The use of “High Dose” Dexmedetomidine in a Patient with Critical Tracheal Stenosis and Anterior Mediastinal Mass

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Abstract: The anterior mediastinal mass patient continues to offer great challenges for the anesthesiologist. As such, newer and safer methods of providing anesthetic care are continually being sought. To this end, there is a growing body of evidence that may suggest that higher than Food and Drug Administration approved dosages of dexmedetomidine may offer another option in the arsenal of the anesthesiologist in this patient population.

We recently cared for a middle aged male who presented with a large mediastinal mass, extrinsic compression critical tracheal stenosis, superior vena cava syndrome, and massive supraclavicular lymphadenopathy, scheduled for tracheal stent placement, biopsy, and diagnostic evaluation of the esophagus. After reviewing anesthetic options, we deemed the safest technique available to us to be the use of a high dose dexmedetomidine based technique with continuous infusion rate of 2mcg/kg/hr. Spontaneous respirations were maintained throughout the case, with a stable heart rate and blood pressure, and our patient tolerated the procedure without complications.

Keywords: Alpha-2 agonist, clonidine, alpha-2 receptor, dexmedetomidine, mediastinal mass.

INTRODUCTION

General anesthesia in patients with an anterior mediastinal mass has been associated with hemodynamic and airway collapse. The anterior mediastinal space is largely composed of the thymus, the middle mediastinum contains the pericardium, heart, ascending aorta, aortic arch, and the great vessels, while the posterior mediastinum contains the tracheobronchial tree, esophagus, descending aorta, and neural structures. As such, compressive physiology may originate from masses of the thymus, thyroid, lung, airway, pleura, pericardium, lymphatic, or possibly other tissues. Morbidity is secondary to compression of the vital structures within the middle and posterior mediastinum.

In limited case series, the incidence of serious complications with general anesthesia in this patient population is up to 20% [1]. Positional dyspnea or orthopnea and stridor are ominous signs that may predict the probability of complications [2-5]. Patients develop symptoms, and have elevated risk of perioperative complications, when the reduction in tracheal cross-sectional area exceeds 50%, while a reduction in tracheal cross-sectional area less than 50% indicates of a lower risk of perioperative complications [1, 3, 6-9]. However, if the patient has coexisting compression of a mainstem bronchi, the perioperative risk for complete airway collapse may be significantly higher [4]. The combination of left mainstem bronchial compression and right pulmonary artery compression has been reported to cause catastrophic complete ventilation-perfusion mismatch [1, 10, 11]. Additionally, separate from airway compression, the presence of a pericardial effusion may be associated with intraoperative cardiovascular complications [3].

Unfortunately, there is a paucity of evidence providing guidance on quantifying risk and planning the safe conduct of anesthesia in patients with a symptomatic mediastinal mass [1]. It is currently believed that high risk patients are best managed with an anesthetic plan that emphasizes the maintenance of spontaneous ventilation, with the availability of cardiopulmonary bypass as the option of last resort [1]. This is largely because during general anesthesia with volatile agents, the functional residual capacity (FRC) is reduced by approximately 20% [12]. The most likely mechanism is the loss of inspiratory muscle tone of the muscles acting on the rib cage, elastic recoil of the chest wall, cephalad displacement of the diaphragm, with gas trapping acting as an additional mechanism [12]. The effect is compression atelectasis and increases in intrapulmonary shut and areas of low ventilation to perfusion. Neuromuscular blocking agents, if used in a multimodal plan for general anesthesia, can further compromise this physiology, as can many intravenous anesthetic agents with the possible exception of ketamine used in low doses. Furthermore, the abolishment of spontaneous (negative pressure) breathing decreases the transpleural pressure gradient which can lead to airway collapse. Additionally, the use of mechanical ventilation (positive pressure) may further increase intrathoracic pressures worsening the already high intrathoracic pressures related to the thoracic mass physiology [13].
When biopsy is desired for the planning of medical management, avoidance of general anesthesia by the use of local anesthesia alone or in combination with sedation has been described in case series of both adults and children [3-5]. Should a patient present with an already life threatening airway compromise, airway stenting can be undertaken as a temporizing measure. This procedure requires significantly more anesthetic depth to allow the patient to tolerate this course of action while attempting to maintain spontaneous ventilation.

In 1988, a new alpha-2 adrenoreceptor (\(\alpha_2\)) agonist anesthetic, dexmedetomidine, was introduced [14]. Currently, the chief clinical application of dexmedetomidine is for sedation and anaesthesia [15, 16]. Upon presentation of a middle aged male with a large mediastinal mass, extrinsic compression critical tracheal stenosis, superior vena cava syndrome, and massive supraclavicular lymphadenopathy, scheduled for tracheal stent placement and diagnostic evaluation of the esophagus, we determined that the use of a higher than current Food and Drug Administration (FDA) approved dose dexmedetomidine based technique was the best option for our patient. Currently, this technique has been described best in the pediatric population, with only a few published adult reports.

**CASE**

A 55 year old male, 65kg, American Society of Anesthesiologist’s Class IV patient, with a past medical history significant for gastroesophageal reflux disease, a recent deep venous thrombosis, 30 pack year tobacco use, alcoholism, on no medications upon admission, presented with progressive dysphagia over a 1-2 month period, with interval weight loss of 50 pounds during the past year. Initial dysphagia was to solid foods, which progressed to soft foods, followed by fluids, with eventual difficulty in handling saliva. Over the past 2-4 weeks, the patient also developed massive neck swelling and bilateral upper extremity edema, with dyspnea on exertion and vocal hoarseness.

A contrast enhanced computerized tomographic imaging (CT) scan of the chest revealed extensive abnormal soft tissue attenuation in the mediastinum extending to the neck base and supraclavicular regions, bilateral thrombi in the upper extremity veins, and tracheal lumen narrowing, with the narrowest portion being only 3.1mm in diameter (Fig. 1). This represented a greater than 87% narrowing (patient’s normal tracheal diameter was 24.5mm, within the normal range for males of 22.3-25.5mm) [17]. In addition, circumferential mid to distal esophageal wall thickening was noted extending downward to the proximal stomach.

Due the patient’s risk of pending catastrophic airway collapse, he was scheduled for tracheal stent placement, diagnostic evaluation of the esophagus (EGD), and needle biopsy. We were consulted to provide his anesthetic care.

Airway exam revealed Malampati Class III, limited neck extension and flexion, neck circumference over 51cm, hypomandibular space firmness, inability to handle salivary gland secretions, and diffuse erythematic swelling of all visualized oral pharyngeal structures. Upon reclining toward the supine position, at approximately 75 degrees he became immediately orthopneic and experienced a severe choking sensation. There was no position, supine, prone, or lateral, in which the patient could tolerate if he declined below the 75 degree erect position. After additional surgical consultation regarding airway management, a primary airway via cricothyriodotomy or tracheostomy was not deemed feasible.

Our general anesthetic plan was to maintain our patient’s supine position as tolerated (75-90 degree position), and maintain spontaneous ventilation throughout the case. To

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**Fig. (1). External Compression Tracheal Stenosis.** This contrast enhanced computed tomographic image shows external tracheal compression. In image A, the narrowest portion of tracheal compression was measured at 3.1mm. Image B shows an anterior mediastinal mass measuring 34mm by 37mm, with a tracheal narrowing of 4.2mm. Esophagus (eso), Aortic Valve Outflow Track (AVOT).
accomplish this goal, we choose to use a “high dose” dexmedetomidine based anesthetic.

Dexmedetomidine was delivered, based on actual patient body weight, at 1mcg/kg/hr for 10 min, and raised to 2mcg/kg/hr for the remainder of the 60 minute case. This regimen was supplemented by 15mcg/kg/min of propofol, used primarily as a means to provide for quicker deepening of anesthetic depth if needed, and 4mg of midazolam.

Throughout the procedure, our patient maintained spontaneous respirations, and was non-responsive to surgical manipulation. We also encountered stable hemodynamics in which heart rate and blood pressure were maintained within twenty percent of baseline (systolic blood pressure 112-130, diastolic blood pressure 68-80, heart rate 112-120). The initial deployment of the tracheal stent proceeded uneventful, however, original placement, as confirmed by fluoroscopy, revealed the stent was placed to distally. The stent was then manually retracted into proper positioning, again with our patient being non-responsive to this stimulation. EGD and biopsy then followed, again with the patient being able to fully tolerate these procedures without the need for increased anesthetic requirements.

DISCUSSION

In 1999, the US FDA approved the use of dexmedetomidine for two indications and usages: sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting, continuous infusion not to exceed 24 hours, and, sedation of non-intubated patients prior to and/or during surgical and other procedures. Approved dosages are as follows.1) For intensive care unit sedation: generally initiate at 1 mcg/kg over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hr. 2) For procedural sedation: generally initiate at 1 mcg/kg over 10 minutes, followed by a maintenance infusion initiated at 0.6 mcg/kg/hr and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/hr. 3) Dosage reduction may need to be considered in the elderly.

Since dexmedetomidine can maintain a patient’s spontaneous ventilation with normal PaCO₂, it is an ideal agent for use in attempts to secure a critically compromised airway. Even at very high doses of dexmedetomidine, the respiratory system can remain relatively unchanged. (See Table 1) Its additional antissialagogue properties are beneficial as well. As such, its value has been recognized in use as the sole sedative in awake intubation in the management of the difficult and critical airway in FDA approved dosages [18]. However, in true airway catastrophes, as presented in the case here, the level of analgesia and sedation achieved with the FDA recommended dosage may not be sufficient for the prescribed procedure. To this end, only a small handful of reports exist in the literature on the use of higher than FDA approved doses of dexmedetomidine in adults [19-25].

Higher doses of dexmedetomidine appear to be better studied in the pediatric literature, where a large scale retrospective study of 747 pediatric patients scheduled for magnetic resonance imaging (MRI), in which doses of 2mcg/kg/hr are used as the sole sedative in their protocol, had a 97.6% success rate [26]. Also within the pediatric literature, as judged by MRI, it has been noted that with the use of dexmedetomidine in doses of 1mcg/kg/hr or 3mcg/kg/hr, upper airway changes in children with no OSA are small in magnitude and do not appear to be associated with clinical signs of airway obstruction [27]. This said, caution is advised, as has been shown in goats with the use of clonidine, α2 stimulation preferentially decreased the activity of the posterior cricoarytenoid, cricothyroid, and inferior pharyngeal constrictor muscles while increasing thyroarytenoid and middle pharyngeal constrictor electromyogram activities [28]. As such, clonidine-induced apneas were shown to be associated with continuous tonic activation of laryngeal thyroarytenoid and middle pharyngeal constrictor adductors, leading to airway closure and arterial oxygen desaturation; these effects being reversed by selective α2 blockade with SKF-86466 [28]. It is postulated that these effects are due to hyperpolarization or attenuation of the activity of central respiratory-related neurons that have been shown to slow or inhibit breathing in animals and humans [15, 29-39]. This said, it is important to note that the effects of α2 agonists appear to be species specific [40, 41]. As such, though α2 agonists are ubiquitously distributed throughout the CNS in humans, including in brainstem regions which are instrumental in control of breathing, such as the nucleus tractus solitaries, nucleus ambiguous, and ventrolateral medulla, their function in the control of respiration has not yet been fully ascertained [15, 42].

In adults, infusion doses of dexmedetomidine up to 10mcg/kg/hr and plasma levels of up to 14.7mg/ml have been reported in which apnea and airway obstruction has not ensued [15, 19-21, 43-45]. Despite the appeal of dexmedetomidine as a sedative that does not induce respiratory depression, it is stressed that central apnea and airway obstruction can occur. It is also important to clarify that the risk of apnea, as demonstrated by Belleville and Ramsay, appears to be related to both the dose and rate of dexmedetomidine infusion. Ebert noted that more pronounced respiratory effects have been reported when dexmedetomidine is rapidly infused to high concentrations [21]. The case we report demonstrates intact respiratory function on a “high-dose” dexmedetomidine infusion of 2mcg/kg/hr. In comparison, Ramsay reported airway obstruction due to dexmedetomidine at infusions of 10 mcg/kg/hr and Belleville reported obstructive apnea following an IV bolus of 2mcg/kg over 2 minutes [15, 19]. These doses are five to thirty-fold greater than doses administered in this case report, though it is certainly possible that apnea can ensue at a dose of 2mcg/kg/hr, or within the range of the approved FDA doses. In Ramsay’s article the single report of airway obstruction was associated with desaturation, and this was resolved with a basic chin-lift. Ebert concluded that because the α2 adrenoceptor does not have an active role in the respiratory center, respiratory depression is more likely to be due to profound sedation [21, 46]. These observations are echoed by Bellivile noting that their subjects did not experience any central apneic episodes with dexmedetomidine doses up to 2ug/kg over two minutes, however, apnea was noted secondary to airway obstruction [15]. With clonidine, used in a single FDA approved oral dose of 0.3mcg, or with dexmedetomidine used within its FDA approved dosing, this same obstructive pattern of breathing has also been noted [38, 47, 48]. Lastly, it is important to note that the majority of these studies were conducted in young healthy adults, suggesting that though many of the
Table 1. The Respiratory Response to Clonidine and Dexmedetomidine in Humans

<table>
<thead>
<tr>
<th>Clonidine*</th>
<th>FDA Approved Dose</th>
<th>Above FDA Approved Dose***</th>
<th>FDA Approved Dose</th>
<th>Above FDA Approved Dose***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Rate</td>
<td>Unchanged-Minor Decrease** [38, 56, 71-74]</td>
<td>Decreased** [75, 76]</td>
<td>Unchanged [21, 41, 78, 79]</td>
<td>Increased** (Statistically significant at target 1.25ng/ml) [21, 78]</td>
</tr>
<tr>
<td>Tidal Volume</td>
<td>Unchanged-Minor Decrease** [38, 73]</td>
<td>Not specified</td>
<td>Unchanged [78]</td>
<td>Decreased** [15] (1 and 2ug/kg bolus over 2 mins)</td>
</tr>
<tr>
<td>Ventilation (liters/minute)</td>
<td>Minor Decrease** [38, 56, 61, 71, 80]</td>
<td>Not specified</td>
<td>Unchanged [78]</td>
<td>Decreased** [15] (1 and 2ug/kg bolus over 2 mins)</td>
</tr>
<tr>
<td>SpO2***</td>
<td>Unchanged [38, 56, 74, 80, 81]</td>
<td>Unchanged [46] (dose range 400-900ug given epidurally)</td>
<td>Unchanged [78, 79]</td>
<td>Decreased (Statistically Significant at target 0.5ng/ml) [21]</td>
</tr>
<tr>
<td>PaO2</td>
<td>Unchanged [46, 81, 82]</td>
<td>Unchanged [46] (dose range 400-900ug given epidurally)</td>
<td>Unchanged [21, 41, 78]</td>
<td>Changes not statistically significant with continuous infusions or bolus doses [15, 21, 78]</td>
</tr>
<tr>
<td>PaCO2</td>
<td>Unchanged [46, 56, 71, 74]</td>
<td>Unchanged [46] (dose range 400-900ug given epidurally)</td>
<td>Unchanged [41]</td>
<td>Increased (Statistically Significant at target 0.8ng/ml) [21]</td>
</tr>
<tr>
<td>pH</td>
<td>Unchanged [46]</td>
<td>Unchanged [46] (Dose range 400-900ug given epidurally)</td>
<td>Unchanged [41, 78]</td>
<td>Decreased (Statistically Significant at target 0.5ng/ml)</td>
</tr>
<tr>
<td>Desaturation (SpO2&lt;90%)</td>
<td>Unchanged [71, 72, 80]</td>
<td>Unchanged [46] (Dose range 400-900ug given epidurally)</td>
<td>Unchanged [15, 21, 41, 78]</td>
<td>Unchanged [15, 19, 21, 78]</td>
</tr>
<tr>
<td>Oxygen Consumption</td>
<td>Decreased [73, 83]</td>
<td>Not specified</td>
<td>Unchanged [15]</td>
<td>Increased at 10mins, Decreased by 60mins [15] (1 and 2ug/kg bolus over 2 mins)</td>
</tr>
<tr>
<td>Carbon Dioxide Production</td>
<td>Decreased [73]</td>
<td>Not specified</td>
<td>Unchanged [15]</td>
<td>Decreased [15] (0.25, 0.5, 1, and 2ug/kg bolus over 2 mins)</td>
</tr>
<tr>
<td>Pulmonary Vascular Resistance</td>
<td>Decreased [84]</td>
<td>Not specified</td>
<td>Unchanged [21]</td>
<td>Increased (Statistically significant at 1.9ng/ml) [21]</td>
</tr>
<tr>
<td>Hypercapnic Ventilatory Response†</td>
<td>Conflicting reports [56, 71-72, 80, 85]</td>
<td>Decreased [71]</td>
<td>Unchanged [78]</td>
<td>Decreased [15] (0.25, 0.5, 1, and 2ug/kg bolus over 2 mins)</td>
</tr>
</tbody>
</table>
negative effects of the $\alpha_2$ agonists on respiration are mild in nature, these effects could be detrimental to more frail patients with pre-existing respiratory disease or other major systemic comorbidities [15]. This documented risk of apnea and airway obstruction, especially at higher than FDA approved doses, should guide each clinician’s judgment on a case-by-case basis when considering to use dexmedetomidine for procedures in which other sedatives would carry an otherwise prohibitive risk of apnea.

Dexmedetomidine has an affinity for the $\alpha_2$, $\alpha_1$ of 1620:1, and a half-life of 2.3 hr [49]. Within the three receptor subtypes of the $\alpha_2$, $\alpha_2a$, $\alpha_2b$, $\alpha_2c$, dexmedetomidine's binding affinity differs only moderately, with a 10-fold preference for $\alpha_2a$ [50, 51]. Unlike other current sedative agents, dexmedetomidine produces a state closely resembling physiological stage 2 sleep in humans. Stage 2 sleep, which occupies 45-55% of total sleep in adults, is characterized by sleep spindles and K-complexes, with muscular activity decreasing, and loss of awareness of the external environment. This evidence has suggested that dexmedetomidine produces its sedative effect via activation of normal non-rapid eye movement (non-REM) sleep-promoting pathways [52]. Indeed, since non-REM sleep causes a decrease in the slope and a shift to the right of the hypercapnic ventilatory response curve (HCVR), the effects attributed to clonidine and dexmedetomidine on HCVR may be ascribed to the sleep state induced by these agents [15, 53-55]. However, since it has been shown in some studies with clonidine that a decrease in the slope of the ventilatory response to carbon dioxide (Ve/PeCO$_2$) occurs, a direct effect of $\alpha_2$ agonists on respiratory centers is possibly at least partly responsible for their respiratory depressant properties [56]. In addition to promoting non-REM sleep, clonidine suppresses rapid eye movement (REM) sleep in a dose dependent manner [56, 57].

Dexmedetomidine also has analgesic properties, with the $\alpha_2a$ subtype most likely being responsible for this effect both in the periphery and in central sites [58-60]. The mechanism of action appears to be activation of potassium channels, via G-protein inhibitory (G$_i$) channel coupling with subsequent hyperpolarization of neuronal membranes, and inhibition of N-type voltage-sensitive calcium channels, via G-protein null effect (G$_n$) channel coupling with decreased calcium influx and neurotransmitter release [61-64]. Furthermore, Aley and Levine have suggested that $\alpha_2$ antinociception is closely related to that of opioid and adenosine receptors as these receptors exhibit cross tolerance and dependence, suggesting that their underlying mechanisms are related [65]. Neuraxially, $\alpha_2$ receptors are located in the dorsal horn of the spinal cord in both pre- and post-synaptic neurons where their activation causes antinociception. Supraspinally, activation of $\alpha_2$ receptors in the locus coeruleus produces analgesia as well [58, 66-68]. Pharmacokinetic and pharmacodynamic studies support the spinal site of action as the primary location for antinociception of $\alpha_2$ agonists [58].

In humans, it has been noted by Ebert, in a study of ten healthy young volunteers, that increasing plasma concentrations of dexmedetomidine, targeted ranges of 0.5, 0.8, 1.25, 2, 3.2, 5, 8 ng/ml, resulted in progressive increases in sedation and analgesia, decreases in heart rate, cardiac output, and memory with a biphasic (low, then high) dose response relation for mean arterial pressure, pulmonary arterial pressure, and vascular resistances [21]. This biphasic response is
due to the different $\alpha_2$ receptor subtypes, where $\alpha_{2a}$, and/or possibly $\alpha_{2c}$, located on the presynaptic nerve ending, decrease sympathetic outflow and blood pressure, whereas the $\alpha_{2b}$ subtype, located on the post synaptic nerve terminal, increases blood pressure [69]. This apparent effect may be due to the 10-fold higher affinity of dexmedetomidine for the $\alpha_{2c}$, which produces hypotension, whereas following higher plasma levels, $\alpha_{2b}$ may be activated causing the hypertensive response. Another possibility is that the sympatholytic effects of dexmedetomidine offset any direct effect on the peripheral vasculature at lower doses, but not higher doses. Of note, 10/10 patients in this study were able to tolerate a targeted infusion level of 1.25ng/ml, with a progressive decline in tolerance in which only 2/10 tolerated the 8.0ng/ml targeted infusion.

Sedation increases progressively with rising dexmedetomidine concentrations. Ebert found that beginning at a targeted plasma level of 1.25ng/ml, some patients will begin to become unarousable. In terms of recall, at a plasma targeted level of 0.8ng/ml, only 2/10 patients they studied had recall, and at a targeted plasma level of 1.25ng/ml, none of the study subjects had recall.

In the presented case, our primary physiologic anesthetic goal was achieved in which our patient maintained spontaneous respirations. Given the risk of pending airway collapse, and the infeasibility of securing an endotracheal or primary surgical airway, the attributes of the use of higher doses of dexmedetomidine proved very useful. If our initial anesthetic plan failed, we intended to progressively increase the dose of dexmedetomidine and employ local anesthetics in a “spray as you go” fashion through the bronchoscope. We also had ketamine available to use in small quantities if we felt that it was needed. The combined use of FDA approved doses of dexmedetomidine and low-dose ketamine has been described for awake fiberoptic intubations [70]. Ultimately, cardiopulmonary bypass was available in the event of total airway collapse.

CONCLUSIONS

Higher doses of dexmedetomidine, above that which is currently FDA approved, can result in progressive increases in sedation and analgesia, with resultant unresponsiveness to some surgical stimuli, and decreases in memory, with the potential for minimal to no clinical effects on spontaneous respirations, and stable hemodynamics, though apnea is possible. This case report adds to a growing body of literature, suggesting that if properly selected patients, higher than FDA recommended doses of dexmedetomidine may be safe for adult use, and in cases where spontaneous respiration must be maintained, may offer the safest anesthetic option when other sedatives carry a prohibitive risk of apnea. Ultimately, large randomized controlled studies are needed to more definitively answer these questions.

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DECLARATION OF INTEREST

The authors declare no conflicts of interest.

REFERENCES


Morley AE, Levine JD. Multiple receptors involved in peripheral alpha 2, mu, and A1 antinociception, tolerance, and withdrawal. J Neurosci 1997; 17: 735-44.


The use of “High Dose” Dexmedetomidine in a Patient with Critical


