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The Use of Dexmedetomidine in Anesthesia and Intensive Care: A Review

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Abstract: The alpha-2 agonist dexmedetomidine is being increasingly used for sedation and as an adjunctive agent during general and regional anesthesia. It is used in a number of procedures and clinical settings including neuroanesthesia, vascular surgery, gastrointestinal endoscopy, fiberoptic intubation, and pediatric anesthesia. The drug is also considered a nearly ideal sedative agent in the intensive care setting. However, the drug frequently produces hypotension and bradycardia, and also decreases cerebral blood flow without concomitantly decreasing the cerebral metabolic rate for oxygen. This review discusses recent advances in the use of dexmedetomidine in anesthesia and intensive care settings, as well as discuss potential problems with its use.

Keywords: Anesthesia, dexmedetomidine, surgery.

INTRODUCTION

Dexmedetomidine is a novel alpha-2 agonist drug with important properties that make it increasingly popular for both procedural sedation as well as an adjunctive agent during general and regional anesthesia. Additionally, the drug is commonly used in the intensive care setting. However, the fact that the drug frequently produces hypotension and bradycardia, and decreases cerebral blood flow are issues that must be considered with its use. This review discusses technical (e.g., pharmacokinetic) and clinical issues with the use of dexmedetomidine in anesthesia and intensive care settings, as well as potential difficulties that may be encountered with its use.

PHARMACOKINETIC PROPERTIES OF DEXMEDETOMIDINE

Following IV administration in adults, dexmedetomidine's volume of distribution (Vd) at steady state is 1.31 L/kg [1]. Dexmedetomidine clearance exhibits first-order kinetics; that is, clearance remains constant within the anticipated therapeutic range. However, a diminished clearance by about 20% was noted in a maximum-tolerated dose study that included concentrations 13 times the upper limit of therapeutic range [2]. Dexmedetomidine exhibits a rapid distribution phase with distribution half-life of 6 min. The terminal elimination half-life is 2–2.5 h in adults, although this half-life in children is 1.8 h [3]. The clearance in neonates is approximately one-third of that in adults, consistent with immature elimination pathways [4]. That said, by one year of age, values approached those reported in adults. Therefore maintenance dosing, which is a function of clearance, should be reduced in neonates and infants when a target concentration approach is used.

It is notable that since the total plasma clearance of dexmedetomidine is independent of age except in neonates, infants and elderly patients, similar rates of infusion can be used in older children and adults to maintain a steady-state concentration of dexmedetomidine [5,6]. Patients with hypoalbuminemia usually have an increased volume of distribution which might prolong dexmedetomidine elimination half-life [7]. Maternal-to-fetal transfer of dexmedetomidine is much less than for clonidine. This difference is attributed to the higher lipophilicity of dexmedetomidine, which results in greater placental tissue retention [8]. A dexmedetomidine dose is 94% protein bound, and is almost completely metabolized to inactive metabolites in the liver via CYP2A6 and N-methylation, then eliminated in the urine as a glucuronide. Ninety-five percent of a dexmedetomidine dose is excreted in the urine and 4% in the feces. In patients with hepatic impairment, the mean clearance for the free drug is diminished by 41%, 49%, and 68% in mild, moderate and severe Child-Pugh categories respectively [2]. The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment differed little from volunteers with normal renal function, although the authors encountered more prolonged sedation in subjects with renal disease [9].

ROUTES OF ADMINISTRATION

Dexmedetomidine is primarily administered intravenously. However, it can be absorbed systemically via intranasal, transdermal, buccal, or intramuscular routes, with a mean bioavailabilty from the last 2 routes of 82% and almost 100%, respectively. Oral bioavailability is 15% due to first–pass metabolism. Transdermal bioavailability is 51% [10]. The onset of action after administration of dexmedetomidine intravenously or intranasally is 15 minutes and 45-60 minutes, respectively, with peak levels reached within 1 hour after IV administration and after 90-105 minutes for intranasal administration [10].

DRUG INTERACTIONS

Because dexmedetomidine inhibits CYP2D6 and CYP2DA4 enzymes, care should be exercised with the concurrent use of drugs metabolized by these same enzymes. In particular, the analgesic effect of tramadol and oxycodone may be compromised with the concomitant use of dexmedetomidine, as their metabolism is dependent on the CYP2D6 enzyme.

CARDIOVASCULAR EFFECTS OF DEXMEDETOMIDINE

Alpha-2 adrenoceptor agonists mediate their cardiovascular effects by activating receptors in the central and peripheral nervous system and in postsynaptic receptors in target organs. Activation of presynaptic alpha-2 adrenoceptors on sympathetic nerves and the central nervous system induces sympatholysis, whereas activation of vascular postsynaptic receptors causes both vasoconstriction [11], through activation of alpha-2 adrenoceptors on vascular smooth muscle cells, and vasodilatation, through activation of alpha-2 adrenoceptors on endothelial cells [12]. Because of these counteracting mechanisms, the overall effect of alpha-2 adrenoceptor activation on organ blood flow is complex and difficult to predict, depending on the specific alpha-2 agonist.

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Dexmedetomidine is a highly selective alpha-2 adrenoreceptor agonist, and possesses hypnotic, sedative, anxiolytic, sympatholytic, and analgesic properties without producing significant respiratory depression [11-14]. Its sympatholytic effect decreases mean arterial blood pressure (MAP) and heart rate (HR) by reducing norepinephrine release [15]. The central hypotensive effect from dexmedetomidine is dependent on endothelial nitric oxide synthase [16]. In a study of the hemodynamic effects of low (measured mean plasma concentration 0.5 ng/ml) and high (measured mean plasma concentration 5 ng/ml) plasma concentrations of dexmedetomidine in healthy volunteers [17], dexmedetomidine had a biphasic effect expressed by reduced blood pressure and HR with low concentrations, while in the high concentration setting substantial elevations in blood pressures (systemic, pulmonary, and venous) were encountered, with increased peripheral vascular resistance and decreases in HR, mixed venous oxygen saturation, and CO. The low dexmedetomidine concentration produced a 22% increase in coronary vascular resistance and a 27% reduction in myocardial blood flow [17]. The high dexmedetomidine concentration did not affect myocardial blood flow, but coronary vascular resistance was further increased during the high concentration dexmedetomidine infusion phase. Plasma levels of epinephrine and norepinephrine decreased on average by approximately 70% during low dexmedetomidine conditions, and only slight additional decreases were noted during high dexmedetomidine conditions.

The low concentration of dexmedetomidine reduces myocardial perfusion, and at the same time reduces myocardial oxygen demand, estimated by the rate–pressure product. The high dexmedetomidine plasma concentration did not further attenuate myocardial perfusion from low dexmedetomidine. Systolic myocardial function was attenuated by sympatholysis during the low infusion rate and was further attenuated by a combination of sustained sympatholysis and increased afterload during the high infusion rate. Diastolic function was minimally affected at all concentrations of dexmedetomidine. It is important, however, to avoid extrapolating the myocardial effects of dexmedetomidine from healthy volunteers to patients with coronary artery disease and impaired coronary endothelial functions.

In patients undergoing vascular surgery, continuous perioperative infusion of dexmedetomidine attenuated increases in heart rate and plasma norepinephrine concentrations during emergence from anesthesia [18]. However, patients receiving dexmedetomidine required greater intraoperative pharmacologic interventions to support blood pressure and heart rate [19]. While the alpha-2 adrenergic agonist mivazerol was shown to reduce perioperative cardiac morbidity following noncardiac surgery [20], large randomized trials are lacking on the effect of dexmedetomidine on cardiac morbidity and mortality after cardiac and noncardiac surgery. In a recent meta-analysis of the cardiac protective effect of dexmedetomidine in noncardiac surgery, the use of dexmedetomidine was associated with improved cardiac outcomes, but perioperative hypotension and bradycardia significantly increased [21]. Any such trials evaluating the beneficial effects of dexmedetomidine on perioperative hemodynamics must also address their effect on vital organ (brain, kidney) perfusion, their overall effect on mortality, and the need for perioperative for pharmacologic support.

Patients undergoing carotid endarterectomy under regional anesthesia who were randomized to dexmedetomidine sedation were less likely to require intervention for hypertension and/or tachycardia than patients randomized to fentanyl and midazolam sedation [22]. A preliminary observational report suggests that dexmedetomidine may play a potential therapeutic role in the acute phase of perioperative atrial and junctional tachyarrhythmias during congenital cardiac surgery for either HR control or conversion to NSR [23].

In a randomized, multicenter, double-blind study to evaluate the safety and efficacy of two doses of dexmedetomidine for sedation in patients undergoing procedures requiring MAC, 326 patients were randomized to dexmedetomidine 0.5μg kg^{-1}, dexmedetomidine 1μg kg^{-1}, or saline placebo initial loading dose, followed by a maintenance infusion of 0.2–1.0 g kg^{-1} over 1 h. Seventeen patients (13.2%) in the 1 μg kg^{-1} group and 17 patients (12.6%) in the 0.5 μg kg^{-1} group received interventions for treatment of hypotension and/or bradycardia during the infusion period (titration of study drug, IV fluid bolus, or pharmacologic treatment), compared with two patients (3.2%) in the placebo group—a comparison which highlighted the hypotension and bradycardia caused by clinical sedation doses of dexmedetomidine.

There was no significant increase in the incidence of hypotension or bradycardia when dexmedetomidine was administered to patients taking chronic antihypertensive therapy, including beta blockers. Dexmedetomidine, through its central sympatholytic activity, has proved effective in abolishing the increased sympathetic activity caused by intranasal cocaine, as evidenced by a reduction in mean arterial pressure, heart rate, and skin vascular resistance caused by cocaine [24]. Kurnik and colleagues [25] found substantial interindividual variability in the reduction of systolic blood pressure (range, 1 to 34 mm Hg) and plasma norepinephrine concentrations with dexmedetomidine. However, they were unable to find any ethnic or genetic differences in hemodynamic responses to dexmedetomidine. Wong and colleagues studied the cardiovascular effects of dexmedetomidine sedation in children undergoing radiologic procedures [26]. Dexmedetomidine sedation for procedures lasting longer than 10 minutes reduced heart rate (24 [8.3to 39.6] bpm) and cardiac index (1.51 [0.96 to 2.06] L/min/m^2), and both effects continued through recovery. In addition, the stroke index decreased (8.01[1.71to 14.31] ml/m2) and the systemic vascular resistance index increased (776.0 [271.9 to 1280.4] dynes /cm^5/m^2); both remained unchanged at recovery. However, in this study the authors used larger than usual doses of dexmedetomidine; specifically, 2 mcg/kg bolus and an infusion rate of 1mcg/kg/hr, and they administered a second bolus if needed. The high dexmedetomidine dosages in this study suggest the need for caution against using high dexmedetomidine doses, especially in children or in adults who have compromised cardiovascular function.

NEUROPROTECTIVE EFFECTS OF DEXMEDETOMIDINE

The neuroprotective effect of dexmedetomidine during cerebral ischemia is primarily related to decreased peripheral catecholamine levels. Suppression of catecholamine concentrations may be neuroprotective in that it balances cerebral oxygen demand and oxygen supply, thereby reducing excitotoxicity, ameliorating toxic effects, or improving perfusion in the ischemic penumbra [27,28]. Dexmedetomidine stimulates astrocytic α-2 adrenergic receptors, which in turn raise astrocytic calcium concentrations. These elevated concentrations then stimulate glutaminase activity and the ability of astrocytes to eliminate glutamine by oxidative metabolism, thereby reducing the availability of glutamine as a precursor of neurotoxic glutamate [29]. Furthermore, dexmedetomidine inhibits evoked glutamate release by stimulating alpha-2 a-receptors though a mechanism involving the suppression of Ca_v 2.2 and Ca_v 2.1 channels and mitogen-activated protein kinase activity (Fig. **1**) [30]. Dexmedetomidine increases the concentration of anti-apoptotic factor BCL-2 during ischemia. Increasing the concentration of BCL-2 during ischemia facilitates the decrease of mitochondrial membrane permeability and the release of cytochrome C from the mitochondria into the cytosol [31,32]. Dexmedetomidine increases extracellular-signal-regulated kinase (ERK) 1/2 phosphorylation, a key mitogen-activated protein kinase involved in cell survival and memory. This effect is mediated via activation of protein kinase C, and probably imidazoline receptors [33]. Dexmedetomidine also increases the expression of growth factors such as epidermal growth factor and brain-derived neurotrophic factors, which participate in these protective effects. The unique neuroprotective feature of dexmedetomidine is that it inhibits neuroapoptosis induced by

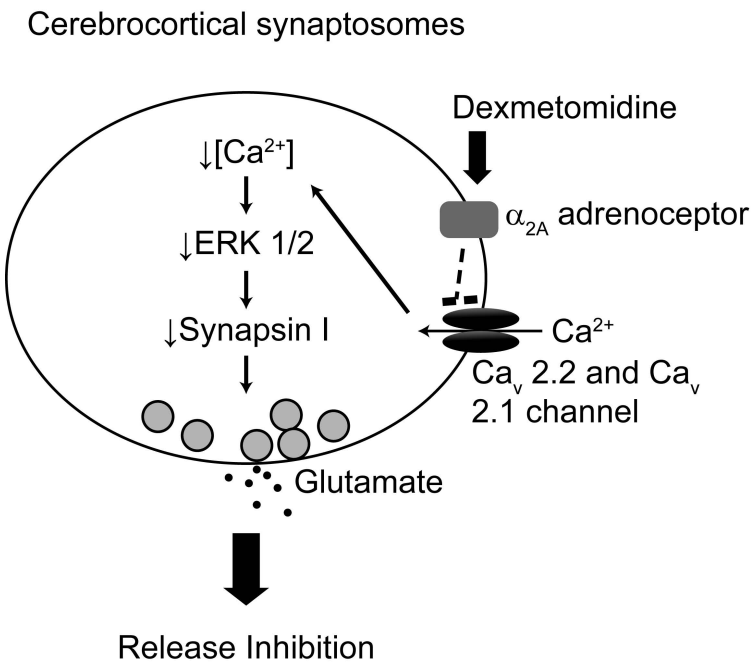

Fig. (1). A schematic diagram of mechanism of dexmedetomidine-induced inhibition of glutamate release in cerebrocortical synaptosomes. In synaptic terminals, the depolarization of neurons induces Ca2+ entry through the Cav2.2 and Cav2.1 channels. Ca2+ influx consequently activates protein kinases and triggers the release of glutamate. In the present study, dexmedetomidine acts at α2A adrenoceptors present on cerebrocortical nerve terminals to effect a reduction of 4-aminopyridine-evoked glutamate release. This effect is linked to a decrease in [Ca2+]i contributed by Ca2+ entry through the Cav2.2 and Cav2.1 channels and to the subsequent suppression of the ERK/synapsin I signaling cascade. Reprinted with permission. European Journal of Pharmacology 2011; 670: Fig. (**8**). page 146.

isoflurane in the growing brain. This effect might be useful in pediatric anesthesia to protect against the neuroapoptosis induced by anesthetics in the growing brain [34,35].

DEXMEDETOMIDINE AND CEREBRAL BLOOD FLOW

Studies in animals have raised concern over the potential of α-2 agonists to reduce CBF out of proportion to their effect on CMRO2. Karlsson and colleagues [36] measured canine global CBF and CMRO2 during 1 minimal alveolar concentration (MAC) of halothane anesthesia. Dexmedetomidine caused a significant reduction in CBF without influencing CMRO2. (Decreasing halothane concentration to 0.1% caused no changes in CBF reduction, but instead increased CMRO2 by 19%.) Asano and colleagues [37] compared the effects of locally applied dexmedetomidine with systemically administered dexmedetomidine on pial arterioles with and without local application of the specific α-2 antagonist atipamezole. The results of this study suggested that the vasoconstrictive response to systemically administered dexmedetomidine might be due to its direct actions via α-2 receptors in the pial arterioles. McPherson and colleagues [38] studied the effect of intraventricular dexmedetomidine on CBF during normoxia and hypoxia in dogs anesthetized by 1.4% isoflurane. After dexmedetomidine administration CBF was reduced during hypoxemia by 52-55% of its baseline value ($P < 0.05$). However, there was no change during hypoxia. In other words, the absolute change in tone resulting from hypoxia was unaltered by dexmedetomidine, which suggests that dexmedetomidine does not alter the underlying mechanism of cerebrovascular response to hypoxemia. The authors speculated that the reduction in CBF by dexmedetomidine stemmed mainly from its inhibitory effect on the locus coeruleus.

Ogawa and colleagues [39] studied the effect of low-dose dexmedetomidine (loading 3μ kg^{-1} over 1 h for 10 min, maintenance 0.2 μ kg^{-1} over 1 h for 60 min) and high-dose dexmedetomidine (loading 6μ kg^{-1} over 1 h for 10 min, maintenance 0.4 μ kg^{-1} over 1 h for 60 min) on dynamic cerebral autoregulation by using the transfer function analyzer and the thigh cuff method in 14 healthy male volunteers. The authors demonstrated that dexmedetomidine weakens dynamic cerebral autoregulation and delays restoration in CBF velocity during temporary decreases in arterial pressure. Dexmedetomidine was also shown to decrease cerebrovascular CO2 reactivity more than propofol sedation in patients with septic shock. This finding is important, as maintaining CBF is crucial to avoiding encephalopathy in septic shock patients [40]. Hiroki and colleagues [41] evaluated pial vessel diameters, cerebral oxygen extraction, and systemic hemodynamics in dogs anesthetized with pentobarbital and mechanically ventilated before and after cardiac arrest (5 min) and resuscitation in the presence or absence of dexmedetomidine. Use of dexmedetomidine during CPR did not alter the changes in cerebral arteriolar diameters and cerebral oxygen extraction that occurred after cardiac arrest at resuscitation. The major finding in this study was that dexmedetomidine did reduce the dose of phenylephedrine used to maintain BP during CPR, and it also reduced the number of ventricular ectopic beats observed after CPR. The authors suggested that dexmedetomidine-induced stabilization of systemic circulation and maintenance of optimal cerebral perfusion pressure after CPR might improve CPR outcomes. A recently published report by Chi and colleagues [42] has shown that the use of dexmedetomidine caused a proportionate decrease in regional cerebral blood flow (rCBF) and O2 consumption in normovolemia. In addition, dexmedetomidine prevented rCBF and O2 consumption from decreasing after hemorrhage. Thus the use of dexmedetomidine may provide optimal O2 supply and consumption balance during hemorrhage.

Drummond and colleagues [43] investigated the relationship between middle cerebral artery velocity and cerebral metabolic rate equivalent (CMRe) in 6 volunteers under dexmedetomidine sedation. Dexmedetomidine was found to cause a dose-related reduction in both cerebral blood flow (CBF) and cerebral metabolic rate (CMR) in healthy subjects. However, the authors cautioned that the results of their study do not ensure that dexmedetomidine will not

have adverse effects on the CBF/CMR ratio in patients with neurologic diseases.

Disagreements among available studies, especially animal ones, can likely be attributed to the following factors:

1. Larger doses of dexmedetomidine were used in animals than in human trials.
2. Dexmedetomidine causes greater reduction in CBF in dogs anesthetized with isoflurane and halothane than in those anesthetized with pentobarbital [44].
3. There are species differences in α-2 receptor concentrations in cerebral arteries. Specifically, dogs have higher concentrations than humans have.

Randomized control studies are thus needed to guide the use of dexmedetomidine in patients with neurologic disorders in whom maintaining normal CBF is crucial [45].

THE USE OF DEXMEDETOMIDINE IN THE ICU

Dexmedetomidine represents a suitable sedative for the postoperative period and in ICU settings. The major goals of an ideal sedative for patients in the PACU and ICU are to provide anxiolysis and analgesia and to facilitate therapeutic and diagnostic procedures with minimal effects on cardiorespiratory systems [2]. Dexmedetomidine and other α-2 agonists induce sedation by initiating processes similar to those found during natural sleep [46]. Studies evaluating electroencephalogram (EEG) patterns revealed that dexmedetomidine-induced hypnosis resembles non-rapid eye movement sleep [1]. The maintenance of natural sleep is crucial to speedy recovery in the ICU and counteracts the effects of sleep deprivation in the postoperative period [47].

The unique sedative effect of dexmedetomidine makes it a good candidate for management of ICU sleep disturbance and its putative consequences on long-term cognitive functions in ICU patients [33]. Dexmedetomidine increases activity in the pulvinar nucleus of the thalamus. As this region mediates the ability of arousal stimuli to produce attention, a sedative state with good patient cooperation might result [48]. In the MENDS randomized controlled trial (Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction), Pandharipande and colleagues [49] randomized 103 adults in medical and surgical ICUs into either dexmedetomidine or lorazepam groups for periods greater than 4 h. This prospective randomized study showed no difference in overall mortality; however, the numbers of days free of coma or delirium were both markedly increased in the dexmedetomidine group. (On the other hand, a study by Ruokonen and colleagues [50] found no effect of dexmedetomidine sedation on length of ICU stay compared with propofol/midazolam.) However, in contrast to Ruokonen *et al*., recent studies have confirmed that patients treated with dexmedetomidine spent less time on the ventilator, experienced less delirium and agitation, and developed less tachycardia and hypertension [51-54]. Compared with morphine sedation after cardiac surgery, dexmedetomidine was found to reduce the duration but not the incidence of delirium; compared with morphine sedation, dexmedetomidine sedation was associated with effective analgesia and sedation, less hypotension, less vasopressor requirement, and more bradycardia [55]. Dexmedetomidine-based sedation for ICU patients was found to be less costly than a continuous infusion of midazolam. The reduction was attributed mainly to reduced mechanical ventilation and shorter stay in the ICU [56]. Dexmedetomidine sedation in the ICU could be beneficial for patients with sepsis, as dexmedetomidine has anti-inflammatory properties. Preemptive administration of dexmedetomidine in a murine model of cecal ligation and puncture-induced (CLP-induced) sepsis was accompanied by a reduction in the pro-inflammatory mediators IL-1B, IL-6 and TNF–α as well as a decrease in NF-RB binding activity [57]. Dexmedetomidine also has anti-inflammatory effects in spinal cord injury [58].In addition, it decreases lung permeability induced by intracranial hypertension [59].Dexmedetomidine confers renal protection by decreasing the secretion of vasopressin and antagonizing its action on renal tubules [60]. Dexmedetomidine inhibits the release of renin and enhances the release of atrial natriuretic peptide [61,62]. It might also confer renal protection against radio-contrast nephropathy (RCN) [63]. These renal protective effects can be considered a unique feature of dexmedetomidine sedation in the ICU. The anti-shivering effect of dexmedetomidine via its central sympatholytic action makes it suitable for sedating patients when induced therapeutic hypothermia is required to manage massive increases in ICP after traumatic brain injury or for comatose patients after cardiac arrest [64].Dexmedetomidine infusion has the same effect as propofol infusion on gastric emptying time in critically ill patients but with less gastric volume measured at the end of the infusion of both drugs [65].

THE USE OF DEXMEDETOMIDINE IN NEUROANESTHESIA

Dexmedetomidine has a MAC-sparing effect [66] which helps to reduce the anesthetic requirements during multimodal neurophysiologic monitoring. Dexmedetomidine was shown to have no effect on sensory evoked potentials [67]. We have previously shown that 0.6 ng/ml plasma concentration of dexmedetomidine had no clinically significant effect on SSEPs and MEPs during complex spine surgery [68]. Dexmedetomidine infusion at a dose up to 0.5 μg kg^{-1} over 1 h allowed successful sedation for craniotomy and electrocorticography (ECOG) [69]. It seems that dexmedetomidine at conventional doses does not adversely impact evoked potential recordings; however, higher doses or boluses could abolish the evoked potentials.

Dexmedetomidine provides sedation, analgesia and anxiolysis with minimal effect on respiratory function during awake craniotomy. It was used successfully as a primary anesthetic for brain mapping of the cortical speech area in children undergoing awake craniotomy [70]. In patients undergoing awake craniotomy, dexmedetomidine was shown to improve patient comfort and safety with minimal effects on respiratory function, while facilitating sophisticated neurologic testing [71-73]. Dexmedetomidine inhibits hypercapnic cerebral vasodilatation, a finding that could be very important in facilitating brain resection during awake craniotomy [74]. At the authors' institution anesthesia for awake craniotomy is commonly accomplished using propofol and dexmedetomidine infusions during the tumor exposure with minimal doses of benzodiazepines and opiates so as to allow better neurological assessment. During the neurological assessment period we usually stop the propofol infusion and keep the patient on 0.2 μ/kg/ hr dexmedetomidine infusion. If the patient is not awake enough we stop the dexmedetomidine infusion as well. Dexmedetomidine also significantly attenuated isoflurane and sevoflurane-induced dilatation of cerebral arterioles [75]. Therefore, it can be a very useful anesthetic adjunct in craniotomies performed under general inhalation anesthesia. The properties of dexmedetomidine make it well suited for sedation during deep brain stimulation (DBS), procedures for Parkinson disease and other chronic neurologic diseases such as dystonia, depression, chronic pain syndromes, and minimally conscious states [76,77]. At doses up to 0.3-0.6 μg kg^{-1} over 1 h dexmedetomidine did not interfere with microelectrode recordings (MER), and had little effect on a patient's motor symptoms. It maintained normal respiratory status and yet created an environment in which the patient felt comfortable and relaxed [69, 70].

THE USE OF DEXMEDETOMIDINE FOR GASTROINTESTINAL ENDOSCOPY

Upper endoscopy can be an unpleasant experience because of air insufflations and gastric irritation caused by the endoscope. The gastric walls are distended and this stimulates the vomiting center via sympathetic and vagal afferents [78]. Dexmedetomidine de-

creases the retching reflex by its sympatholytic and vagomimetic effects. In a prospective, randomized study, 50 adult patients were randomized to receive dexmedetomidine (bolus 1μg kg^{-1} over 10 min then 0.2 μg kg^{-1} over 1 h) or midazolam(0.07 mg kg^{-1} total 5 mg) as a sedative during upper endoscopy. Both groups also had minimal perceived procedural gagging, little discomfort, low anxiety scores, and high satisfaction levels (90.1±3.0 for dexmedetomidine versus 84.9±4.5 for midazolam;P>0.05). Retching and endoscopist satisfaction were significantly better in patients receiving dexmedetomidine versus those receiving midazolam (88.8± 6.5 versus 73.5±16.4, P< 0.05; and 20.6±4.4 versus 45.2±6.0; P<0.001). In the midazolam group, the number of patients who experienced adverse effects like apnea and low oxygen saturation was higher than in the dexmedetomidine group. It was therefore concluded that dexmedetomidine might be a good alternative to midazolam for upper endoscopy sedation [79]. Dexmedetomidine was observed to provide a relatively satisfactory level of analgesia and conscious sedation without clinically observed respiratory side effects in patients undergoing colonoscopy. However, fentanyl supplementation for analgesia was administered in 47% of individuals in the dexmedetomidine group [80].

OTHER USES FOR DEXMEDETOMIDINE IN CLINICAL ANESTHESIA

Dexmedetomidine has been used successfully for fiberoptic intubation. In a multicenter randomized, double-blind study, the safety and efficacy of dexmedetomidine for sedation versus placebo during elective awake fiberoptic intubation was evaluated Fewer patients in the dexmedetomidine group required midazolam to achieve a Ramsay Sedation Scale score of ≥ 2 for either nasal or oral awake fiberoptic intubation. The most common adverse events were hypotension (27.3%) with dexmedetomidine, and hypertension (28.3%) and tachycardia (24.0%) with placebo [81]. A recent, randomized double-blinded comparative study has demonstrated that the use of dexmedetomidine during flexible bronchoscopy can reduce the incidence of oxygen desaturation, airway secretion, and cough; and improve bronchoscopist satisfaction scores compared with remifentanil infusion. However, dexmedetomidine was associated with a greater requirement for topical anesthesia and a prolonged recovery time [82].

Dexmedetomidine is considered an ideal sedative agent during awake fiberoptic intubation and awake airway procedures for several reasons: It induces no respiratory depressant effect, it provides a dry field for the anesthesiologist, it is an antisialagogue, and it creates a comfortable environment during the procedure [83-87]. Dexmedetomidine decreased MAC of inhalation anesthetics in a dose-dependent manner [88-91]. Dexmedetomidine also reduced the propofol dose required for sedation and suppression of motor response. Therefore, the propofol dose required for sedation and induction and for maintenance of anesthesia may have to be reduced in the presence of dexmedetomidine [92]. Dexmedetomidine enhances the neuromuscular blocking action of rocuronium, an action attributed to decreased hepatic blood flow during dexmedetomidine administration, which reduces the availability of rocuronium to be metabolized by the liver. However, it is unlikely that these effects have clinical significance [93,94].

Spinal and epidural administration of dexmedetomidine exerts a powerful antinociceptive effect, mediated by stimulating alpha-2 receptors at the spinal level. However, it causes severe demyelinization of the myelin sheaths in the white matter when it is administered via the epidural route. This effect could be related to the vasoconstriction of the medullary spinal vessels [95-97].

Preliminary studies after spinal administration of the novel α- 2 agonist fadolmidine showed potent antinociceptive effects, with only minor cardiovascular and sedative side effects [98-99]. A single intraperitoneal dose of dexmedetomidine has a long-term antinociceptive effect in acute heat pain (tail-flick test) and on carrageenan-induced inflammatory thermal hyperalgesia (paw withdrawal test) [100]. Dexmedetomidine enhances the local anesthetic effects first by hyperpolarization of nerve fibers by stimulating α2-adrenoceptor receptors in peripheral nerves, and second due to its anti-inflammtory properties [101].

Addition of dexmedetomidine to the local anesthetic solution during intravenous regional analgesia improved the quality of analgesia and decreased the analgesic requirements, but did not affect the onset and regression times of sensory and motor blocks [102,103]. The use of low-dose intravenous dexmedetomidine (1mcg/kg) prior to spinal anesthesia, with 1.2 ml of bupivacaine (5mg/ml) in elderly patients, prolonged the duration of spinal anesthesia and improved postoperative analgesia. However, in patients given dexmedetomidine, more profound sedation with desturation, along with more frequent bradycardia and delayed recovery, were observed in comparison to the control group [104].

Similarly, dexmedetomidine decreases the dosage of opioids perioperatively. In 34 patients who had elective inpatient surgery, those in the dexmedetomidine group required less morphine in the PACU than patients in the control group, who received intraoperative morphine (PACU dexmedetomidine group, 4.5 +/- 6.8 mg; morphine group, 9.2 +/- 5.2 mg). [105].Dexmedetomidine administered intraoperatively during hypospadias surgery repair in pediatric patients under general anesthesia decreased intraoperative and postoperative analgesic requirements. However, dexmedetomidine lowered the heart rate and blood pressure.[106]. The opioid-sparing effect of dexmedetomidine may be very beneficial in certain patient populations, including those undergoing bariatric surgery, because these patients are sensitive to the respiratory depression induced by opioids [107]. A small study of 20 bariatric surgery patients demonstrated that the patients who received intraoperative dexmedetomidine required less morphine in the recovery unit than those patients who received intraoperative fentanyl(6.1±3.5 mg in dexnedetomidine group vs 14.6±5.9 mg morphine in fentanyl group; p<0.05) [108]. However, large studies are still needed to prove that dexmedetomidine has an opioid-sparing effect, with better preserved respiratory function, in bariatric patients or in patients with significant respiratory disease.

Dexmedetomidine has been used extensively in pediatric anesthesia, although this is an off-label indication (*vide infra*). The bioavailabilty of buccal or nasal administration of dexmedetomidine is 82% compared with intravenous administration [109]. A recent study showed that dexmedetomidine can be administered in children through an intranasal route and produces more sedation than oral midazolam but with similar and acceptable cooperation [110]. Dexmedetomidine has been considered the ideal sedative outside the operating room; for example, in MRI and repetitive radiation therapy [111-113]. A study on the use of dexmedetomidine as a sedative agent in children undergoing ablation of supraventricular accessory pathways showed that dexmedetomidine significantly depressed sinus and AV nodal function. However, the authors of the study did not recommend using dexmedetomidine to provide sedation for electrophysiology studies, as the drug caused undesirable and misleading measurements for cardiac conduction and might also interfere with the inducibility of some tachyarrhythmias [114]. Dexmedetomidine was used to provide sedation in children in the post-anesthesia care unit (PACU) to decrease the incidence of agitation following sevoflurane anesthesia [115]. Dexmedetomidine was used successfully in pediatric intensive care to enable early extubation after cardiac surgery. However, the study group had a higher rate of bradycardia and hypotension, most probably due to the alpha-2 agonist effects of dexmedetomidine [116]. For additional data on the use of dexmedetomidine in pediatric anesthesia and intensive care, other review articles are also helpful [117,118].

REGULATORY ISSUES

Clinicians may wish to take guidance from the following labeling statements for dexmedetomidine (Precedex) provided by the US Food and Drug Administration (FDA):

- Precedex is indicated for sedation in nonintubated patients prior to and during surgical and other procedures and in intubated and mechanically ventilated patients during treatment in an intensive care setting.
- Precedex should be administered by continuous infusion not to exceed 24 hours.
- Caution should be exercised when administering Precedex to patients with advanced heart block and/or severe ventricular dysfunction.
- Clinically significant episodes of bradycardia, sinus arrest and hypotension have been associated with Precedex infusion and may necessitate medical intervention.
- Caution should be exercised when administering Precedex to patients with advanced heart block and/or severe ventricular dysfunction. Because Precedex decreases sympathetic nervous system activity, hypotension and/or bradycardia may be expected to be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension and in elderly patients.
- The efficacy, safety, and pharmacokinetics of Precedex in pediatric patients less than 18 years of age have not been established. Therefore, Precedex should not be used in this population.
- The safety of Precedex during labor and delivery has not been studied.
- It is not known whether Precedex is excreted in human milk. Radio-labeled dexmedetomidine administered subcutaneously to lactating female rats was excreted in milk. Because many drugs are excreted in human milk, caution should be exercised when Precedex is administered to a nursing woman.
- Since Precedex clearance decreases with increasing severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function

CONCLUSION

Dexmedetomidine is a nearly ideal sedative agent for critically ill patients and as an adjunct in clinical anesthesia. However, the safety profile of its effects on CBF and CMRO2, especially in patients with neurologic diseases and sepsis, has not yet been determined. Randomized studies are needed to prove or disprove its safety in such patients.

CONFLICT OF INTEREST

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