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Editorial

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

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ANESTHETIC DOSE OF DEXMEDETOMIDINE: HOW HIGH IS HIGH ENOUGH?

Patients who present with an anterior mediastinal mass requiring surgical intervention continue to be a challenge for anesthetic care. The risk for airway and hemodynamic collapse during general anesthesia with inhaled agents complicates the management of these patients. Anesthetics that maintain spontaneous ventilation are optimal in this setting. Dexmedetomidine, a selective alpha$_2$ agonist, which is devoid of significant respiratory depression at clinically approved doses, may have a role. However, there is a paucity of data quantifying level of anesthesia, as well as respiratory and hemodynamic response with high dose dexmedetomidine in adult patients. Previous case reports demonstrate a wide range of doses necessary to provide anesthesia [1-3]. Voscopoulos *et al*., described a case involving an adult patient with critical tracheal stenosis and a large mediastinal mass undergoing a tracheal stent placement and diagnostic evaluation of the esophagus. They utilized a high dose dexmedetomidine infusion to facilitate the procedure (1 mcg/kg/hr for 10 minutes followed by 2 mcg/kg/hr for 60 minutes).

This case adds to a growing field of evidence that dexmedetomidine, at higher than labeled doses, is effective as the sole anesthetic during surgical manipulation without inducing significant respiratory depression or hemodynamic instability. An infusion rate of 2 mcg/kg/hr provided deep anesthesia and the patient was unresponsive. This contrasts to previous work by Ebert *et al*., and Ramsay *et al*., who demonstrated that dexmedetomidine required much higher titration to provide adequate anesthesia [1-3]. Ebert *et al*. investigated the effects of increasing plasma concentrations of dexmedetomidine in 10 young healthy volunteers. The authors found that plasma concentrations of 8 ng/ml were required before patients became unarousable, although dexmedetomidine diminished memory recall and recognition at concentrations of 1.2 ng/ml [1]. A plasma concentration of 8 ng/ml is approximately equivalent to 4.5 mcg/kg/hr in a 70 kg patient, based on an elimination half-life of 2.67 hours and volume of distribution of 152 L. In a case series published by Ramsay *et al*., the infusion of dexmedetomidine ranged from 5 to 10 mcg/kg/hr until patients were fully anesthetized [2]. In a morbidly obese patient undergoing a tracheal resection, dexmedetomidine was titrated to 10 mcg/kg/hr, before the patient became unresponsive. Following an anterior neck incision, the level of anesthesia began to lighten, requiring the addition of 1% sevoflurane [3]. It is evident that the level of anesthesia achieved with doses as high as 10 mcg/kg/hr may not be sufficient for deep surgical incisions. The wide range of dosing in these case reports suggests significant interpatient variability in levels of anesthesia. More data is needed to fully understand the dose of dexmedetomidine and plasma concentration that correlates with level of anesthesia in adults.

The risk of hemodynamic instability and respiratory depression has been previously described with high dose dexmedetomidine in a small sample of adult patients [1,2,4,5]. These effects are likely precipitated by bolus doses and higher rates of administration. At clinical doses, dexmedetomidine's preferential affinity toward alpha$_{2a}$ decreases sympathetic outflow and causes hypotension. At higher doses, selectivity may be lost, activating alpha$_{2b}$ receptors that induce hypertension and reflex bradycardia [6]. The mechanism of high dose dexmedetomidine on respiratory depression has not been fully elucidated. It has been suggested that alpha$_2$ adrenoceptors have minimal direct function in neural pathways involved in central control of breathing [4].

Dexmedetomidine's effects on hemodynamics at high doses have been well documented [5]. A rate of 2 mcg/kg infused over 2 minutes produced a biphasic response in blood pressure in 28 healthy male participants. Mean arterial pressure increased transiently for 3 minutes by 24 $\pm$ 10 mmHg followed by a maximum reduction in mean arterial pressure of 27% at 60 minutes post infusion. The transient increase in blood pressure was associated with a reduction in cardiac output by 41% and heart rate by 22%. Interestingly, there was an absence of significant hemodynamic side effects in this case presented by Voscopoulos *et al.* Two potential mechanisms may explain the lack of hemodyamic instability. First, this patient's elevated baseline heart rate and low vagal tone may have buffered the drug's effect on bradycardia and fluctuations in blood pressure. Bloor *et al*., concluded that patients with lower resting heart rates and

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1874-3218/11

higher vagal tone may be more susceptible to bradycardia caused by high doses of dexmedetomidine as shown in a group of young subjects [5]. Second, as demonstrated by Ebert, increasing concentrations of dexmedetomidine up to 8 ng/ml (approximately equivalent to infusion rate of 4.5 mcg/kg/hr) caused progressive increases in mean arterial pressures, decreases in heart rate, and reduction of cardiac output [1]. A mean steady state plasma concentration of 1.25 ng/ml correlates with a dexmedetomidine rate of 0.7 mcg/kg/hr infused up to 24 hours [7]. However, in this case, a dexmedetomidine infusion over 60 minutes produced an estimated concentration of 1.15 ng/ml. It is unclear if the plasma concentrations of dexmedetomidine would reach levels associated with significantly more hemodynamic instability had the infusion exceeded 60 minutes.

The mechanism of respiratory depression with high dose dexmedetomidine is not fully understood. In a study by Belleville *et al.*, a dexmedetomidine infusion of 2 mcg/kg infused over 2 minutes produced short periods of apnea in healthy volunteers [4]. Additionally, a case report utilizing a continuous infusion of dexmedetomidine at 10 mcg/kg/hr resulted in significant oxygen desaturation [2]. The cause of apneic episodes in these reports was due to airway obstruction at deeper levels of sedation, but not secondary to central apnea. The function of $alpha_2$ adrenoceptors on respiratory control is likely minimal, even at higher doses of dexmedetomidine [4]. The case report by Voscopoulos *et al.*, further supports this data.

It might be possible that respiratory depression is secondary to inhibiting effects of dexmedetomidine on noradrenergic arousal pathways, resulting in sedation. Those effects on global brain states can switch local recurrent networks such as upper airway muscle control into different regimes *via* direct neuromodulation. Avoidance of rapid titration and utilization of a relatively lower infusion rate compared to previous cases, minimized the potential for apneic episodes. Further research is required to evaluate the risk of apnea in patients who are deeply sedated or have pre-existing respiratory disease.

Dexmedetomidine is an attractive alternative for anesthesia in patients with a compromised airway requiring less invasive procedures. The infusion rate, 2 mcg/kg/hr, is higher than labeled doses, but lower than anesthetic doses used in previous literature. The case by Voscopoulos *et al*., demonstrated this dose of dexmedetomidine was effective for providing anesthesia without causing significant respiratory depression or hemodynamic instability.

CONFLICT OF INTEREST

Dr. Levine has no conflict of interest associated with the topic of this editorial.

ACKNOWLEDGEMENT

None declared.

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Received: November 24, 2011 Revised: December 14, 2011 Accepted: December 14, 2011