Dexemedetomidine use inside operation theatre.

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Abstract

Statement of the Problem: Use of Dexemedetomidine (Precedex) medication for procedural sedation in non-intubated patients prior to or during surgical procedures.

Methodology and Theoretical Orientation: Start loading dosage of 0.5-1 mcg/kg IV over 10 minutes then Maintenance 0.2-0.4 mcg/kg/hr. IV titrate to effect. (Generally initiate at 0.5-1 mcg/kg over 10 minutes, followed by a maintenance infusion initiated at 0.6 mcg/kg/hour and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/hour).

Target population: Adults.

Findings: 41 cases observed for vital signs, depth of sedation, patient response, and arousal effect. Results showed 30 cases got good smooth deep sedation without complications. 11 cases got low blood pressures with low heart rates needed stopping infusion, pressor support medications.

Conclusion and Significance: Precedex dosing should be individualized and titrated to desired clinical response. It should be administered using a controlled infusion device with full monitoring devices and oxygen supplement.

Keywords: Dexemedetomidine- DEX, Precedex®, Hospira, Procedural sedation, Operation theatre, Surgical procedures, Controlled infusion, Clonidine, α- alpha receptors - α2-agonist, Awake intubation, Fiber-optic intubation.

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Introduction

Anesthesia for short procedures or ambulatory surgery as (awake fiber-optic bronchoscopy, ophthalmic procedures, back injections, awake craniotomy and other minor procedures) has several challenges to an anesthetist. The patient must be sedated to a state where patient can tolerate the surgical procedure, alert responding and co-operative like in awake craniotomy for neurocognitive testing [1].

Adequate anesthesia and analgesia have to be achieved to level that patient is alert, comfortable, responding without pain. The depth of sedation, anxiolysis should be titrated to avoid adverse events as obtunded airway, affection of respiration, high carbon dioxide, coughing, low blood pressure and other hemodynamic abnormalities [2,3].

Dexemedetomidine has some characters of ideal anesthetic for perioperative use as rapid start of action and termination with low lipid solubility, easy to give by infusion, achieve a well-balanced sedation, can maintain airway reflexes, and less effect on respiration [4].

Now, it has been found that DEX without any known active or toxic metabolites therefore; it is USA Food and Drug Administration (FDA) approved for sedation via IV bolus and continuous administration up to 24 h on intubated patients and for procedural anxiolysis in locations outside the critical care unit (ICU) and operation theatre [2,5].

Structure-organic chemistry

Precedex (Dexemedetomidine hydrochloride) in 0.9% Sodium Chloride Injection is a clear solution tolerable for intravenous injection after dilution. Dexemedetomidine HCL is the S-isomer of medetomidine and is chemically characterized as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride [6].

Precedex has an empirical formula is $C_{13}H_{16}N_2$ • HCl and the structural formula is (Figure 1)

Dexemedetomidine hydrochloride is a white or almost white powder that is freely soluble in water and has a PKa of 7.1. Its partition coefficient in-octanol: water at pH 7.4 is 2.89.

Precedex injection is supplied as a clear, colorless, isotonic solution with a pH of 4.5 to 7.0. Each mL contains 118 mcg of Dexemedetomidine hydrochloride equivalent to 100 mcg (0.1 mg) of Dexemedetomidine and 9 mg of sodium chloride in water and is to be used after dilution (Figure 2). The solution is preservative-free and contains no additives or chemical stabilizers [7,8].

It is related chemically to clonidine (Figure 3), but it is more attar-actability for α2 over α1-receptors (with ratio of 1,600:1, compared to 200:1 for clonidine) [9].

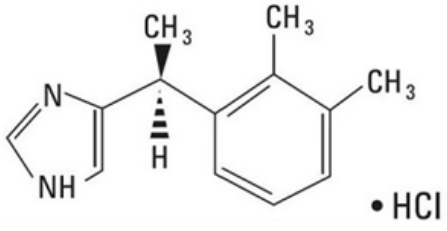

Figure 1. *Formula of Precedex.*

Mechanism of action

Dexemedetomidine is a selective alpha$_2$-adrenergic receptor drug agonist. It is active at a variety of sites throughout the central neuronal system. The sedative and anxiolytic effects of Dexemedetomidine result primarily from its action on the locus ceruleus of the brainstem. Stimulation of α_2-adrenergic receptors at this location inhibits central sympathetic output, leading to more firing of inhibitory neurons. The action of Dexemedetomidine at α_2-adrenergic receptors in the dorsal horn of the spinal cord modifies release of substance P and produces its painless effects [9,10] (Figure 4).

Figure 2. *Precedex Injection Solution.*

Pharmacokinetics

With intravenous (IV) injection, Dexemedetomidine has a rapid distribution, with a 50% distribution time of approximately 6 minutes in adults [11,12].

It is extensively distributed, with a volume of distribution of 118 L and protein binding of 94%. Dexemedetomidine exhibits linear kinetics over the recommended dosage range of 0.2 to 0.7 mcg/kg/h. It is extensively metabolized through both the cytochrome P450 enzyme system, by aliphatic hydroxylation via CYP2A6, and direct glucuronidation. N-glucuronidation produces inactive metabolites, while aliphatic hydroxylation produces active 3-hydroxy-dexmedetomidine, which then undergoes glucuronidation, and 3-carboxy-dexmedetomidine. N-methylation produces active 3-hydroxy-N-methyl-dexmedetomidine, 3-carboxy-N-methyl-dexmedetomidine, and Dexemedetomidine-N-methyl-O-glucuronide. These metabolites are excreted in urine (95%) and feces (4%). Dexemedetomidine has a terminal elimination half-life of approximately 2 hours and a clearance of 39 L/h in adults. Dose reduction is needed for patients with hepatic impairment [12].

Indications

DEX can be used for anxiolysis, relief of pain and stress intraoperative for many as following [13,14]

Airway procedures as rigid bronchoscopy, awake fiber-optic bronchoscopy;

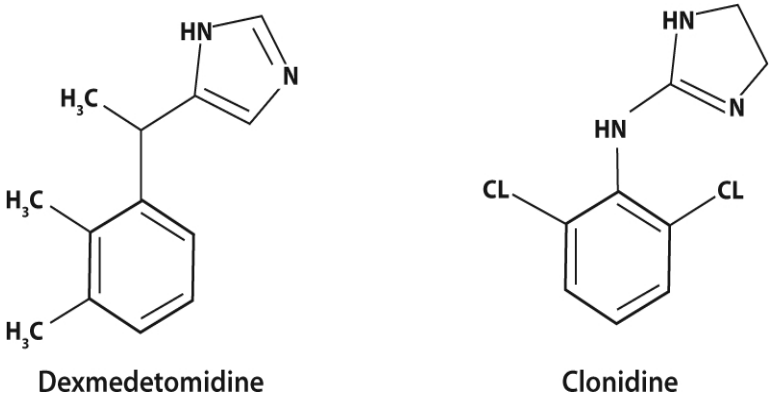

Figure 3*. Comparison of Chemical Structure of Dexemedetomidine and Clonidine [8,9].*

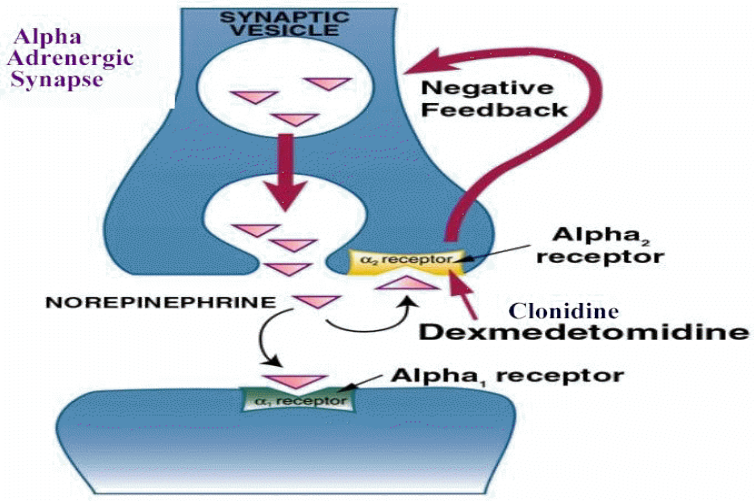

Figure 4. *Action of DEX on the α2-adrenoceptor agonist receptor [11].*

Difficult intubation algorithm;

Anesthetic adjuvant in Bariatric surgery and sleep apnea patients [15-17];

Arthroscopic knee surgery [18,19];

Neurosurgical procedures as awake craniotomy;

Posterior spine fusions; DEX Lowers requirements for propofol and inhalation agents;

Cardiac surgery induction;

Painful procedures as extracorporeal shock-wave lithotripsy;

Burn dressing change;

Lumbar puncture;

Bone marrow biopsy;

Central venous line placement;

Chest tube insertion.

Dental procedures

Monitored Anesthesia Care as gynecological, urological, burns patients, trauma patients, ophthalmic procedures, back injections, awake craniotomy, drug-induced sleep endoscopy, magnetic resonance imaging (MRI) and Anterior mediastinal mass biopsy [12,15].

Dosage regimens

Initiation of procedural sedation: For adults: a loading infusion of one mcg/kg over 10 minutes. For less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 mcg/kg given over 10 minutes. For awake fiber optic intubation in adult patients: a loading infusion of one mcg/kg over 10 minutes. For patients over 65 years of age: a loading infusion of 0.5 mcg/kg over 10 minutes.

For adult patients with impaired hepatic function: a dose reduction should be done [6,7,17].

Maintenance of procedural sedation:

For adult patients: Maintenance infusion is started at 0.6 mcg/kg/hour and titrated according to best level of sedation, dose adjustment needed in renal patients. For intubation: a maintenance infusion of 0.7 mcg/kg/hour is preferred till the endotracheal tube is secured.

For patients over 65 years of age: doses range from 0.2 to 1 mcg/kg/hour [17,18].

Clinical effects

Centrally: Dexemedetomidine lowers cerebral blood flow and cerebral metabolic oxygen consumption with limited effect on intracranial pressure (ICP). Dexemedetomidine modulates cognitive performance with sedative, analgesic, and anxiolytic effects. Studies found that DEX has some neuroprotective effects through lowering circulating and brain catecholamines levels [18-21].

Cardiovascular: Dexemedetomidine has a biphasic blood pressure effect in form of a short high blood pressure phase with following lower. The two staged effect is mediated by two different α2-AR subtypes' receptors: α-2B AR which mediates initial high blood pressure stage and later lower blood pressure is mediated by the α2A-AR. In young age with high levels of parasympathetic tone; low heart rate and sometimes cardiac arrest have been reported but they were well treated with anti-parasympathetic agents as atropine, glycopyrrolate [19].

Respiratory: Dexemedetomidine can affect respiration as deep sleep state does without depression. It doesn't affect respiration rate or ventilation in spontaneously breathing critical care patients postoperative. It can facilitate weaning and removal of endotracheal tube (recovery) in trauma/ surgical critical care unit patients with stable hemodynamics and preserved respiration [22-24] (Figure 5).

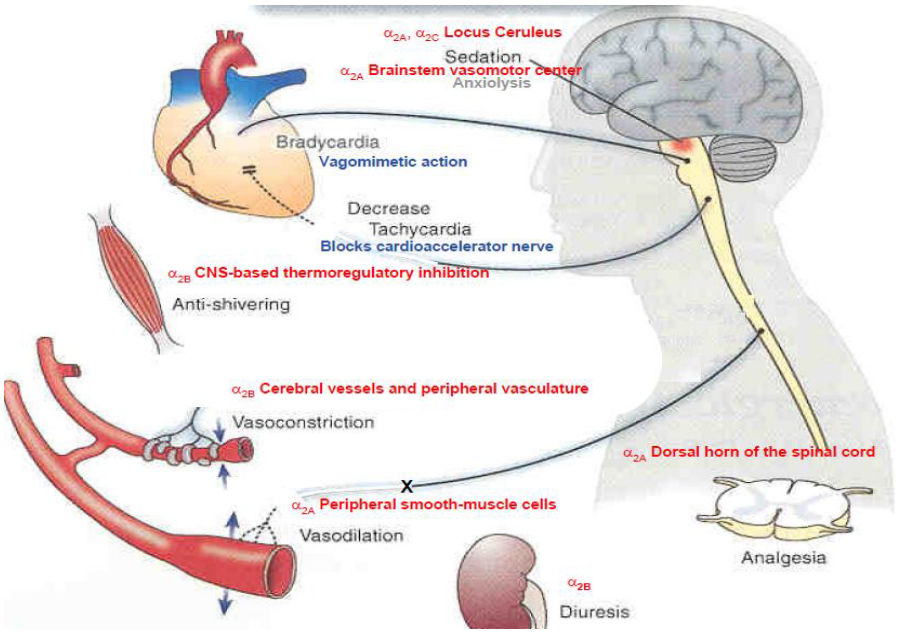

Figure 5. *Clinical effects of DEX on various α2 -adrenergic receptors (physiological view) [18,19].*

Others: Dexemedetomidine enhances peripheral pre-synaptic α2-AR which inhibit the firing catecholamines leading to diminished sympathetic response to surgery. Some studies concluded that DEX can cause more excretion of water and salt in urine (more urine output). It was found that DEX doesn't inhibit production of steroids if used as intravenous infusion for short time; although it is imidazole form (unlike etomidate) [25,26].

Adverse effects

DEX may cause unwanted systemic effects as low or high blood pressure, slow heart rate, dry oral cavity, sense of vomiting or gastric discomfort, high temperature, rigors, cyanosis and weak muscles.

It was also reported that DEX can cause cardiac abnormalities, heart block or even cardiac arrest, inverted T-wave, rapid heart rate, myocardial ischemia, syncopal attacks and rare heart failure.

It may cause airway obstruction, inadequate respiration, tingling nerve sensation or slight paralysis and high blood levels of potassium, glucose or lactic acid [14,27].

Methodology

41 patients of either sex, aged 18 to 60 years of ASA grade I and II were used as a sample; all adults over 18 years (most surgical patents coming at that time).

All pediatrics, patients with multiple comorbidities, Patient's refusing; known or admitted alcohol or drug abusers, allergic to the drugs involved in the study and prisoners were excluded.

41 Patients were randomized to receive a Loading dose of 0.5 to 1 mcg/kg IV over 10 minutes then maintenance IV infusion in dosage regimen of 0.2 to 0.4 mcg/kg/hour IV, titrate to effect.

Start loading dosage of 0.5-1 mcg/kg IV over 10 minutes then Maintenance 0.2-0.4 mcg/kg/hour IV titrate to effect.

35 patients did not need any midazolam adjuvant as sedative during procedure. Other 6 patients needed only 2 mg IV boluses.

Generally initiate at 0.5-1 mcg/kg over 10 minutes, followed by a maintenance infusion initiated at 0.6 mcg/kg/hour and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/hour.

Discussion and Results

Research study is a prospective case study.

Study was done on adults over 30 years (target population) with total 41 cases in number.

Precedex administration for sedation of non-intubated patients prior to and/or during surgical and other procedures under monitored anesthesia care was evaluated in randomized clinical trial including safety and efficacy. Precedex in patients undergoing awake fiber-optic intubation prior to a surgical or diagnostic procedure also was included in the study.

41 Patients were randomized to receive a Loading dose of 0.5 to 1 mcg/kg IV over 10 minutes then maintenance IV infusion in dosage regimen of 0.2 to 0.4 mcg/kg/hour IV, titrate to effect.

DEX injection is available in 200 mcg/2 mL clear glass vials (100 mcg/ml); for single use only.

11 patients of total 41 cases in the study had marked bradycardia with slow heart rate reached 30 to 40 beats per min and lower blood pressure (systolic blood pressure dropped to 80 to 90 mmHg) on monitor. Other 30 cases got good smooth deep sedation without complications.

It was found to be noted adverse effect but tolerable controlled not affecting surgery or study outcome.

It was found that giving rapid bolus over short time can cause rapid affection on heart rate and blood pressure; that's why tapered IV infusion was preferred mode of DEXA administration with good monitoring of vital signs and giving IV fluids with standby pressor agents beside patient.

Most of patients responded well to IV fluids, pressor agents as ephedrine or phenylephrine with oxygen therapy during procedure.

DEX may be used as a total intravenous anesthetic agent in certain patients if doses are increased to a high tolerable level [16].

Previous studies on assessing Dexemedetomidine as a general anesthetic found that supplementary agents were necessary, but the doses of Dexemedetomidine had not reached the high levels of administration reported here [12,16].

Scoring Questionnaire at 24 h post. Op: - 29

1. How did you feel Precedex sedation: Excellent-Good-Fair-Poor
2. Do you think that sedation dosage was less or more: Needed less- Right amount- Needed more
3. Do you remember anything during procedure / any awareness: No-Yes
4. Do you remember any events before, during, with recovery from procedure: Yes-No
5. Any discomfort you got during procedure: No-Yes.

Overall, using visual analog scale, where zero end is completely dissatisfied and other end is completely satisfied how you rate your satisfaction with sedation?

0=complete Dissatisfaction

10=complete Satisfaction.

Conclusion:

Dexemedetomidine is a very useful medication enlisted in the family of drugs used in anesthesia. It can be utilized in a wide range of applications as discussed before at the same time requiring caution during its use. High cost is its limiting factor.

Decreases in heart rate and blood pressure were modest, predictable and well treated. Some patients were arousable, responding to calls. DEX produced good sedation with anxiolysis and lowered need for other sedatives.

DEX should be used with caution in patients with low circulatory volume, shock or accompanied with hypnotics and analgesics.

DEX dosage should be individualized and titrated to desired clinical response. DEX is not indicated for infusions longer than 24 hours. Precedex should be administered using a controlled infusion device.

Arterial Blood pressure, Heart rate, Respiratory rate and Oxygen saturation levels should be monitored during and after the infusion as clinically applicable.

Besides, patients should be instructed to report symptoms occurring within 48 hours after DEX injection as weakness, disorientation, more sweating, weight loss, abdominal pain, diarrhea, constipation, affected level of consciousness.

Dexemedetomidine has become a part of ambulatory anesthesia, offers anesthetic sparing and maintains hemodynamics.

As pharmacological effects of Dexemedetomidine can be reversed by α2-AR antagonist atipamezole, addition of Dexemedetomidine with atipamezole can provide titratable form of sedation in the future.

Limitations of the study

The patient population was small and a larger trial testing Dexemedetomidine with other agents is warranted to detect greater differences in these agents.

References

1. Piccioni F, Fanzio M. Management of anesthesia in awake craniotomy. Minerva Anestesiol. 2008;74:393-408.
2. Kallapur BG, Bhosale R. Use of dexmedetomidine infusion in anesthesia for awake craniotomy. Indian J Anaesth 2012;56(4):413.
3. Mack PF, Perrine K, Kobylarz E, et al. Dexemedetomidine and neurocognitive testing in awake craniotomy. J Neurosurg Anaesthesiol. 2004;16:20-5.
4. Mahmoud M, Mason KP. Dexemedetomidine:review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. British Journal of Anaesthesia. 2015;115(2):171-82
5. Sanders RD, Sun P, Patel S, et al. Dexemedetomidine provides cortical neuroprotection:impact on anesthetic-induced neuroapoptosis in the rat developing brain. Acta Anaesthesiol Scand. 2010;54:710-69.
6. Roychowdhury P, Cedergren RA. Dexmedetomidine premix formulation. United States patent.2017.
7. Aantaa R, Kallio A, Virtanen R. Dexemedetomidine, a novel α-2-adrenergic agonist. A Review of its Pharmacodynamic Characteristics. Drugs of the Future. 1993;18(1):49-56.
8. Aantaa R. Dexmedetomidine, a novel alpha 2-adrenergic agonist. A review of its pharmacodynamic characteristics. Drugs Future. 1993:49-56.
9. Horlocker TT, Wedel DJ, Schroeder DR, et al. Preoperative antiplatelet therapy does not increase the risk of spinal hematoma associated with regional anesthesia. Anesthesia & Analgesia. 1995;80(2):303-9.
10. Smith CM. The pharmacology of sedative/hypnotics, alcohol, and anesthetics:Sites and mechanisms of action. InDrug addiction I. 1977:413-587.
11. Aho M, Erkola O, Kallio A, et al. Dexmedetomidine infusion for maintenance of anesthesia in patients undergoing abdominal hysterectomy. Anesthesia and Analgesia. 1992;75(6):940-6.
12. Paul S, Bhattacharjee DP, Ghosh S, et al. Efficacy of intra-articular dexmedetomidine for postoperative analgesia in arthroscopic knee surgery. Ceylon Med J. 2010;55(4).
13. Shagufta Naaz, Erum Ozair. Dexemedetomidine in Current Anesthesia Practice- A Review. J Clin Diagn Res. 2014;8(10):GE01-GE04.
14. Bergese SD, Khabiri B, Roberts WD, et al. Dexmedetomidine for conscious sedation in difficult awake fiberoptic intubation cases. J Clin Anesth. 2007;19(2):141-4.
15. Ramsay MA, Luterman DL. Dexmedetomidine as a total intravenous anesthetic agent. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2004;101(3):787-90.
16. Candiotti KA, Bergese SD, Bokesch PM, et al. Monitored Anesthesia Care with Dexemedetomidine:A Prospective, Randomized, Double- Blind, Multicenter Trial. Anesthesia & Analgesia. 2010;110(1):47-56.
17. Kaur M, Singh PM. Current role of dexmedetomidine in clinical anesthesia and intensive care. Anesthesia, Essays and Researches. 2011;5(2):128.
18. Philipp M, Brede M, Hein L. Physiological significance of alpha(2)-adrenergic receptor subtype diversity: One receptor is not enough. Am J Physiol Regul Integr Comp Physiol. 2002;283:287-95.
19. Franowicz JS, Arnsten AF. The alpha-2a noradrenergic agonist, guanfacine, improves delayed response performance in young adult rhesus monkeys. Psychopharmacology. 1998;136:8-14.
20. Bekker A, Sturaitis MK. Dexemedetomidine for neurological surgery. Neurosurgery. 2005;57:1-10.
21. Venn RM, Hell J, Grounds RM. Respiratory effects of Dexemedetomidine in the surgical patient requiring intensive care. Crit Care. 2000;4:302-8.
22. Hsu YW, Cortinez LI, Robertson KM, et al. Dexemedetomidine pharmacodynamics: Part I: Cross-over comparison of the respiratory effects of Dexemedetomidine and remifentanil in healthy volunteers. Anesthesiology. 2004;101:1066-76.
23. Siobal MS, Kallet RH, Kivett VA, et al. Use of Dexemedetomidine to facilitate extubation in surgical intensive-care-unit patients who failed previous weaning attempts following prolonged mechanical ventilation: A pilot study. Respir Care. 2006;51:492-6.
24. Ebert TJ, Hall JE, Barney JA, et al. The effects of increasing plasma concentrations of Dexemedetomidine in humans. Anesthesiology. 2000;93:382-94.

25. Venn R, Bryant A, Hall GM, et al. Effects of Dexemedetomidine on adrenocortical function and the cardiovascular, endocrine and inflammatory responses in post-operative patients needing sedation in the intensive care unit. Br J Anaesth. 2001;86:650-6.

26. Morgan GE, Mikhail MS, Murray MJ. Preoperative Medication in Clinical Anaethesia. New York: Mcgraw Hill. 2006:248.

27. Akeju O, Pavone KJ, Westover MB, et al. A comparison of propofol- and Dexemedetomidine-induced electroencephalogram dynamics using spectral and coherence analysis. Anesthesiology 2014;121:978-89.

28. Singh P, Punia TS, Kaur B, et al. A randomised comparative study of dexmedetomidine and midazolam for sedation during awake fiberoptic intubation in laproscopic cholecystectomy patients. 2015.

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