Dexmedetomidine use inside operation theatre.

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Abstract

Statement of the Problem: Use of Dexmedetomidine (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: Dexmedetomidine- DEX, Precedex®, Hospira, Procedural sedation, Operation theatre, Surgical procedures, Controlled infusion, Clonidine, α- alpha receptors - α2-agonist, Awake intubation, Fiber-optic intubation.

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].

Dexmedetomidine 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 (Dexmedetomidine hydrochloride) in 0.9% Sodium Chloride Injection is a clear solution tolerable for intravenous injection after dilution. Dexmedetomidine 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).

Dexmedetomidine 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 Dexmedetomidine hydrochloride equivalent to 100 mcg (0.1 mg) of Dexmedetomidine 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**

Dexmedetomidine is a selective alpha₂-adrenergic receptor drug agonist. It is active at a variety of sites throughout the central neuronal system. The sedative and anxiolytic effects of Dexmedetomidine result primarily from its action on the locus ceruleus of the brainstem. Stimulation of α₂-adrenergic receptors at this location inhibits central sympathetic output, leading to more firing of inhibitory neurons. The action of Dexmedetomidine at α₂-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.](image)

**Pharmacokinetics**

With intravenous (IV) injection, Dexmedetomidine 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%. Dexmedetomidine 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 Dexmedetomidine-N-methyl-O-glucuronide. These metabolites are excreted in urine (95%) and feces (4%). Dexmedetomidine 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].](image)

**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 biopsy;
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: Dexmedetomidine lowers cerebral blood flow and cerebral metabolic oxygen consumption with limited effect on intracranial pressure (ICP). Dexmedetomidine 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: Dexmedetomidine 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: Dexmedetomidine 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).
Dosage regimen of 0.2 to 0.4 mcg/kg/hour IV, titrate to effect.

1 mcg/kg IV over 10 minutes then maintenance IV infusion in

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diagnostic procedure also was included in the study.

undergoing awake fiber-optic intubation prior to a surgical or

clinical trial including safety and efficacy. Precedex in patients

monitored anesthesia care was evaluated in randomized

prior to and/or during surgical and other procedures under

Methodology

41 patients of either sex, aged 18 to 60 years of ASA grade I and

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.

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1 mcg/kg IV over 10 minutes then maintenance IV infusion in
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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 mcg 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
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\[
\text{Scoring Questionnaire at 24 h post. Op: - 29}
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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**


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