Received: 28 February 2022 | Revised: 29 March 2022 | Accepted: 31 March 2022

DOI: 10.1002/phar.2684

PHARMACOTHERAPY accp

ORIGINAL RESEARCH ARTICLE

A pilot study of *ADRA2A* genotype association with doses of dexmedetomidine for sedation in pediatric patients

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Abstract

Study Objective: Dexmedetomidine is titrated to achieve sedation in the pediatric and cardiovascular intensive care units (PICU and CVICU). In adults, dexmedetomidine response has been associated with an ADRA2A polymorphism (rs1800544); CC genotype is associated with an increased sedative response compared with GC and GG. To date, this has not been studied in children.

Design: We conducted a pilot study to determine whether ADRA2A genotype is associated with dexmedetomidine dose in children.

Measurements and Main Results: Forty intubated PICU or CVICU patients who received dexmedetomidine as a continuous infusion for at least 2 days were genotyped for ADRA2A with a custom-designed TaqMan® Assay. Ten (25%) subjects were wildtype (GG), 15 (37.5%) were heterozygous (GC), and 15 (37.5%) were homozygous (CC) variant. The maximum dexmedetomidine doses (mCg/kg/h) were not different between genotype groups CC (1, 0.3–1.2), GC (1, 0.3–1.3), and GG (0.8, 0.3–1.2), ($p = 0.37$); neither were mean dexmedetomidine doses for these respective genotype groups 0.68 (0.24–1.07), 0.72 (0.22–0.98), 0.58 (0.3–0.94), ($p = 0.67$).

Conclusions: These findings did not confirm the results from adult studies where ADRA2A polymorphisms correlate with dexmedetomidine response, therefore highlighting the need for pediatric studies to validate PGx findings in adults prior to implementation in pediatrics.

KEYWORDS
adrenergic, alpha-2, child, dexmedetomidine, pharmacogenetics, receptor

1 | INTRODUCTION

Children admitted to the pediatric intensive care unit (PICU) and cardiovascular intensive care unit (CVICU) often require mechanical ventilation and invasive procedures. The discomfort and anxiety caused by these procedures requires sedation with various opioids, benzodiazepines and other drugs to ensure patient comfort. Although recommended starting doses are available for pain and sedation in critically ill pediatric patients, doses are often titrated to the desired effect.[1] Patient response is variable, with some patients requiring a small cumulative dose of these drugs to achieve sufficient sedation and others requiring higher doses or multiple medications.[2]

Dose titrations are adjusted as needed, therefore increasing the risk for both under- and over-sedation and associated adverse events. Under-sedation can cause increased stress, pain, unplanned extubation and catheter dislodgment. Over-sedation is associated with tolerance, withdrawal and delays in recovery. Adverse events associated with both over- and under-sedation can result in a longer PICU or CVICU stay.

Recent efforts to decrease use of benzodiazepines in children have resulted in dexmedetomidine becoming a mainstay in sedation regimens in critically ill children,[3] despite a lack of dosing and pharmacokinetic data in critically ill pediatric patients. Dexmedetomidine is an alpha-2-adrenergic agonist. Effects are produced after binding to the G Protein-coupled protein of the alpha-2-adrenergic gene (ADRA2A). This gene does not have introns and is located on chromosome 10q25.2. Alpha 2A receptors are predominant in the central nervous system, and physiological functions controlled by different α2-AR subtypes are subject to interindividual variability.[4,5] In a phase III clinical trial in postsurgical ventilated ICU patients, dexmedetomidine produced clinically effective sedation and significantly reduced analgesic needs.[5] Additionally, dexmedetomidine is 8–10 times more selective toward α-2A than clonidine, does not suppress respiratory function, and has favorable cardiovascular effects.[6] The most recent U.S. Food and Drug Administration labeling for dexmedetomidine states that it should be used for adult patients for procedural sedation or continuous infusion in the ICU but not to exceed 24 h; safety and efficacy of dexmedetomidine has not been established for procedural or ICU sedation in pediatric patients.[7] Despite these label recommendations, dexmedetomidine is widely used for long-term sedation in the PICU and CVICU.[1]

In two adult studies, sedative response to dexmedetomidine has been associated with an *ADRA2A* polymorphism (rs1800544).[8,9] Homozygous wild-type (GG) and heterozygous (GC) allele carriers were found to have a decreased sedative response to dexmedetomidine, whereas homozygous (CC) variant allele carriers had an increased response (MAF C = 0.39).[8-10] Yet, there is a paucity of data in pediatrics. In this small pilot study, we aimed to determine if polymorphism of the *ADRA2A* genotype (rs1800544) is associated with dexmedetomidine response in critically ill children. We hypothesized that similar to adults, children with the presence of the wild-type allele (G) would require larger doses of dexmedetomidine and may take longer to achieve desired sedation compared to patients with the homozygous variant.

2 | METHODS

2.1 | Patient information

This study received expedited approval from the institutional review board. Patients were screened for eligibility using admitting data. Patients were eligible to be enrolled if they were admitted to PICU or CVICU; this includes patients who were at least 1 week through 25 years of age, which is inclusive of the population admitted to the PICU and CVICU at our institution and received dexmedetomidine as a continuous infusion for sedation for 2 or more days while mechanically ventilated. All patients or their legal guardian provided informed consent prior to enrollment. The patient's medical record was accessed retrospectively, post-enrollment to obtain demographic data including age, weight, sex, race, ethnicity, sedative medication dosing, pediatric state behavioral scale (SBS) sedation scores (when available), critical care admitting diagnosis, Pediatric Logistic Organ Dysfunction (PELOD) and Pediatric RIsk of Mortality (PRISM) III critical illness scores, PICU/CVICU length of stay (LOS), and hospital LOS.

2.2 | Genotyping

A biological sample was collected from each patient. When available, a scavenged sample from a previously scheduled clinical test was collected from the clinical laboratory. If leftover blood was not available, a saliva sample was collected using a commercially available kit (DNA Genotek, Ontario Canada).[11] In some cases, a tracheal aspirate was collected from mechanically-ventilated patients as previously described.[9] Genomic DNA was extracted from blood, saliva, or tracheal aspirate using validated methods and quantified using commercially available kits following manufacturer's instructions. The specific single nucleotide polymorphisms (SNPs) were determined based on adult studies showing correlation of genotype and sedative response to dexmedetomidine.[8,9] Following quantification, 10 ng DNA was used to genotype for rs1800544 with a custom-designed TaqMan® Assay (Life Technologies, Waltham MA) on the QuantStudio 12K Flex (Applied Biosystems, Waltham MA) platform following manufacturer's instructions. Patient genotype was determined using TaqMan® Genotyper software version 1.5.0 (Life Technologies, Waltham MA).

2.3 | Dose analysis

Dose as continuous infusion rate was retrospectively collected on dexmedetomidine, midazolam, ketamine, propofol, hydromorphone, morphine, and fentanyl. Single doses of these drugs administered as part of the scheduled medication regimen and/or administered as needed were also collected. The mean dexmedetomidine dose was determined for each patient by averaging the continuous infusion rate at, or around noon daily, by the number of days received. The maximum dexmedetomidine dose received was collected. The time to effective dose (12 h of continuous dexmedetomidine infusion without dose change) was also collected. To determine all individual and cumulative sedation medications used for each patient, *z*-scores were used to assess the population average dose of each medication and compare each patient day to this population average as previously described by our group.[12] The *z*-scores allowed us to assess the population average dose of each medication and compare each patient day to the overall study population average. A

z-score is representation of how far a data point is from the population mean, or a measure of how many standard deviations below or above an individual raw score is from the population mean. A *z*-score typically has a normal distribution curve.[13] We first calculated *z*-scores for each of the drugs (midazolam, ketamine, propofol, hydromorphone, morphine, and fentanyl) used as continuous infusions for each patient on each day. A cumulative medication burden score (summation *z*-score) was then calculated for each patient (medication burden = midazolam *z*-score + ketamine *z*-score + propofol *z*-score + hydromorphone *z*-score + morphine *z*-score + fentanyl *z*-score) in order to compare multiple sedative regimens received by patients. A *z*-score for each drug (midazolam, ketamine, propofol, hydromorphone, morphine, and fentanyl) was also calculated to determine the individual sedative regimens received by patient and divided by the number of days of mechanical ventilation to normalize to a patient's average *z*-score per ventilator days. We used this calculation method as measure of the sedation load that we have previously published to serve as an objective way to compare individual patients' medication loads to the rest of the population.[12]

2.4 | Data analysis

As the data followed non-normal distribution, nonparametric tests were used with a significance of $p = 0.05$ using SAS 9.4 (SAS Institute, Cary NC). In separate analyses, Pearson's correlation was used to determine the relationship between (i) dexmedetomidine mean dose, (ii) dexmedetomidine maximum dose, and (iii) cumulative *z*-score with time of effective dose, days of mechanical ventilation, PELOD score, PRISM score, ICU LOS, and age. In separate analyses, Wilcoxon signed-rank test was used to determine the relationship between (i) dexmedetomidine mean dose, (ii) dexmedetomidine maximum dose, and (iii) cumulative-*z*-score to patient genotype, gender, race, ethnicity, and critical care unit (i.e., PICU or CVICU).

Wilcoxon signed-rank test was also used to determine the relationship between (i) dexmedetomidine mean, and (ii) dexmedetomidine maximum dose to individual drug *z*-scores. Fisher's exact test was used to determine the relationship between patient genotype and gender, race, ethnicity, and critical care unit. Last, Fisher's exact test was also used to determine the relationship between patient genotype and individual drug *z*-score. There were not enough samples to conduct a meaningful Hardy–Weinberg analysis.

3 | RESULTS

Forty intubated pediatric critical care patients (34 PICU, 6 CVICU) who met the inclusion criteria were enrolled in this pilot study. The median age of patients was 2.7 (range, <1–18.4) years. One patient was Hispanic or Latino, 38 (95%) were not Hispanic or Latino, and 1 ethnicity was not reported. Seven (17.5%) of the patients were black or African American, 31 (77.5%) were white, and 2 (5%) races were unknown or not reported. Seventeen (42.5%) of patients were female and 23 (57.5%) were male. Patient demographic data are shown in Table 1.

Patient genotype results are as follows: 10 (25%) patients were wild-type (GG), 15 (37.5%) were heterozygous (GC), and 15 (37.5%) were homozygous variant (CC). The maximum dexmedetomidine doses (mCg/kg/h) were not different between genotype groups CC (1, range 0.3–1.2), GC (1, 0.3–1.3), and GG (0.8, 0.3–1.2), ($p = 0.37$). The mean dexmedetomidine doses (mCg/kg/h) for these respective genotype groups were 0.68 (0.24–1.1), 0.72 (0.22–0.98), and 0.58 (0.3–0.94) and were also nonsignificant ($p = 0.67$). Dexmedetomidine data according to genotype is shown in Table 2. The cumulative medication burden scores for CC, GC, and GG genotypes were 0.56 (−1.65, 1.47), 0.64 (−3.37, 1.47), and 0.60 (−4.44, 1.47), respectively ($p = 0.62$) (Table 2).

The patient age was significantly correlated with cumulative *z*-score ($r = -0.51$) and dexmedetomidine mean dose ($r = 0.37$) (Table 3). Time to effective dose was significantly correlated with cumulative drug score ($r = -0.42$); time to effective dose was also correlated with dexmedetomidine mean dose ($r = 0.38$) (Table 3). Hydromorphone *z*-score was significantly correlated with dexmedetomidine mean dose ($r = -0.341$) and dexmedetomidine maximum dose ($r = -0.318$) (Table 3). Patient genotype was not correlated with individual drug *z*-scores (Table 1).

4 | DISCUSSION

We report in a heterogeneous PICU population that *ADRA2A* polymorphisms did not correlate with dexmedetomidine response. Specifically, our results highlight three key findings: (i) mean and maximum doses of dexmedetomidine were not significantly different between children with wild-type versus variant genotype of *ADRA2A*; (ii) time to achieve effective dexmedetomidine doses was not significantly different between children with wild-type versus variant genotype of *ADRA2A*; and (iii) cumulative medication burden *z*-scores were highly variable between groups with a large range.

In our study, we included a diverse PICU population that introduces many clinical variables, most notably multiple pain and sedative medications, varying degrees of pain, and baseline neurological status that would be better controlled in a homogeneous population. Thus, the heterogenicity of our patient population may have contributed to the lack of association of *ADRA2A* polymorphisms and dexmedetomidine response despite our genotype results being comparable to adult studies. In adult studies, an association between *ADRA2A* polymorphisms and dexmedetomidine response was conducted in homogeneous populations.[8,9] In adult patients undergoing cardiac surgery, patients with the *ADRA2A* C-1291G (rs1800544) gene polymorphism had higher Ramsay sedation scores and longer periods of sleep compared to patients with the wild-type *ADRA2A* genotype.[9] Second, in a study of Chinese women post-cesarean section, those with an *ADRA2A* CC genotype had significantly increased pain thresholds and significantly reduced pain scores post-cesarean section compared to women

TABLE 1 Patient data by *ADRA2A* genotype variant

	Genotype		
Demographics	**CC (*n* = 15, 37.5%)**	**GC (*n* = 15, 37.5%)**	**GG (*n* = 10, 25%)**
Age, years, median (range)	2.0 (<0.1–18.4)	6.5 (<0.1– 17.9)	1.5 (<0.1–15.4)
Sex *n* (%)			
Female	5 (29.4)	6 (35.3)	6 (35.3)
Male	10 (43.5)	9 (39.1)	4 (17.4)
Race *n* (%)			
White	14 (45.2)	10 (32.3)	7 (22.6)
Other	1 (11.1)	5 (55.6)	3 (33.3)
Ethnicity *n* (%)			
Hispanic	0 (0)	0 (0)	1 (100)
Non-Hispanic	15 (38.5)	15 (38.5)	9 (23.1)
ICU *n* (%)			
PICU	11 (73)	14 (93)	9 (90)
CVICU	4 (27)	1 (7)	1 (10)
Admitting diagnosis			
Respiratory failure			
Chronic	2	3	1
Infectious	2	6	1
Malignancy	2	2	2
Neurological	2	3	3
Cardiac Surgery	4	0	1
Other	3	1	2
Illness Severity median (range)			
ICU LOS (days)	22.7 (10.0–121.8)	19.5 (6.0–63.0)	12.2 (4.2–96.0)
Hospital LOS (days)	28.7 (6–197.8)	33.6 (13.3–246)	22.9 (5.3–90.4)
MV Days	15.6 (3.0 –121.8)	12.6 (2.6–31.6)	8.2 (3.1–18.0)
Time to SS (hours)	7.8 (0–61)	8.5 (0–52)	8.5 (0–57.5)
CVICU/PICU *n* (%)			
PICU	11 (73.3)	14 (93.3)	9 (90.0)
CVICU	4 (26.7)	1 (6.7)	1 (10.0)
PELOD median (range)	11 (0–22)	11 (0–32)	11 (1–21)
PRISM median (range)	7 (0–16)	5 (0–34)	7 (0–18)
Z-scores (mean ± SD)			
Fentanyl	0.14 (0.39)	−0.22 (0.84)	−0.38 (0.96)
Morphine	0.17 (0.12)	0.07 (0.57)	0.00 (0.58)
Hydromorphone	−0.06 (0.79)	0.05 (0.56)	0.35 (0)
Midazolam	−0.05 (0.53)	−0.02 (0.41)	0.11 (0.01)
Ketamine	0.12 (0.03)	0.04 (0.34)	−0.12 (0.80)
Propofol	0.05 (0.23)	−0.03 (0.47)	0.05 (0.21)

Abbreviations: CVICU, cardiovascular intensive care unit, ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; PELOD, Pediatric Logistic Organ Dysfunction; PICU, pediatric intensive care unit; PRISM, Pediatric Risk of Mortality; SD, standard deviation; SS, steady state or effective dexmedetomidine dose.

with the GC or GG genotypes.[8] Due to the differences in our heterogeneous PICU population compared to the previous studies in surgical adult patients having dexmedetomidine titrated in a very controlled protocol, our lack of congruence with respect to validating the genotype to phenotype is not unexpected. The variability in dosing of other sedative and pain medications in the PICU adds confounding factors. Due to current trends for opioid-sparing protocols, one may hypothesize that dexmedetomidine

TABLE 2 *ADRA2A*genotype and response to dexmedetomidine

	CC ($n = 15$) median (range)	GC ($n = 15$) median (range)	GG ($n = 10$) median (range)	p-value
Maximum Dexmedetomidine dose (mcg/kg/h)	1.00 (0.30–1.20)	1.00 (0.30–1.30)	0.80 (0.30–1.20)	0.3733
Mean Dexmedetomidine dose (mcg/kg/h)	0.68 (0.24–1.07)	0.72 (0.22–0.98)	0.58 (0.30–0.94)	0.6710
Time to achieve dose (h)	7.8 (0–61)	8.5 (0–52)	8.5 (0–57.5)	0.9140
Cumulative *z*-score[a]	0.56 (−1.65–1.47)	0.64 (−3.37–1.47)	0.60 (−4.44–1.47)	0.6197

[a]Cumulative *z*-score = (midazolam *z*-score + ketamine *z*-score + propofol *z*-score + hydromorphone *z*-score + morphine *z*-score + fentanyl *z*-score).

TABLE 3 Patient data by cumulative *z*-scores and dexmedetomidine doses

Demographics	Cumulative *z*-score	Dexmedetomidine Mean Dose	Dexmedetomidine Max Dose
Age	−0.514*	0.373*	0.309
Sex median (range)			
Female	0.69 (−4.45–2.13)	0.77 (0.30–0.96)	1.00 (0.30–1.30)
Male	0.84 (−2.72–2.35)	0.58 (0.22–1.07)	0.80 (0.30–1.20)
Race median (range)			
White	0.69 (−4.45–2.30)	0.68 (0.24–1.07)	1.00 (0.30–1.30)
Other	1.12 (−3.25–2.35)	0.55 (0.22–0.94)	1.00 (0.30–1.20)
Ethnicity median (range)			
Hispanic	−2.00 (−2.00–−2.00)	0.94 (0.94–0.94)	1.20 (1.20–1.20)
Non-Hispanic	0.72 (−4.45–2.35)	0.59 (0.22–1.07)	1.00 (0.30–1.30)
Illness severity			
ICU LOS	0.156	−0.056	−0.036
MV Days	0.309	−0.151	−0.148
Time to SS	−0.419*	0.376*	0.305
CVICU/PICU median (range)			
PICU	0.69 (−4.45–2.35)	0.59 (0.22–1.07)	1.00 (0.30–1.20)
CVICU	1.31 (−0.13–1.98)	0.74 (0.40–0.83)	1.00 (0.40–1.30)
PELOD	−0.054	0.095	0.228
PRISM	−0.140	0.245	0.212
Z-scores			
Fentanyl		−0.097	−0.108
Morphine		−0.204	−0.168
Hydromorphone		−0.341*	−0.318*
Midazolam		−0.204	−0.120
Ketamine		−0.007	−0.118
Propofol		−0.071	−0.008

Note: Values are correlation coefficients when both variables are continuous, and medians (ranges) for one continuous with a categorical.

Abbreviations: CVICU, cardiovascular intensive care unit, ICU, intensive care; LOS, length of stay; MV, mechanical ventilation; PELOD, Pediatric Logistic Organ Dysfunction, SS, steady state or effective dexmedetomidine dosePICU, pediatric intensive care unit; PRISM, Pediatric Risk of Mortality.

*Significant $p < 0.05$.

doses may have potentially been titrated to the maximum dose prior to adding other agents. Although interesting, our data does not support this hypothesis. Even if dexmedetomidine response cannot be explained by genetic variability due to *ADRA2A*, there was a wide variety of maximum dexmedetomidine dosing ranging from 0.3 to 1.3 mcg/kg/h in our population.

The time to achieve effective dexmedetomidine doses was not significantly different between children with wild-type versus variant genotype of *ADRA2A*. Discussed above, dexmedetomidine titration often takes several hours to achieve adequate sedation. At our institution, intubated patients receive sedative medications until a goal SBS of 0 to −1 is achieved. Unfortunately, a limitation of this study is that sedation scores were not readily recorded and available in the electronic medical record (EMR).

Recent studies evaluating the effect of protocolizing sedation have shown minimal impact on length of mechanical ventilation or ICU length of stay.[14,15] In our study, we included both PICU and CVICU patients and, while at the same institution, these are two independent critical care units with varying degrees of protocolization for sedation. Additionally, our study included patients with a diverse cause of respiratory failure such as infection, structural airway abnormalities, and neurological cases such as head trauma. These respiratory failure etiologies are associated with varying degrees of pain as well as neurological status. The significance between time to effective dose and cumulative *z*-score may be indicative of the need to quickly titrate dexmedetomidine to achieve adequate patient sedation to avoid adverse effects associated with over-sedation when other sedatives are also being utilized.

Dosing of dexmedetomidine for continuous infusion can vary widely from doses of 0.2–1.5 mcg/kg/h.[16,17] At our institution, dexmedetomidine is often capped at 1 to 1.2 mcg/kg/h and this dose is rarely exceeded. In instances where the maximum dexmedetomidine dose is received, other drugs are added to achieve desired sedation. It is especially challenging to calculate and correlate the sedation medication burden when multiple medications from different drug classes are used in numerous combinations. In order to calculate the cumulative medication burden, *z*-scores were used to assess the population average dose of each medication and compare each patient's medication burden to the population average.[12] The cumulative *z*-scores were variable between the wild-type (GG), heterozygous (GC), and homozygous variant (CC) groups with a large range. This may indicate a potential association but identifies the need for a larger and potentially more focused study population. The individual *z*-score for hydromorphone was correlated with dexmedetomidine mean and maximum dose. As hydromorphone is more potent and offers higher sedative effects compared to other opioids, less dexmedetomidine would be utilized in clinical practice to achieve sedation.

Developmental changes in dexmedetomidine clearance also likely contribute to the variability in dosing in pediatric patients. Children have known developmental and ontogeny changes that affect drug metabolism and PGx.[18] Weerink et al.,[4] found dexmedetomidine clearance and distribution to have high inter-individual variability, especially in ICU populations. Additionally, patients under 1 year of age are reported to have reduced dexmedetomidine clearance.[18] In a dose escalation pharmacokinetic (PK) study of term neonates and infants with congenital heart disease, dexmedetomidine clearance was decreased in term newborns and rapidly increased within the first few weeks of life.[19] In a population PK model that included both children and adults, genes involved in dexmedetomidine metabolism included *CYP2A6*, *UGT2B10*, *CYP1A2*, *CYP2E1*, *CYP2C19*, and *CYP2D6*, but the receptor gene *ADRA2A* was not included.[20] In a population PK model of dexmedetomidine in critically ill children, investigators found that inclusion of *UGT2B10* but not *CYP2A6* or *UGT1A4* improved the fit of the model.[21] However, neither of these studies assessed the effect of *ADRA2A* variants on pharmacodynamic response. We observed a relationship between dexmedetomidine mean dose and time to effective dose, indicating that either (i) dexmedetomidine was started on low dose titrations and time to effective dose was reached with escalating dose, or (ii) the patient's sedative needs increased over time. A similar relationship was observed between patient age and cumulative dexmedetomidine *z*-score, as older patients had a lower cumulative *z*-score due to lower mcg/kg/h dosing, under the assumption that older patients weighed more and doses are normalized to adult dosing. These data are consistent with clinical practice. To fully elucidate the association of *ADRA2A* and dexmedetomidine response in pediatric patients, a prospective pharmacokinetic and pharmacodynamic study including multiple clinical correlates and potential genetic variants is needed.

This pilot study was limited as some patients were prospectively enrolled whereas others were retrospectively enrolled. Sedation scores were not documented for all patients, we did not quantify dexmedetomidine or other sedative drug dosing with plasma concentrations, and the diverse PICU population introduces many clinical variables, most notably varying degrees of pain and baseline neurological status. Overall, our study population was more heterogeneous and the study was more pragmatic compared with the two adult studies evaluating *ADRA2A* gene polymorphism on the effects of dexmedetomidine.[8,9] Thus, an adequately powered prospective study in a homogeneous pediatric population is needed to determine the association of *ADRA2A* and other genetic variants with dexmedetomidine response. In summary, our findings did not confirm adult studies where *ADRA2A* polymorphisms correlate with dexmedetomidine response, therefore highlighting the need for pediatric studies to validate PGx findings in adults prior to implementation in pediatrics.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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How to cite this article: Gallaway KA, Skaar TC, Biju A, Slaven J, Tillman EM. A pilot study of *ADRA2A* genotype association with doses of dexmedetomidine for sedation in pediatric patients. *Pharmacotherapy*. 2022;42:453–459. doi:10.1002/phar.2684