Sedation Analgesia and Neuromuscular Blockade in Pediatric Critical Care

Overview and Current Landscape

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KEYWORDS

• Sedation • Critical illness • Benzodiazepine • Opiate

KEY POINTS

- Sedation is a mainstay of therapy for critically ill children. Drugs of many classes are available to sedate children cared for in the PICU, and are used in various combinations to achieve the desired effect.
- Although necessary in the care of the critically ill child, sedative drugs are associated with adverse effects, such as disruption of circadian rhythm, altered sleep, delirium, potential neurotoxicity, and immunosuppression.
- Optimal approaches to the sedation of the critically ill child should include identification of sedation targets and sedation interruptions, allowing for a more individualized approach to sedation.
- Further research is needed to better understand the relationship between critical illness and sedation pharmacokinetics and pharmacodynamics, the impact of sedation on immune function, and the genetic implications on drug disposition and response.

In 2006 the consensus guidelines on sedation and analgesia in critically ill children was published, providing guidance for sedative use in the pediatric intensive care unit (PICU).[1] This guidance included statements supporting the assessment of sedation level using validated sedation scales, specifying that the "desired level of sedation should be identified for each patient and should be regularly reassessed" and "doses

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of sedative agents should be titrated to produce the desired level of sedation." In addition, the concepts of tolerance and withdrawal were detailed, with the recommendation for medication tapering after 7 days of therapy. These overarching concepts to sedation in the PICU still hold true a decade later. However, recent changes in knowledge about potentially deleterious effects of sedative medications in combination with addition of newer medications, such as dexmedetomidine, suggest that previous guidance in 2006 may not apply today.

In 2016, the Pediatric Cardiac Intensive Care Society 2014 consensus statement "Pharmacotherapies in Cardiac Critical Care: Sedation, Analgesia and Muscle Relaxant" was published.[2] Analgesic guidance for morphine, fentanyl, remifetanil, ketamine, and methadone was provided. In addition, guidance on the benzodiazepines midazolam, lorazepam, and diazepam was also given. Dexmedetomidine was highlighted in this statement, with an in-depth review of its pharmacokinetics and dynamics, and its potential as an antiarrhythmic especially in this setting. In conclusion, it was stated that sedation should be tailored to the individual needs of the patient.

This article provides an overview of the various drug classes that are used in the sedation of the critically ill child, and details regarding select drugs within each class. Analgesics, or medications that provide relief from pain, are also included because these agents are often included as sedation adjuncts regardless of whether there is an indication to treat pain. Afterward, an overview of concepts and issues surrounding sedation in the PICU is discussed, providing the reader with the current state of knowledge and areas that require additional scientific inquiry.

BENZODIAZEPINES

Benzodiazepines are often used to provide sedation and amnesia, and exert their anxiolytic, amnestic, anticonvulsant, and muscle-relaxing effects through interaction at specific binding sites on neuronal γ-aminobutyric acid (GABA) receptors.[3] Chronic administration of benzodiazepines can lead to decreased receptor activity and drug tolerance. Tolerance is a common finding in intensive care unit (ICU) patients receiving benzodiazepines or other sedative agents for periods longer than 24 hours, although most commonly seen clinically after 3 to 7 days. Withdrawal syndromes have been reported with cessation of midazolam and other benzodiazepine infusions. Risk factors for acute withdrawal include high infusion rates, prolonged duration, and abrupt cessation. For these reasons, gradual tapering of sedative infusions is suggested to reduce the chance of withdrawal reactions.

Midazolam undergoes extensive metabolism by the cytochrome P-450 (CYP) 3A (CYP3A) subfamily to a major (1-OH-midazolam) and a minor hydroxylated metabolite (4-OH-midazolam), both of which are subsequently metabolized to their respective glucuronide metabolites by uridine diphosphate-glucuronosyltransferases and renally cleared. The major metabolite 1-OH-glucorinide also seems to have sedative properties when concentrations are high, as has been observed in adult patients with renal failure.[4] The elimination half-life is prolonged and clearance reduced in adolescents as compared with younger children.[5] The elimination half-life of midazolam is 2 hours in young, healthy adults but increases rapidly in the elderly and following major surgery.[6] CYP3A activity reaches adult levels between 3 and 12 months of postnatal age.[7] Developmental differences in CYP3A activity may therefore alter the pharmacokinetics of midazolam in PICU patients of different ages.[4] In addition, polymorphisms in CYP3A impact midazolam disposition and response, but unfortunately are not currently accounted for in dosing decisions at the bedside.[4,8,9] The most dramatic changes in the pharmacokinetics of midazolam in the critically ill may result from