ISSN: 1607-8322, e-ISSN: 2220-5799 Anaesthesia, Pain & Intensive Care
Vol 27(4); August 2023 DOI: 10.35975/apic.v27i4.1901

CASE REPORT NEUROANESTHESIA

Dexmedetomidine related apnea and desaturation during awake craniotomy: a case report

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ABSTRACT

Dexmedetomidine (Dex) is regarded as a novel sedative agent since the drug preserves respiration and makes 'conscious sedation' possible. This drug is widely used for monitored anesthesia care (MAC). We report a case of apnea and desaturation in awake craniotomy surgery under MAC after loading of Dex with 1 mg/kg over 10 min and discuss possible explanations. We advocate using Dex with a lower loading dose over a prolonged duration and the up-titration of the drug according to the patient's response particularly in those who are underweight or elderly. Meticulous judgement for possible interactions of Dex with antiepileptics, opioids and other sedative agents is essential during MAC.

Abbreviations: BIS- Bispectral Index; Dex- Dexmedetomidine; DBS- Deep Brain Stimulation; MAC- Monitored Anesthesia Care; TCI- Targeted-Controlled Infusion

Key words: Dexmedetomidine; Craniotomy; Apnea; Conscious sedation; Balanced anesthesia; Anticonvulsant

Citation: Hasyizan HM, Mohd Nazaruddin WHWM, Laila AM, Zamzuri I, Zulfakar MM. Dexmedetomidine related apnea and desaturation during awake craniotomy: a case report. Anaesth. pain intensive care 2023;27(4):609−612; **DOI:** 10.35975/apic.v27i4.1901

Received: May 30, 2022; **Reviewed:** December 28, 2022; **Accepted:** May 22, 2023

1. INTRODUCTION

Dexmedetomidine (Dex) is a highly selective α_2 adrenoceptor agonist that activates guanine-nucleotide regulatory binding proteins (G proteins), leading to potassium efflux, hyperpolarization of the membrane, and suppression of the neuronal firing. Dex is a specific α_2 receptor agonist, and the sedative and hypnotic effects of Dex are attributed to the activation of receptors in the nucleus coeruleus.[1] Moreover, Dex modulates nociception and causes release of endogenous opioids at the spinal cord level, leading to reduced intraoperative and postoperative opioid requirements.[1,2] The combination of Dex with other sedative agents reduces the dose of the agent required, while preserving respiration and improving patient satisfaction.[3]

Dexmedetomidine has a good respiratory profile, preserving respiration and adequate oxygenation.[2,4] Because of this, Dex is a novel sedation agent that is widely used in procedural sedation, in operations under monitored anesthesia care (MAC) and for sedation in the intensive care unit (ICU). In a surgery requiring MAC, the patient needs to be adequately sedated but have an

unobstructed airway, spontaneous breathing and good oxygenation. In awake craniotomy, Dex helps in the provision of conscious sedation when opening the brain, and it allows rapid recovery from sedation, thereby facilitating the brain mapping process and neurological assessment. This drug is widely used in awake craniotomies in situations that include tumor resection, epilepsy surgery and deep brain stimulation (DBS) surgery.[5] We report a case of apnea and desaturation in a patient undergoing awake craniotomy under MAC employing Dex. The message to the anesthetists is clear; vigilance is the price of safety. No drug should be taken as granted for its absolute safety

2. CASE REPORT

A 50-year-old lady, with no known prior medical illness, presented with sudden onset of a brief, unprovoked seizure during sleep, associated with the drooling of saliva, which was spontaneously aborted. She did not have any symptoms of increased intracranial pressure (ICP), and her clinical and neurological examinations were unremarkable, showing intact cranial nerves. Her hematological parameters were unremarkable, renal profile was normal, but contrasted computerized tomography (CT) and magnetic resonance imaging (MRI) of the brain showed an ill-defined, non-enhancing intra-axial hypodense lesion in the left frontoparietal region with a mass effect and a surrounding white-matter edema. Diagnosis of the left insular lesion established the likelihood of a low-grade glioma, and the patient was subsequently subjected to an awake craniotomy with tumor debulking under MAC. She was classified as ASA 1, with a weight of 38 kg, a height of 140 cm, a stable hemodynamic profile and no potential difficulties in intubation. The patient was on levetiracetam 500 mg BID and dexamethasone 4 mg TDS, and no anxiolytic or premedication was given preoperatively. The written informed consent including taking photos, videos and patient's speech for academic and publication purposes was obtained from the patient.

Upon arrival at the operation theatre, standard non-invasive blood pressure (NIBP), electrocardiogram (ECG) and pulse oxygen saturation (SpO_2) monitoring was set up, and a 16G IV cannula was inserted. Oxygen was supplied via a nasal prong @ 3 L/min. Capnography trace was monitored. After positioning for the surgery, a loading dose of Dex 40 µg (1 µg/kg) was infused over 10 min. However, at eight minutes of the infusion, we noted that the patient became unresponsive, apneic, with no capnographic trace and desaturated down to SpO_2 88%. The blood pressure was, however, stable at 110/70 mmHg and the heart rate was maintained at 60–70 bpm. The Dex infusion was stopped, an oropharyngeal airway was inserted, and ventilation was manually assisted with a bag and mask until the SpO_2 rose to 100%. She regained full consciousness after three minutes and claimed to have been totally asleep during the incident. The nasal prong was then replaced with a non-rebreathing face mask with end tidal carbon dioxide ($EtCO_2$) connection, and the intravenous infusion of Dex was restarted at 0.3 µg/kg/h. Remifentanil was infused at a rate of 0.2 ng/ml for the insertion of the right central venous line cannulation and the administration of the scalp block, which was performed using bupivacaine 0.5% with adrenaline 1;200000, in a total volume of 24 ml. Entropy was monitored for the patient and maintained at around 65 to 85 at initiation of surgery until opening of the dura. The patient was fully sedated yet cooperative and comfortable throughout the operation with the Dex infusion of 0.3 µg/kg/h and targeted-controlled infusion (TCI) of remifentanil at 0.2 ng/ml. Twenty minutes prior to the neurological testing, Dex and the remifentanil infusion were stopped, and her entropy level went up to 95. The Observer's Assessment of Alertness/Sedation (OAA/S) and the Richmond Agitation Sedation Scale (RASS) were 5 and 0, respectively. The awake left craniotomy and tumor resection with an intraoperative depth electrode and electrocorticogram (ECOG) reading was completed in six hours with a total estimated blood loss of 600 ml. The tumor was debulked inferiorly until the middle temporal gyrus, superiorly until the inferior frontal gyrus, medially until the external capsule, and anteriorly until the bifurcation of the internal carotid artery. The tumor was also debulked in the hippocampus and insular region. Intraoperative language and memory assessment were conducted by a neuropsychologist during the debulking process. No further intraoperative incidents were encountered. Postoperatively, she was sent to the neurocritical care unit (NCCU) for close monitoring, and a CT scan of the brain revealed complete evacuation of the tumor. She was discharged from the NCCU to the general ward at day one post-surgery. She was discharged from the hospital after day four, and her follow-up at three months postoperatively, revealed complete resolution of her symptoms.

3. DISCUSSION

Dex is a highly selective α2 adrenoreceptor agonist that activates guanine-nucleotide regulatory binding proteins and causes inhibition of adenylate cyclase and decreased formation of 3,5-cyclic adenosine monophosphate (cAMP) through a second messenger system.[1] The efflux of potassium through an activated channel hyperpolarizes the membrane and leads to the suppression of neuronal firing. The sedative and hypnotic effect of Dex is attributed to the activation of an α2 receptor in the nucleus coeruleus.[1] The specificity of Dex for the α_2 receptor, especially for the 2A subtype of this receptor, causes it to be a far more effective

sedative and analgesic agent than clonidine. Dex causes sedation but preserves spontaneous breathing at even high doses.[2,4] These special properties favor usage of this drug in awake fiberoptic intubation, in surgical procedures under MAC, while it is widely used in intensive care sedation.

In the context of pain, Dex modulates nociception and causes release of endogenous opioids in the dorsal horn neurons at the spinal cord level, consequently, leading to reduced intraoperative and postoperative opioid requirements.[1] In addition, Dex is also proven to reduce the opioid requirement in opioid-induced hyperalgesia.[6] Ho et al. postulated that an incident of apnea post-operatively in a patient who had received a loading dose of Dex 1 μg/kg over 30 min and the infusion of 0.5 μg/kg/h was due to intraoperative opioids.[7] Chun et al. found that, in a patient given a combination of Dex-midazolam-fentanyl infusion, a lower Bispectral Index (BIS) score and a better sedation profile were observed.[8] In our patient, although TCI remifentanil was planned for analgesic purposes, the infusion was only started prior to insertion of the subclavian central venous cannulation and administration of the scalp block. We were cautious about the remifentanil and avoided initiation prior to any significant pain stimulation.

Some studies have reported an effect of Dex on respiration. A non-blinded randomized cross-over study by Lodenios et al. revealed the possibility of upper airway collapse with a Dex dose of 0.5 μg/kg/h.[9] Another of the patients in that study developed apnea after seven minutes of a loading dose of Dex at 0.6 μg/kg/h. However, numerous studies in both pediatric and adult patients have shown the preservation of upper airway reflexes.

We postulated a few possible explanations for the incident of apnea in this patient. First, the loading dose of 1 mg/kg for 10 min might have been excessive for this patient, especially for a patient who was naive to previous sedation. In a randomized controlled trial in elderly patients who received Dex after spinal anesthesia, the ED50 and ED95 for the loading dose were 0.29 μg/kg and 0.87 μg/kg, respectively.[10] In another study comparing loading doses of 0.5 μg/kg for 10 min as compared to over 20 min, the time taken to reach a Ramsay Sedation Score of 3 did not differ between the two groups.[11] In our patient, a loading dose of 1 μg/kg was given over 10 min, suggesting a possible reason for the central apnea. Thus, we advocate the use of a lower loading dose over a prolonged duration in elderly patients to reduce the incidence of adverse cardiorespiratory effects. Furthermore, our patient's requirement for intraoperative Dex and remifentanil was very low for a craniotomy and the opening of the dura, suggesting the need for careful titration to avoid excessive sedation and cardio-respiratory side effects.

Second, there might have been a drug interaction between the Dex and levetiracetam in our patient. Most antiepileptics are enzyme inducers. However, levetiracetam has insignificant protein binding, an absence of enzyme induction or drug interaction and is effective for refractory partial-onset seizures.[12] Its novelty as an antiepileptic is caused by its modulation of synaptic neurotransmitter release by binding to the protein SV2A vesicle in the brain. Although Carl et al. demonstrated an insignificant effect on sleep structure in healthy subjects, another study of its tolerability by the elderly with a CNS disorder found that somnolence was a frequent adverse reaction.[13,14] Levetiracetam is usually given in two divided doses of 20 mg/kg, with the commercial preparation being 500 mg tablets. This patient presented with only one episode of seizure, and no subsequent seizure was observed after the initiation of the antiepileptic. Thus, there is the possibility that this patient was overdosed, as she was a small lady with a weight of only 38 kg. This might have aggravated the incidence of apnea after Dex. After surgery, she was free of fits and a trial with the cessation of the antiepileptic did not lead to any recurrent seizure episode.

Premedication with midazolam will also affect dexmedetomidine. In this patient, we avoided premedication with midazolam. A combination of Dex with midazolam during elective awake fiber-optic intubation is associated with better patient cooperation and satisfaction.[15] Osamu et al. found that a combination of Dex with midazolam in elderly patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) decreased the incidence of respiratory complications as compared to conventional sedation.[3]

4. CONCLUSION

In conclusion, we advocate using Dex with a lower loading dose over a prolonged duration and the up-titration of the drug according to the patient's response to avoid incidents of central apnea. We also suggest the initiation of TCI remifentanil with DEX upon pain stimulation. Although DEX has a safer respiratory profile compared to other sedative agents, judicious use and meticulous monitoring are essential to ensure good quality MAC.

5.Consent for publishing

Written consent was obtained from the patient to publish this case report for the academic purposes.

6. Authors' contribution

All authors participated in the conduct of this case, data collection and preparation of the manuscript.

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