Sedation and Analgesia in Pediatric Cardiac Critical Care

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Objectives: This review will focus on the pharmacokinetics (with an emphasis on the context-sensitive half-time), pharmacodynamics, and hemodynamic characteristics of the most commonly used sedative/hypnotic, analgesic, and IV anesthetics used in cardiac intensive care. In addition, the assessment of pain and agitation and withdrawal will be reviewed.

Data Source: MEDLINE, PubMed.

Conclusions: Children in the cardiac ICU often require one or more components of general anesthesia: analgesia, amnesia (sedation and hypnosis), and muscle relaxation to facilitate mechanical ventilation, to manage postoperative pain, to perform necessary procedures, and to alleviate fear and anxiety. Furthermore, these same children are often vulnerable to hemodynamic instability due to unique underlying physiologic vulnerabilities. An assessment of hemodynamic goals, postoperative procedures to be performed, physiologic vulnerabilities, and the intended duration of mechanical ventilation should be made. Based on this assessment, the optimal selection of sedatives, analgesics, and if necessary, muscle relaxants can then be made. (*Pediatr Crit Care Med* 2016; 17:S225–S231)

Key Words: amnesia; analgesia; cardiac intensive care; pharmacodynamics; pharmacokinetics; sedation

Children in the ICU undergo painful interventions, often require mechanical ventilation, and are exposed to multiple strangers while separated from their caregivers and their normal environment. Some and often all three components of general anesthesia: analgesia, amnesia (sedation and hypnosis), and muscle relaxation must be administered to children in the cardiac ICU (CICU). Managing their pain, fear, and anxiety and maintaining hemodynamic stability is challenging. Both under-treatment and over-treatment can have deleterious effects. Under-treatment can result in delayed healing and stress for the patient and the caregivers, whereas overtreatment can cause tolerance and possibly withdrawal upon discontinuation of therapy, delay recovery, and induce cardiopulmonary instability (1–3). An assessment of hemodynamic goals, postoperative procedures to be performed such as tube/line removal and chest closure, cardiopulmonary status, physiologic vulnerabilities, and the intended duration of mechanical ventilation should be made. Based on this assessment, the projected trajectory for each patient can be determined. Intelligent choices regarding use of sedatives, analgesics, and if necessary, muscle relaxants can then be made. Since no one drug can provide analgesia, sedation, and muscle relaxation, the use of multiple agents is necessary. With the large choice of agents available, practitioners should understand the mechanism of action, pharmacokinetic profile, and advantages and disadvantages of each agent that may be used, as well as the hemodynamic profile of the individual patient.

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ASSESSMENT OF PAIN AND AGITATION

Assessing pain and agitation in children is challenging. Children in the CICU are unable to self-report pain due to several factors: they are nonverbal, mechanically ventilated, or unable to give reliable responses secondary to sedation. However, pain and sedation scales exist and have been validated in children (4). They should be used along with clinical indicators upon initiation of sedation or pain treatment and after subsequent change in dosing of the medications to determine appropriate management. The COMFORT-Behavioral Scale is the only validated scale used to assess both pain and sedation in ventilated and non-ventilated children (5, 6). It assesses alertness, calmness/agitation, respiratory response, crying, physical movement, muscle tone, and facial tension.

PHARMACODYNAMIC AND PHARMACOKINETIC DIFFERENCES IN CHILDREN

The pharmacokinetics of drugs in infants and children are strongly influenced by developmental changes in input, distribution, and elimination. The physiologic changes that

influence the pharmacokinetics and the effects of maturation on these processes have been summarized by Anderson et al (7) (**Table 1**). By 2 years of age, in normal children, these developmental changes are largely complete and consequently from a pharmacokinetic perspective children differ from adults only in size (7). An important consideration with the use of a continuous infusion in the CICU is the concept of context-sensitive half-time. The context-sensitive half-time is the time required for blood or plasma concentrations of a drug to decrease by 50% after discontinuation of drug administration. During an infusion, IV drugs with multi-compartmental pharmacokinetics initially distribute in the central compartment with subsequent redistribution to peripheral compartments. When these peripheral redistribution sites become saturated and the concentration of drug in them reaches equilibrium with the central compartment, the context-sensitive half-time becomes equal to the terminal elimination half-life. A practical example is fentanyl, which is highly lipophilic and initially has a short half-life due to redistribution from the central compartment to adipose tissue. Once adipose tissue becomes saturated fentanyl loses its short duration characteristics such that after a 3-hour infusion the "short acting opioid" fentanyl has a longer half-time than a morphine infusion once the infusions are stopped (8).

ANALGESIA

Analgesics commonly used in the ICU can be characterized as opioid and non-opioid. **Table 2** describes the mechanism of action, dosing, pharmacokinetic, and adverse effects of these agents. Non-opioid analgesics include acetaminophen and ketorolac. Acetaminophen exerts its analgesic effects by centrally inhibiting prostaglandin production via the cyclooxygenase pathway and is widely used as an analgesic and antipyretic (4). It is available in oral, rectal, and IV formulations (9). The recent IV formulation with a peak effect at 15 minutes following administration makes it a useful adjunct therapy for pain management in postoperative cardiac patients who are unable to tolerate enteral administration (10). Ketorolac is a nonsteroidal anti-inflammatory drug and exhibits both analgesic and anti-inflammatory properties by inhibiting prostaglandin synthesis via the cyclooxygenase pathway. It has been studied in multiple prospective and retrospective studies involving cardiac patients suggesting that it can be safely used in infants and children undergoing cardiothoracic surgery (11–16). Of note, it has been shown that ketorolac does not increase the risk of bleeding or the prevalence of renal complications.

Opioids are commonly used in clinical practice. They bind to the μ_1-receptor subtype producing analgesia, the μ_2-receptor causing analgesia and respiratory depression, and to the κ-receptor inducing sedation (4, 17). The most commonly used opioids are described below. Morphine is considered the prototypical opiate. Morphine is metabolized in the liver to active and inactive metabolites morphine-6-glucuronide and morphine-3-glucuronide, which are renally excreted and therefore should be used with caution in patients with impaired renal function (4). A limited cardiac output affecting hepatic flow may decrease clearance of morphine causing a prolonged duration of action and increasing the risk of respiratory depression (18, 19). When used for pain management, morphine has little effect on blood pressure and heart rate in supine, normovolemic patients. However, high doses in critically ill patients can lead to decreased arterial resistance, increased venous capacitance, and inhibition of baroreceptor reflexes causing hypotension. In addition, morphine stimulates the release of histamine, which contributes to the development of hypotension. Fentanyl is 70–100 times more potent than morphine. It is a synthetic opioid that is metabolized by the liver and does not cause histamine release and thus is less likely to cause hypotension and is therefore commonly used intraoperatively during cardiac surgery and postoperatively in the CICU (4, 9, 17). However, bradycardia and chest wall rigidity can occur. In cardiac patients, the presence of acidosis and hypothermia are common and lead to an increased plasma concentration (9). Tolerance to fentanyl develops more rapidly and the risk of dependence and withdrawal is greater than with morphine (20). Remifentanil is a very short acting, pure μ-receptor agonist that is equipotent to fentanyl. Its rapid onset and offset times and lack of significant hemodynamic effects makes it particularly useful for procedural analgesia and anesthesia, and less useful for prolonged sedation in the CICU (17–19), and its context-sensitive half-time remains constant at 4 minutes regardless of infusion duration. However, it has been associated with bradycardia and hypotension during rapid

TABLE 1. Childhood Physiologic Changes Influencing Pharmacokinetics (7)

Pharmacokinetic Process	Developmental Change
Input	Reduced gastric emptying
	Intestinal transit time increased
	Transporter expression immature
	Intestinal permeability increased
	Bioavailability may be increased in neonates
Distribution	Body composition
	Increased extracellular fluid in neonates
	Reduced fat in neonates
	Dramatic increase muscle bulk (5–15 yr)
	Increased blood-brain barrier permeability
	Reduced α-1 acid glycoprotein and albumin concentrations
Elimination	Immature hepatic enzyme systems responsible for clearance
	Glomerular filtration and tubular excretion immature

TABLE 2. Opioids

Drug	Mechanism of Action	Bolus Dose	Infusion	Pharmacokinetic Properties	Adverse Effects
Fentanyl	μ-agonist κ-agonist	1–2 μg/kg	1–3 μg/kg/hr	Onset, 30 s; short duration of action; half-life, 2 hr; context-sensitive half-life, 21 hr	Nausea, constipation, respiratory depression
Remifentanil	μ-agonist	1–3 μg/kg	0.4–1 μg/kg/min	Very quick onset; half-life, 5–10 min; steady state, 10–15 min after administration of a continuous infusion	Bradycardia, respiratory depression
Morphine	μ-agonist κ-agonist δ-agonist	0.05–0.2 mg/kg	0.01–0.03 mg/kg/hr	Peak at 20 min; half life, 1–3 hr in infants and children and 10–20 hr in preterm neonates	Nausea, constipation, respiratory depression, bronchospasm, vasodilation, hypotension, puritus
Methadone	μ-agonist κ-agonist δ-agonist	Initiated at 0.05–0.1 mg/kg orally or IV	No infusion	Peak at 1–2 hr, half life = 19 hr	Bradycardia, hypotension, and arrhythmias (prolonged QT interval)

infusion (17). Methadone is a long-acting opioid that is typically used to treat or prevent opioid withdrawal. Methadone is equipotent to morphine with a longer half-life (4, 9). Methadone is hepatically metabolized by the cytochrome P450 system (21). Rapid IV administration increases the risk of cardiovascular toxicities, therefore enteral administration is preferred (9). Methadone can be useful in patients who require long-term analgesia as a replacement for morphine infusions.

SEDATION

Sedation can be achieved with benzodiazepines, IV anesthetics such as ketamine and propofol and the α_2-agonist dexmedetomidine. Benzodiazepines are used as sedative-hypnotic agents in children in the CICU. They bind to the postsynaptic γ-aminobutyric acid (GABA) receptors inhibiting the central nervous system and have dose-dependent anxiolytic, amnestic, sedative, hypnotic, and anticonvulsant properties (9, 11, 22). They produce spinally-mediated muscle relaxation. However, they do not possess any intrinsic analgesic properties (**Table 3**). Diazepam was the first benzodiazepine used for pediatric sedation, but since the arrival of midazolam, it is currently rarely used in the CICU due to its long and variable half-life, which can result in prolonged sedation (22, 23). In addition, diazepam needs dose adjustments in patients with hepatic (metabolism) and renal (excretion) impairment (4, 9). Midazolam is the most commonly used benzodiazepine in the CICU. It has a rapid onset of action, a short duration of action, and a short half-life (9, 22, 23). It can be administered via IV, oral, intranasal, intramuscular, and rectal routes. Midazolam is metabolized in the liver by the cytochrome p450 isoenzyme 3A4 and is highly-protein bound. An increase in free fraction can occur in patients receiving other highly protein-bound medications, and in patients with liver and renal failure (4, 9, 22, 24–26). Adverse effects include hypotension, tolerance, and withdrawal. It can also cause respiratory depression

TABLE 3. Benzodiazepines

Drug	Bolus Dose	Infusion	Pharmacokinetic Properties	Adverse Effects
Midazolam	0.025–0.1 mg/kg	0.05–0.2 mg/kg/hr	Onset, 1–5 min Peak effect, 3–5 min Duration of action, 10–30 min Half-life varies with the child's age, 2.5–10 hr	Increase accumulation in hepatic and renal impairment
Lorazepam	0.02–0.1 mg/kg	0.025 mg/kg/hr	Onset, 15–30 min Duration of action, 8–12 hr Half-life, 10.5–40.2 hr	Contains propylene glycol. Toxicity can cause acidosis, seizures, and renal failure.
Diazepam	0.04–0.3 mg/kg	Not recommended	Onset, 1–3 min Peal effect, 30–90 min Half-life, 15–95 hr	Pain, tissue necrosis during IV administration. Accumulation in liver/renal failure

leading to hypoxia if given in conjunction with opioids (23, 25). Midazolam is the only benzodiazepine with a pharmacokinetic profile that permits administration via continuous infusion without excessive accumulation. Lorazepam has a long duration of action and half-life making it an ideal agent for intermittent administration and as a replacement for midazolam infusions (4). It is metabolized in the liver via a phase II reaction involving glucuronyl transferase that is less likely to be affected in patients with liver dysfunction (22). The context-sensitive half-lives of lorazepam is very long making it inappropriate for administration as a continuous infusion. The additive propylene glycol in lorazepam and diazepam has been associated with development of thrombophlebitis and toxicities including lactic acidosis and hyperosmolality during high-dose administration (4, 22, 27).

IV ANESTHETICS

IV anesthetics are commonly used in the CICU for sedation and during bedside procedures. They differ in their mechanisms of action (**Table 4**). Ketamine is structurally related to phencyclidine and blocks the N-methyl-D-aspartate receptor. It acts on the cortex and limbic system leading to a dissociative anesthetic state with strong analgesic, sedative, and antegrade amnestic effects during which there is maintenance of the airway reflexes (4, 22, 23, 28). Multiple routes of administration are available including IV, intramuscular, oral, rectal, intranasal, and intraspinal. IV and intramuscular administrations are preferred for procedural sedation and analgesia due to better predictability (29). Its hepatic metabolism is via N-methylation forming nor-ketamine, which is from one third to one fifth as potent as ketamine. It is hydroxylated and conjugated and then finally excreted in the urine. Ketamine, similar to that of propofol, has a short context-sensitive half-time (40 min after discontinuation of an 8 hr infusion), making it an ideal agent for a continuous infusion. Support for the use of ketamine in pediatric patients with congenital heart disease is found in multiple reports in infants and children receiving ketamine during cardiac catheterization that describe minimal effects on respiration and hemodynamics (22, 30–33). The misconception that ketamine raises the pulmonary artery pressure is derived from adult studies. This effect is attenuated or absent in children when normocarbia and normoxia are maintained (34). In addition, the reported dose-related increases in heart rate are generally clinically insignificant (4, 33). Although ketamine may cause a dose-related increase in blood pressure due to the release of endogenous catecholamines, it can cause hypotension in patients with depletion of catecholamine stores due to the direct myocardial depressive effects of the drug (22).

Propofol is an IV administered sedative-hypnotic agent. It has no intrinsic analgesic properties. Propofol has a fast onset time with an effect seen within 40 seconds of injection. It has a large volume of distribution and an increased clearance in children when compared with adults. It takes 1–3 minutes for blood-brain equilibration to occur and therefore dose adjustments are not recommended sooner than 3–5 minutes, allowing time for a clinical effect (35). The context-sensitive half-time for an infusion duration of up to 8 hours is less than 40 minutes allowing rapid emergence from its effects. Unfortunately, the very narrow therapeutic index of this drug leaves little margin for error with sedation rapidly progressing to unconsciousness and apnea (35–37). Despite this and other risks that accompany the use of propofol in critically ill cardiac patients, including bradycardia, decreased systemic vascular resistance and hypotension, and reduced clearance, it is safe to use in early tracheal extubation protocols (38, 39). In 2001, the Food and Drug Administration (FDA) advised against the use of propofol for prolonged sedation in critically ill children. The FDA stance on this issue has not changed and the current package insert for propofol contains the following language: "Propofol injectable emulsion is not indicated for use in PICU sedation since the safety of this regimen has not been established." Nonetheless, propofol is used at low doses (< 4 mg/kg/hr) alone or in combination with other drugs, generally in older patients, to provide short-sedation in the pediatric CICU (40). Enthusiasm for the use of propofol in critically ill children must be tempered with the concern for the development of the propofol infusion syndrome, which appears to be dose and infusion duration related (41–43). Risk factors for the propofol infusion syndrome in children appear to be an infusion rate of 4 mg/kg/hr for longer than 48 hours, young age, critical

TABLE 4. IV Anesthetic Agents

Drug	Dose	Pharmacodynamic Properties	Cardiac Effect	Adverse Effects
Propofol (sedative/hypnotic)	Bolus: 0.5–1 mg/kg Infusion: 125–300 μg/kg/min	Onset, 30 s Half-life, 30–60 min	Cardiovascular depressant	Respiratory depression, apnea, propofol infusion syndrome
Dexmedetomidine (sedative)	Bolus: 0.5–1 μg/kg Infusion: 0.2–2.5 μg/kg/hr	Onset, 30 min Half-life, 2–2.65 hr	Prevention of arrhythmias	IV bolus associated with bradycardia and hypertension
Ketamine (analgesic/sedative/dissociative agent)	Bolus: IV, 0.5–2 mg/kg IM, 3–7 mg/kg	Onset, 30 s Half-life, 2.5 hr	Cardiac stimulant, no effect on pulmonary arterial pressure and pulmonary vascular resistance	Nausea, salivation, bronchospasm, hypotension in catecholamine depleted patients

illness, concomitant catecholamine infusions, and concomitant steroids (44, 45). Many institutions do not encourage or allow propofol infusions for sedation of children for more than 24–48 hours.

Dexmedetomidine is a highly selective central nervous system α_2 adrenergic receptor agonist with a large volume of distribution (necessitating a loading dose), an initial short half-life allowing titration during continuous infusion, and a prolonged context-sensitive half-time (4 hr after an 8 hr infusion). It produces sedation and weak analgesia by increasing GABA inhibition in the central nervous system and spinal cord. The central nervous system effects of therapeutic plasma levels of dexmedetomidine resemble those of non-rapid eye movement stage 2 (light) sleep (46). It is metabolized by CYP450 and direct N-glucuronidation. Dosing adjustments are needed in patients with hepatic impairment. Severe renal impairment does not affect the pharmacokinetics of dexmedetomidine (47–49).

Dexmedetomidine has been studied in a variety of pediatric populations including those in the CICU in the context of procedural sedation, postoperative sedation, sedation prior to extubation, as well as in the management of arrhythmias (49). It has been shown that the pharmacokinetics in older children and adolescents are similar to adults; however, infants less than 2-years old exhibit a greater volume of distribution and longer terminal half-life thus requiring larger initial loading doses but lower maintenance doses (50). Initiation of dexmedetomidine treatment can decrease heart rate and blood pressure; the initiation of a continuous infusion without a loading dose does not affect the prevalence of these adverse effects (47–51). Although dexmedetomidine can be used safely and efficaciously in pediatric cardiac patients, vigilance and appropriate monitoring during infusions is required (52–57). Dexmedetomidine is approved for the sedation of mechanically ventilated adult patients for less than 24 hours and for the sedation of non-intubated patients during procedures (58). Additional off-label uses of prolonged infusions in a variety of settings for neonates, infants, and children are increasingly being reported (49). It has been suggested that dexmedetomidine may be useful in the prevention and treatment of perioperative arrhythmias. The mechanism for antiarrhythmic effects is speculative and may in part be related to enhancement of vagal neural activity (59). Retrospective and observational studies suggest that the prevalence of perioperative junctional ectopic tachycardia and supraventricular tachycardia is lower in patients receiving dexmedetomidine and that dexmedetomidine administration may be useful in terminating arrhythmias (60–62). However, prospective studies are necessary to better define the role of dexmedetomidine in the management of perioperative arrhythmias. The main advantage of dexmedetomidine is its minimal effect on respiratory function, and its opioid and benzodiazepine sparing effects. However, although patients receiving dexmedetomidine receive significantly lower amounts of opioid and benzodiazepine infusions when compared with those not receiving dexmedetomidine, no differences in heart rate, blood pressure, duration of mechanical ventilation, or ICU length of stay have been demonstrated (48, 63)). Provision of sedation in children with dexmedetomidine alone is not practical in the intensive care setting given that large doses of dexmedetomidine (2–3 μg/kg/hr), with its associated hemodynamic effects, are necessary (49). Adverse effects such as transient hypertension and agitation along with tachyarrhythmias are seen after discontinuation of prolonged infusion of dexmedetomidine and they appear to be more common after abrupt discontinuation when compared with slow weaning (64). Further studies are needed to better define the long-term effects of prolonged dexmedetomidine infusions.

Clonidine is indicated for sedation, analgesia, control of opiate and/or benzodiazepine withdrawal, and hypertension and does not cause respiratory depression (65–67). Clonidine is a mixed α_1 and α_2 adrenoreceptor agonist with predominant α_2 activity. It is metabolized in the liver and excreted through the urine. The sedative and analgesic effects of clonidine are dose-dependent and influenced by the route of administration (66). Clonidine is most commonly used orally. Although it has been shown to be safe in cardiac patients, there is limited evidence available regarding its IV use (66, 68).

WITHDRAWAL IN THE CICU

Patients in the CICU unit can become tolerant with increased metabolism leading to an increase in medication requirements and development of physical dependence. The absence of weaning after prolonged treatment can lead to the iatrogenic withdrawal syndrome (IWS). Risk factors leading to IWS include patient's age, duration of therapy cumulative dose, type of drugs used, single versus multiple agents, sedation protocols, and compliance. The duration of therapy and cumulative dose have been shown to be the most predictive of IWS (69). A number of algorithms and recommendations have been proposed for short-term and long-term extubation goals in the ICU (24, 70, 71). They are intended to promote continuous assessment and evaluation with the goal of decreasing the frequency of prolonged mechanical ventilation and sedation and potentially decreasing the prevalence of withdrawal.

CONCLUSION

In the CICU, balancing sedation and analgesia while maintaining cardiopulmonary stability and avoiding withdrawal is challenging. Algorithms and protocols can help guide therapy and limit overdosing. Multiple pharmacologic agents exist and should be used in combinations based on the projected short or long-term trajectory of the patient.

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