BRIEF REPORT

OPEN

Effect of Enteral Guanfacine on Dexmedetomidine Use in the ICU

Megan B. Fetters, PharmD[1]
Calvin Diep, PharmD, BCCCP[1]
Ran Ran, MD[2]
Amy Kloosterboer, MD[3]

OBJECTIVES: Describe the efficacy and safety of guanfacine for dexmedetomidine weaning in critically ill patients.

DESIGN: Retrospective descriptive analysis.

SETTING: Six hundred thirteen–bed academic medical center from October 2020 to October 2021.

PATIENT/SUBJECTS: All Adult patients on IV dexmedetomidine who received at least one dose of guanfacine for sedation or agitation were included.

INTERVENTIONS: Enteral guanfacine.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was discontinuation of dexmedetomidine therapy within 48 hours after guanfacine initiation. Secondary outcomes assessed included adjunctive medication use, rate of dexmedetomidine reinitiation, and safety outcomes. One hundred five patients were included in the analysis. Median age was 59 years old, 66% were male, and median daily dose of guanfacine was 1.5 mg. Dexmedetomidine was discontinued within 48 hours in 58% of patients ($n = 61$) and within 72 hours in 71% of patients ($n = 75$). Fifty-five percent of patients ($n = 58$) required rescue medications for poorly controlled agitation, sedation, or pain while on guanfacine. Dexmedetomidine withdrawal occurred in 2% of patients ($n = 2$) while on guanfacine. Adverse effects attributed to guanfacine occurred in 8% of patients ($n = 8$), all experiencing hypotension leading to medication discontinuation.

CONCLUSION: Dexmedetomidine was successfully weaned within 48 hours of guanfacine initiation in 58% of patients with minimal withdrawal or adverse effects. Guanfacine may be an effective and safe enteral option for dexmedetomidine weaning in critically ill patients.

KEY WORDS: adrenergic alpha-2 receptor agonists; critical illness; dexmedetomidine; drug withdrawal symptoms; guanfacine

Dexmedetomidine is an IV alpha-2 agonist commonly used in critically ill patients for the management of sedation and agitation (1–5). Dexmedetomidine use for greater than 24 hours can lead to withdrawal symptoms including hypertension, tachycardia, agitation, and nausea (6, 7). Enteral alpha-2 agonist agents, such as clonidine, have been shown to facilitate dexmedetomidine weaning in critically ill patients (8–12). However, use of clonidine maybe limited by hypotension with rates reported as high as 44% when used for dexmedetomidine weaning (10–12). Guanfacine, another enteral alpha-2 agonist, may be an alternative to clonidine with less cardiovascular adverse effects (13–16). Currently, data regarding the use of guanfacine for this indication are limited to published abstracts (14–16).

Dexmedetomidine, clonidine, and guanfacine are all alpha-2 receptor agonists often used to manage agitation, anxiety, and sedation in mechanically ventilated patients and hypertension. Variation in therapeutic

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KEY POINTS

- **Question:** What is the efficacy and safety of guanfacine for dexmedetomidine weaning in critically ill patients?
- **Findings:** This retrospective, descriptive analysis of 105 ICU patients found that dexmedetomidine was discontinued within 48 hours of guanfacine initiation in 61 patients (58%) with minimal withdrawal or adverse effects.
- **Meanings:** Guanfacine may be an effective and safe enteral option for dexmedetomidine weaning in critically ill patients.

action can be attributed to differing affinity for the three alpha-2 adrenoceptors subtypes: $\alpha2_a$ located in the prefrontal cortex and locus coeruleus, $\alpha2_b$ in vascular smooth muscle, and $\alpha2_c$ located in the striatum and the hippocampus (13). Although dexmedetomidine and clonidine both bind on all three receptor subtypes, guanfacine acts primarily on $\alpha2_a$. Guanfacine's minimal activity on the $\alpha2_b$ and $\alpha2_c$ receptors may lead to less effects on heart rate and blood pressure, making guanfacine an attractive alternative to clonidine, particularly in patients with hypotension.

At Stanford Healthcare, dexmedetomidine, clonidine, and/or guanfacine are included in our benzodiazepine sparing protocol for management of alcohol withdrawal (17). Guanfacine is frequently recommended by the psychiatry service for management of hyperactive delirium, agitation, and anxiety at doses ranging from 0.5–1 mg twice to tid. In line with this, guanfacine use to wean patients off dexmedetomidine has become a common practice due to its favorable pharmacodynamic profile, although no formal protocol is in place. The primary aim of this study is to describe the efficacy and safety of guanfacine for dexmedetomidine weaning in critically ill patients.

MATERIALS AND METHODS:

This was a retrospective descriptive study at a 613-bed academic medical center. Patients were included if they were greater than or equal to 18 years old, admitted to the ICU, were on dexmedetomidine, and received at least one dose of guanfacine for sedation or agitation from October 1, 2020, to October 1, 2021. Patients were excluded if they were in active alcohol or substance withdrawal, taking guanfacine prior to admission, received propofol or midazolam continuous infusions at the time of guanfacine initiation, or passed away while on dexmedetomidine. Guanfacine use and dosing was at the discretion of the treating team. Dexmedetomidine was titrated by the unit nurse(s) assigned to each patient generally by increments of no more than 0.2 μg/kg/hr every 15 minutes to achieve target a Richmond Agitation-Sedation Scale goal of –1 to 1 (doses range 0–1.2 μg/kg/hr).

The primary outcome assessed was discontinuation of dexmedetomidine therapy within 48 hours of guanfacine initiation defined as discontinuation of dexmedetomidine infusion order in the electronic medical record (EMR) without reinitiation within 72 hours. Secondary outcomes included discontinuation or reinitiation of dexmedetomidine within 72 hours of guanfacine initiation, medication dosing, and safety outcomes. Frequency of dexmedetomidine withdrawal was based on daily provider progress note, as withdrawal symptoms may be confounded by other disease states in critically ill patients (see **supplement** for full methods description, http://links.lww.com/CCX/B79). This study protocol was approved by the Stanford Institutional Review Board (IRB no. 62857, approval date 11/15/2021). This study was conducted in accordance with the ethical standards of the Stanford IRB and with the Helsinki Declaration of 1975.

IBM SPSS Statistics 22 (IBM Analytics, Armonk, NY) was used to perform all statistical analyses with a predefined significance level of 0.05 by two-tailed asymptotic or exact tests. Nonparametric continuous variables were analyzed using Mann-Whitney *U* test, and categorical variables were analyzed using Pearson chi-square test or Fisher exact test.

RESULTS

A total of 305 patients were screened for inclusion and 105 were included in the final analysis. The most common reason for exclusion was use of concurrent midazolam or propofol infusion (n = 107) (**Supplemental Fig. 1**, http://links.lww.com/CCX/B79). Median time on dexmedetomidine infusion prior to guanfacine initiation was 90 hours, and median dexmedetomidine

TABLE 1.
Baseline Characteristics

Variables	Results (*N* = 105)
Demographics	
Age, median (IQR)	59 (41–72)
Male, *n* (%)	69 (66)
Body mass index, median (IQR)	26 (22–31)
Pertinent medical history	
Comorbidities, *n* (%)	
Severe acute respiratory syndrome coronavirus 2 infection	11 (10)
Depression	9 (9)
Bipolar disorder	2 (2)
Other psychiatric disorder[a]	7 (7)
Prior to admission medication use, *n* (%)	
Benzodiazepine	2 (2)
Selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor/dopamine norepinephrine reuptake inhibitor[b]	9 (9)
Antipsychotic[c]	3 (3)
Clonidine	1 (1)
Clinical characteristics	
Admitting ICU type, *n* (%)	
Cardiovascular ICU	34 (32)
Medical ICU	33 (31)
Surgical ICU	13 (12)
Neuro ICU	19 (18)
Cardiac ICU	6 (6)
Reason for ICU admission, *n* (%)	
Surgery	25 (24)
Respiratory failure	22 (21)
Cardiogenic shock	19 (18)
Intracerebral hemorrhage/stroke	12 (11)
Sepsis	10 (10)
Trauma	5 (5)
Other[c]	12 (11)
Invasive mechanical ventilation, *n* (%)	43 (41)
Vasopressor use, *n* (%)	36 (34)
Richmond Agitation-Sedation Scale at time of guanfacine initiation, median (IQR)	0 (–1 to 1)
Time on dexmedetomidine prior to guanfacine, hr, median (IQR)	90 (43–201)
Dexmedetomidine dose at guanfacine initiation, µg/kg/hr, median (IQR)	0.6 (0.35–1)
Confusion Assessment Method + at time of guanfacine initiation, *n* (%)[d]	36 (41)
Psychiatry consult, *n* (%)	53 (50)

IQR = interquartile range.

[a]Other psychiatric disorders—patients with prior diagnosis of any other psychiatric disorder included in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition.

[c]Includes both typical and atypical antipsychotics.

[c]Liver failure (3), malignancy (6), autoimmune (1), unable to determine (2).

[d]Eight-seven patients with available data.

dose at guanfacine initiation was 0.6 µg/kg/hr. All baseline characteristics are shown in **Table 1**.

Dexmedetomidine order in the EMR was discontinued within 48 hours of guanfacine initiation in 58% of patients (*n* = 61). Dexmedetomidine was reordered in 10% of patients (*n* = 11) within 72 hours of discontinuation. Dexmedetomidine withdrawal occurred in 2% of patients (*n* = 2). Hypotension occurred in 23% of patients (*n* = 24) with 8% (*n* = 8) being attributed to guanfacine as indicated by physician notes. Guanfacine was continued at hospital discharge for 18% of patients (*n* = 19): 12 discharged to another care facility, two discharged home with taper plans to stop within 7 days, and five discharged with no discontinuation plan. All outcomes are shown in **Table 2**.

The median daily dose of guanfacine administered was 1.5 mg with a maximum total daily dose of 3 mg. Median time to dexmedetomidine order discontinuation was 41 hours from guanfacine initiation. Rescue psychoactive medications were administered in 55% of patients (*n* = 58), and scheduled psychoactive medications were administered in 53% of patients (*n* = 56). See **Supplemental Table 1** (http://links.lww.com/CCX/B79) for medication dosing and use.

DISCUSSION

In this study including critically ill patients on IV dexmedetomidine, approximately half of patients were successfully weaned off dexmedetomidine within 48 hours of guanfacine initiation with minimal incidence of withdrawal or adverse effects. A total of five patients were discharged from the hospital on guanfacine with no discontinuation plan. A taper or discontinuation plan should be in place to reduce unnecessary therapy, adverse events, and polypharmacy. This study shows the potential use of guanfacine as an oral agent to wean patients off IV dexmedetomidine.

Currently, there are limited studies investigating the use of guanfacine for weaning dexmedetomidine. A single-centered retrospective study of 48 patients presented as a meeting abstract reported successful discontinuation of dexmedetomidine in 62.5% of patients within 24 hours of initiating guanfacine (14). Guanfacine dosing or use of concomitant psychoactive medications was not described in the previous study. The median guanfacine dose observed in this study was 1.5 mg per day, and approximately 50% of patients in this study received adjunctive psychoactive

TABLE 2.
Outcomes

Outcomes	Results (*N* = 105)
Primary outcome	
Discontinuation of dexmedetomidine order within 48 hr, *n* (%)	61 (58)
Secondary outcomes	
Discontinuation of dexmedetomidine order within 72 hr, *n* (%)	75 (71)
Restart dexmedetomidine within 72 hr, *n* (%)	11 (10)
Hospital length of stay, d, median (IQR)	24 (14–36.5)
ICU length of stay, d, median (IQR)	13 (8–22)
ICU mortality, *n* (%)	12 (11)
Medication use	
Guanfacine daily dose, mg, median (IQR)	1.5 (1–2.17)
Titration of guanfacine in first 72 hr, *n* (%)	30 (29)
Change in dexmedetomidine dose after guanfacine initiation, µg/kg/hr, median (IQR)	
24 hr	−0.3 (0.02–0.5)
48 hr	−0.4 (0.2–0.8)
72 hr	−0.5 (0.28–0.8)
Time to dexmedetomidine discontinuation from guanfacine initiation, hr, median (IQR)	41 (19–84)
Use of as needed rescue agentsa, *n* (%)	58 (55)
Scheduled psych medsa, *n* (%)	56 (53)
Safety Outcomes	
Dexmedetomidine withdrawalb, *n* (%)	2 (2)
Bradycardiac, *n* (%)	2 (2)
Hypotensiond, *n* (%)	24 (23)
Required vasopressors	11 (10)
Related to guanfacine	8 (8)
Escalation in ventilatione, *n* (%)	4 (4)
ICU deliriumf, *n* (%)	23 (22)
Continuation of guanfacine at hospital discharge, *n* (%)	19 (18)

IQR = interquartile range.

[a]See Supplemental Table 1 (http://links.lww.com/CCX/B79) for breakdown of medications.

[b]Dexmedetomidine withdrawal defined as suspicion of or signs and symptoms of withdrawal within in progress notes.

[c]Bradycardia defined as heart rate < 60 beats per minute.

[d]Hypotension defined as mean arterial pressure < 65, systolic blood pressure < 90 mm Hg, or blood pressure requiring initiation of vasopressors.

[e]Escalation in ventilation defined as need for initial intubation or reintubation not related to other procedures while on guanfacine therapy.

[f]ICU delirium was defined as a positive Confusion Assessment Method-ICU score at any time during guanfacine therapy, documented every four hours as assessed by the bedside nurse.

medications, which may be attributed to institutional tendency to use multimodal therapy to manage ICU agitation and anxiety. In this study, the time frame of 48 hours used to assess the primary outcome was chosen based on the half-life of guanfacine (10 to 30 hr), resulting in a time to steady state concentration of approximately 50–150 hr (~5 half-lives) (19, 20). Both these studies showed successful weaning of dexmedetomidine in greater than 50% of patients within 24–48 hours of guanfacine initiation.

Current literature describing the use of non-IV agents to wean off dexmedetomidine focuses on clonidine. Studies have reported successful transition off dexmedetomidine in up to 75% of patients within 8–48 hours of receiving clonidine with minimal withdrawal symptoms (10–12). Oral clonidine has a shorter half-life (12–16 hr) compared with guanfacine, resulting in a shorter time to steady state levels and potentially faster onset (18, 21). Guanfacine has a higher selectivity for $\alpha 2_a$ receptor, potentially minimizing cardiovascular side effects. Terry et al (10) reported hypotension in 35–44% of patients receiving clonidine for dexmedetomidine tapering. In this study, hypotension was reported in 23% of patients with 8% being potentially related to guanfacine administration. The reduced effects on cardiovascular hemodynamics of guanfacine may offer an advantage as many critically ill patients are hypotensive and require vasopressor support.

There were several limitations to our study, including its single-centered retrospective nature and the potential confounders inherent to such a design. During the study period, guanfacine initiation and dosing was at the discretion of the treating team. It is difficult to determine whether the addition of guanfacine was necessary as dexmedetomidine weaning without an oral transition maybe possible in some cases. Approximately half of patients received adjunctive psychoactive and opioid medications which could confound the efficacy of guanfacine for weaning dexmedetomidine. Although other psychoactive medications maybe used to manage symptoms of dexmedetomidine withdrawal, guanfacine maybe an ideal option given its similar mechanism of action and favorable side effect profile. Although the pharmacologic profile of guanfacine may suggest less cardiovascular adverse effects compared with clonidine, this was not a comparative study and that conclusion cannot be definitely made.

CONCLUSIONS

This study, which investigated the use of guanfacine for dexmedetomidine weaning, showed that 58% of patients were weaned off dexmedetomidine within 48 hours of guanfacine initiation with minimal withdrawal or adverse effects. Guanfacine may be an effective and safe enteral option for dexmedetomidine weaning in critically ill patients. Although the use of guanfacine is promising, further studies are needed to confirm these findings and to determine optimal dosing of guanfacine for dexmedetomidine weaning.

1 *Department of Pharmacy, Stanford Health Care, Palo Alto, CA.*

2 *Department of Critical Care Medicine, Oregon Health & Science University, Portland, OR.*

3 *Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University, Palo Alto, CA.*

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Drs. Fetters and Diep led the development of the project, collected, and analyzed data and contributed to and reviewed the article. Dr. Ran contributed to the study design, analyzed data, and contributed to and reviewed the article. Dr. Kloosterboer contributed to the study design and contributed to and reviewed the article.

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For information regarding this article, E-mail: cdiep@stanfordhealthcare.org

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