Chapter 6
Alpha-Agonists in Pediatric Critical Care

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Introduction

Alpha-agonists are a class of sedatives whose unique mechanism of action in addition to advantageous non-sedative properties has led to them gaining substantial popularity among pediatric critical care providers in recent years. For many years, the only α-agonist available was clonidine, and its primary uses were for the management of a sleep or behavior disorders in children with diagnoses such as attention deficit with hyperactivity disorder, autism spectrum disorder, and Tourette's syndrome among others [1–4]. Additional uses included treatment of hypertension [5, 6] and noninvasive procedural sedation, particularly for electroencephalography [7, 8]. While available as an enteral or intravenous (IV) agent, use until recently has been primarily enteral. In the late 1990s, however, dexmedetomidine was developed and rapidly expanded the applications of α-agonists into the anesthesia and critical care environments. While it is currently only approved by the United States Food and Drug Administration (FDA) for sedation up to 24 hours in critically ill adults and for procedural sedation in non-intubated adults, uses in pediatrics and pediatric critical care have risen rapidly since the first reports of its use in the pediatric setting in 2002 [9] and for pediatric intensive care unit (PICU) sedation in 2004 [10]. It is currently a mainstay for PICU sedation in many ICUs globally; in an analysis of dexmedetomidine use among 37 PICUs contributing to the public hospital information system (PHIS) database, from 2007 to 2013 dexmedetomidine use for PICU sedation increased over sixfold [11].

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Pharmacology

The primary mechanism by which clonidine and dexmedetomidine elicit their effects is selective agonism of the α_2 receptor. Three subtypes of the α_2 receptor exist (A, B, and C), and both drugs have agonistic effects on all three subtypes, albeit in different proportions [12]. The sedative and anxiolytic effects of α-agonists are mediated via binding to central α_{2B} receptors in the locus coeruleus, whereas their most common adverse effects, bradycardia and hypotension, are mediated via both the central (bradycardia) and peripheral (hypotension) α_{2A} receptors [13]. The cardiovascular effects, especially peripherally, are dose dependent. At lower drug doses, peripheral α_{2A} binding results in vasodilation and hypotension, whereas at high doses, peripheral α_{2B} binding occurs, resulting in vasoconstriction and hypertension. This likely explains the clinical findings that, during rapid bolus dose administration of dexmedetomidine, hypertension often occurs early, presumably due to higher plasma drug levels, while hypotension is a later finding, occurring as drug levels diminish as bolus doses dissipate or drug infusions are discontinued [14, 15]. Cellular effects of agonism of all three α_2 receptor subtypes are mediated by intracellular G-proteins. In addition to their sedative and anxiolytic effects, α-agonists confer modest analgesic effects via stimulation of α_2 receptors within the spinal cord which are mediated via substance P and result in inhibition of both Aδ and C pain fibers [16]. In contrast to other sedatives, α-agonists also appear to have limited effects on the electroencephalogram (EEG) and produce a sedation that closely simulates EEG patterns seen during natural sleep [17, 18]. From a clinical perspective, children tend to rouse from this sedation more easily and with significantly less potential for post-sedation confusion, agitation, and delirium than is seen during sedation with many other agents. They also tend to be more easily rousable with stimulation during ongoing sedation and return to their sedated state upon stimulus cessation with minimal need for resedation, a pattern that some have coined “cooperative sedation” [19].

Despite many similar pharmacodynamic effects, significant differences exist in the relative potencies of these effects between clonidine and dexmedetomidine. The primary reason for this lies in the significantly greater α_2 selectivity of dexmedetomidine which has a roughly eightfold greater α_2:α_1 receptor specificity compared to clonidine at 1620:1 vs 220:1 [20]. This facilitates greater sedative effects with, theoretically, fewer cardiovascular effects.

While primarily utilized as an oral agent, in some parts of the world (Europe, Australia), clonidine is also available in IV form [21] and has recently seen increased interest for use in the sedation of PICU patients. Following IV administration, onset of action is relatively rapid (minutes). High lipid solubility leads to rapid tissue redistribution, including the central nervous system, and the potential for prolonged clinical effects with longer-term use. Metabolism is primarily via hydroxylation of the phenyl ring following splitting of the imidazoline ring [22]. While metabolites are excreted in the urine, roughly half of the drug is excreted unchanged in the urine. Dosing may be initiated with a loading dose of 3–5 mcg/kg, followed by an infusion

of 1–3 mcg/kg/hr [23]. Plasma elimination $t_{1/2}$ ranges from 12 to 24 hrs [24]. Onset is slower following enteral administration, peaking at 60–90 min although bioavailability is good at 75–90% [25]. Clearance varies with age. Neonatal clearance is slow with an elimination $t_{1/2}$ of 44–72 hrs which decreases rapidly such that by 1 year of age, elimination nears the 12–16 hrs seen in adults [25]. Clinical duration of action is much shorter at 60–90 minutes [7]. Dosing for sedation is 3–5 mcg/kg, while that for treatment of withdrawal syndromes is typically lower (1–2 mcg/kg/dose) but depends on the dosages of other IV alpha-agonists being received prior to transitioning to enteral clonidine.

While enteral, intranasal, and intramuscular use have been reported for procedural sedation use with dexmedetomidine, for PICU sedation it is utilized almost exclusively as an intravenous agent. Following bolus dosing, onset of action is rapid (within minutes) although the vast majority of practitioners forego the loading dose and use the drug as an infusion only. This is likely contributed to by findings that bolus dosing may be associated with significant hemodynamic changes as well as prolonged sinus pauses if done too rapidly [15]. Like clonidine, dexmedetomidine is highly lipophilic and rapidly redistributes in tissues. In contrast to clonidine, its elimination $t_{1/2}$ is relatively short at 2–2.5 hours in both healthy volunteers [14, 26] and the critically ill [27], making titration to clinical effect easier than with clonidine. Also, unlike clonidine, dexmedetomidine undergoes almost complete metabolism in the liver via glucuronidation and cytochrome P2A6 oxidation into inactive metabolites which are renally excreted [28]. Consequently, elimination is prolonged in liver but not renal disease. Non-IV use is almost exclusively limited to procedural sedation and includes primarily intranasal and oral/buccal use. While discussed elsewhere in this book in more depth, one factor that must be considered when administering orally is that bioavailability via buccal absorption is markedly higher (82%) than it is from gastric absorption (16%, Ref. 29). This significantly limits the appeal of enteral dexmedetomidine compared to clonidine in the PICU setting. If utilized, bolus dosing in the PICU is 1–2 mcg/kg administered over no more than 10 minutes. Continuous infusion rates range from 0.2 to 2 mcg/kg/hr with recommendations being to start low and titrate up to clinical effect.

Clinical Applications

Like many other sedative/anxiolytic agents used in the PICU, α-agonists have multiple beneficial actions beyond just their sedative effects. In particular, the sympatholytic effects appear to be beneficial in reducing the incidence of clinically significant tachydysrhythmias, and the minimal respiratory-depressing effects make the class appealing for use in the non-intubated patient to facilitate cooperation with sometimes irritating therapies, especially noninvasive ventilation. Additionally, they can be used to manage symptoms of iatrogenic withdrawal associated with benzodiazepine and/or opioid use and may decrease the risk of ICU-associated delirium.

The effectiveness of both dexmedetomidine and clonidine for PICU sedation during mechanical ventilation has been well described. As a primary sedative agent, clonidine has seen relatively limited use in pediatric critical care with most early studies concentrating on use to manage iatrogenic withdrawal from opioids and/or benzodiazepines [30, 31]. These studies have reported use as both enteral [30] or as an IV infusion [21, 32] and as an adjunct to opioid and/or benzodiazepine "failure" or in an attempt to decrease opioid/benzodiazepine use several days into the PICU course. Only two studies have evaluated the addition of clonidine early in the course of PICU sedation. A retrospective review compared usual sedation with or without addition of an α-agonist (primarily clonidine) and reported slightly improved sedation efficacy but no morphine- or midazolam-sparing effects [33]. A single RCT has compared clonidine versus midazolam infusions for sedation during mechanical ventilation in critically ill children [34]. While sedation quality and time at adequate sedation was similar with each regimen, in both groups, sedation quality was suboptimal much of the time, and patients receiving clonidine required more inotropic support than those in the midazolam group. Dosing of clonidine in all the above studies included oral and IV use as well as intermittent dosing or continuous infusion. For enteral use, dosing was 3–5 mcg/kg every 6–8 hours. For intermittent IV use, dosing was 1–2 mcg/kg every 6–8 hours and continuous infusion doses ranged from 1 to 3 mcg/kg/hr.

Substantially more experience has been published regarding the use of dexmedetomidine for PICU sedation and has revealed a large, albeit likely expected, evolution in use and dosage patterns as experience increases. Initially approved in 1999 for sedation in mechanically ventilated adults, the first case reports of use in the PICU appeared in 2002 [9] followed in 2004 by the first RCT comparing two doses of dexmedetomidine infusion versus midazolam infusion in addition to intermittent morphine boluses. Time inadequately sedated and total morphine use was lower in the high dexmedetomidine dose group compared to midazolam, while no differences were observed between low-dose dexmedetomidine and midazolam groups [10]. Over the next few years, several more case series were published describing effective and apparently safe (defined as limited adverse hemodynamic effects) use of dexmedetomidine as a primary sedative agent, many describing initiation soon after arrival to the PICU. Two cohorts of postoperative cardiac surgical patients received dexmedetomidine as their primary sedative with additional analgesia via either continuous infusion or intermittent dosing of opioids [35, 36]. Sedation and analgesia were assessed as adequate in the vast majority of patients. In one cohort, compared to patients receiving midazolam sedation, dexmedetomidine use was also found to be opioid-sparing [36]. Doses required in infants were found to be slightly higher than those required in older children. Subsequently, the use of dexmedetomidine was more specifically evaluated in neonates and infants following cardiothoracic surgery to better understand safety in this population [37]. While not overtly stated as a study motivation, this question is of special interest as the sympatholytic effects of dexmedetomidine (particularly bradycardia) might, theoretically, be less well tolerated due to the greater dependence on heart rate for cardiac output in younger children. Approximately ¼ of patients in this cohort also received fentanyl

infusions, although this addition did not alter either the quality of sedation/analgesia or the mean dexmedetomidine doses required to achieve adequate sedation. In more mixed PICU populations, dexmedetomidine use has been reported as either a primary sedative or adjunct to benzodiazepine and/or opioid infusions [38, 39]. Sedation quality in these populations also was reported as adequate, with dexmedetomidine use also facilitating reductions in other sedative agents. In one study this reduction was a stated goal so that the limited respiratory-suppressing effects of dexmedetomidine compared to opioids and/or benzodiazepines could be taken advantage of in order to facilitate earlier extubation. A common thread in all of these studies was that dexmedetomidine doses used were relatively low (0.1 to 0.75 mcg/kg/hr) and likely reflected both published experience in critically ill adults [40, 41] and the initial FDA label. In addition, early use tended to be time-limited, with mean infusion durations ranging from 13 to 32 hours [36, 38, 39].

Subsequent reports have described expansions in terms of both dexmedetomidine dosing and duration in multiple critically ill pediatric populations. Following burn injury, dexmedetomidine initiation after failure of opioid and benzodiazepine infusions to maintain adequate comfort was associated with improved sedation quality and maintained adequacy of sedation using doses titrated up to 2 mcg/kg/hr and infusions continued for a mean duration of 11 days [42]. In a second report following burn injury, dexmedetomidine and midazolam were both able to maintain acceptable sedation, with each drug being used for mean durations of just over 20 days. Hypotension was reported less often in patients receiving dexmedetomidine although the mean dose was relatively low at 0.44 mcg/kg/hr [43]. Similarly, safe and effective use of prolonged dexmedetomidine infusions (mean duration of 9 days) following laryngotracheal reconstruction has been reported with no differences in adverse events compared to sedation with benzodiazepines although, unlike the above reported use in burn patients, iatrogenic withdrawal was a frequent finding regardless of sedation regimen utilized [44]. In general PICU populations, prolonged (>72 hr) dexmedetomidine infusions have also been reported to be well tolerated, including hemodynamically, at doses ranging up to 2.5 mcg/kg/hr although withdrawal symptoms were, again, not uncommon and tended to correlate with rate of weaning of the infusion or failure to transition off the infusion using enteral equivalents [45–47]. In addition to withdrawal with longer-term use, the major adverse effects described in these studies were hypotension and/or bradycardia, occurring in up to 40% of patients receiving dexmedetomidine although, due to coadministration of other cardioactive medications, it is unclear what proportion of hypotension is solely attributable to dexmedetomidine (38 39, 47).

Use of dexmedetomidine for sedation of the cardiac surgical patient has been an area of special interest since its arrival. While the efficacy of sedation has been well described, the increased incidence of bradycardia and hypotension compared to many other sedative/analgesic agents used could limit usefulness in this population. However, the sympatholysis which is responsible for these adverse events could also be of benefit, particularly in reducing the risk of catecholamine-sensitive dysrhythmia development. From a sedation perspective, dexmedetomidine appears to be as well tolerated in the cardiac surgical population as in other PICU populations.

Compared to patients receiving "conventional" sedation with benzodiazepine and opioid infusions, addition of dexmedetomidine to these therapies allowed reductions in both benzodiazepine and opioid doses without any significant hemodynamic changes [48, 49]. In studies comparing sedation regimens with a dexmedetomidine/opioid versus a midazolam/opioid-based regimen, patients receiving the dexmedetomidine-based protocol were equally well sedated compared to those receiving midazolam [50, 51]. One of these studies also reported significant reductions in the need for adjunct analgesia or sedative agents to maintain comfort but also found increased rates of hypotension and/or bradycardia development with dexmedetomidine, even though interventions for these events were rarely required [50].

As alluded to above, dexmedetomidine is of particular interest in the cardiac surgical patient with respect to postoperative dysrhythmias, particularly junctional ectopic tachycardia (JET). This is particularly malignant tachydysrhythmia that is unique to the pediatric population, occurring in up to 15% of children undergoing cardiac surgery. While decreasing, mortality rates of 8–13% have been reported in patients developing JET [52, 53]. Pathophysiologically, JET is associated with atrioventricular dissociation and progressive decreases in cardiac output as heart rates rise, making management difficult as the addition of catecholamine-based inotropic agents can exacerbate instability [54]. Treatment has focused on decreasing catecholamine levels by patient cooling, aggressively treating pain, deepening sedation, and reducing inotrope infusion rates [55]. Additional pharmacologic management focuses on reducing heart rate to enhance ventricular filling time, with amiodarone being the currently accepted standard [54]. The sympatholytic effects of dexmedetomidine are especially appealing here as, in addition to providing sedation, sympatholysis-induced catecholamine reductions may also contribute to heart rate control. In a retrospective cohort study, patients who received dexmedetomidine for postoperative sedation had a markedly reduced risk of JET development (OR 0.17) compared to non-dexmedetomidine-based sedation regimens [56]. In a subsequent trial randomizing patients to receive dexmedetomidine or placebo as an intraoperative load plus a 48-hour postoperative infusion, the incidence of JET in the dexmedetomidine group was significantly reduced (16.7% vs 3.3%) without increases in other adverse events including bradycardia and hypotension [57]. In a placebo-controlled randomized comparison of prophylactic dexmedetomidine or amiodarone following cardiac surgery, the incidence of postoperative JET was identical in the two treatment groups (6.7% each) compared to 33.3% in the placebo group [58]. All of the above studies suggest that dexmedetomidine is effective in reducing the risk of JET development. However, inadequate data exist to comment on the impact of addition of dexmedetomidine to patients who develop JET. In addition to the impacts of JET, dexmedetomidine use following cardiac surgery has been associated with reductions in other tachydysrhythmias, tachydysrhythmias requiring intervention, and ventricular tachycardia [59, 60]. In two meta-analyses of dexmedetomidine use in cardiac surgical patients, additional dexmedetomidine benefits included reductions in length of mechanical ventilation, duration of PICU and hospital stay, opioid and benzodiazepine requirements, and delirium development [61, 62]. A single study has reported that the occurrence and severity of acute kidney injury following pediatric cardiac surgery was lower in children sedated with

dexmedetomidine compared to other agents, the proposed mechanisms being a combination of anti-inflammatory effects, cytoprotection via α_2-receptor-mediated cell survival signaling, and sympatholysis-mediated increased renal blood flow [63].

The absence of clinically relevant respiratory depression associated with α-agonists compared to most other sedatives available to the critical care provider has been well described and contributes largely to the basis for their use in procedural sedation. This property has also been taken advantage of in the PICU, with dexmedetomidine use described either for non-intubated patients in whom agitation control was required or as a bridge to extubation in patients deemed at higher risk of inadvertent device removal during the sedation lightening and ventilator weaning process [38, 45, 64, 65]. More recently, in correlation with the increasing use of noninvasive ventilation (NIV) for acute respiratory failure in the PICU [66], use of α-agonists has expanded to facilitate cooperation with NIV strategies, including high flow nasal cannula and continuous/bilevel positive airway pressure (CPAP/BiPAP) via nasal or full face mask. In three studies, dexmedetomidine infusions were utilized in over 600 critically ill children requiring NIV support for either primary lung disease or systemic diseases such as sepsis and septic shock [67–69]. The average doses administered to these cohorts ranged from 0.6 to 1 mcg/kg/hr with reported maximum doses of 1–1.5 mcg/kg/hr, which is similar to doses reported during use for procedural sedation. Median infusion durations ranged from 35 to 48 hrs with numerous patients requiring infusion durations of >96 hours. Two of the 3 studies provided data regarding progression of lung disease; in 242 patients initially managed with NIV and dexmedetomidine sedation, only 9 required subsequent endotracheal intubation [67, 68], and, of these, 8 were deemed to be a result of primary disease progression rather than adverse effects of dexmedetomidine use. These data suggest that, similar to its well-established respiratory safety record during procedural sedation, longer-term use of moderate-dose dexmedetomidine infusions can be safely used to facilitate cooperation with NIV therapies.

The development of tolerance and iatrogenic withdrawal syndromes following prolonged use of many sedative or analgesic agents is a well-recognized phenomenon within pediatric critical care, occurring in up to half of patients [69, 70]. To date, most literature regarding iatrogenic sedative withdrawal has focused on benzodiazepines and opioids, as they remain the most commonly utilized agents in the PICU setting. Typically, management of withdrawal is two-pronged. Firstly, prevention of symptoms is aimed for, usually by slow weaning of the sedative/analgesic agent(s) with or without transition from IV to enteral equivalents. Alongside this, a validated withdrawal scoring tool is used so that, if symptoms do develop, interventions to mitigate them such as increasing doses or reinitiation of the presumed responsible agent can be implemented. Concerns for the development of benzodiazepine and opioid withdrawal may have adverse effects on the intubated patient. In addition to potential ongoing agent-related adverse effects, endotracheal extubation may be delayed due to worries that respiratory depression may develop if infusions must be continued following extubation. Alpha-agonists, especially clonidine, have a relatively well-established history of benefit in treating withdrawal associated with substances of abuse [71–73]. More recently, these properties have been utilized to manage tolerance to, and withdrawal from, benzodiazepine and opioid infusions

in PICU patients. Use of a dexmedetomidine infusion to manage iatrogenic withdrawal in the PICU setting was first described over 15 years ago [74]. Subsequent small case series describe success with IV or subcutaneous dexmedetomidine infusions [75, 76] with more rigorous data remaining limited. While it is commonly utilized, published data regarding the use of clonidine for prevention/treatment of iatrogenic withdrawal are also relatively limited, including just over 100 patients in 10 reports [77]. Both enteral and transdermal clonidine applications have been described. Regardless of which agent is used, strategies should be tailored to the unique patient situation. Dosing needs will vary depending on both the doses and duration of time the other sedative and/or analgesic agents have been administered. Unless concerns regarding hemodynamic tolerance exist, it is typically recommended that once the α-agonist is added, the benzodiazepine and opioid infusions be weaned and discontinued first so that ventilator weaning can continue with a lower likelihood of respiratory depression. It is acceptable to initiate therapy with dexmedetomidine given that it is most easily titratable. Subsequent conversion to enteral or transdermal clonidine can then occur at the practitioners discretion and patients ability to tolerate enteral intake.

Despite their value for the management of iatrogenic withdrawal, it has also been increasingly recognized that tolerance and withdrawal to α-agonists may develop. Initial descriptions of possible withdrawal occurred over 10 years ago with two case reports. In the first case, tachycardia, hypertension, and emesis developed in a 2-year-old male shortly following abrupt discontinuation of a 6-day dexmedetomidine infusion [78]. In the second, an 8-week-old female developed agitation, tachycardia, diarrhea, pupillary dilation, and seizure in the first several hours after abrupt discontinuation of a 3.5-day infusion of dexmedetomidine [79]. In both cases, symptoms resolved with reinitiation of dexmedetomidine and did not recur with a slower wean. Subsequent to these reports, several larger series have reported presumed withdrawal in patients either following abrupt discontinuation or weaning of dexmedetomidine infusions, although consensus regarding what constitutes a true withdrawal syndrome to α-agonists does not yet exist. Multiple symptoms have been described with the most common including tachycardia, hypertension, agitation, tremor, fever, and sleep disturbances [46, 48, 65, 80]. Many of these symptoms are also seen with withdrawal from either benzodiazepines or opioids. Since these medications are often coadministered with α-agonists, determination of which agent is the primary offender in terms of withdrawal development may be difficult. Use of conventional withdrawal scoring tools such as the Finnegan score for neonatal abstinence syndrome and the Modified Withdrawal Assessment Tool (M-WAT) may also be problematic as they were not specifically designed for assessing withdrawal to α-agonists and do not necessarily assess for all of the symptoms which have been described with possible α-agonist withdrawal. Thus, their use may result in an under-recognition of α-agonist-based withdrawal, which underscores the importance of practitioner being especially aware of the potential for withdrawal development during α-agonist weaning and/or termination. Similar to use for opioid and benzodiazepine withdrawal, transition from IV dexmedetomidine to enteral or transdermal clonidine is a potentially useful strategy for mitigation of withdrawal.

While initially recognized/appreciated in adult critical care, delirium in PICU patients has also come to be appreciated as a significant problem with numerous associated morbidities including prolonged ICU and hospital lengths of stay [81, 82], prolonged psychological sequelae [83], and possibly even mortality [81]. With data increasingly suggesting an association between benzodiazepine use and pediatric delirium [82, 84] and data in critically ill adults suggesting sedation that dexmedetomidine may be protective regarding delirium development [85], increased understanding of the impact of α-agonists on pediatric delirium is needed. Limited data to date have addressed this. In a small study comparing midazolam to dexmedetomidine-based sedation following scoliosis surgery, patients receiving dexmedetomidine experienced significantly less delirium [86]. In a larger meta-analysis of dexmedetomidine use in pediatric cardiac surgical patients, the odds ratio of experiencing delirium was 0.39 in patients sedated with dexmedetomidine compared to other sedatives [61]. Further study into the benefits of α-agonists for pediatric delirium remains an ongoing need and priority.

Conclusion

Alpha-agonists are increasingly utilized for pediatric ICU sedation. Useful applications include sedation efficacy, reduced risk of tachydysrhythmias following cardiac surgical procedures, treatment of withdrawal syndromes associated with benzodiazepine and opioid exposure, and possibly reductions in delirium. Their limited respiratory-suppressing properties make this class of sedatives appealing for use during noninvasive ventilation or to facilitate ventilator weaning and extubation in the otherwise potentially behavior-challenged patient. For IV sedation in the PICU, dexmedetomidine is the preferred agent due to more favorable pharmacokinetics compared to clonidine although, to facilitate termination of IV infusions, transition to enteral or transdermal clonidine is viable and useful. Significant adverse effects associated with α-agonists are limited to cardiovascular effects, particularly hypotension and bradycardia. While not uncommon, these issues usually do not require intervention other than dose reductions.

As with other sedative and analgesic agents, prolonged use can be associated with tolerance and iatrogenic withdrawal development, which can be mitigated by slow weans and/or addition of enteral α-agonist equivalents.

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