins is different. Except for the effects of these drugs on neuroapoptosis mediators, the hemodynamic profile may also be related to miRNA expression in cardiovascular system. Propofol and etomidate are intravenous anesthetic agents with different cardiovascular effects. These differences are particularly important for cardiovascular and critically ill patients. MiRNAs up and down regulation were studied in patients who received propofol or etomidate. This study showed that these drugs have different effects on circulatory miRNA. Regarding this, further animal studies are needed to determine which one of the miRNAs changes (Yao et al. 2018).

Due to rapid onset and rapid recovery of propofol, it is a common anesthetic drug for induction and maintenance. However, propofol infusion is not recommended for critically ill children. In recent years, the anti-inflammatory effect of propofol has been considered. Propofol can upregulate Annexin A1 protein, which is an anti-inflammatory protein, and prevent the phosphorylation of P53 and inflammatory factors (IL6, IL1β, and TNFα) release (Tang et al. 2011).

Ketamine is a widely used anesthetic agent that antagonizes the N-Methyl-D-aspartate glutamate (NMDA) receptors. It has many clinical applications, especially providing analgesia and cooperation for short procedures in children, because of hemodynamic stability and preservation of patient's spontaneous breathing. CYP3A4, CYP2B6 and CYP2C9 enzyme isoforms metabolize ketamine through N-demethylation in the liver. Its metabolite is norketamine. CYP2B6*6 allele is associated with a reduction of enzyme expression. It may lead to individual differences in metabolism and clinical response to ketamine (Hijazi and Boulieu 2002; Li et al. 2013). Studies have shown no significant association between genotype and incidence of emergence phenomena. High dose and long duration administration of ketamine, were predictors in this case (Aroke et al. 2017). However, in chronic pain patients who use long duration subcutaneous ketamine, CYP2B6*6 allele was associated with significant reduction in ketamine steady state plasma clearance. It may cause elevation of plasma level and increase in adverse effects of ketamine e.g. increased salivary secretions and cerebrospinal fluid pressure. However, the effect of this allele on precision medicine and ketamine is still controversial (Li et al. 2015; Cook-Sather et al. 2016). Ketamine induced neuronal apoptosis will discussed in the neuroapoptosis section.

Muscle Relaxants

Since introducing succinylcholine to clinical practice in 1950, it has been used as a gold standard drug for rapid and profound muscle relaxation. Succinylcholine is considered for rapid sequence induction, due to its rapid onset and short duration of action. Succinylcholine adverse effects such as prolonged muscle paralysis and fatal

hyperkalemia were reported from the same decade. It recommended for emergency control of the airway in infants and children (Dierdorf and McNiece 2018).

Succinylcholine and mivacurium (a short acting non depolarizing neuromuscular blocker) are hydrolyzed by plasma cholinesterase. Also, butyrylcholinesterase heterozygote variant expression leads to less effect of this enzyme and prolonged recovery time after succinylcholine and mivacurium administration. In homozygotes, this time can be up to 60 times longer(Palmer et al. 2005). Pseudocholinesterase deficiency will discussed later.

Individual differences, resistance and sensitivity in the response to muscle relaxants aren't uncommon. Except of the nature and properties of muscle relaxants, individual factors including age, sex, smoking, race, nutrition, obesity and body temperature can affect onset time of neuromuscular blockers (Kim et al. 2017).

In the case of nondepolarizan muscle relaxants, a study was performed by considering the association of liver transporter polymorphism and its effect on the clinical use of rocuronium. SLCO1B1, ABCB1, and CHRNA1 polymorphism has no effect on rocuronium onset. In patients with ABCB1 rs1128503TT, SLCO1B1 rs2306283 AG, and GG genotype; recovery time is prolonged. Accordingly, the most important genotype with effect on rocuronium is ABCB1 rs1128503C>T (Mei et al. 2015; Awad et al. 2019).

Pseudocholinesterase Deficiency

Butyrylcholinesterase or pseudocholinesterase is an enzyme produced in the liver and can be found in most of the tissues except red blood cells. The defect of this enzyme can be hereditary or acquired. The most obvious clinical effect of pseudocholinesterase deficiency is prolonging the effect of relaxants including mivacurium and succinylcholine. Among pseudocholinesterase deficient patients, the defect cannot be diagnosed until they are exposed to succinylcholine or mivacurium. In these patients, prolonged paralysis and apnea are observed after the administration of these drugs (Zhang et al. 2018).

Pseudocholinesterase deficiency is important to the anesthesia providers including emergency department, anesthesiologists, and intensive care unit. In acquired cases, this defect was due to chronic infectious, kidney disease, hepatic disease, malnutrition, cancer, severe burns, or using a variety of drugs. In neonates, blood levels of the enzyme are usually lower.

Inheriting the defect of pseudocholinesterase is autosomal recessive that is associated with mutations in the butyrylcholinesterase gene BChE, which lies in q 26.1–26.23 position in ch3. Accordingly, Polymorphism of this gene has many variations. An individual can inherit 65 variants and their clinical pattern ranges from mild to severe paralysis and apnea. 96% of the population are homozygote for normal pseudocholinesterase, which is EuEu designate. The remaining 4% carry atypical alleles as heterozygote or homozygote (Zencirci 2009).

The most common variant is the Atypical variant A in which mutation occurs at nucleotide 209 and Guanine replaces Adenine and Glycine substitutes for Aspartic

acid at position of 70 of the enzyme. The Kalow variant (variant K) can reduce the enzyme level by 30%; and other types are fluoride and silent resistant. In the traditional method, the patient and his family history of prolonged anesthesia and apnea is examined.

Blood sample and the activity of pseudocholinesterase enzyme, which is measured using a dibucaine and fluoride inhibition test, are employed for diagnosis. Although DNA analysis is not routine, it can be used to diagnose a variety of genetic defects such as heterozygotes or atypical alleles. New variants of the butyrylcholinesterase genotype are being discovered (Alvarellos et al. 2015).

A study on a 12-year-old child and his family has shown a new mutation. Two heterozygous mutations had occurred and stopped the translation and production of active protein (double heterozygotes recessive mutation).

- Exon2, C.734> T and C.401-402insA

This mutation can be related to the intellectual disability phenotype (Yu et al. 2018).

Malignant Hyperthermia

Malignant hyperthermia is a pharmacogenetic disorder in metabolism of calcium in the skeletal muscle, and it is a particular concern to a pediatric anesthesiologist.

Accordingly, it was first introduced as a clinical entity by Denborough in 1960. An Australian young man who was afraid of anesthesia due to the death of several members of his family, had symptoms such as hypotension, tachycardia, and high fever during anesthesia. However, he was rescued using aggressive cooling, and genetic tests showed that a dominant autosomal disorder is the main reason underpinning death during anesthesia. This disorder starts with MH triggers (volatile anesthetics or succinylcholine) and is rarely associated with hypermetabolism symptoms and death in the absence of medications and anesthetic triggers.

The symptoms of malignant hyperthermia emerge as hypermetabolic creases with rapid onset and uncontrollable release of myoplasmic calcium of skeletal muscle cells. If predisposition for MH is diagnosed in the patient before anesthesia, it is preventable (Rosenberg et al. 2015; Kaur et al. 2019). Molecular etiology and genetics of MH have made significant progress in the recent decades.

RYR1 (ryanodine receptor1), CACNA1s (calcium voltage gated channel subunit alpha1s), and STAC3 (stromal antigen3) are three genes associated with susceptibility to MH. The RYR1 gene encodes the Ryanodine receptor of skeletal muscle. Ryanodine receptors mediate the release of calcium ions from sarcoplasmic reticulum and endoplasmic reticulum, which is an essential step in muscle contracture. Mutation of this gene is located at chromosome 19q13.2 and is associated with various diseases, pharmacogenetic disorder, malignant hypertension, and three congenital myopathy, including Central Core disease (CCD), and Multiminicore disease (MMD), an isolated case of congenital myopathy (Robinson et al. 2006; Toppin et al. 2010; Riazi et al. 2018).

A coagulopathy disorder with a variant of RYR1, which is implicated in predisposition for MH, has been recently reported. This report has increased the spectrum of clinical disorder, which currently includes myopathies and exertional rhabdomyolysis. The RYR1 Ryanodine receptor is mainly found in skeletal muscle, but it can also be seen in smaller quantities in immune cells and smooth muscles, and it is hypothesized that RYR1 mutations have wider effects compared to those that have been previously identified (Lopez et al. 2016).

A small number of MH-prone families carry a variant in the CACNA1s gene, which encodes the α-1 subunit of voltage-dependent channels (α-1subunit of the T tabular cell voltage-gated Ca+ channel). It is also known as the dihydropyridine receptor. α-1 subunit is very important for voltage sensing and conduction of hydropyridine receptor (Stewart et al. 2001; Gillies et al. 2015).

Approximately 50% of MH probands rescued from an MH and individuals who are MH-prone based on the contracture tests that carried no RYR1 or CANCA1S variants and their genetic basis remain unknown to MH (Klingler et al. 2014; Rosenberg et al. 2015).

Stac3 protein is required for excitation-contraction coupling in skeletal muscle. Its function is due to effect on CACNA1channel activity and also normal calcium release from the sarcoplasmic reticulum (Fig. 7.1). A homozygote STAC3 mutation

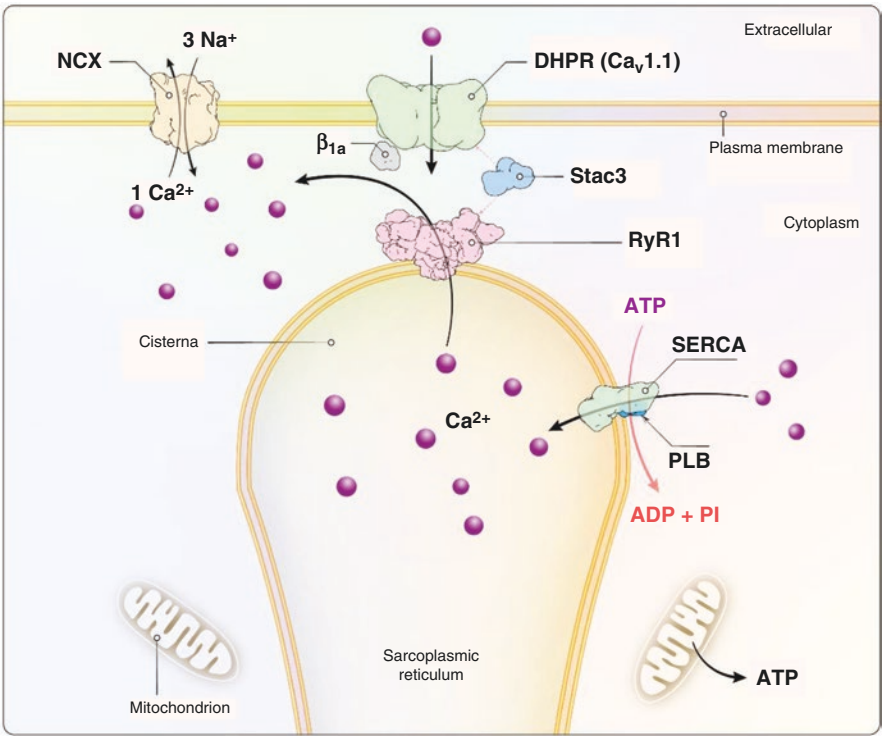

Fig. 7.1 DHPR, Ryanodine receptor and stac3 protein interaction in excitation-contraction coupling

has been recently linked to the American native myopathy, which was associated with predisposition for MH in a Native American family (Horstick et al. 2013).

STAC3 encodes stac3 protein and it is necessary for the efficient arrangement of dihydropyridine receptors and RYR1s. Also, the necessary components of skeletal muscle excitation contraction coupling underlying MH are the interruption of excitation contraction coupling and the sudden and severe increase in toxic sarcoplasmic calcium via RYR1, which occur in response to the endogenous or exogenous stimulus. Currently, more than 200 RYR1 variants have been found in association with MH, but only 35 RYR1 variants and 2 CACNA1s variants were recognized as being functionally characterized to be used in diagnostic genetic testing for MH (Gillies et al. 2015; Hopkins et al. 2015; Riazi et al. 2018).

Anyone carrying one of the MH pathogenic variants is susceptible to MH. When a variant of the familial pathogen is identified, genetic testing is required for all the family members. However, having a predisposition for MH cannot be rejected for those who are not carriers of the familial variant, because there is a possibility for more than one pathogen variants in the same family. Therefore, a contracture test must be done for these patients. Accordingly, DNA-based MH susceptibility detection is an attractive choice, especially in children as it can be an alternative to muscle biopsy and in vitro contracture caffeine halothane test (Stowell 2014).

Maintenance of Anesthesia, Traditional and Personalized Approach

Amnesia

Midazolam is a water soluble, short acting benzodiazepine that provides amnesia during children's anesthesia. It is metabolized in the liver through CYP450 enzyme. Clearance of midazolam, significantly depends on the patient's age. Preterm infants have the lowest metabolism rate, due to immaturity of CYP3A4 metabolism. Midazolam pharmacogenomic has been discussed in preoperative section (Shin et al. 2013b; Brussee et al. 2018).

Analgesia

The response of pediatric patients to opioids is highly variable. In addition to immaturity of organs such as brain and liver in neonates and its important effect on drug metabolism; pharmacogenetic issues are also important. A well-known pharmacogenetic example of pediatric morbidity is the administration of codeine conventional doses to ultra-rapid metabolizer children. In ultra-rapid metabolizers, most of the prodrug become active form and toxicity sharply increases. This will be discussed in pediatric personalized pain management (Kirchheiner et al. 2007; Iravani et al. 2017).

Fentanyl is a common and potent narcotic for pediatric intraoperative analgesia due to more hemodynamic stability compared to morphine and the other opioids. it is metabolized by CYP3A4/5. The patient's response to fentanyl and perioperative dose is highly variable (Mieda et al. 2016). Fentanyl clearance has decreased in preterm infants, but reaches to 80% of adults in term infants.

Synthetic opioids dose should be reduced in the first 4 weeks of life and for premature infants at least until to 44 weeks post conceptual age. Remifentanil is metabolized by nonspecific plasma and tissue esterase and has a very short half-life. The importance of liver and kidney maturity is negligible. Its metabolism is not affected by butyrylcholinesterase deficiency. Effective half-life of remifentanil in neonates is similar to older children and adults and it requires no dose adjustment (Kamata and Tobias 2016; Cravero et al. 2019).

Morphine

Morphine is a practical opioid to control pain in pediatric patients. There is a large variation in its pharmacokinetic in neonates and young infants. Morphine dose should be adjusted in neonates, because of lower glomerular filtration rate and hepatic enzymes immaturity (Elkomy et al. 2016; Cravero et al. 2019).

It is very difficult to link morphine function to a single gene. To understand the function of morphine in relation to one's genetic, it should be followed from the times that enters the circulation to the effect site. After intravenous injection of morphine, it is first metabolized in the liver. Glucuronidation is the major pathway of morphine metabolism. A change in UDGT (uridine diphosphate glycosyl transferase) can increase morphine glucuronidation and reduce its effect. To enter the brain cells, cassette transporter (ABBC1) is necessary. Investigations in the transporter polymorphism is in its infancy. However, it has been shown up to know that, polymorphism of the transporter can increase morphine dose up to twice. The effect site of morphine and other opioids is the μ receptor. OPRM1 gene encodes this receptor and A118G polymorphism results in reduced opioid sensitivity. Opioids, in order to be effective, must send a signal from μ receptor to brain and activate the analgesic effect. This internal signal is β Arrestin. C8622T polymorphism encodes β Arrestin, and increases morphine efficacy. The interaction of these four target sites is very complex and further research is needed in the future to clarify the relation between drug signal relationship and receptor (Galinkin et al. 2010; Kaye et al. 2019).

Hypnotics

Inhalation agents such as isoflurane are widely used in pediatric anesthesia maintenance. Anesthesia maintenance with desflurane is an effective agent with rapid recovery due to lower blood-gas and tissue-blood solubility compared to the other common anesthetics, but it isn't approved for induction and maintenance of anesthesia in non-intubated pediatric patients. The incidence of respiratory adverse

events, including coughing, laryngospasm and secretions is significantly higher with desflurane (Kapoor and Vakamudi 2012; Khan and Liu 2020).

Effect of these agents on neuronal apoptosis in different doses and duration of administration has been studied. Various studies have shown long term exposure to isoflurane can induce behavioral and cognitive impairment (Coleman et al. 2017; Demirgan et al. 2019). Neuroapoptosis will be discussed later.

MAC (minimum alveolar concentration) of inhalation anesthetics is age dependent. MAC rises during the neonatal period, peaking in infancy and then decreases throughout life (Nickalls and Mapleson 2003). Studies have shown inhalation anesthetics resistance in redheads. Melanocortin1 receptors are members of the rhodopsin family of 7-transmembrane G protein-coupled receptors. MC1R (melanocortin1 receptor) is associated with pigmentation genetics. MC1R gene polymorphism is associated with the increase of the required dose of desflurane. This mutation occurs more frequently in redheads (Liem et al. 2004). Less than 5% of inhaled anesthetics is metabolized in the body and the elimination is through the lungs. Inhalation anesthetics are also metabolized by CYP2E1. This elimination is trivial. 20–50% of halothane, 2% of sevoflurane, less than 1% of isoflurane and 0.1% of desflurane are metabolized by CYP. Genetic variations of this enzyme have no significant clinical effect (Nair 2019).

N2O is the oldest and also the most common anesthetic used worldwide. It is an adjunct to other agents during induction and maintenance of anesthesia. Nitrous oxide increases plasma homocysteine via vitaminB_{12} irreversible inactivation. It seems an acute elevation in homocysteine appears to increase the risk of cardiac complication such as ischemia (Nagele et al. 2013). C677T or A1298C variant homozygote patients for MTHFR (methylene tetrahydrofolate reductase) gene, have higher levels of homocysteine after N2O administration. Nitrous oxide administration is very dangerous and has severe complications among MTHFR deficient children. N2O is not metabolized and irreversibly oxidizes vitamin B12 in these patients. Vitamin B12 is essential for methionine synthetase function. The active form of methionine, s-adenosylmethionine, is critical for methylation in many biochemical reactions, neurotransmission, and DNA synthesis. Two infant deaths following anesthesia with nitrous due to preoperative undiagnosed MTHFR have been reported. This diagnosis should be warranted in infants with clinical symptoms e.g. hypotonia, seizure, and psychomotor retardation. 29 mutations of MTHFR are associated with methionine severe deficiency (Selzer et al. 2003).

Local Anesthetics

Regional and neuraxial blocks have many advantages in pediatric anesthesia, such as reduction of the anesthetic agent requirement and better postoperative experience for children and their parents. The quality of these blocks depends on the dose and characteristics of the used local anesthetic and site of the effect. In several cases, despite the ideal block condition, the response to local anesthetics is inadequate. Local anesthetics can act by blocking sodium channels. Resistance to local

anesthetics is uncommon. It is assumed that LA resistance is related to variations in voltage gated sodium channels (NaV). In this regard, through one family whole-exome sequencing, a genetic variant was identified in NaV. A572D mutation in SCN5A gene, which encodes NaV1.5. More incidence of local anesthetic resistance has been reported in Ehlers-Danlos syndrome with unknown cause. Further research is needed (Batas et al. 2007; Clendenen et al. 2016; Schubart et al. 2019).

NaV plays an important role in action potential formation in neurons and muscle cells. Mutation in NaV1.7 encoding gene, SCN9A, is associated with pain perception disorders such as congenital analgesia, paroxysmal pain disorder, and primary erythermalgia. Also, NaV mutations is responsible for some genetic epileptic syndromes (Catterall et al. 2010; Marković et al. 2015).

Intraoperative Awareness

Occasionally, despite the administration of a sufficient dose of anesthetic drugs during operation; the patient experiences awareness, and this is so unpleasant. Few genetic variants may be involved in intraoperative awakening and inadequate explicit memory suppression during anesthesia. Studies have found no gene having a strong association with intraoperative awareness. The authors identified 29 genetic variants in these patients including CACNA1A, CACNA1S variations, and genes encoding calcium and purinergic receptors (Sleigh et al. 2019).

Antagonists of Neuromuscular Blockers

Neostigmine is the most widely used anticholinesterase for nondepolarizing muscle relaxant reverse. It reduces the risk of residual paralysis and associated adverse respiratory events. Neostigmine has many benefits including the ability to reverse all nondepolarizing muscle relaxants, low cost and availability. A lower dose of neostigmine is required in children compared to adults, due to neuromuscular junction differences: The number and quantity of nicotinic receptors, amount of acetylcholine reserve and acetylcholinesterase enzyme activity (Wu et al. 2014; Luo et al. 2018).

Postoperative Care, Traditional and Personalized Approach

Post Anesthesia Care Unit for Stable Patients

The patients are transferred to post anesthetic care unit after deep or awake extubation (according to patients' situation). Post anesthesia care period is a high-risk time for pediatrics. Oxygen desaturation, nausea, vomiting, temperature instability may be occurred. Recovery time varies widely among different patients, (Jain et al. 2018)

Anesthesia recovery may have a presynaptic mechanism. Similar patients do not have similar recovery times. Synaxin-1A is a protein encoded by STX1A gene. Synaptic vesicles store neurotransmitters that are released during calcium-regulated exocytosis. The specificity of neurotransmitter release requires the localization of both synaptic vesicles and calcium channels to the presynaptic active zone. Syntaxin acts in this vesicle process and plays a key role in neurotransmitter release. Mutation in STX1A gene have influences on the anesthesia effect in vitro and in vivo. This mutation facilitates isoflurane recovery in Drosophila melanogaster and resistance to volatile anesthetics and intravenous anesthetic drugs (Troup et al. 2019; Templeton et al. 2019).

Emergence agitation is a common complication immediately after waking in preschool pediatric patients, and happens more with sevoflurane anesthesia. Although it is self-limited, it can be associated with severe complications such as self-injury, pulling out of intravenous line or fully (Templeton et al. 2019). In addition, there is a need for more sedative and anxiolytic drugs that prolongs recovery time in children. Also, the exact mechanism is not clear. Some studies have shown that midazolam, which its target effect site is $GABA_A\gamma_2$ subunit, reduces emergence agitation, and flumazenil reverses this effect; however, this is a controversy issue. It may be $GABR_2$ genetic polymorphism involved in emergence agitation development. A study conducted on pre-school children who underwent tonsillectomy, showed genetic polymorphism, SNP (single nucleotide polymorphism) 211037C/T, nucleotide position 3145 in intron A (G) may affect incidence and intensity of emergence agitation through GABA receptor function (Araki et al. 2005; Park et al. 2008).

PONV

Postoperative nausea and vomiting (PONV) is the most common complication of anesthesia in children. PONV incidence in this group of age is twice that of adults. Predictive factors include: age of 3 years, positive family history of PONV, history of motion sickness, type of surgery such as strabismus and adenotonsillectomy, duration of surgery equal to 30 min, opioid administration (Wiesmann et al. 2015; Chau et al. 2017).

For prophylaxis against PONV, intravenous serotonin receptor (5-HT3) antagonists such as ondansetron and granisetron given intraoperatively. 5HT3 antagonists are highly effective in prophylaxis and treatment of PONV with minor adverse effects. The other drugs such as intravenous dexamethasone decrease the incidence of PONV (Gan et al. 2014; Frelich et al. 2018). However, prophylaxis and treatment failure with ondansetron is sometimes observed. Individual variations in response to treatment is multifactorial. One of the possible mechanisms is ultra-rapid metabolism via CYP450 system especially CYP2D6 enzyme. The patients with multiple copies of the CYP2D6 allele, are ultra-rapid metabolizers and have higher incidence of treatment failure. The receptors that may play a role in PONV incidence are 5HT3B, dopamine type 2 and mu-opioid receptor. Preoperative polymerase chain reaction (PCR) and restriction length polymorphism (RFLP) test can define

CYP2D6 allele genotype (Candiotti et al. 2005; Wesmiller et al. 2013; Niewinski et al. 2018; Zhou et al. 2018a; Awad et al. 2019).

Postoperative Care in Critical Patients

Inflammation and sepsis are one of the causes leading to death in critically ill patients during perioperative period. Epigenetic modifications such as DNA methylation, histone modification and miRNAs are emerging as important players in modulating the immune responses and inflammation that ultimately result in multi organ failure in critical ill patients. Using the biomarkers for early detection of organ damage and overall prognosis is a new idea. Therapeutic strategies targeting epigenetic mechanisms are very interesting and still at early stages. Identification of epigenetic changes in personalized therapeutic approach, with the aim of using precise treatments, can improve critical care in the future. Several studies have shown that miRNAs are involved in adaptive immune response regulation and dynamically modulate the proliferation, differentiation, and the function of immune cells. Depending on the target gene, miRNAs can ameliorate proinflammatory or anti-inflammatory responses, so miRNAs exacerbate or decrease inflammatory responses (Fazi et al. 2005; Boldin et al. 2011).

MiRNA223 modifies innate immune response in two levels. It directly controls granulocytes differentiation and maturation, in addition to regulating granulocytes function (Fazi et al. 2007).

Caspase1 enzyme regulates IL_8 level, and plays a role in inflammation and apoptosis. NLRP3 is a multiprotein complex, which senses cellular stress and mediates inflammatory responses. NLRP3 is an important caspase1 regulator. NLRP3 play a role in pathogens of hereditary cryoprinopathies (a spectrum of auto inflammatory syndromes), and is associated with some disease such as gout, DM_{II}, and atherosclerosis. MiRNA223 suppresses NLRP3 through 3′UTR, thus restricts auto inflammatory processes. MiRNA223 deletion, increases susceptibility to infection in mice (Bauernfeind et al. 2012).

Postoperative *pulmonary complications* such as acute respiratory distress syndrome (ARDS) and ventilator associated pneumonia (VAP) are associated with high mortality and morbidity rate. These patients are managed by various treatments such as antibiotic therapy and lung protective ventilation strategies. In several studies, the effect of intravenous administration of selenium has been investigated with the aim of modulating inflammatory responses to ARDS. Selenium can reduce inflammatory responses in pneumonia, and significantly improve the respiratory mechanics; however, it has no effect on patient's survival (Trivedi et al. 2017; Mahmoodpoor et al. 2018, 2019a).

In order to ventilator associated pneumonia prophylaxis, administration of probiotics has been investigated in adults and children. Probiotics contain non-pathogenic flora that compete with pathogens and modulate the local and systemic immune system. Probiotic administration is a novel intervention for VAP and other

nosocomial infections prophylaxis, and especially in children can decrease VAP incidence and ICU and hospital stay (Mahmoodpoor et al. 2019a).

After major surgeries, especially open-heart surgery in children, *acute kidney injury* can increase mortality and morbidity. Clinicians try to prevent this complication by keeping stability of hemodynamic and maintaining fluid and acid-base balance in these patients. Also, early diagnosis and intervention are critical in this case. We need biomarkers for early detection of postoperative acute kidney injury, because serum creatinine is a delayed biomarker. In recent years, protein biomarkers have been investigated and used for this purpose. Three proteins including: $\alpha_1$acid glycoprotein, urinary $\alpha_1$microglubuline, and albumin can detect early acute kidney injury, which are also useful in determining the prognosis and the length of hospital stay (Devarajan et al. 2010; Greenberg and Parikh 2017).

Various studies have shown the role of inflammatory biomarkers, especially IL_8, to evaluate treatment response in patients with acute kidney injury. Serum CysC (sCys C), Serum neutrophil gelatinase lipocalin (s NGAL), Urine neutrophil gelatinase lipocalin (s NGAL), Urine liver fatty acid binding protein (UL-FABP), and Urine kidney injury molecules (UKIM) have been used to predict AKI and its severity after cardiopulmonary bypass in children (Peco-Antic et al. 2013; Greenberg et al. 2018).

Pediatric Personalized Pain Management

The progression of fields such as epigenetics, proteomics, transcriptomics, and metabolomics, has enhanced our appreciation of the complexity of acute, chronic and neuropathic pain response and its relation to individual genetic. Omics studies are relatively limited in the field of children's pain. The most prominent clinical cases in children include different responses to codeine. *Codeine* is a prodrug that converts to its active metabolites, morphine, and morphine 6-glucoronide in the liver. Most of the administrated codeine is converted to inactive metabolites by glucuronidation and N-demethylation and 10–20% of codeine metabolizes to active metabolites by CYP2D6 (Cytochrome P450 2D6) enzyme (Fig. 7.2). CYP2D6 gene is highly polymorphic with more than 100 CYP2D6 different alleles. Alleles are characterized as normal function (wild type), reduced function, and non-functional. Patients are divided into poor, intermediate, extensive, and ultra-rapid metabolizer in terms of the enzyme activity score. In poor metabolizers, activity score is lower than 0.5 and patients with activity score between 0.5 and 1 are considered intermediate metabolizer, those between 1.0 and 2.0 are extensive metabolizer and those with score greater than 2 are ultra-rapid metabolizers. In poor metabolizer patients, codeine has no analgesic effect, whereas ultra-rapid metabolizers are at high risk of serious adverse effect such as respiratory depression. There are allele's variations between racial and ethnic groups. Normal function alleles (wild type) are more frequent among European Caucasians compared to Asian and African-Americans. Genetic studies conducted on East Africa population showed that 29% of studied

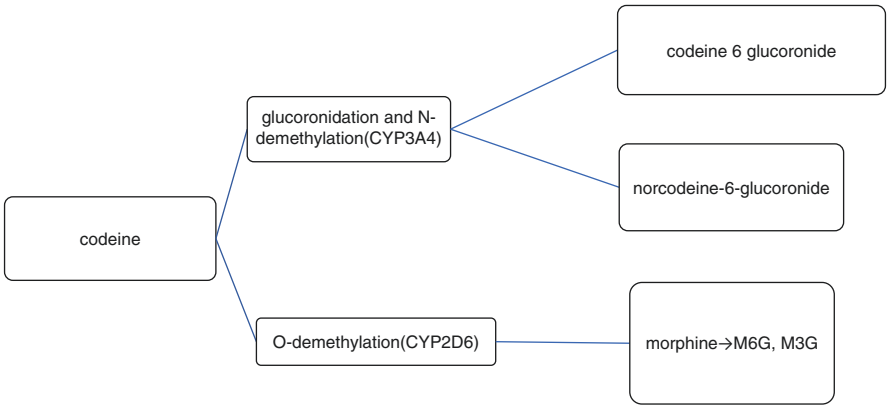

Fig. 7.2 Codeine metabolism. 10–20% of codeine converts to active metabolites by CYP2D6

subjects are ultra-rapid metabolizer and susceptible to serious adverse complications. Over the past years, several cases of respiratory depression, anoxic brain injury, and even death in pediatric patients who received appropriate doses of codeine has been reported, especially in post tonsillectomy analgesia administration. A case of infant death due to codeine consumption by the breast feeding, ultra-rapid metabolizer mother has been reported. In this regard, FDA warned of codeine use in nursing mothers due to the risk of neonatal deaths. In 2013 the use of codeine for post tonsillectomy analgesia was contraindicated in children, and in 2017, codeine and tramadol were banned in children under 12. In addition to codeine; tramadol, hydrocodone, and oxycodone are metabolized by CYP2D6 and affected by polymorphism of this gene (Aklillu et al. 2002; Bradford 2002; Thorn et al. 2009; Crews et al. 2014; Mele and Goldschmidt 2017).

Although routine preoperative genotyping is only performed in a limited number of centers, CYP2D6 pharmacogenetics can be used as a guideline for treatment of opioid use in children, especially in certain groups such as sickle cell patients, which codeine is one of the most commonly used drugs (Gammal et al. 2016; Chidambaran et al. 2017a).

Most studies among pediatric patients have focused on investigating genetic polymorphism in genes related to *morphine* metabolism, transport across membranes, and effector sites; and interesting results have been achieved (Table 7.2) Morphine is metabolized in the liver by Uridine diphosphate glucuronyl transferase. The uridine glucuronyl transferase (UGT) enzymes are subdivided into 4 families, and each of these can be categorized into subfamilies. The UGT2B7 isoform of the UGT2 family is the principle isoform responsible for morphine metabolism. Morphine is metabolized to morphine 6 glucuronide (M6G) and morphine 3 glucuronide (M3G). In patients with UGT2B7 variant in position-79 M6G/morphine and M3G/morphine ratio reduced, compared to non-carriers (De Gregori et al. 2016; Talebi et al. 2017). Studies regarding the effects of UGT2B7 on morphine glucuronidation activity are limited, and it is not clear how its genetic variant affects

Table 7.2 Genes that their polymorphism affects pharmacokinetic of morphine in children

Gene	Protein action	Polymorphism effect
UGT2B7	Morphine metabolism	Variations in the effect of morphine
ABCB1(MDR1)	Drug transporter at the BBB	Greater risk of respiratory depression
OCT1	Hepatic uptake transporter	Lower morphine clearance
ABCC3	Efflux M6G and M3G into the blood	Higher M6G plasma level
OPRM1	μ opioid receptor	Poor response to morphine

morphine metabolism. In adult studies, polymorphism of this gene has been associated with variations in clearance of morphine. Morphine is common opioid for post-operative pain management, and despite its long history of use, there is still no concordance between dose and analgesic effect in adult and children. It is used in various forms, and respiratory depression, post-operative nausea, and vomiting are its common complications. Other genes including gene coding for transport proteins such as ATP binding cassette, subfamily B, member 1(ABCB1), which is a transporter in the blood brain barrier and organic cationic transporter 1 (OCT1), which functions as a hepatic uptake transporter. ABCC3 facilitate hepatic morphine metabolites efflux. In children with rs4148412AA and rs4973665CC genotype, the likelihood of respiratory depression and long-term ICU is increasing. The effect of ABCB1 genetic variations on respiratory depression after intravenous morphine administration has also been demonstrated in children. Children with GG and GA genotype of ABCB1 polymorphism rs9282564, have a greater risk of respiratory depression (Sadhasivam et al. 2015) The efflux of morphine glucuronide from the hepatocyte cell is an ATP dependent process, mediated by ATP binding cassette transporter including ABCC3. In some literatures, the authors have demonstrated that ABBC3 gene variants contribute to variability in morphine, M6G and M3G pharmacokinetics and can potentially affect serious adverse effects of morphine. The presence of allele A at rs4148412 and allele G at rs729923 increase the risk of prolonged respiratory depression and PACU stay after pediatric tonsillectomy (Venkatasubramanian et al. 2014; Chidambaran et al. 2017a).

Organic cationic transporter (OCT) can transport morphine from blood to hepatocytes. OCT1 polymorphism causes higher risk of respiratory depression and PONV after morphine administration. Pharmacokinetic studies among pediatric patients of diverse racial and ethnic backgrounds have shown differences in morphine administration side effects. Caucasian and AA children significantly differ in the incidence of obstructive sleep apnea and total morphine use. A study on Caucasian and African American children showed association between OCT1 gene polymorphisms and the presence of side effects in Caucasian children. OCT1 polymorphism rs12208357 was associated with post-operative nausea and vomiting (PONV) and prolonged PACU stay. A significant association was also found, between rs72552763 GAT deletion and high incidence of respiratory depression (Balyan et al. 2017).

Studies showed that polymorphism of OPRM1 gene (the gene coding for mu opioid receptor type1) was associated with pain sensitivity. An association between

the A118G single nucleotide polymorphism in the OPRM1 gene and pain sensitivity was reported in children who carry the G-allele have higher postoperative pain scores (Table 7.2) (Lee et al. 2016).

Nonsteroidal anti-inflammatory drugs (NSAIDS) prevents prostaglandin production and decrease of peripheral pain and inflammation. NAIDS use as a part of multimodal analgesia. Most of NSAIDS are metabolized by CYP450 enzymes, including CYP2C8 and CYP2C9. The patients with CYP2C8*2,*3, CYP2D9*2 or *3, are poor metabolizers. The recommended treatment start dose for these patients, is half the normal dose to avoid adverse effects such as bleeding, cardiovascular or gastrointestinal events (Wyatt et al. 2012).

Acetaminophen is widely used in pediatric practice. It metabolizes in the liver extensively by glucuronosyltransferase (UGT), cytochrome P(CYP), sulfotransferases(SULT) and glutathione-s-transferase(GST). Polymorphisms of these enzymes can cause individual differences in the response to acetaminophen administration (Krasniak et al. 2014; Awad et al. 2019).

Epigenetic changes do not affect or alter DNA sequence. DNA methylation is one of the epigenetic mechanisms, which occurs in OPRM1 gene in chronic pain patients, which is correlated with increased chronic pain score, suggesting that opioids may improve pain through a direct effect on DNA transcription (Chidambaran et al. 2017a).

Toll like receptors are the members of the pattern recognition receptor (PRR) family, which play a critical role in innate immune system and their main function is to identify pathogen molecules and initiate an immune response against them; therefore, they are involved in various physiologic and pathologic processes such as septic shock. MD-2 is a glycoprotein required for response to lipopolysaccharides, which binds to LPS and extracellular domain of TLR4; therefore, it is essential for TLR4 activation. TLR4 is widely present in the cell surface and endosomes of immune and nonimmune cells, especially in human nervous system. Recent studies indicated a fundamental role of TLR4 in several chronic neuropathic pain model. Peripheral nerve injury can induce spinal microglia/astrocyte activation, so inhibition of TLR4 can develop less neuropathic pain and decrease expression of pain related cytokines. In this regard, FDA approved TLR4 inhibitors were investigated, and the authors demonstrated that these drugs can be considered as a good choice for further in-vitro and in-vivo neuropathic pain studies (Bagheri et al. 2016; Sezari 2017; Zali et al. 2019).

Gene expression leading to protein production in multiple studies of pain in rat was examined. CCL2 and Reg3b genes are correlated to the protein's monocyte chemoattractant protein 1 and pancreatic-associated protein. These proteins can be used as biomarkers of pain response in rats (LaCroix-Fralish et al. 2011).

Among the metabolite examined in rats' chronic pain, it was found that endogenous metabolite N, N-dimethyl sphingosine (DMS) production (a catabolite of ceramide) was significantly altered. DMS was intrathecally injected into healthy rats. Within 24 hours, rats developed persistent allodynia, so DMS inhibition can be considered as a novel target for reduction of neuropathic pain. Metabolomics are potential for developing new drugs and therapeutics in chronic pain (Patti et al. 2012).

TAOK3 gene encodes serine/threonine protein kinase and TAO3, an amino acid protein. TAO3 is a member of the large mammalian kinase family that is present in the cytoplasm and cell membrane, which is similar to regulating pain and analgesia proteins. Mu-opioid receptor (MOR) is an opioid receptor plays an important role in the effectiveness of opioids, especially morphine. Also, MOR and TAO3 interactions are interesting. MOR has more than 15 serine/ threonine residues, available for protein kinases. TAO3 variants can alter the phosphorylation pattern of MOR and cause desensitization of this receptor and morphine resistance phenotype. Genome wide association study in a pediatric surgery center, demonstrated an association between rs795484 and rs1277441 at TAOK3 locus and total increase morphine requirement (Cook-Sather et al. 2014).

Special Considerations

Neuroapoptosis and Developing Brain

Anesthesia drugs are extensively used in infants and children for a wide range of procedures; however, little is known about their effects on the developing brain. Millions of pediatric surgeries are annually performed worldwide. In USA, 6 million children that 1.5 million of them are infants, undergo surgery each year (Loepke et al. 2009; Kodama et al. 2011; Andropoulos and Greene 2017). Normal brain development involved neurogenesis and synaptogenesis. Non-physiological exposure to various drugs and stressors such as pain, the mother separation, hypoglycemia, hypoxia, and ischemia during the critical periods of brain development, can cause neurodegeneration. Animal studies showed that anesthesia drugs can cause neurologic and cognitive adverse effects under certain conditions such as prolonged anesthesia among infants and young children. Central nervous system has not evolved at birth and continues to grow during the early postnatal years. A large volume of experimental and laboratory studies over the past decade have demonstrated the association between general anesthesia during rapid brain development and increased neuronal apoptosis and long-term complications in mice, guinea pigs or primates (Loepke et al. 2009; Kodama et al. 2011; Andropoulos and Greene 2017). Regarding, the effect of GABA agonist or NMDA antagonist drugs e.g. midazolam, ketamine, propofol, etomidate, isoflurane, sevoflurane, desflurane, and N2O has been investigated and evidence of apoptosis and synaptic dysfunction has been obtained (Sun 2010; Wang et al. 2014; Creeley 2016; Andropoulos 2018). These drugs block neuronal transmission that result in synaptic deprivation, and then intrinsic neuroapoptosis pathway is activated due to lack of neuronal stimulation. Anesthetic drugs increase mitochondrial permeability through bcl2 proteins. The B-cell lymphoma-2(BCL-2) family protein control the intrinsic apoptosis pathway. The pro-apoptotic BCL-2 proteins, BAX and BAK can commit a cell to its programmed death by permeabilizing the outer mitochondrial membrane, release of

cytochrome c into cytosol and subsequent initiation of caspase cascade. This phenomenon rapidly occurs within 2 h of anesthetic drug exposure (Zhang et al. 2010; Boscolo et al. 2012; Zhang et al. 2012; Kajimoto et al. 2014).

N2O is a NMDA antagonist drug that its neurotoxicity effect is related to increased homocysteine levels. Homocysteine can cause cell death and cognitive dysfunction (Savage and Ma 2014). The neuroprotection effect of α_2 agonists (clonidine, dexmedetomidine) has been shown in various animal studies (Laudenbach et al. 2002; Men'shanov et al. 2007; Sanders et al. 2009).

An important question facing the pediatric anesthetist is the potential neurotoxicity of anesthetic drugs. Unfortunately, translation of bench finding to bedside is limited. It is impossible to study histologic anesthetized pediatric patients; therefore, alternative approaches such as biomarkers should be used to evaluate this important issue. Also, the safest and the most effective method should be chosen for pediatric anesthesia (Levy et al. 2016). Detectable biomarkers in blood or CSF are ideal for this purpose. Biomarkers that are sensitive and elevate shortly after drug exposure are used, and out of this, $S_{100\text{-}\beta,}$ neuron specific enolase, glial fibrillary acidic protein, myelin basic protein, α_{II}-spectrin breakdown products, apolipoprotein E, and Ubiquitin (carboxyl-terminal hydrolyze isozyme L1) can assess damage severity and outcome prediction in adult and pediatric brain trauma patients. Many of these proteins have been used to determine the prognosis of other conditions e.g. neonatal hypoxic ischemic encephalopathy (Kovesdi et al. 2010; Looney et al. 2015; Zhou et al. 2016; Fani et al. 2018). Nowadays, biomarkers such as miRNAs are used in ongoing studies. In addition, the roles of genetic and epigenetic in neuroapotosis have been investigated. Epigenetic changes are heritable, which target gene expression and function without alternation in DNA sequence. Major epigenetic mechanisms include DNA methylation, histone modification, and non-coding RNAs. The epigenetic implications for susceptibility to injury and its severity are important. Epigenetic may lead to the identification of novel markers in the field of neuroapoptosis. Animal studies have shown exposure to general anesthesia during the critical period of brain development, modulates expression, and function of the cAMP-responsive element binding protein (CREB) and CREB-binding protein (CBP), which are important in the regulation of expression several genes required for memory formation. In fact, the two key transcription factors are CREB and CBP. Accordingly, their modulation results in epigenetic changes and histone hypoacetylation, and consequently causes down regulation of c-Fos and brain-derived neurotrophic factor (BDNF). Regarding, both play a critical role in neuronal formation and function (Dalla Massara et al. 2016; Wu and Zhao 2018).

MiRNA-124 can reduce isoflurane and ketamine induced neurologic disorder. Treatment with miRNA-124 agomir enhances memory capacity and resistance to apoptosis. Accordingly, it is due to brain-derived neurotrophic factor (BDNF) elevation and decreased expression of neuroapoptotic factors including cleaved-caspase3 and Bax. MiRNA24 reduces isoflurane induced neurological deficit through prevention of early growth response 1(EGR1) expression. EGR1 gene encoded EGR family of Cys_2His_2type zinc finger proteins. Several studies suggested that it plays a role

in neuronal plasticity and synaptic exocytosis (Xu et al. 2015; Dabbagh 2016; Yang et al. 2019).

miRNA137 plays an important role in ketamine induced hippocampal neurodegeneration. Excessive use of ketamine causes severe hippocampal neuron apoptosis and also long-term memory deficit. Repeated anesthesia induced the miRNA down regulation. Cell division control protein 42 (CDC42) is the molecular target of miRNA137 and drops with ketamine usage. Neuroprotective effect against anesthesia induced through miRNA137 up regulation. In this regard, lentiviruses injection of miR137-mimics and miR137-NC into cortex have neuroprotective αIn sevoflurane anesthesia, miRNA-410-3p showed neuroprotective effect through PI3K/Akt (phosphoinositide 3-kinase/ serine, threonine kinase) signaling pathway and targeting CXCR5(C-X-C motif chemokine receotor5). This pathway can be activated by many types of cellular stimuli or toxic insults, and can also regulate many fundamental cellular functions. Activated PI3K phosphorylates AKT, thereby activating it. Akt controls a number of downstream cellular processes including apoptosis, protein synthesis, metabolism, and cell cycle, by phosphorylating a range of substrates. $IL_{6,}$ TNF-$\alpha_{,}$ $IL_{1\beta}$ have increased during sevoflurane anesthesia, in contrast miRNA-410-3p agomir attenuate inflammation (Su et al. 2019).

Sevoflurane anesthesia in new-born have significant effect on hippocampal and total brain miRNA expression that occurs immediately after exposure while in adults appears in longer duration (Lin et al. 2018). Protective role of miRNA665 through PI3K/AKt signaling pathway, by targeting Insulin like growth factor2 (IGF2) has been demonstrated; therefore, it can be used as a potential target in sevoflurane induced cognitive disorder (Lu et al. 2017). In contrast, miRNA34a up regulation increases sevoflurane induced hippocampal apoptosis; therefore, miRNA-34a inhibitor may prevent sevoflurane induced apoptosis via activation of Wnt/β catenin pathway. This pathway plays an important role in neurogenesis and hippocampal neurodegenerative disorder (Jiang et al. 2014; Libro et al. 2016).

MiRNA34-a by targeting Wnt1 and inactivation of Wnt/β catenin pathway, can suppress tumor growth. This miRNA inducts down regulation of fibroblast growth factor receptor1 (FGFR1), so anesthetic apoptosis is exacerbated. MiRNA34-a inhibitor can be considered as a novel treatment for sevoflurane neuroapoptosis (Chen and Hu 2012; Zhao et al. 2018).

MiRNA 34c is involved in the Alzheimer pathogenesis, and can be increased obviously with ketamine anesthesia. Down regulation of miRNA34c activate protein kinase C-extracellular signal regulated kinase (PKC/ERK) pathway and up regulate Bcl2 protein, thus attenuate ketamine induced apoptosis. Bcl2 is localized to the outer membrane of mitochondria, where it plays an important role in promoting cellular survival and inhibiting the actions of proapoptotic proteins. The proapoptic proteins in the Bcl2 family including Bax and Bak. Bcl2 is an antiapoptotic protein (Cao et al. 2015).

MiRNA96 augment sevoflurane effect on hippocampal neurons through insulin like growth factor receptor (IGF1R) down regulation (Xu et al. 2019). MiRNA125b-5p and miRNA188-3p are related to sevoflurane induced cognitive disorder, so

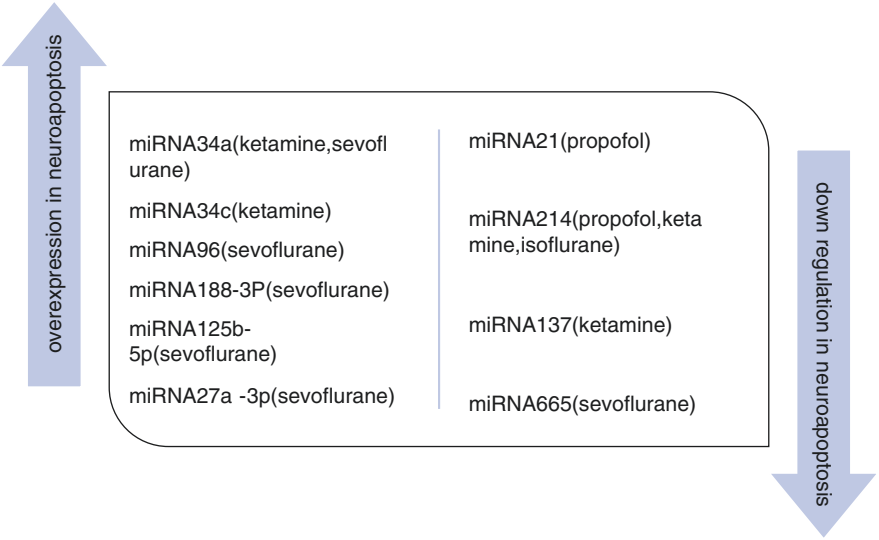

Fig. 7.3 The miRNAs alternations in anesthesia induced neuronal apoptosis

accordingly, their inhibitors can be used for apoptosis reduction. MiRNAs that affected neuroapoptosis are summarized in Fig. 7.3 (Wang et al. 2018; Xiong et al. 2019).

Anesthetic drugs induced cognitive disorder is associated with hippocampal neuroinflammation. Glycyrrhizin is used for the treatment of neurodegenerative or inflammatory diseases. It can activate hippocampal high mobility group box1 protein/ nuclear factor kappa-light-chain-enhancer of activated B cells (HMGB1/ NFKβ) signaling pathway and attenuate inflammatory cytokines and Isoflurane induced neurotoxicity. Also, it can be a potential treatment for neuroapoptosis (Wang et al. 2016a; Kong et al. 2017).

Isoflurane and other volatiles cause permanent and long-lasting changes in hippocampal proteins, similar to changes observed in Alzheimer's disease. Isoflurane induces biological processes involving synaptic plasticity, stress response, detoxification, and cytoskeleton (Kalenka et al. 2010). After exposure to isoflurane and halothane, metabolic proteins alter (Dabbagh and Rajaei 2013). Down regulation of fructose-bisphosphate aldolase and upregulation of glyceraldehyde-3-phosphate-dehydrogenase (GAPDH) and GST occur. Synaptic proteins also change, and the suggesting that synapse can act as a cellular target in anesthesia, is enhanced. Voltage dependent anion channel (VDAC) is a membrane protein that is likely to be involved as an apoptotic regulator in neurodegenerative diseases. Also, its interaction with sevoflurane can cause apoptosis.

Expression of three proteins change with both halothane and isoflurane.

- Tubulin B2A chains
- Heat shock protein cognate 71 KD

– N acetylneuraminate tidylyl transferase: It is responsible for sialoglycoprotein synthesis that is necessary for prenatal brain development and postnatal synaptogenic (Kalenka et al. 2007; Pan et al. 2008).

Ketamine and Developing Brain

Ketamine is an NMDA antagonist that is recognized as one of the potent drugs in developing brain neuroapoptosis. Many studies have been done on the effects of ketamine on the fetus and neonatal brain. The fetal and neonatal brain is sensitive to ketamine, and it has been shown that exposure for 5 h is sufficient for inducing significant neuroapoptosis. Animal studies have shown that the use of NMDA antagonists or GABA agonists by the pregnant mother in clinically dose, even single or brief exposure, can trigger neuroapoptosis. Drugs such as ethanol, phencyclidine, ketamine, N2O, barbiturates, benzodiazepines, and many of anticonvulsants and sedatives can induce apoptosis and long-term neurocognitive disorders. An animal study has shown that ketamine induced apoptosis is more diffuse and wider in fetal brain that of rhesus macaque neonates, using Activated caspase-3(AC3) immunohistochemistry, that identifies drug induced developmental neuronal death. The peak sensitivity of the fetus to NMDA antagonists is the third trimester, which is known as the development period (Zou et al. 2009; Brambrink et al. 2010; Joselyn et al. 2010; Brambrink et al. 2012).

Safety of ketamine as adjunct drug in neuraxial children block especially caudal block is in doubt. Ketamine dose used in the neuraxial block (0.5–1 mg/kg) in close to the intravenous anesthesia induction dose (2 mg/kg), and because ketamine is a lipid-soluble drug, its concentration rapidly rises in plasma and CSF, after epidural injection. In addition, animal studies have shown neuroapoptotic effect of ketamine on the spinal cord in rat neonates (Sanders et al. 2008; Lönnqvist and Walker 2012).

Glycogen synthase kinase-3β (GSK-3β) is a multifunctional enzyme that regulate neurogenesis, neuronal polarization, axon development, and synaptogenesis in developing brain. This kinase is related to neurodegenerative disorders and ketamine enhances GSK-3β induced neuroapoptosis. Ketamine decreases GSK-3β phosphorylation dependent on during of exposure. Coadministration of lithium, which is an inhibitor of GSK-3β, decreases this response (Liu et al. 2012, 2013).

Neuroprotective Agents

– Dexmedetomidine: A selective α_2 agonists attenuate sevoflurane induced cognitive disorder. Pre-treatment with dexmedetomidine is neuroprotective against volatiles and propofol in rat neonates.

Antiapoptotic expression agents, Bcl2 and PERK protein reserve by dexmedetomidine; however it is not FDA approved for neonates and children yet, and maybe causes dose dependent bradycardia and hypotension (Li et al. 2014; Wang et al. 2016a).
- Melatonin: stabilizes mitochondrial membrane and reduces apoptosis.
- Estradiol (17-β estradiol), xenon, L-Carnitine, lithium, and hypothermia are neuroprotective via various mechanisms.
- Naringenin, that is a flavonoid, can protect isoflurane induced neuroapoptosis through the regulation of PI3K/AKt pathway, decreasing inflammatory mediators and elevation of the level of antiapoptotic proteins such as Bcl2 and Bcl-xl (Hua et al. 2016).

Research on neuroapoptosis is rapidly growing and it is hoped that the results of molecular and animal studies will be applied in clinical practice.

Retinopathy of Prematurity

ROP is an eye vasoproliferative disorder affecting the premature neonates. It is one of the visual loss causes in children even in developed countries. Also, ROP pathogenesis is not fully understood. Associated environmental factors include preterm gestational age and supplemental oxygen exposure, but these factors cannot predict severity of ROP necessarily. In this case, the possible roles of other factors including genetic variants have been considered. Familial exudative vitreoretinopathy (FEVR) is an inherited disorder with clinical symptoms similar to ROP. Three genes involved in wingless/int1 (wnt) receptor signaling pathway are associated with FEVR progression. FZD4 for frizzled 4, LRP5 for low density lipoprotein receptor related protein 5, and ND for Norrie disease protein (Bizzarro et al. 2006, Hiraoka et al. 2010; Shastry 2010). The role of these genes variation in advanced ROP is demonstrated. Further studies involving genomics, transcriptomics, and proteomics are needed to obtain better understanding of the pathophysiology and management of ROP (Hiraoka et al. 2001; Kondo et al. 2013).

References

Afshari A. Clonidine in pediatric anesthesia: the new panacea or a drug still looking for an indication? Curr Opin Anaesthesiol. 2019;32(3):327–33.

Aghajani M, Imani A, Faghihi M, Vaez Mahdavi MR, Mahboubi S, Moradi F, Kazemi Moghaddam E. Does increased nitric oxide production and oxidative stress due to high fat diet affect cardiac function after myocardial infarction? J Cell Mol Anesth. 2017;2(1):3–8.

Aklillu E, Herrlin K, Gustafsson LL, Bertilsson L, Ingelman-Sundberg M. Evidence for environmental influence on CYP2D6-catalysed debrisoquine hydroxylation as demonstrated by phenotyping and genotyping of Ethiopians living in Ethiopia or in Sweden. Pharmacogenetics. 2002;12(5):375–83.

Alvarellos ML, McDonagh EM, Patel S, McLeod HL, Altman RB, Klein TE. PharmGKB summary: succinylcholine pathway, pharmacokinetics/pharmacodynamics. Pharmacogenet Genomics. 2015;25(12):622–30.

Ama T, Bounmythavong S, Blaze J, Weismann M, Marienau MS, Nicholson WT. Implications of pharmacogenomics for anesthesia providers. AANA J. 2010;78(5):393–9.

Andropoulos DB. Effect of anesthesia on the developing brain: infant and fetus. Fetal Diagn Ther. 2018;43(1):1–11.

Andropoulos DB, Greene MF. Anesthesia and developing brains—implications of the FDA warning. N Engl J Med. 2017;376(10):905–7.

Araki H, Fujiwara Y, Shimada Y. Effect of flumazenil on recovery from sevoflurane anesthesia in children premedicated with oral midazolam before undergoing herniorrhaphy with or without caudal analgesia. J Anesth. 2005;19(3):204–7 (0913-8668 (Print)).

Arboleda VA, Garner OB. Ensuring the quality of point-of-care testing in a large and decentralized ambulatory care setting. Am J Clin Pathol. 2017;148(4):336–44.

Aroke EN, Crawford SL, Dungan JR. Pharmacogenetics of ketamine-induced emergence phenomena: a pilot study. Nurs Res. 2017;66(2):105–14.

Atkins JH, Johansson JS. Technologies to shape the future: proteomics applications in anesthesiology and critical care medicine. Anesth Analg. 2006;102(4):1207–16.

Awad H, Ahmed A, Urman RD, Stoicea N, Bergese SD. Potential role of pharmacogenomics testing in the setting of enhanced recovery pathways after surgery. Pharmgenomics Pers Med. 2019;12:145–54.

Bagheri B, Razavi S, Gohari A, Salarian S, Dabbagh A. Toll-like receptor 4 in ventilator-induced lung injuries: mechanism of disease. J Cell Mol Anesth. 2016;1(1):34–9.

Balyan R, Zhang X, Chidambaran V, Martin LJ, Mizuno T, Fukuda T, Vinks AA, Sadhasivam S. OCT1 genetic variants are associated with postoperative morphine-related adverse effects in children. Pharmacogenomics. 2017;18(7):621–9.

Bamedi T, Dadashizadeh G, Sarabandi A, Tabibian S, Shams M, Dorgalaleh A. Genetic risk factors for inhibitor development in patients with hemophilia and rare bleeding disorders. J Cell Mol Anesth. 2017;2(1):19–23.

Basel A, Bajic D. Preoperative evaluation of the pediatric patient. Anesthesiol Clin. 2018;36(4):689–700.

Batas D, Nejad MR, Prabhu PK. Resistance to local anaesthetics: a case report. BJA Br J Anaesth. 2007; 99(eLetters Suppl).

Bauernfeind F, Rieger A, Schildberg FA, Knolle PA, Schmid-Burgk JL, Hornung V. NLRP3 inflammasome activity is negatively controlled by miR-223. J Immunol. 2012;189(8):4175–81.

Bilkey GA, Burns BL, Coles EP, Mahede T, Baynam G, Nowak KJ. Optimizing precision medicine for public health. Front Public Health. 2019;7:42.

Bizzarro MJ, Hussain N, Jonsson B, Feng R, Ment LR, Gruen JR, Zhang H, Bhandari V. Genetic susceptibility to retinopathy of prematurity. Pediatrics. 2006;118(5):1858–63.

Bogusaite L, Razlevice I, Lukosiene L, Macas A. Evaluation of preoperative information needs in pediatric anesthesiology. Med Sci Monit. 2018;24:8773–80.

Boldin MP, Taganov KD, Rao DS, Yang L, Zhao JL, Kalwani M, Garcia-Flores Y, Luong M, Devrekanli A, Xu J, Sun G, Tay J, Linsley PS, Baltimore D. miR-146a is a significant brake on autoimmunity, myeloproliferation, and cancer in mice. J Exp Med. 2011;208(6):1189–201.

Boscolo A, Starr JA, Sanchez V, Lunardi N, DiGruccio MR, Ori C, Erisir A, Trimmer P, Bennett J, Jevtovic-Todorovic V. The abolishment of anesthesia-induced cognitive impairment by timely protection of mitochondria in the developing rat brain: the importance of free oxygen radicals and mitochondrial integrity. Neurobiol Dis. 2012;45(3):1031–41.

Bradford LD. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. Pharmacogenomics. 2002;3(2):229–43.

Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, Zhang X, Dissen GA, Creeley CE, Olney JW. Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. Anesthesiology. 2010;112(4):834–41.

Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, Martin LD, Dissen GA, Creeley CE, Olney JW. Ketamine-induced neuroapoptosis in the fetal and neonatal rhesus macaque brain. Anesthesiology. 2012;116(2):372–84.

Brussee JM, Vet NJ, Krekels EHJ, Valkenburg AJ, Jacqz-Aigrain E, van Gerven JMA, Swart EL, van den Anker JN, Tibboel D, de Hoog M, de Wildt SN, Knibbe CAJ. Predicting CYP3A-mediated midazolam metabolism in critically ill neonates, infants, children and adults with inflammation and organ failure. Br J Clin Pharmacol. 2018;84(2):358–68.

Callis TE, Pandya K, Seok HY, Tang RH, Tatsuguchi M, Huang ZP, Chen JF, Deng Z, Gunn B, Shumate J, Willis MS, Selzman CH, Wang DZ. MicroRNA-208a is a regulator of cardiac hypertrophy and conduction in mice. J Clin Invest. 2009;119(9):2772–86.

Candiotti KA, Birnbach DJ, Lubarsky DA, Nhuch F, Kamat A, Koch WH, Nikoloff M, Wu L, Andrews D. The impact of pharmacogenomics on postoperative nausea and vomiting: do CYP2D6 allele copy number and polymorphisms affect the success or failure of ondansetron prophylaxis? Anesthesiol J Am Soc Anesthesiol. 2005;102(3):543–9.

Cao SE, Tian J, Chen S, Zhang X, Zhang Y. Role of miR-34c in ketamine-induced neurotoxicity in neonatal mice hippocampus. Cell Biol Int. 2015;39(2):164–8.

Caplan LA, Felberg M. Anesthetic considerations in medium-chain acyl-CoA dehydrogenase deficiency. J Cell Mol Anesth. 2017;2(2):69–76.

Catterall WA, Kalume F, Oakley JC. NaV1.1 channels and epilepsy. J Physiol. 2010;588(Pt 11):1849–59.

Chatrath V, Kumar R, Sachdeva U, Thakur M. Intranasal fentanyl, midazolam and dexmedetomidine as premedication in pediatric patients. Anesth Essays Res. 2018;12(3):748–53.

Chau DF, Reddy A, Breheny P, Young AR, Ashford E, Song M, Zhang C, Taylor T, Younes A, Vazifedan T. Revisiting the applicability of adult early post-operative nausea and vomiting risk factors for the paediatric patient: a prospective study using cotinine levels in children undergoing adenotonsillectomies. Indian J Anaesth. 2017;61(12):964–71.

Chen F, Hu SJ. Effect of microRNA-34a in cell cycle, differentiation, and apoptosis: a review. J Biochem Mol Toxicol. 2012;26(2):79–86.

Chennou F, Bonneau-Fortin A, Portolese O, Belmesk L, Jean-Pierre M, Cote G, Dirks MH, Jantchou P. Oral lorazepam is not superior to placebo for lowering stress in children before digestive endoscopy: a double-blind, randomized, controlled trial. Paediatr Drugs. 2019;21(5):379–87.

Chidambaran V, Ngamprasertwong P, Vinks AA, Sadhasivam S. Pharmacogenetics and anesthetic drugs. Curr Clin Pharmacol. 2012;7(2):78–101.

Chidambaran V, Costandi A, D'Mello A. Propofol: a review of its role in pediatric anesthesia and sedation. CNS Drugs. 2015;29(7):543–63.

Chidambaran V, Sadhasivam S, Mahmoud M. Codeine and opioid metabolism: implications and alternatives for pediatric pain management. Curr Opin Anaesthesiol. 2017a;30(3):349–56.

Clendenen N, Cannon AD, Porter S, Robards CB, Parker AS, Clendenen SR. Whole-exome sequencing of a family with local anesthetic resistance. Minerva Anestesiol. 2016;82(10):1089–97.

Coleman K, Robertson ND, Dissen GA, Neuringer MD, Martin LD, Cuzon Carlson VC, Kroenke C, Fair D, Brambrink AM. Isoflurane anesthesia has long-term consequences on motor and behavioral development in infant rhesus macaques. Anesthesiol J Am Soc Anesthesiol. 2017;126(1):74–84.

Cook-Sather SD, Li J, Goebel TK, Sussman EM, Rehman MA, Hakonarson H. TAOK3, a novel genome-wide association study locus associated with morphine requirement and postoperative pain in a retrospective pediatric day surgery population. Pain. 2014;155(9):1773–83.

Cook-Sather SD, Adamson PC, Li J, Hakonarson H. CYP2B6*6 or not CYP2B6*6-that remains a question for precision medicine and ketamine! Anesthesiology. 2016;125(6):1085–7.

Cravero JP, Agarwal R, Berde C, Birmingham P, Cote CJ, Galinkin J, Isaac L, Kost-Byerly S, Krodel D, Maxwell L, Voepel-Lewis T, Sethna N, Wilder R. The Society for Pediatric Anesthesia recommendations for the use of opioids in children during the perioperative period. Paediatr Anaesth. 2019;29(6):547–71.

Creeley CE. From drug-induced developmental neuroapoptosis to pediatric anesthetic neurotoxicity—where are we now? Brain Sci. 2016;6(3):32.
Crews KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, Haidar CE, Shen DD, Callaghan JT, Sadhasivam S, Prows CA, Kharasch ED, Skaar TC. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther. 2014;95(4):376–82.
Dabbagh A. Clonidine: an old friend newly rediscovered. Anesth Pain. 2011;1(1):8–9.
Dabbagh A. Microglial cells: the bridge between the immune system and pain in the central nervous system. J Cell Mol Anesth. 2016;1(4):135–6.
Dabbagh A, Rajaei S. The role of anesthetic drugs in liver apoptosis. Hepat Mon. 2013;13(8): e13162.
Dahmani S, Delivet H, Hilly J. Emergence delirium in children: an update. Curr Opin Anaesthesiol. 2014;27(3):309–15.
Dalla Massara L, Osuru HP, Oklopcic A, Milanovic D, Joksimovic SM, Caputo V, DiGruccio MR, Ori C, Wang G, Todorovic SM, Jevtovic-Todorovic V. General anesthesia causes epigenetic histone modulation of c-fos and brain-derived neurotrophic factor, target genes important for neuronal development in the immature rat hippocampus. Anesthesiology. 2016;124(6):1311–27.
Dave NM. Premedication and induction of anaesthesia in paediatric patients. Indian J Anaesth. 2019;63(9):713–20.
de Fontnouvelle CA, Greenberg JH, Thiessen-Philbrook HR, Zappitelli M, Roth J, Kerr KF, Devarajan P, Shlipak M, Coca S, Parikh CR. Interleukin-8 and tumor necrosis factor predict acute kidney injury after pediatric cardiac surgery. Ann Thorac Surg. 2017;104(6):2072–9.
De Gregori M, Diatchenko L, Ingelmo PM, Napolioni V, Klepstad P, Belfer I, Molinaro V, Garbin G, Ranzani GN, Alberio G, Normanno M, Lovisari F, Somaini M, Govoni S, Mura E, Bugada D, Niebel T, Zorzetto M, De Gregori S, Molinaro M, Fanelli G, Allegri M. Human genetic variability contributes to postoperative morphine consumption. J Pain. 2016;17(5):628–36.
Demirgan S, Akyol O, Temel Z, Şengelen A, Pekmez M, Demirgan R, Sevdi MS, Erkalp K, Selcan A. Isoflurane exposure in infant rats acutely increases aquaporin 4 and does not cause neurocognitive impairment. Bosn J Basic Med Sci. 2019;19(3):257–64.
Devarajan P, Krawczeski CD, Nguyen MT, Kathman T, Wang Z, Parikh CR. Proteomic identification of early biomarkers of acute kidney injury after cardiac surgery in children. Am J Kidney Dis. 2010;56(4):632–42.
Dierdorf SF, McNiece WL. Succinylcholine-induced hyperkalemia in children: the case that led to the studies. J Anesth Hist. 2018;4(2):147.
Dinis-Oliveira RJ. Metabolism and metabolomics of ketamine: a toxicological approach. Forensic Sci Res. 2017;2(1):2–10.
Elens L, van Gelder T, Hesselink DA, Haufroid V, van Schaik RH. CYP3A4*22: promising newly identified CYP3A4 variant allele for personalizing pharmacotherapy. Pharmacogenomics. 2013;14(1):47–62.
Elkomy MH, Drover DR, Glotzbach KL, Galinkin JL, Frymoyer A, Su F, Hammer GB. Pharmacokinetics of morphine and its metabolites in infants and young children after congenital heart surgery. AAPS J. 2016;18(1):124–33.
Fani K, Hashem-Aghaei M, Jelveh-Moghaddam HA, Radmand G, Foroughi M, Rajaei S, Dabbagh A. The relationship between s100β and cerebral oximetry trend in patients undergoing CABG with cardiopulmonary bypass. J Cell Mol Anesth. 2018;3(2):47–53.
Fazi F, Rosa A, Fatica A, Gelmetti V, De Marchis ML, Nervi C, Bozzoni I. A minicircuitry comprised of microRNA-223 and transcription factors NFI-A and C/EBPalpha regulates human granulopoiesis. Cell. 2005;123(5):819–31.
Fazi F, Racanicchi S, Zardo G, Starnes LM, Mancini M, Travaglini L, Diverio D, Ammatuna E, Cimino G, Lo-Coco F, Grignani F, Nervi C. Epigenetic silencing of the myelopoiesis regulator microRNA-223 by the AML1/ETO oncoprotein. Cancer Cell. 2007;12(5):457–66.
Frelich M, Divák J, Vodička V, Masárová M, Jor O, Gál R. Dexamethasone reduces the incidence of postoperative nausea and vomiting in children undergoing endoscopic adenoidectomy under

general anesthesia without increasing the risk of postoperative hemorrhage. Med Sci Monit. 2018;24:8430–8.
Gabriel RA, Ehrenfeld JM, Urman RD. Preoperative genetic testing and personalized medicine: changing the care paradigm. J Med Syst. 2017;41(12):185.
Galinkin JL, Demmer L, Yaster M. Genetics for the pediatric anesthesiologist: a primer on congenital malformations, pharmacogenetics, and proteomics. Anesth Analg. 2010;111(5):1264–74.
Gammal RS, Crews KR, Haidar CE, Hoffman JM, Baker DK, Barker PJ, Estepp JH, Pei D, Broeckel U, Wang W, Weiss MJ, Relling MV, Hankins J. Pharmacogenetics for safe codeine use in sickle cell disease. Pediatrics. 2016;138(1)
Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, Watcha M, Chung F, Angus S, Apfel CC, Bergese SD, Candiotti KA, Chan MT, Davis PJ, Hooper VD, Lagoo-Deenadayalan S, Myles P, Nezat G, Philip BK, Tramèr MR. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2014;118(1):85–113. (1526-7598 (Electronic))
Gaynor JW, Kim DS, Arrington CB, Atz AM, Bellinger DC, Burt AA, Ghanayem NS, Jacobs JP, Lee TM, Lewis AB, Mahle WT, Marino BS, Miller SG, Newburger JW, Pizarro C, Ravishankar C, Santani AB, Wilder NS, Jarvik GP, Mital S, Russell MW. Validation of association of the apolipoprotein E epsilon2 allele with neurodevelopmental dysfunction after cardiac surgery in neonates and infants. J Thorac Cardiovasc Surg. 2014;148(6):2560–6.
Gillies RL, Bjorksten AR, Du Sart D, Hockey BM. Analysis of the entire ryanodine receptor type 1 and alpha 1 subunit of the dihydropyridine receptor (CACNA1S) coding regions for variants associated with malignant hyperthermia in Australian families. Anaesth Intensive Care. 2015;43(2):157–66.
Giudice G, Petsalaki E. Proteomics and phosphoproteomics in precision medicine: applications and challenges. Brief Bioinform. 2019;20(3):767–77.
Greenberg JH, Parikh CR. Biomarkers for diagnosis and prognosis of AKI in children: one size does not fit all. Clin J Am Soc Nephrol. 2017;12(9):1551–7.
Greenberg JH, Zappitelli M, Jia Y, Thiessen-Philbrook HR, de Fontnouvelle CA, Wilson FP, Coca S, Devarajan P, Parikh CR. Biomarkers of AKI progression after pediatric cardiac surgery. J Am Soc Nephrol. 2018;29(5):1549–56.
Grueter CE, van Rooij E, Johnson BA, DeLeon SM, Sutherland LB, Qi X, Gautron L, Elmquist JK, Bassel-Duby R, Olson EN. A cardiac microRNA governs systemic energy homeostasis by regulation of MED13. Cell. 2012;149(3):671–83.
Hijazi Y, Boulieu R. Contribution of CYP3A4, CYP2B6, and CYP2C9 isoforms to N-demethylation of ketamine in human liver microsomes. Drug Metab Dispos. 2002;30(7):853–8.
Hiraoka M, Berinstein DM, Trese MT, Shastry BS. Insertion and deletion mutations in the dinucleotide repeat region of the Norrie disease gene in patients with advanced retinopathy of prematurity. J Hum Genet. 2001;46(4):178–81.
Hiraoka M, Takahashi H, Orimo H, Hiraoka M, Ogata T, Azuma N. Genetic screening of Wnt signaling factors in advanced retinopathy of prematurity. Mol Vis. 2010;16:2572–7.
Holliday SF, Kane-Gill SL, Empey PE, Buckley MS, Smithburger PL. Interpatient variability in dexmedetomidine response: a survey of the literature. ScientificWorldJournal. 2014;2014:805013.
Hopkins PM, Ruffert H, Snoeck MM, Girard T, Glahn KP, Ellis FR, Muller CR, Urwyler A. European Malignant Hyperthermia Group guidelines for investigation of malignant hyperthermia susceptibility. Br J Anaesth. 2015;115(4):531–9.
Horstick EJ, Linsley JW, Dowling JJ, Hauser MA, McDonald KK, Ashley-Koch A, Saint-Amant L, Satish A, Cui WW, Zhou W, Sprague SM, Stamm DS, Powell CM, Speer MC, Franzini-Armstrong C, Hirata H, Kuwada JY. Stac3 is a component of the excitation-contraction coupling machinery and mutated in Native American myopathy. Nat Commun. 2013;4:1952.
Hua FZ, Ying J, Zhang J, Wang XF, Hu YH, Liang YP, Liu Q, Xu GH. Naringenin pre-treatment inhibits neuroapoptosis and ameliorates cognitive impairment in rats exposed to isoflurane anesthesia by regulating the PI3/Akt/PTEN signalling pathway and suppressing NF-kappaB-mediated inflammation. Int J Mol Med. 2016;38(4):1271–80.

Huang C, Zhang X, Zheng J, Chen C, Chen Y, Yi J. Upregulation of miR-137 protects anesthesia-induced hippocampal neurodegeneration. Int J Clin Exp Pathol. 2014;7(8):5000–7.
Iravani M, Lee LK, Cannesson M. Standardized care versus precision medicine in the perioperative setting: can point-of-care testing help bridge the gap? Anesth Analg. 2017;124(4):1347–53.
Jabbary Moghaddam M, Ommi D, Mirkheshti A, Dabbagh A, Memary E, Sadeghi A, Yaseri M. Effects of clonidine premedication upon postoperative shivering and recovery time in patients with and without opium addiction after elective leg fracture surgeries. Anesth Pain Med. 2013;2(3):107–10.
Jain A, Gombar S, Ahuja V. Recovery profile after general anaesthesia in paediatric ambulatory surgeries: desflurane versus propofol. Turk J Anaesthesiol Reanim. 2018;46(1):21–7.
Jiang XL, Du BX, Chen J, Liu L, Shao WB, Song J. MicroRNA-34a negatively regulates anesthesia-induced hippocampal apoptosis and memory impairment through FGFR1. Int J Clin Exp Pathol. 2014;7(10):6760–7.
Joselyn AS, Cherian VT, Joel S. Ketamine for labour analgesia. Int J Obstet Anesth. 2010;19(1):122–3.
Kajimoto M, Atkinson DB, Ledee DR, Kayser EB, Morgan PG, Sedensky MM, Isern NG, Des Rosiers C, Portman MA. Propofol compared with isoflurane inhibits mitochondrial metabolism in immature swine cerebral cortex. J Cereb Blood Flow Metab. 2014;34(3):514–21.
Kalenka A, Hinkelbein J, Feldmann RE, Jr, Kuschinsky W, Waschke KF, Maurer MH. The effects of sevoflurane anesthesia on rat brain proteins: a proteomic time-course analysis. Anesth Analg. 2007;104(5):1129–35, tables of contents.
Kalenka A, Gross B, Maurer MH, Thierse HJ, Feldmann RE Jr. Isoflurane anesthesia elicits protein pattern changes in rat hippocampus. J Neurosurg Anesthesiol. 2010;22(2):144–54.
Kamata M, Tobias JD. Remifentanil: applications in neonates. J Anesth. 2016;30(3):449–60.
Kapoor MC, Vakamudi M. Desflurane—revisited. J Anaesthesiol Clin Pharmacol. 2012;28(1):92–100.
Kaur H, Katyal N, Yelam A, Kumar K, Srivastava H, Govindarajan R. Malignant hyperthermia. Mo Med. 2019;116(2):154–9.
Kaye AD, Garcia AJ, Hall OM, Jeha GM, Cramer KD, Granier AL, Kallurkar A, Cornett EM, Urman RD. Update on the pharmacogenomics of pain management. Pharmgenomics Pers Med. 2019;12:125–43.
Kaymak C, Karahalil B, Ozcan NN, Oztuna D. Association between GSTP1 gene polymorphism and serum alpha-GST concentrations undergoing sevoflurane anaesthesia. Eur J Anaesthesiol. 2008;25(3):193–9.
Khan J, Liu M. Desflurane. StatPearls. Treasure Island, FL: StatPearls; 2020.
Khan MS, Zetterlund EL, Green H, Oscarsson A, Zackrisson AL, Svanborg E, Lindholm ML, Persson H, Eintrei C. Pharmacogenetics, plasma concentrations, clinical signs and EEG during propofol treatment. Basic Clin Pharmacol Toxicol. 2014;115(6):565–70.
Kim YB, Sung TY, Yang HS. Factors that affect the onset of action of non-depolarizing neuromuscular blocking agents. Korean J Anesthesiol. 2017;70(5):500–10.
Kim S, Hahn S, Jang MJ, Choi Y, Hong H, Lee JH, Kim HS. Evaluation of the safety of using propofol for paediatric procedural sedation: a systematic review and meta-analysis. Sci Rep. 2019;9(1):12245.
Kirchheiner J, Schmidt H, Tzvetkov M, Keulen JT, Lotsch J, Roots I, Brockmoller J. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. Pharmacogenomics J. 2007;7(4):257–65.
Klingler W, Heiderich S, Girard T, Gravino E, Heffron JJ, Johannsen S, Jurkat-Rott K, Ruffert H, Schuster F, Snoeck M, Sorrentino V, Tegazzin V, Lehmann-Horn F. Functional and genetic characterization of clinical malignant hyperthermia crises: a multi-centre study. Orphanet J Rare Dis. 2014;9:8.
Kodama M, Satoh Y, Otsubo Y, Araki Y, Yonamine R, Masui K, Kazama T. Neonatal desflurane exposure induces more robust neuroapoptosis than do isoflurane and sevoflurane and impairs working memory. Anesthesiology. 2011;115(5):979–91.

Kondo H, Kusaka S, Yoshinaga A, Uchio E, Tawara A, Tahira T. Genetic variants of FZD4 and LRP5 genes in patients with advanced retinopathy of prematurity. Mol Vis. 2013;19:476–85.
Kong ZH, Chen X, Hua HP, Liang L, Liu LJ. The oral pretreatment of glycyrrhizin prevents surgery-induced cognitive impairment in aged mice by reducing neuroinflammation and Alzheimer's-related pathology via HMGB1 inhibition. J Mol Neurosci. 2017;63(3–4):385–95.
Kovesdi E, Luckl J, Bukovics P, Farkas O, Pal J, Czeiter E, Szellar D, Doczi T, Komoly S, Buki A. Update on protein biomarkers in traumatic brain injury with emphasis on clinical use in adults and pediatrics. Acta Neurochir (Wien). 2010;152(1):1–17.
Krasniak AE, Knipp GT, Svensson CK, Liu W. Pharmacogenomics of acetaminophen in pediatric populations: a moving target. Front Genet. 2014;5:314.
LaCroix-Fralish ML, Austin JS, Zheng FY, Levitin DJ, Mogil JS. Patterns of pain: meta-analysis of microarray studies of pain. Pain. 2011;152(8):1888–98.
Laudenbach V, Mantz J, Lagercrantz H, Desmonts JM, Evrard P, Gressens P. Effects of alpha(2)-adrenoceptor agonists on perinatal excitotoxic brain injury: comparison of clonidine and dexmedetomidine. Anesthesiology. 2002;96(1):134–41.
Le KN, Moffett BS, Ocampo EC, Zaki J, Mossad EB. Impact of dexmedetomidine on early extubation in pediatric cardiac surgical patients. Intensive Care Med. 2011;37(4):686–90.
Lee MG, Kim HJ, Lee KH, Choi YS. The influence of genotype polymorphism on morphine analgesic effect for postoperative pain in children. Korean J Pain. 2016;29(1):34–9.
Levy RJ, Herbstman JB, Bosnjak ZJ, Loepke AW, McGowan FX. Biomarkers, genetics, and epigenetic studies to explore the neurocognitive effects of anesthesia in children. J Neurosurg Anesthesiol. 2016;28(4):384–8.
Li Y, Coller JK, Hutchinson MR, Klein K, Zanger UM, Stanley NJ, Abell AD, Somogyi AA. The CYP2B6*6 allele significantly alters the N-demethylation of ketamine enantiomers in vitro. Drug Metab Dispos. 2013;41(6):1264–72.
Li Y, Zeng M, Chen W, Liu C, Wang F, Han X, Zuo Z, Peng S. Dexmedetomidine reduces isoflurane-induced neuroapoptosis partly by preserving PI3K/Akt pathway in the hippocampus of neonatal rats. PLoS One. 2014;9(4):e93639.
Li Y, Jackson KA, Slon B, Hardy JR, Franco M, William L, Poon P, Coller JK, Hutchinson MR, Currow DC, Somogyi AA. CYP2B6*6 allele and age substantially reduce steady-state ketamine clearance in chronic pain patients: impact on adverse effects. Br J Clin Pharmacol. 2015;80(2):276–84.
Libro R, Bramanti P, Mazzon E. The role of the Wnt canonical signaling in neurodegenerative diseases. Life Sci. 2016;158:78–88.
Liem EB, Lin CM, Suleman MI, Doufas AG, Gregg RG, Veauthier JM, Loyd G, Sessler DI. Anesthetic requirement is increased in redheads. Anesthesiology. 2004;101(2):279–83.
Lin D, Liu J, Hu Z, Cottrell JE, Kass IS. Neonatal anesthesia exposure impacts brain microRNAs and their associated neurodevelopmental processes. Sci Rep. 2018;8(1):10656.
Liu JR, Liu Q, Li J, Baek C, Han XH, Athiraman U, Soriano SG. Noxious stimulation attenuates ketamine-induced neuroapoptosis in the developing rat brain. Anesthesiology. 2012;117(1):64–71.
Liu JR, Baek C, Han XH, Shoureshi P, Soriano SG. Role of glycogen synthase kinase-3β in ketamine-induced developmental neuroapoptosis in rats. BJA Br J Anaesth. 2013;110(suppl_1):i3–9.
Liu Y, Li P, Cheng X, Yu W, Yang L, Zhu H. Plasma microRNA-21 predicts postoperative pulmonary complications in patients undergoing pneumoresection. Mediators Inflamm. 2016.
Loepke AW, Istaphanous GK, McAuliffe JJ 3rd, Miles L, Hughes EA, McCann JC, Harlow KE, Kurth CD, Williams MT, Vorhees CV, Danzer SC. The effects of neonatal isoflurane exposure in mice on brain cell viability, adult behavior, learning, and memory. Anesth Analg. 2009;108(1):90–104.
Lönnqvist P-A, Walker SM. Ketamine as an adjunct to caudal block in neonates and infants: is it time to re-evaluate? BJA Br J Anaesth. 2012;109(2):138–40.

Looney AM, Ahearne C, Boylan GB, Murray DM. Glial fibrillary acidic protein is not an early marker of injury in perinatal asphyxia and hypoxic-ischemic encephalopathy. Front Neurol. 2015;6:264.

Lopez RJ, Byrne S, Vukcevic M, Sekulic-Jablanovic M, Xu L, Brink M, Alamelu J, Voermans N, Snoeck M, Clement E, Muntoni F, Zhou H, Radunovic A, Mohammed S, Wraige E, Zorzato F, Treves S, Jungbluth H. An RYR1 mutation associated with malignant hyperthermia is also associated with bleeding abnormalities. Sci Signal. 2016;9(435):ra68.

Lu X, Lv S, Mi Y, Wang L, Wang G. Neuroprotective effect of miR-665 against sevoflurane anesthesia-induced cognitive dysfunction in rats through PI3K/Akt signaling pathway by targeting insulin-like growth factor 2. Am J Transl Res. 2017;9(3):1344–56.

Luo J, Chen S, Min S, Peng L. Reevaluation and update on efficacy and safety of neostigmine for reversal of neuromuscular blockade. Ther Clin Risk Manag. 2018;14:2397–406.

Mahmoodpoor A, Hamishehkar H, Sanaie S, Behruzizad N, Iranpour A, Koleini E, Nader ND. Antioxidant reserve of the lungs and ventilator-associated pneumonia: a clinical trial of high dose selenium in critically ill patients. J Crit Care. 2018;44:357–62.

Mahmoodpoor A, Hamishehkar H, Asghari R, Abri R, Shadvar K, Sanaie S. Effect of a probiotic preparation on ventilator-associated pneumonia in critically ill patients admitted to the intensive care unit: a prospective double-blind randomized controlled trial. Nutr Clin Pract. 2019a;34(1):156–62.

Marković D, Janković R, Veselinović I. Mutations in sodium channel gene SCN9A and the pain perception disorders. J Adv Anesthesiol. 2015;2015:6.

Mei Y, Wang SY, Li Y, Yi SQ, Wang CY, Yang M, Duan KM. Role of SLCO1B1, ABCB1, and CHRNA1 gene polymorphisms on the efficacy of rocuronium in Chinese patients. J Clin Pharmacol. 2015;55(3):261–8.

Mele C, Goldschmidt K. Personalized perioperative pediatric pain management: myth or reality? J Pediatr Nurs. 2017;32:85–7.

Men'shanov PN, Bannova AV, Il'inykh FA, Dygalo NN. Negative regulation of caspase-3 expression in the neonatal cerebral cortex by alpha2A-adrenoceptors. Bull Exp Biol Med. 2007;143(3):277–9.

Merchant ML, Brier ME, Slaughter MS, Klein JB, McLeish KR. Biomarker enhanced risk prediction for development of AKI after cardiac surgery. BMC Nephrol. 2018;19(1):102.

Miao J, Jin Y, Marunde RL, Gorski CJ, Kim S, Quinney S, Radovich M, Li L, Hall SD. Association of genotypes of the CYP3A cluster with midazolam disposition in vivo. Pharmacogenomics J. 2009;9(5):319–26.

Mieda T, Nishizawa D, Nakagawa H, Tsujita M, Imanishi H, Terao K, Yoshikawa H, Itoh K, Amano K, Tashiro J, Ishii T, Ariyama J, Yamaguchi S, Kasai S, Hasegawa J, Ikeda K, Kitamura A, Hayashida M. Genome-wide association study identifies candidate loci associated with postoperative fentanyl requirements after laparoscopic-assisted colectomy. Pharmacogenomics. 2016;17(2):133–45.

Mikstacki A, Skrzypczak-Zielinska M, Zakerska-Banaszak O, Tamowicz B, Skibinska M, Molinska-Glura M, Szalata M, Slomski R. Impact of CYP2E1, GSTA1 and GSTP1 gene variants on serum alpha glutathione S-transferase level in patients undergoing anaesthesia. BMC Med Genet. 2016;17(1):40.

Moghadam MJ, Ommi D, Mirkheshti A, Shadnoush M, Dabbagh A. The effect of pretreatment with clonidine on propofol consumption in opium abuser and non-abuser patients undergoing elective leg surgery. J Res Med Sci. 2012;17(8):728–31.

Montgomery RL, Hullinger TG, Semus HM, Dickinson BA, Seto AG, Lynch JM, Stack C, Latimer PA, Olson EN, van Rooij E. Therapeutic inhibition of miR-208a improves cardiac function and survival during heart failure. Circulation. 2011;124(14):1537–47.

Mottaghi K, Safari F, Sezari P, Gholizadeh N, Nashibi M. Anesthetic management of patients with Klippel-Feil syndrome, a case series. J Cell Mol Anesth. 2017;2(2):63–8.

Naderi M, Tabibian S, Alizadeh S, Dorgalaleh A. Coagulation factor XIII-a tyr204phe gene variation shows ethnic heterogeneity, an Iranian based study. J Cell Mol Anesth. 2016;1(1):19–22.

Nagele P, Brown F, Francis A, Scott MG, Gage BF, Miller JP. Influence of nitrous oxide anesthesia, B-vitamins, and MTHFR gene polymorphisms on perioperative cardiac events: the vitamins in nitrous oxide (VINO) randomized trial. Anesthesiology. 2013;119(1):19–28.
Nair AS. Pharmacogenomics of inhalational anesthetic agents. Med Gas Res. 2019;9(1):52–3.
Nasr VG, DiNardo JA, Faraoni D. Development of a pediatric risk assessment score to predict perioperative mortality in children undergoing noncardiac surgery. Anesth Analg. 2016;124(5):1514–9.
Nashibi M, Tajbakhsh A, Safari F, Mottaghi K. Anesthetic consideration of Niemann-Pick disease type C. J Cell Mol Anesth. 2016;1(1):73–7.
Nelson K, Nicholls C, Muckler VC. Pediatric review and perioperative considerations. J Perianesth Nurs. 2018;33(3):265–74.
Neudecker V, Brodsky KS, Kreth S, Ginde AA, Eltzschig HK. Emerging roles for microRNAs in perioperative medicine. Anesthesiology. 2016;124(2):489–506.
Nickalls RW, Mapleson WW. Age-related iso-MAC charts for isoflurane, sevoflurane and desflurane in man. Br J Anaesth. 2003;91(2):170–4.
Niewinski PA, Wojciechowski R, Sliwinski M, Hurkacz ME, Glowacka K, Orzechowska-Juzwenko K, Wiela-Hojenska AK. CYP2D6 basic genotyping as a potential tool to improve the antiemetic efficacy of ondansetron in prophylaxis of postoperative nausea and vomiting. Adv Clin Exp Med. 2018;27(11):1499–503.
Pacifici GM. Clinical pharmacology of midazolam in neonates and children: effect of disease-a review. Int J Pediatr. 2014;2014:309342.
Palmer SN, Giesecke NM, Body SC, Shernan SK, Fox AA, Collard CD. Pharmacogenetics of anesthetic and analgesic agents. Anesthesiology. 2005;102(3):663–71.
Pan JZ, Xi J, Eckenhoff MF, Eckenhoff RG. Inhaled anesthetics elicit region-specific changes in protein expression in mammalian brain. Proteomics. 2008;8(14):2983–92.
Park C, Park H, Kim K, Kang H, Lee S. The influence of GABA A γ2 genetic polymorphism on the emergence agitation induced by sevoflurane. Korean J Anesthesiol. 2008;55.
Park SK, Hur M, Kim E, Kim WH, Park JB, Kim Y, Yang JH, Jun TG, Kim CS. Risk factors for acute kidney injury after congenital cardiac surgery in infants and children: a retrospective observational study. PLoS One. 2016;11(11):e0166328.
Patti GJ, Yanes O, Shriver LP, Courade JP, Tautenhahn R, Manchester M, Siuzdak G. Metabolomics implicates altered sphingolipids in chronic pain of neuropathic origin. Nat Chem Biol. 2012;8(3):232–4.
Peco-Antic A, Ivanisevic I, Vulicevic I, Kotur-Stevuljevic J, Ilic S, Ivanisevic J, Miljkovic M, Kocev N. Biomarkers of acute kidney injury in pediatric cardiac surgery. Clin Biochem. 2013;46(13-14):1244–51.
Piazza O, De Benedictis G, Marinosci GFZ. Proteomics in anaesthesia and intensive care medicine; 2013.
Rahmatizadeh S, Valizadeh-Haghi S, Dabbagh A. The role of artificial intelligence in management of critical COVID-19 patients. J Cell Mol Anesth. 2020;5(1):16–22.
Rhee AJ, Kahn RA. Laboratory point-of-care monitoring in the operating room. Curr Opin Anaesthesiol. 2010;23(6):741–8.
Riazi S, Kraeva N, Hopkins PM. Malignant hyperthermia in the post-genomics era: new perspectives on an old concept. Anesthesiology. 2018;128(1):168–80.
Roberts JD, Wells GA, Le May MR, Labinaz M, Glover C, Froeschl M. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. Lancet Digital Health. 2012;379(9827):1705–11.
Robinson R, Carpenter D, Shaw MA, Halsall J, Hopkins P. Mutations in RYR1 in malignant hyperthermia and central core disease. Hum Mutat. 2006;27(10):977–89.
Ronaghi A, Karamzadeh S, Jowkar S, Mousavi Z, Naderi N. Midazolam-induced learning and memory impairment is modulated by cannabinoid CB1 receptor agonist and antagonist. J Cell Mol Anesth. 2016;1(1):3–11.

Rosenberg H, Pollock N, Schiemann A, Bulger T, Stowell K. Malignant hyperthermia: a review. Orphanet J Rare Dis. 2015;10:93.
Sadhasivam S, Chidambaran V, Zhang X, Meller J, Esslinger H, Zhang K, Martin LJ, McAuliffe J. Opioid-induced respiratory depression: ABCB1 transporter pharmacogenetics. Pharmacogenomics J. 2015;15(2):119–26.
Safari F, Mottaghi K, Fallahinejadghajari R, Nashibi M. Crouzon syndrome: a fibroblast growth factor receptor 2 gene mutation. J Cell Mol Anesth. 2017;1(2):15–8.
Sanders RD, Xu J, Shu Y, Fidalgo A, Ma D, Maze M. General anesthetics induce apoptotic neurodegeneration in the neonatal rat spinal cord. Anesth Analg. 2008;106(6):1708–11.
Sanders RD, Xu J, Shu Y, Januszewski A, Halder S, Fidalgo A, Sun P, Hossain M, Ma D, Maze M. Dexmedetomidine attenuates isoflurane-induced neurocognitive impairment in neonatal rats. Anesthesiology. 2009;110(5):1077–85.
Sandritter TL, Dinh JC, Wagner JA, Lowry JA. Description of an innovative pediatric individualized therapeutics clinic: working toward precision drug therapy. Children (Basel). 2019;6(2).
Satoh M, Minami Y, Takahashi Y, Tabuchi T, Nakamura M. Expression of microRNA-208 is associated with adverse clinical outcomes in human dilated cardiomyopathy. J Card Fail. 2010;16(5):404–10.
Savage S, Ma D. The neurotoxicity of nitrous oxide: the facts and "putative" mechanisms. Brain Sci. 2014;4(1):73–90.
Schubart JR, Schaefer E, Janicki P, Adhikary SD, Schilling A, Hakim AJ, Bascom R, Francomano CA, Raj SR. Resistance to local anesthesia in people with the Ehlers-Danlos syndromes presenting for dental surgery. J Dent Anesth Pain Med. 2019;19(5):261–70.
Selzer RR, Rosenblatt DS, Laxova R, Hogan K. Adverse effect of nitrous oxide in a child with 5,10-methylenetetrahydrofolate reductase deficiency. N Engl J Med. 2003;349(1):45–50.
Seng KY, Hee KH, Soon GH, Sapari NS, Soong R, Goh BC, Lee LS. CYP3A5*3 and bilirubin predict midazolam population pharmacokinetics in Asian cancer patients. J Clin Pharmacol. 2014;54(2):215–24.
Serafini G, Ingelmo PM, Astuto M, Baroncini S, Borrometi F, Bortone L, Ceschin C, Gentili A, Lampugnani E, Mangia G, Meneghini L, Minardi C, Montobbio G, Pinzoni F, Rosina B, Rossi C, Sahillioglu E, Sammartino M, Sonzogni R, Sonzogni V, Tesoro S, Tognon C, Zadra N. Preoperative evaluation in infants and children: recommendations of the Italian Society of Pediatric and Neonatal Anesthesia and Intensive Care (SARNePI). Minerva Anestesiol. 2014;80(4):461–9.
Sezari P. The role of Toll-like receptors in pain control. J Cell Mol Anesth. 2017;2(1):24–9.
Sezari P, Dabbagh A. Personalized medicine: the paradigm shift in medicine mandating lifelong learning. J Cell Mol Anesth. 2019;4(2):31–2.
Shastry BS. Genetic susceptibility to advanced retinopathy of prematurity (ROP). J Biomed Sci. 2010;17:69.
Shaw JLV. Practical challenges related to point of care testing. Pract Lab Med. 2016;4:22–9.
Shenfield GM. Genetic polymorphisms, drug metabolism and drug concentrations. Clin Biochem Rev. 2004;25(4):203–6.
Shin YH, Kim MH, Lee JJ, Choi SJ, Gwak MS, Lee AR, Park MN, Joo HS, Choi JH. The effect of midazolam dose and age on the paradoxical midazolam reaction in Korean pediatric patients. Korean J Anesthesiol. 2013b;65(1):9–13.
Sleigh JW, Leslie K, Davidson AJ, Amor DJ, Diakumis P, Lukic V, Lockhart PJ, Bahlo M. Genetic analysis of patients who experienced awareness with recall while under general anesthesia. Anesthesiology. 2019;131(5):974–82.
Smith T, Rajakaruna C, Caputo M, Emanueli C. MicroRNAs in congenital heart disease. Ann Transl Med. 2015;3(21):333.
Stewart SL, Hogan K, Rosenberg H, Fletcher JE. Identification of the Arg1086His mutation in the alpha subunit of the voltage-dependent calcium channel (CACNA1S) in a North American family with malignant hyperthermia. Clin Genet. 2001;59(3):178–84.

Stoica SC, Dorobantu DM, Vardeu A, Biglino G, Ford KL, Bruno DV, Zakkar M, Mumford A, Angelini GD, Caputo M, Emanueli C. MicroRNAs as potential biomarkers in congenital heart surgery. J Thorac Cardiovasc Surg. 2019;159(4):1532–1540.e7.

Stowell KM. DNA testing for malignant hyperthermia: the reality and the dream. Anesth Analg. 2014;118(2):397–406.

Su F, Gastonguay MR, Nicolson SC, DiLiberto M, Ocampo-Pelland A, Zuppa AF. Dexmedetomidine pharmacology in neonates and infants after open heart surgery. Anesth Analg. 2016;122(5):1556–66.

Su R, Sun P, Zhang D, Xiao W, Feng C, Zhong L. Neuroprotective effect of miR-410-3p against sevoflurane anesthesia-induced cognitive dysfunction in rats through PI3K/Akt signaling pathway via targeting C-X-C motif chemokine receptor 5. Genes Genomics. 2019;41(10):1223–31.

Sucharov CC, Sucharov J, Karimpour-Fard A, Nunley K, Stauffer BL, Miyamoto SD. Micro-RNA expression in hypoplastic left heart syndrome. J Card Fail. 2015;21(1):83–8.

Sun L. Early childhood general anaesthesia exposure and neurocognitive development. Br J Anaesth. 2010;105(Suppl 1):i61–8.

Talebi Z, Peyvandi H, Dabbagh A. Cellular and molecular mechanisms in perioperative hepatic protection: a review of current interventions. J Cell Mol Anesth. 2017;2(2):82–93.

Tang J, Chen X, Tu W, Guo Y, Zhao Z, Xue Q, Lin C, Xiao J, Sun X, Tao T, Gu M, Liu Y. Propofol inhibits the activation of p38 through up-regulating the expression of annexin A1 to exert its anti-inflammation effect. PLoS One. 2011;6:e27890.

Templeton TW, Goenaga-Diaz EJ, Downard MG, McLouth CJ, Smith TE, Templeton LB, Pecorella SH, Hammon DE, O'Brien JJ, McLaughlin DH, Lawrence AE, Tennant PR, Ririe DG. Assessment of common criteria for awake extubation in infants and young children. Anesthesiology. 2019;131(4):801–8.

Thorn CF, Klein TE, Altman RB. Codeine and morphine pathway. Pharmacogenet Genomics. 2009;19(7):556–8.

Toppin PJ, Chandy TT, Ghanekar A, Kraeva N, Beattie WS, Riazi S. A report of fulminant malignant hyperthermia in a patient with a novel mutation of the CACNA1S gene. Can J Anaesth. 2010;57(7):689–93.

Trivedi P, Gottlieb E, Mossad E. Anesthesia for pediatric lung transplantation: case presentation and review of the literature. J Cell Mol Anesth. 2017;2(3):124–33.

Troup, M., Zalucki OH, Kottler BD, Karunanithi S, Anggono V, van Swinderen B. Syntaxin1A neomorphic mutations promote rapid recovery from isoflurane anesthesia in Drosophila melanogaster. Anesthesiology. 2019;131(3):555–68 (1528-1175 (Electronic)).

Twaroski DM, Yan Y, Olson JM, Bosnjak ZJ, Bai X. Down-regulation of microRNA-21 is involved in the propofol-induced neurotoxicity observed in human stem cell-derived neurons. Anesthesiology. 2014;121(4):786–800.

van Hoff SL, O'Neill ES, Cohen LC, Collins BA. Does a prophylactic dose of propofol reduce emergence agitation in children receiving anesthesia? A systematic review and meta-analysis. Paediatr Anaesth. 2015;25(7):668–76.

van Rooij E, Sutherland LB, Qi X, Richardson JA, Hill J, Olson EN. Control of stress-dependent cardiac growth and gene expression by a microRNA. Science. 2007;316(5824):575–9.

Valencia E, Staffa SJ, Faraoni D, DiNardo JA, Nasr VG. Prospective external validation of the pediatric risk assessment score in predicting perioperative mortality in children undergoing noncardiac surgery. Anesth Analg. 2019;129(4):1014–20.

Venkatasubramanian R, Fukuda T, Niu J, Mizuno T, Chidambaran V, Vinks AA, Sadhasivam S. ABCC3 and OCT1 genotypes influence pharmacokinetics of morphine in children. Pharmacogenomics. 2014;15(10):1297–309.

Wang X, Xu Z, Miao CH. Current clinical evidence on the effect of general anesthesia on neurodevelopment in children: an updated systematic review with meta-regression. PLoS One. 2014;9(1):e85760.

Wang W, Chen X, Zhang J, Zhao Y, Li S, Tan L, Gao J, Fang X, Luo A. Glycyrrhizin attenuates isoflurane-induced cognitive deficits in neonatal rats via its anti-inflammatory activity. Neuroscience. 2016a;316:328–36.
Wang L, Zheng M, Wu S, Niu Z. MicroRNA-188-3p is involved in sevoflurane anesthesia-induced neuroapoptosis by targeting MDM2. Mol Med Rep. 2018;17.
Wei Z, Jiang S, Zhang Y, Wang X, Peng X, Meng C, Liu Y, Wang H, Guo L, Qin S, He L, Shao F, Zhang L, Xing Q. The effect of microRNAs in the regulation of human CYP3A4: a systematic study using a mathematical model. Sci Rep. 2014;4:4283.
Wesmiller SW, Henker RA, Sereika SM, Donovan HS, Meng L, Gruen GS, Tarkin IS, Conley YP. The association of CYP2D6 genotype and postoperative nausea and vomiting in orthopedic trauma patients. Biol Res Nurs. 2013;15(4):382–9.
Wiesmann T, Kranke P, Eberhart L. Postoperative nausea and vomiting—a narrative review of pathophysiology, pharmacotherapy and clinical management strategies. Expert Opin Pharmacother. 2015;16(7):1069–77.
Wu Z, Zhao P. Epigenetic alterations in anesthesia-induced neurotoxicity in the developing brain. Front Physiol. 2018;9:1024.
Wu X, Oerding H, Liu J, Vanacker B, Yao S, Dahl V, Xiong L, Claudius C, Yue Y, Huang Y, Abels E, Rietbergen H, Woo T. Rocuronium blockade reversal with sugammadex vs. neostigmine: randomized study in Chinese and Caucasian subjects. BMC Anesthesiol. 2014;14:53.
Wyatt JE, Pettit WL, Harirforoosh S. Pharmacogenetics of nonsteroidal anti-inflammatory drugs. Pharmacogenomics J. 2012;12(6):462–7.
Xiong J, Wang H, Mu F, Liu Z, Bao Y, Sun Y. MiR-125b-5p inhibitor might protect against sevoflurane-induced cognitive impairments by targeting to LIMK1. Curr Neurovasc Res. 2019;16(4):382–91.
Xu H, Zhang J, Zhou W, Feng Y, Teng S, Song X. The role of miR-124 in modulating hippocampal neurotoxicity induced by ketamine anesthesia. Int J Neurosci. 2015;125(3):213–20.
Xu C, Niu JJ, Zhou JF, Wei YS. MicroRNA-96 is responsible for sevoflurane-induced cognitive dysfunction in neonatal rats via inhibiting IGF1R. Brain Res Bull. 2019;144:140–8.
Yang W, Guo Q, Li J, Wang X, Pan B, Wang Y, Wu L, Yan J. microRNA-124 attenuates isoflurane-induced neurological deficits in neonatal rats via binding to EGR1. J Cell Physiol. 2019; 234.
Yao Y, Yang N, Han D, Ni C, Wu C, Guo X. Effects of propofol and etomidate anesthesia on cardiovascular miRNA expression: the different profiles? BMC Anesthesiol. 2018;18(1):149.
Yu KS, Cho JY, Jang IJ, Hong KS, Chung JY, Kim JR, Lim HS, Oh DS, Yi SY, Liu KH, Shin JG, Shin SG. Effect of the CYP3A5 genotype on the pharmacokinetics of intravenous midazolam during inhibited and induced metabolic states. Clin Pharmacol Ther. 2004;76(2):104–12.
Yu R, Guo Y, Dan Y, Tan W, Mao Q, Deng G. A novel mutation in the BCHE gene and phenotype identified in a child with low butyrylcholinesterase activity: a case report. BMC Med Genet. 2018;19(1):58.
Yuen VM, Bailey CR. Premedication in children: does taste matter? Anaesthesia. 2018;73(12):1453–6.
Zali H, Golchin A, Farahani M, Yazdani M, Ranjbar MM, Dabbagh A. FDA approved drugs repurposing of Toll-like receptor4 (TLR4) candidate for neuropathy. Iranian J Pharm Res. 2019;18(3):1639–47.
Zencirci B. Pseudocholinesterase enzyme deficiency: a case series and review of the literature. Cases J. 2009;2:9148.
Zeng L, Cui J, Wu H, Lu Q. The emerging role of circulating microRNAs as biomarkers in autoimmune diseases. Autoimmunity. 2014;47(7):419–29.
Zhang Y, Dong Y, Wu X, Lu Y, Xu Z, Knapp A, Yue Y, Xu T, Xie Z. The mitochondrial pathway of anesthetic isoflurane-induced apoptosis. J Biol Chem. 2010;285(6):4025–37.
Zhang Y, Xu Z, Wang H, Dong Y, Shi HN, Culley DJ, Crosby G, Marcantonio ER, Tanzi RE, Xie Z. Anesthetics isoflurane and desflurane differently affect mitochondrial function, learning, and memory. Ann Neurol. 2012;71(5):687–98.

Zhang C, Cao H, Wan ZG, Wang J. Prolonged neuromuscular block associated with cholinesterase deficiency. Medicine (Baltimore). 2018;97(52):e13714.
Zhao X, Sun Y, Ding Y, Zhang J, Li K. miR-34a inhibitor may effectively protect against sevoflurane-induced hippocampal apoptosis through the Wnt/beta-catenin pathway by targeting Wnt1. Yonsei Med J. 2018;59(10):1205–13.
Zhong Q, Chen X, Zhao Y, Liu R, Yao S. Association of polymorphisms in pharmacogenetic candidate genes with propofol susceptibility. Sci Rep. 2017;7(1):3343.
Zhong Q, Qu X, Xu C. Effect of preoperative visiting operation room on emergence agitation in preschool children under sevoflurane anesthesia. Int J Pediatr Otorhinolaryngol. 2018;104:32–5.
Zhou S, Bao J, Wang Y, Pan S. S100beta as a biomarker for differential diagnosis of intracerebral hemorrhage and ischemic stroke. Neurol Res. 2016;38(4):327–32.
Zhou S, Skaar DJ, Jacobson PA, Huang RS. Pharmacogenomics of medications commonly used in the intensive care unit. Front Pharmacol. 2018a;9:1436.
Zou X, Patterson TA, Divine RL, Sadovova N, Zhang X, Hanig JP, Paule MG, Slikker W Jr, Wang C. Prolonged exposure to ketamine increases neurodegeneration in the developing monkey brain. Int J Dev Neurosci. 2009;27(7):727–31.