Published in final edited form as:
Am J Crit Care. 2014 March ; 23(2): 160–165. doi:10.4037/ajcc2014678.

Identification of Patient Predictors for Dexmedetomidine Effectiveness for ICU Sedation

Pamela L. Smithburger, PharmD, BCPS [Assistant Professor],
University of Pittsburgh School of Pharmacy

Randall B. Smith, PhD [Senior Associate Dean of the School of Pharmacy],
Pharmaceutical Sciences, University of Pittsburgh

Sandra L. Kane-Gill, PharmD, MSc [Associate Professor], and
University of Pittsburgh School of Pharmacy

Philip E. Empey, PharmD, PhD, BCPS [Assistant Professor]
University of Pittsburgh School of Pharmacy

Abstract

Background—Effective sedation is paramount in the care of critically ill patients. Dexmedetomidine, a selective α2- adrenergic receptor agonist, is an agent that is being increasingly used in the ICU despite its variability of patient response.

Objective—To report dexmedetomidine effectiveness and to identify specific patient characteristics that play a role in the achievement of adequate sedation with dexmedetomidine.

Methods—We conducted a 6 month, pilot, prospective observational study in a medical intensive care unit (MICU) at an academic medical center. Patients receiving dexmedetomidine were followed until drug discontinuation and were grouped into non-responders and responders. Effective sedation was defined as the achievement of a Sedation Agitation Scale (SAS) score of 3-4 after the addition of dexmedetomidine. Patient characteristics, laboratory values, home and inpatient medications, and dexmedetomidine dosing information were collected to identify predictors of clinical response.

Results—Thirty eight patients received dexmedetomidine in a 6 month time period, with dexmedetomidine being ineffective in 19/38 (50%) patients, effective in 11/38 (28.95%) patients, and effectiveness was unable to be assessed in 8 patients due to clinical confounders. Based upon the standard multiple logistic regression analysis, patients with a lower APACHE II (β coefficient −0.24; 95% CI, −0.39 to −0.03) and patients that received home antidepressants (β coefficient 2.33; 95% CI, 0.23 to 4.43) were more likely to achieve successful sedation with dexmedetomidine as compared to patients with a higher APACHE II score or no home antidepressant use.

Corresponding Author: Pamela L. Smithburger, PharmD, BCPS Assistant Professor, University of Pittsburgh 200 Lothrop Street, Pittsburgh PA 15213 smithburgerpl@upmc.edu; 412-647-0899 (p); 412-864-3824 (f).

Conclusions—Variability in effective sedation occurred with dexmedetomidine use. Future large scale investigations should be conducted to confirm the association of a lower APACHE II score and home antidepressant use and dexmedetomidine effectiveness.

Keywords

Dexmedetomidine; critically ill; sedation

To minimize agitation and anxiety, one or more sedative agents are administered to over 50% of critically ill patients.[1,2] The use of sedative agents should facilitate patient comfort while avoiding prolonged and deep sedation.[3,4] The 2013 Society of Critical Care Medicine's Pain, Agitation, Delirium guideline recommended that non-benzodiazepine sedatives, such as propofol and dexmedetomidine, be utilized as first line agents to provide effective sedation for mechanically ventilated, intensive care unit (ICU) patients.[2] Dexmedetomidine is a selective α2-adrenergic receptor agonist that possesses sympatholytic, sedative, as well as analgesic and opioid sparing properties.[5,6] The characteristics of the sedation produced by dexmedetomidine, lack of respiratory depression, and the 2013 Pain, Agitation, Delirium Guideline recommendation, has led to an increased use of dexmedetomidine in the ICU.[2,7,8] However, a wide variability in patient response to dexmedetomidine limits success in achieving sedation goals (treatment failures) in some patients. [8,9,10,11] It is therefore important to identify the patient factors that are associated with treatment response to best differentiate between patients that will achieve effective sedation and those that will not in order to optimize sedation care. The aim of this pilot investigation is to generate hypotheses to drive future large scale, prospective inquires to investigate what specific patient characteristics play a role in the achievement of adequate sedation with dexmedetomidine.

Methods

This was a 6 month, pilot, prospective observational study that was conducted in a medical intensive care unit (MICU) at an academic medical center. This study was IRB approved by the University of Pittsburgh IRB. Patients were included if they were ≥ 18 years old, mechanically ventilated, and received a continuous infusion of dexmedetomidine for ICU sedation for at least 6 hours. The use of dexmedetomidine and the initial infusion rate chosen for ICU sedation were both based on the attending physician's clinical judgment and the unit's standard sedation protocol. Each patient's level of sedation was determined by Sedation Agitation Scale (SAS) scores, which were measured by the bedside nurse every two hours, per standard protocol. The target level of sedation was a SAS score of 3-4, which corresponds to "waking with verbal or physical stimuli" or "easily arousable".[12] Patients were followed from the initiation to discontinuation of dexmedetomidine. Dexmedetomidine's ineffectiveness was defined as the addition of a new continuous infusion sedative at any dose or the re-initiation of previously discontinued sedative while dexmedetomidine was being used at an infusion rate of 0.7 mcg/kg/hr or higher. This dosing rate was selected as it is the United States' Food and Drug Administration maximum recommended infusion rate for ICU sedation.[5] Descriptive statistics, two sample student t-tests, Chi-Square, and Fisher's exact tests were used as appropriate. Potential patient

characteristics predicting dexmedetomidine success were assessed using a univariate logistic regression. Covariates significant at the α level of 0.05 were then entered into a standard multiple logistic regression analysis, which included home antidepressant use and A Modified Acute Physiology and Chronic Health Evaluation (APACHE) II score. Statistical analysis was completed by using STATA software, version 12, College Station, Texas.

Results

Thirty eight mechanically ventilated patients who received dexmedetomidine for ICU sedation in the 6 month time period were included in this study. The average age was 52.0 ± 13.7 years, 50% were female, and 83% were Caucasian. Dexmedetomidine was ineffective in 19/38 (50%) patients, and effective in 11/38 (28.95%) patients. The assessment of dexmedetomidine's effectiveness was unable to be assessed in eight patients due to clinical conditions that confounded patient mental status (hepatic encephalopathy; drug overdoses). The clinical variables between the groups that achieved effective sedation and those that did not are displayed in Table 1. There were no differences in the amount of narcotics, benzodiazepines, antipsychotics, or total propofol use during the dexmedetomidine infusion between patients that experienced effective or ineffective sedation. There was also not a difference in average maximum dexmedetomidine infusion rate or length of time on dexmedetomidine. In the univariate analysis, APACHE II and home antidepressant use were both significant. Based upon the standard multiple logistic regression analysis, a lower APACHE II score (less severe illness) (β coefficient −0.24; 95% CI, −0.39 to −0.03) and patients that received home antidepressants (β coefficient 2.33; 95% CI, 0.23 to 4.43) were more likely to achieve successful sedation with dexmedetomidine as compared to patients with a higher APACHE II score or no home antidepressant use.

Discussion

With recent guidelines recommending non-benzodiazepine sedatives for ICU sedation, the use of dexmedetomidine will continue to increase in many ICUs.[2] Identifying which patients will achieve effective sedation with dexmedetomidine with standard dosing may aid in medication selection, improve patient care, and reduce drug expenditures by not initiating medications that will ultimately need to be transitioned to other agents due to ineffectiveness. In this investigation, a lower severity of illness was independently associated with dexmedetomidine success. Based upon these results, clinicians should take into account a patient's severity of illness score when choosing dexmedetomidine for sedation. Clinicians should also be aware that patients with a higher APACHE II score may require a deeper level of sedation necessitating different dexmedetomidine dosing or alternative sedative therapies. Home antidepressant use was also shown to be independently associated with dexmedetomidine effectiveness in the multiple logistic regression analysis. Prior antidepressant use may alter dexmedetomidine pharmacokinetic or pharmacodynamic relationships leading to enhanced effectiveness, or an association of alpha2-adrenergic receptor activity and depression and/or the treatment of depression exists. Relationships have been demonstrated to exist between the alpha2-adrenergic receptor and antipsychotic and antidepressant efficacy, as well as between alpha2-adrenergic receptor polymorphisms and neuropsychological responsiveness in patients with major depressive disorders. [13,14]

Based upon the results of our study and the established relationships between the alpha2-adrenergic receptor , antidepressant medications, and depression, further investigations need conducted to evaluate the association with dexmedetomidine effectiveness.

Understanding the factors which predict dexmedetomidine effectiveness is critical to the appropriate usage of this medication. In their retrospective study, Tellor and colleagues reported that non-black race was independently associated with treatment failure/intolerance.[10] However, another investigation did not find an association between race and cardiovascular response with dexmedetomidine.[11] Our pilot data supports the latter results. Another possible explanation for the variability in patient response may be genetic factors such as polymorphisms in either the cytochrome P450 2A6 (CYP 2A6) enzyme or alpha2-adrenergic receptor, proteins partially responsible for dexmedetomidine metabolism and activity, respectively.[14-17]

One major limitation of this study was the limited number of patients that received dexmedetomidine in our MICU. An investigation with a larger sample size may provide more robust results. The results of this investigation should be used as a hypotheses-generating evaluation that provides pilot data for future large scale investigations.

Conclusion

With the increasing focus on optimizing patient sedation in the ICU, it is important to efficiently use medications in patients that will receive benefit from them. The observed variability in response to dexmedetomidine makes this an ideal medication to identify patient characteristics that are associated with effective sedation, which will allow clinicians to individualize care. In our investigation, we discovered that a lower severity of illness and home antidepressant use was independently associated with the achievement of successful sedation with dexmedetomidine. Further large-scale investigations need to be conducted to confirm these findings.

Acknowledgments

This work was performed at UPMC Presbyterian Hospital, Pittsburgh, PA. It received approval through the University of Pittsburgh Institutional Review Board.

References

1. Wunsch H, Kahn JM, Kramer AA, Rubenfeld GG. Use of intravenous infusion sedation among mechanically ventilated patients in the United States. Crit Care Med. 2009; 37:3031–9. [PubMed: 19633543]
2. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013; 41:263–306. [PubMed: 23269131]
3. Patel SB, Kress JP. Sedation and analgesia in the mechanically ventilated patient. Am J Respir Crit Care Med. 2012; 185:486–97. [PubMed: 22016443]
4. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): A randomised controlled trial. Lancet. 2008; 371:126–134. [PubMed: 18191684]
5. Precedex [package insert]. Hospira; Lake Forest, IL: 2010. Package insert

6. Khan ZP, Ferguson CN, Jones RM. alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. Anaesthesia. 1999; 54:146–165.
7. Panzer O, Moitra V, Sladen RN. Pharmacology of sedativeanalgesic agents: dexmedetomidine, remifentanil, ketamine, volatile anesthetics, and the role of peripheral mu antagonists. Crit Care Clin. 2009; 25:451–69. [PubMed: 19576524]
8. Venn RM, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. Crit Care. 2000; 4:302–308. [PubMed: 11056756]
9. Dasta JF, Kane-Gill SL, Durtschi AJ. Comparing dexmedetomidine prescribing patterns and safety in the naturalistic setting versus published data. Ann Pharmacother. 2004; 38:1130–1135. [PubMed: 15173557]
10. Tellor BR, Arnold HM, Micek ST, Kolled MH. Occurrence and predictors of dexmedetomidine intolerance and failure. Hospital Practice. 2012; 40(1):186–92. [PubMed: 22406894]
11. Jones GM, Murphy CV, Gerlach AT, et al. High dose dexmedetomidine for sedation in the intensive care unit: an evaluation of clinical efficacy and safety. Ann Pharmaocther. 2011; 45:740–7.
12. Riker RR, Picard JT, Fraser GL. Prospective evaluation of the sedation-agitation scale for adult critically ill patients. Crit Care Med. 1999; 27(7):1325–9. [PubMed: 10446827]
13. Sallinen J, Hoglund I, Engstrom M, et al. Pharmacological characterization and CNS effects of a novel highly selective a2C-adrenoceptor antagonist JP-1302. British Journal of Pharmacology. 2007; 150:391–402. [PubMed: 17220913]
14. Neumeister A, Drevets WC, Belfer I, et al. Effects of a alpha(2C)-adrenoreceptor gene polymorphism on neural responses to facial expressions in depression. Neuropsychopharmacology. 2006; 31:1750–1756. [PubMed: 16407897]
15. Kurnik D, Muszkat M, Sofowora GG, et al. Ethnic and Genetic Determinants of Cardiovascular Response to the Selective 2-Adrenoceptor Agonist Dexmedetomidine. Hypertension. 2008; 51:406–411. [PubMed: 18071056]
16. Kohli U, Panharipande P, Muszkat M, et al. CYP2A6 genetiv variation and dexmedetomidine disposition. Eur JcLIN Pharmacol. 2012; 68:937–942.
17. Yagar S, Yavas S, Karahalil B. The rol of the ADRA2A C1291G genetic polymorphism in response to dexmedetomidine on patients undergoing coronary artery surgery. Mol Biol Rep. 2011; 38:3383–3389. [PubMed: 21104443]

Table 1

Clinical variables investigated between those achieving effective sedation and those that did not.

Clinical Variable	Effective Sedation (n= 11)	Ineffective Sedation (n=19)	p-value
Average age (mean ± SD)	57± 27 years	50.3± 15.7 years	0.217
Female (#; %)	6 (54.54)	7(36.84)	0.287
Caucasian (#; %)	10 (90.91)	16 (84.21)	0.68
Average BMI (mean ± SD)	28.81± 8.00	31.85±9.39	0.3767
Active or history of heavy ETOH use (≥everyday consumption) (#; %)	4 (36.36)	8 (42.11)	0.534
Active or history of smoking (#; %)	6 (54.54)	9 (47.37)	0.500
Illicit drug use (#; %)	4 (36.36)	4 (21.05)	0.31
History of Renal Disease (#; %)	8 (72.73)	17 (89.47)	0.245
History of Liver Disease (#; %)	10 (90.91)	16 (84.2)	0.530
History of COPD (#; %)	6 (54.54)	14 (73.68)	0.250
History of Hypertension (#; %)	7 (63.63)	10 (52.63)	0.421
History of anxiety (#; %)	5 (45.45)	4 (21.05)	0.161
History of Bipolar (#; %)	2 (18.18)	0 (0)	0.126
History of depression (#; %)	6 (54.54)	3 (15.79)	0.042*
Ave. # home meds (mean ± SD)	12.18 ± 5.60	9.79 ± 7.87	0.192
Home benzodiazepines (#; %)	7 (63.63)	6 (31.58)	0.093
Home narcotics (#; %)	3 (27.27)	8 (42.10)	0.341
Home antidepressants (#; %)	9 (81.82)	8 (42.11)	0.040*
APACHE II Score (mean ± SD)	16.36±4.63	21.94±6.08	0.007*
Length of time receiving dexmedetomidine (hrs) (mean ± SD)	108 ± 88.54	84.25 hrs ±102.19	0.26
Average dexmedetomidine Maximum infusion rate (mean ± SD)	0.95 mcg/kg/hr ± 0.46	0.79 mcg/kg/hr ± 0.49	0.2058
Mean narcotic amount received during dexmedetomidine (fentanyl equivalents) (mean ± SD)	7.96 mg ± 9.61	9.21 mg ± 18.83	0.42
Mean benzodiazepine amount received during dexmedetomidine (lorazepam equivalents) (mean ± SD)	42.01 mg ± 49.97	82.12 mg ± 185.87	0.246
Mean antipsychotic amount received during dexmedetomidine (chlorpromazine 100mg equivalents) (mean ± SD)	12.07 mg ± 18.39	8.95 mg ± 23.71	0.36
Mean propofol received during dexmedetomidine (mean ± SD)	75.59 mg ± 162.60	113.46 mg ± 316.40	0.55
Mean # of inpatient medications received (mean ± SD)	11 ± 5.73	14.53 ± 5.50	0.08
Mean # of PRN medications received during dexmedetomidine infusion (mean ± SD)	3 ± 1.945	1.79 ± 1.357	0.057
Reasons for dexmedetomidine use:			

Clinical Variable	Effective Sedation (n= 11)	Ineffective Sedation (n=19)	p-value
Aid in weaning from mechanical ventilator (#; %)	4 (36.4)	5 (26.32)	0.45
Limit benzodiazepine use (#; %)	6 (54.54)	6 (42.11)	0.22
Adverse event on propofol (#; %)	1 (9.10)	3 (15.79)	0.52
History of heavy ETOH or narcotic use (#; %)	0	3 (16)	0.16
History of ICU delirium (#; %)	0	2 (10.53)	0.38

SD= standard deviation; ETOH= alcohol; ICU= intensive care unit;

* = statistically significant at $p < 0.05$ and included in the multiple logistic regression analysis