Use of Dexmedetomidine in a Patient Allergic to Clonidine Presenting for an Awake Craniotomy: a Case Report

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Abstract
The use of dexmedetomidine with concurrent scalp block is increasingly being utilized as an effective and safe anesthetic approach for awake craniotomy (AC). Dexmedetomidine is an alpha-2 adrenergic receptor (α2-AR) agonist with dose-dependent sedative, analgesic, and anxiolytic properties while preserving respiratory function. The challenge with the use of dexmedetomidine arises when the patient has a clonidine allergy, which is also an α2-AR agonist. Currently, there is no published literature regarding the use of dexmedetomidine in a patient allergic to clonidine. A 48-year-old male with chronic obstructive pulmonary disease, obstructive sleep apnea, and body mass index of 54 with clonidine allergy presents for an AC. Given the goals of the surgery and the patient’s comorbidities, we planned for monitored anesthesia care with intravenous (IV) dexmedetomidine, remifentanil, and propofol. We discussed the use of dexmedetomidine with the patient and the potential risk of allergic reaction given his allergy to clonidine. The patient understood the risk and consented to the anesthetic plan. AC was successfully performed with IV dexmedetomidine, remifentanil, and propofol. Although both dexmedetomidine and clonidine have some functional similarities in terms of acting on the central and peripheral nervous system, there are marked differences between the two based on chemical structure, receptor affinity, and metabolism of the drug. This case highlights the successful use of dexmedetomidine in a patient with known allergy of rash to clonidine.

Keywords
Awake craniotomy · Dexmedetomidine · Clonidine · Alpha-2-adrenergic receptor

Introduction
Awake craniotomy (AC) with intraoperative brain mapping and monitoring of neurological function and cognitive performance has been shown to improve efficacy and safety of tumor resection. The primary aim of AC is to achieve maximum resection of tumors or epileptic foci while preserving brain function [1]. Relative contraindications for AC consist of anxiety disorder, poor neurological status, anticipated difficult airway, severe chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), obesity, gastroesophageal reflux (GERD), and large tumor with midline shift [2]. Balancing relative contraindications with the potential benefit of AC presents a challenge for the anesthesiologist. A multitude of tasks need to be accomplished by the anesthesiologist to avoid complications during an AC, including the maintenance of airway, analgesia, sedation, and management of hemodynamics. Therefore, it is critical that the anesthetic regimen for AC be individualized to the patient’s comorbidities and the goals of the surgery.

There have been multiple publications demonstrating the successful use of dexmedetomidine in high-risk patients.
undergoing AC [2–5]. Dexmedetomidine is an alpha-2 adrenergic receptor (α2-AR) agonist with dose-dependent sedative, analgesic, and anxiolytic properties which preserves respiratory function [6]. Its actions make it an ideal anesthetic agent for an AC [5]. Concern with the use of dexmedetomidine arises when you encounter a patient with a documented allergy to clonidine, which is also an α2-AR agonist. In this situation, one must be vigilant regarding the potential for cross reactivity among medications. Cross reactivity with medication occurs when a medication, not previously used, provokes a hypersensitivity reaction due to a sensitization to a structurally similar compound or due to similar pharmacological properties [7].

Currently, there are no case reports or published work discussing the use or avoidance of dexmedetomidine in patients who are allergic to clonidine. In most situations, anesthesia providers would avoid dexmedetomidine in these patients to mitigate any potential adverse reaction, but in circumstances where dexmedetomidine can provide a major advantage to the anesthetic plan, the risk–benefit needs to be weighed.

The goals of this case report are to present a case where dexmedetomidine was successfully used in a patient with a reported allergy to clonidine and to explore the similarities and differences between clonidine and dexmedetomidine.

Written Health Insurance Portability and Accountability Act authorization has been obtained from the patient to publish this case report.

Case Presentation

We report a case of a super morbid obese 48-year-old male with a body mass index of 54, who presents for an AC for a 6-cm lesion involving the left anterior temporal lobe, the basal ganglia, the inferior frontal lobe, and the thalamus. Location of the cranial lesion incorporated sensorimotor and language areas. Therefore, during the resection phase of the surgery, along with neuromonitoring, the patient would have to perform language and vocabulary tasks to optimize tumor resection and minimize neurological complications.

The patient’s past medical history was significant for hemorrhagic stroke, hypertension, COPD on home inhalers, OSA, insulin-dependent diabetes, and GERD. Due to the cranial lesion, the patient was also experiencing seizures despite being on antiepileptics. Airway exam revealed Mallampati score of 3, thick neck, and at least three fingerbreadth thyromental distance. The patient also had a documented allergy to clonidine. The patient mentioned that he was prescribed clonidine for the treatment of hypertension and developed a rash. He was told by his provider to immediately discontinue the medication and the rash resolved. There was not any formal skin testing or evaluation of the allergic reaction.

Given the goals of the surgery and the patient’s comorbidities, we planned for monitored anesthesia care with intravenous (IV) dexmedetomidine, remifentanil, and propofol. We were concerned of the potential allergic reaction with the use of dexmedetomidine given the patient’s documented allergy to clonidine. We researched the use of dexmedetomidine with clonidine allergy in PubMed and were unable to find any published literature regarding its use in a patient allergic to clonidine. We reached out to our institution’s inpatient clinical pharmacist for guidance. Our clinical pharmacist confirmed the lack of published literature but did mention, based on experience, dexmedetomidine had been safely used in two prior patients who were also allergic to clonidine. In these prior patients, we only knew that clonidine was listed as an allergy but unfortunately, we did not know what their specific reaction to clonidine was. Given the time constraint of our planned surgical case, we were unable to refer the patient to immunology or dermatology for further evaluation and work up.

With this information, we discussed the use of dexmedetomidine with the patient and the potential risk of allergic reaction. The patient understood the risk and consented to the anesthetic plan.

Prior to taking the patient to the operating room, the patient had two peripheral IV cannula, and was given an inhaled bronchodilator treatment due to mild expiratory wheezing on auscultation in the preoperative area, 20 mg of IV famotidine, 10 mg of IV metoclopramide, and 4 mg of IV ondansetron. Bilateral nares were prepped with neosynephrine in case nasopharyngeal airway would have to be used during the procedure for airway maintenance. Upon arrival to the operating room, IV infusion of 0.4mcg/kg/h of dexmedetomidine and 0.03mcg/kg/min of remifentanil was immediately started after standard monitors (ECG, pulse oximetry, and noninvasive blood pressure cuff) and salter nasal cannula were placed. Given the patient’s history of diabetes and the need to check blood glucose throughout the case, hemorrhagic stroke, and hemodynamic effects of the IV anesthetic, radial arterial catheter was inserted in the operating room with 1% lidocaine local anesthetic. Video laryngoscopy, intubation equipment along with a supraglottic airway, and emergency medications (epinephrine, diphenhydramine, levetiracetam, and lorazepam) were ready in the operating room.

During the 12-point scalp block and placement of urinary Foley catheter, increments of 5–10 mg of propofol were given for patient comfort while maintaining a Richmond Agitation Sedation Score (RASS) of − 1 to − 2. Throughout the procedure, the goal was to keep the patient arousable so the patient could communicate potential
allergic symptoms. Prior to pinning of the head in the Mayfield Skull Clamp, in addition to the increments of 5–10 mg of propofol, a propofol infusion was also started at a rate of 5 μg/kg/min and titrated upward as tolerated to maintain target RASS. The patient tolerated the scalp block, positioning, and pinning well.

During the opening phase of the dura, the patient tolerated upward of 0.7 mcg/kg/h of dexmedetomidine, 0.03 mcg/kg/min of remifentanil, and 12 mcg/kg/min of propofol. Any increase in the propofol dosing led to airway obstruction. All IV infusions were paused once the dura was opened for the awake phase of the AC. The patient successfully underwent language, memory, and motor testing during mapping and resection. Once resection was completed, and dexmedetomidine and remifentanil infusions were reinitiated at 0.4 mcg/kg/h and 0.3 mcg/kg/min, respectively, for the post-awake phase.

Throughout the procedure, the patient’s oxygenation was maintained with a salter nasal cannula without the need of oral or nasopharyngeal airway. During the intraoperative period, the patient was periodically evaluated for allergic sign symptoms which included skin examination for rashes, pruritus, edema, and subjective dyspnea. The patient remained hemodynamically stable throughout the case without the need of any vasopressors. Toward the end of the post-awake phase, the patient became hypertensive, which was resolved with IV labetalol. After the surgery concluded, the patient was transferred to the post-anesthesia care unit (PACU) for recovery and transferred to the intensive care unit (ICU) for monitoring. Both in the PACU and ICU, the patient was closely monitored for signs and symptoms of allergic reaction. Communication was made to nursing staff to look for cutaneous signs and symptoms of rash, pruritus, edema, and respiratory issues which could indicate an allergic etiology. No signs and symptoms were detected in the PACU period and during the ICU stay. The patient was discharged on post-operative day 6.

### Discussion

This case report highlights the successful use of dexmedetomidine in a patient with history of an adverse reaction of rash with oral clonidine. Currently, there are no publications discussing the use of dexmedetomidine in a patient with history of clonidine rash allergy.

Dexmedetomidine is a full agonist at the α2-AR and it selectively binds to presynaptic α2-AR located in the locus coeruleus of the brain stem for sedative action. It inhibits the release of norepinephrine from synaptic vesicles, which leads to an inhibition of post-synaptic activation of adrenoceptors, which inhibit sympathetic activity, leading to sedation and anxiolysis. Its analgesic effect is mediated by binding to α2-AR in the spinal cord. Dexmedetomidine is 8–10 times more selective for the α2-AR than clonidine. The improved specificity for the α2-AR, especially for the α-2A subtype, may make it a more effective sedative than clonidine. Clonidine is a partial agonist at the α2-AR. It stimulates central alpha receptors in the vasomotor center of the medulla oblongata and hypothalamus, which decreases the efferent sympathetic tone to the heart, kidneys, and peripheral vasculature with a concomitant increase in vagal activity [6].

Though both dexmedetomidine and clonidine work on α2-AR, there are noteworthy differences between the two (Table 1). Dexmedetomidine is an imidazole derivative, while clonidine is an imidazoline derivative as seen in Fig. 1 [8, 9]. When chemically comparing the two drugs, the Tanimoto coefficient, based on atom pairs, is 0.180723 and maximum common substructure is 0.2609 [10]. Tanimoto coefficient is a similarity measure score comparing two chemical structures by means of their chemical fingerprint. Its score ranges from 0 to 1, with values closer to 1 indicating greater similarity between two compounds [11]. Based on the Tanimoto coefficient, the two drugs are not similar. Though there is not any published literature that correlates Tanimoto coefficient as a predictor of cross

### Table 1 Comparison of dexmedetomidine and clonidine

|                  | Dexmedetomidine  | Clonidine           |
|------------------|------------------|---------------------|
| **Structure**    | Imidazole derivative | Imidazoline derivative |
| **Molecular weight (gram/mole)** | 200.2 | 230.09 |
| **pKa**          | 7.1              | 8.05                |
| **Metabolism**   | Hepatic          | <50% Hepatic        |
| **Excretion**    | 95% urine, 4% feces | 50% urine, 20% feces |
| **Solubility in water** | Soluble     | Insoluble           |
| **Elimination half-life (hours)** | 2      | 8                   |
| **Protein binding** | 94%         | 50%                 |
| **Ratio of α2: α1 receptor binding** | 220:1 | 1620:1 |
| **Function at α2 receptor** | Full agonist | Partial agonist |
reactivity, it does provide support to the structural difference of dexmedetomidine to clonidine. Furthermore, dexmedetomidine is water-soluble, while clonidine is insoluble in water. Majority of dexmedetomidine is metabolized in the liver, while less than 50% of clonidine is metabolized in the liver [8, 9].

Although both dexmedetomidine and clonidine have some functional similarities in terms of acting on the central and peripheral nervous system, there are marked differences between the two based on chemical structure, receptor affinity, and metabolism of the drug.

Allergic reactions are classified using Gell and Coombs’ classification system [12]. Classification system includes:

- Immediate-type reaction, also known as type I reaction, which is immunoglobulin E (IgE) antibodies mediated. Clinical symptoms include anaphylaxis, urticaria, angioedema, and bronchospasm, which manifests within minutes to hours.
- Cytotoxic reaction, also known as type II reaction, which is immunoglobulin G (IgG) or immunoglobulin M (IgM) antibodies mediated. Clinical symptoms include anemia, thrombocytopenia, and cytopenia, and its manifestation can be variable.
- Immune-complex reaction, also known as type III reaction, which involves the activation of the complement system through tissue deposition of drug-antibody complex. Clinical symptoms include serum sickness, vasculitis, fever, rash, and arthralgia, which can manifest within 1–3 weeks of drug exposure.
- Delayed-type hypersensitivity reaction, also known as type IV, which is mediated by the recruitment and activation of T cells. Clinical symptoms include contact sensitivity, skin rashes, and organ tissue damage, which can manifest within 2–7 days after drug exposure.

Fig. 1 Chemical structure of dexmedetomidine and clonidine (PubChem Database)

Based on the clinical scenario, it seems that our patient may have had a type IV reaction to clonidine. Given the time constraints of the surgical case, we were unable to send the patient to dermatology or immunology for a more thorough workup to confirm the suspected diagnosis. The potential type IV reaction to clonidine raised the concern of potential reaction or cross reactivity with dexmedetomidine. Cross reactivity is when a drug that is structurally similar to or has a similar pharmacological property to another drug that a patient is allergic to can also provoke a hypersensitivity reaction. Cross reactivity among drugs is mediated by either immunologic mechanisms or non-immunologic mechanisms. Cross reactivity due to immunologic mechanisms is believed to be from the presence of common antigenic determinants in the cross-reacting drug. Cross reactivity mediated by non-immunologic mechanisms can be due to a common pharmacological characteristic, such as having a similar effect on the same receptors or inducing release of histamine which leads to the hypersensitivity reaction. Skin testing and intradermal patch test have been used to evaluate cross reactivity [7].

In this case presentation, we are not concluding that it is clearly safe to use dexmedetomidine in patients with clonidine allergy; we would need more information and research to state that. But until we do have more research and publications, we want to highlight the importance of weighing the risk and benefit of the use of dexmedetomidine in situations where the medication’s benefits may outweigh its risk. As anesthesiologist, we often encounter patient allergies that are not confirmed with testing but documented; therefore, we have to acknowledge the documented facts. Our patient’s reported reaction to clonidine was believed to be type IV hypersensitivity reaction which is not life-threatening and is often resolved with topical creams and avoidance of trigger. The advantage of using dexmedetomidine in the anesthetic...
plan allowed for a successful AC with sedation, anxiolysis, and analgesia, while preserving patient’s respiratory function.

**Author Contribution**  Yasmin Sritapan: writing of the manuscript, literature search, and idea for manuscript. Brett Cornell: writing of the manuscript, literature search, and with critical review of the manuscript. Brittany Maggard: critical review of the manuscript and supervision and organization of the manuscript.

**Data Availability**  Not applicable.

**Code Availability**  Not applicable.

**Declarations**

**Ethical Approval**  Not applicable.

**Consent to Participate**  Not applicable.

**Consent for Publication**  Written consent was obtained from patient to publish the case.

**Conflict of Interest**  The authors declare no competing interests.

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