Rev Bras Anestesiol
2012; 62: 1: 118-133

Dexmedetomidine: Current Role in Anesthesia and Intensive Care

Joana Afonso [1], Flávio Reis [2]

Summary: Afonso J, Reis F – Dexmedetomidine: Current Role in Anesthesia and Intensive Care.

Background and objectives: To update and review the application of dexmedetomidine in anesthesia and intensive care. This study is a comprehensive review of clinical uses, pharmacology, pharmacokinetics, mechanism of action and adverse effects of dexmedetomidine.

Content: The effective use of sedative-hypnotic agents and analgesics is an integral part of comfort and safety of patients. Dexmedetomidine is a potent and highly selective α-2 adrenoceptor agonist with sympatholytic, sedative, amnestic, and analgesic properties, which has been described as a useful and safe adjunct in many clinical applications. It provides a unique "conscious sedation", analgesia, without respiratory depression. The current reviewed uses include sedation at Intensive Care Unit – ICU (both adult and pediatric), emergency department, regional and general anesthesia, neurosurgery, sedation for pediatric procedures, awake fiber-optic intubation, cardiac surgery and bariatric surgery.

Conclusions: Dexmedetomidine offers a unique ability of providing both sedation and analgesia without respiratory depression. It is a new agent with a wide safety margin, excellent sedative capacity and moderate analgesic properties. Although its wide use is currently in patients of surgical and non-surgical intensive care units, dexmedetomidine seems to have promising future applications in neuroprotection, cardioprotection and renoprotection. More detailed studies are required to define its role as sedative in critical, neurosurgical and pediatric patients, as anesthesia adjunct and sedative during procedures.

Keywords: Dexmedetomidine; Anesthesia, Analgesia; Intensive Care.

©2012 Elsevier Editora Ltda. All rights reserved.

INTRODUCTION

Effective use of sedative-hypnotic and analgesic agents is an integral part of providing patient comfort and safety. Choosing the appropriate agent or combination is crucial in order to alleviate noxious stimuli, stress and anxiety, while minimizing the risk of adverse events.

Dexmedetomidine is a potent and highly selective α-2 adrenoceptor agonist with sympatholytic, sedative, amnestic, and analgesic properties [1,2], which has been described as a useful and safe adjunct in many clinical applications. It is the most recently developed and commercialized agent in this pharmacological class. It provides a unique "conscious sedation" (patients appear to be asleep, but are readily roused), analgesia, without respiratory depression. It decreases central nervous system (CNS) sympathetic outflow in a dose-dependent manner and has analgesic effects best described as opioid-sparing. There is increasing evidence of its organ protective effects against ischemic and hypoxic injury, including cardioprotection, neuroprotection and renoprotection [3].

This work aims to update and review the application of dexmedetomidine in anesthesia and intensive care. It is a comprehensive review of current clinical uses, pharmacology, pharmacokinetics, mechanism of action, and side effects of dexmedetomidine.

HISTORY

The first α-2 adrenoceptor agonist was synthesized in the early 1960s to be used as a nasal decongestant. Early application of the new substance, now known as clonidine, showed unexpected side effects, with sedation for 24 hours and symptoms of severe cardiovascular depression. Subsequent testing led to the introduction of clonidine as an antihypertensive drug in 1966. Over the years, clonidine gained acceptance as a powerful therapy not only for high blood pressure but also for the management of alcohol and drug withdrawal, for adjunctive medication in myocardial ischemia, and for pain and intrathecal anesthesia [4].

The use of α-2 adrenoceptor agonists as anesthetics is not new. Veterinarians employed xylazine and detomidine for a long time to induce analgesia and sedation in animals [5], and much of current knowledge was gained from this application. It has recently become evident that complete anesthesia is possible by employing new, more potent α-2 agonists, such as medetomidine and its stereoisomer, dexmedetomidine.

Received from Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Portugal.

1 DESA; Anesthesiology Consultant
2 PhD; Laboratory of Pharmacology & Experimental Therapeutics, IBILI, Medicine Faculty, Coimbra University, Portugal

Submitted on March 28, 2011.
Approved on May 19, 2011.

Correspondence to:
Dra. Joana Afonso
Hospital Pedro Hispano
Rua Dr. Eduardo Torres, 4464-513
Matosinhos, Portugal
E-mail: joanaafonsoo@gmail.com

Dexmedetomidine (Precedex®; Abbott Labs, Abbott Park IL) was approved in the United States, by the Food and Drug Administration (FDA), at the end of 1999, for use in humans as a short-term medication (< 24 hours) for sedation/analgesia in the intensive care unit (ICU) and, thereafter, in some other countries (Czech Republic, for example). Its unique properties render it suitable for sedation and analgesia during the whole perioperative period. Its applications as a premedication, as an anesthetic adjunct for general and regional anesthesia, and as a postoperative sedative and analgesic are similar to those of the benzodiazepines, but a closer look reveals that the α-2 adrenoceptor agonist has more beneficial side effects.

PHYSIOLOGY

α-2 Adrenoceptor agonists

α-2 adrenergic receptors (or adrenoceptors) are transmembrane receptors composed of excitable G-proteins, which cross the cell membrane and link selectively with extracellular ligands: endogenous mediators or exogenous molecules, such as drugs. The α-2 adrenergic receptor consists of three α-2 isoreceptors - α-2a, α-2b and α-2c - which bind α-2 agonists and antagonists with similar affinities and share an amino acid composition homology of approximately 70 to 75%. Sub-receptor specific agonists or antagonists that enhance advantageous effects while limiting deleterious effects may be forthcoming [6].

α-2 adrenoceptors have been implicated in a variety of physiological functions. The pharmacology of α-2 adrenoceptors is complex, but pharmacological studies, helped by the development of genetic mouse models, have elucidated the physiological effects mediated by the different α-2 adrenoceptor subtypes [7].

Specific α-2 receptor subtypes mediate the varied pharmacodynamic effects of dexmedetomidine. For example, agonism at the α-2a receptor appears to promote sedation, hypnosis, analgesia, sympatholysis, neuroprotection and inhibition of insulin secretion. Agonism at the α-2b receptor suppresses shivering centrally, promotes analgesia at spinal cord sites, and induces vasoconstriction in peripheral arteries. The α-2c receptor is associated with modulation of cognition sensory processing, mood and stimulant-induced locomotor activity, and regulation of epinephrine outflow from the adrenal medulla. Inhibition of norepinephrine release appears to be equally affected by all three α-2 receptor subtypes [3].

These receptors appear to possess presynaptic, postsynaptic and extrasynaptic sites of action. In fact, α-2 adrenergic receptors have been found in platelets and in a variety of organs, including the liver, pancreas, kidney and eye and in the central and peripheral nervous system, at autonomic ganglia and presynaptic and postsynaptic sites. The presynaptic sites of action are clinically significant because they modulate the release of norepinephrine and adenosine triphosphate through a negative feed-back mechanism.

The physiological responses regulated by α-2 receptors vary depending on their location. The stimulation of α-2 receptors in the brain and spinal cord inhibit neuronal firing, which leads to hypotension, bradycardia, sedation and analgesia. The responses from other organs containing α-2 receptors include decreased salivation, secretion, and gastric motility; inhibited renin release; increased glomerular filtration rate; increased secretion of sodium and water in the kidney; decreased intraocular pressure; and decreased insulin secretion from the pancreas. The stimulation of α-2 receptors decreases calcium entry into nerve terminals, which may contribute to its inhibitory effect on neurotransmitter release [8].

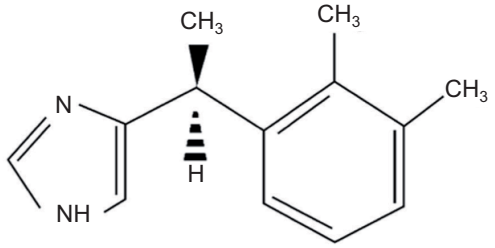
Mechanisms of action

The hypnotic effect of dexmedetomidine is mediated by the hyperpolarization of noradrenergic neurons in the locus ceruleus of the brain stem (a small bilateral nucleus that contains many adrenergic receptors), which is the primary site in modulating wakefulness. When the α-2 adrenergic receptor is activated, it inhibits adenylyl cyclase. This latter enzyme catalyzes the formation of cyclic AMP (cAMP), a crucial second messenger molecule that acts in many catabolic cell processes. By reducing the amount of cAMP in the cell, dexmedetomidine favors anabolic over catabolic pathways. Simultaneously, there is an efflux of potassium through calcium-activated potassium channels and an inhibition of calcium entry into calcium channels in nerve terminals [9]. The change in membrane ion conductance leads to a hyperpolarization of the membrane, which suppresses neuronal firing in the locus ceruleus as well as activity in the ascending noradrenergic pathway [10]. The locus ceruleus is also the site of origin for the descending medullospinal adrenergic pathway, which is known to be a key mechanism in regulating nociceptive neurotransmission. The similar mechanisms of α-2 receptors and opioid receptors in this area of the brain have contributed to the thought that there must also be extra-spinal sites of action. When these sites are stimulated, they decrease the firing of nociceptor neurons stimulated by peripheral A and C fibers and also inhibit the release of their neurotransmitters. The analgesic effects are believed to be in the dorsal horn of the spinal cord.

When a hypnotic dose of dexmedetomidine was administered to laboratory animals, norepinephrine release from the locus ceruleus was inhibited. The absence of inhibitory control over the ventrolateral preoptic nucleus (VLPO) resulted in the release of -aminobutyric acid (GABA) and galanin, which further inhibited the locus ceruleus and tuberomamillary nucleus (TMN). This inhibitory response also causes a decrease in the release of histamine, which results in a hypnotic response. This response is similar to that found in normal sleep in that the reduction of norepinephrine release by the locus ceruleus triggers the release of GABA and galanin by the VLPO. These neurotransmitters further inhibit norepinephrine release by the locus ceruleus and suppress histamine secretion by the TMN. The reduced occupancy of the histamine receptors on the cells of the subcortical areas induces a hypnotic state [11].

PHARMACOLOGY

Dexmedetomidine is chemically described as (+)-4-(*S*)-[1-(2,3-dimethylphenyl)ethyl]-1 *H*-imidazole monohydrochloride. It has a molecular weight of 236.7. It has a pH in the range of 4.5-7. It is water soluble, has a p*K*a of 7.1. Its partition coefficient in octanol: water at pH 7.4 is 2.89 (Figure 1) [12].



Dexmedetomidine is the pharmacologically active dextro enantiomer of medetomidine, the methylated derivative of etomidine. It is considered primarily as α-2 adrenoceptor agonist, but also incorporates an imidazoline structure, thus having an agonist effect on imidazoline receptors.

Dexmedetomidine is chemically related to clonidine, but is approximately eight times more specific for α-2 adrenoceptors with α-2: α-1 selectivity ratio of 1620:1, compared with 200:1 for clonidine, especially for the 2a subtype, which makes dexmedetomidine more effective than clonidine for sedation and analgesia [12]. Its effects are dose-dependently reversed by administration of a selective α-2 antagonist, such as atipamezole [3].

PHARMACOKINETICS

Dexmedetomidine follows linear or zero-order kinetics, meaning that a constant amount of the drug is eliminated per hour rather than a constant fraction of the drug eliminated per hour, which is characteristic of first order kinetics. After intravenous administration (IV) in healthy adult volunteers, dexmedetomidine has an onset of action after approximately 15 minutes. Peak concentrations are usually achieved within 1 hour after continuous IV perfusion. Dexmedetomidine is also absorbed systemically through the transdermal, oral, or intramuscular routes, with a mean bioavailability from the latter two routes of 82 and 104%, respectively [3]. Protein binding to serum albumin and α1-glycoprotein is reported to be approximately 94% and remains constant despite varied concentrations of the drug. The bound fraction is decreased significantly in patients with hepatic dysfunction, compared with healthy patients; therefore, a dose reduction in patients with hepatic dysfunction may be required.

It has a rapid distribution phase. Its steady state volume of distribution is 118 L and its distribution half-life (t ½ α) is 6 min in adults over the manufacturer-suggested dose ranges of 0.2-0.7 μg.kg^{-1}.h^{-1}, an elimination half-life (t ½ β) of between 2.0 and 2.5 hours [13] and a clearance of 39 L.h^{-1}.

Total plasma clearance of dexmedetomidine is age independent; thus, similar rates of infusion can be used in children and adults to effect a steady state plasma concentration [14]. However, in patients aged ≥ 65 years, a greater incidence of hypotension and bradycardia was reported; therefore, a dose reduction in this population may be warranted [12]. In children younger than 2 years of age, the volume of distribution at steady state is increased, suggesting that higher doses are required to achieve steady state; but t ½ β is prolonged, which may result in increased drug accumulation with time [14].

Dexmedetomidine is extensively metabolized in the liver through glucuronide conjugation and biotransformation by the cytochrome P450 enzyme system. There are no known active or toxic metabolites. However, hepatic clearance may be decreased by as much as 50% of normal with severe liver disease. No differences have been seen between healthy patients and those with renal impairment. The metabolites are eliminated to the extent of 95% in the urine and 4% in the feces. Considering that the majority of the metabolites are excreted in the urine, there is a theoretical risk that accumulation may result with prolonged administration [15].

PHARMACODYNAMICS

Hemodynamic effects

A brief biphasic, dose-dependent, cardiovascular response has been reported after the initial administration of dexmedetomidine. The bolus dose of 1 μg.kg^{-1} results in an initial increase in blood pressure and a reflex drop in heart rate. This response is seen more often with young and healthy patients. The stimulation of the α-2b receptors in vascular smooth muscle is postulated to be the cause of the increase in blood pressure. The rise in blood pressure can be attenuated by a slow infusion and by avoiding bolus administration of the drug [8].

This initial response lasts for 5 to 10 minutes and is followed by a slight decrease in blood pressure due to the inhibition of central sympathetic outflow. The presynaptic α-2 receptors are also stimulated, thereby decreasing norepinephrine release, causing a fall in blood pressure and heart rate. The dose-dependent bradycardiac effect of dexmedetomidine is primarily mediated by the decrease in sympathetic tone and partly by baroreceptor reflex and enhanced vagal activity [10,16].

Therefore, the cardiovascular effects of dexmedetomidine are predictable and can be derived from the α-2 adrenoceptor pharmacological effects. Slow bolus loading or omitting bolus loading [17] to prevent initial hypertension and reflex bradycardia as well as drug dosing, rate of drug infusion, adequate volume repletion and careful patient selection and monitoring renders dexmedetomidine a substance with predictable side-effects belonging to a pharmacological class with a wide safety margin [10].

Central nervous system effects

Like other α-2 adrenoceptor agonists, dexmedetomidine provides sedation, hypnosis, anxiolysis, amnesia and analgesia. The dose-dependent sedative/hypnotic effects of dexmedetomidine have been well documented in various experimental

and clinical trials. With increasing doses of dexmedetomidine, profound anesthetic actions have been described, leading to the suggestion that dexmedetomidine could be used as a total intravenous anesthetic [10,18,19].

Interestingly, some similarity with natural sleep was observed with dexmedetomidine-induced sedation. This is in accordance with other findings in rats, which proposed that dexmedetomidine converges on a natural sleep pathway, activating pathways that promote endogenous non-rapid eye movement sleep to exert its sedative effect [20]. It also preserves a cerebral blood flow pattern akin to natural sleep.

The amnestic effects of dexmedetomidine are far less than the benzodiazepines, which provide profound anterograde amnesia that may contribute to confused states on emergence. In contrast, amnesia is achieved with dexmedetomidine only at high plasma levels ($\geq$ 1.9 ng.mL^{-1}), without retrograde amnesia [19].

The analgesic properties of dexmedetomidine in humans are more controversial. It has been suggested that the spinal cord is probably the major site of analgesic action of α-2 adrenoceptor agonists. It appears to exert analgesic effects at the spinal cord level and at supraspinal sites. Dexmedetomidine may also provide antinociception through non-spinal mechanisms – intra-articular administration during knee surgery improves postoperative analgesia, with less sedation than the IV route [21]. Suggested mechanisms are activation of α-2a receptors [22], inhibition of the conduction of nerve signals through C and Aδ fibers, and the local release of encephalin.

Respiratory effects

Despite profound sedative properties, dexmedetomidine is associated with only limited respiratory effects, even when dosed to plasma levels up to 15 times of those normally achieved during therapy, leading to a wide safety margin [23]. Hypercapnic arousal is preserved, and the apnea threshold is actually decreased.

In contrast to infusions of opioids, benzodiazepines, or propofol, dexmedetomidine can safely be infused through tracheal extubation and beyond [3]. Despite the lack of respiratory depression, only later dexmedetomidine was originally approved by the FDA for use in "initially intubated, mechanically ventilated patients," that is, it had to be started on ventilated patients but could be continued through and beyond tracheal extubation. In October 2008, dexmedetomidine was approved by the FDA for procedural sedation in non-intubated patients [3].

Metabolic effects

Dexmedetomidine and other α-2 agonists suppress shivering, possibly by their activity at α-2b receptors in the hypothalamic thermoregulatory center of the brain. Low-dose dexmedetomidine has an additive effect with meperidine on lowering the shivering threshold, when they are combined. It may also be beneficial in decreasing patient discomfort from postoperative shivering and controlling shivering that may delay therapeutic hypothermia for acute stroke or CNS injury [24]. Easley et al. [25], in an open-label prospective pediatric study, found that a single intravenous bolus of dexmedetomidine, 0.5 μg. kg^{-1} over 3-5 min, was effective in the treatment of postanesthesia shivering [9,25].

Organ protective effects

Myocardial ischemia and cardioprotection

The perioperative period is characterized by increased sympathetic activity, leading to stress-induced tachycardia and hypertension. By attenuating sympathetically mediated hyperdynamic responses, α-2 adrenoceptor agonists ameliorate the hemodynamic profile during the perioperative period. Previous studies have shown that hemodynamic stabilization by the application of α-2 adrenoceptor agonists in the perioperative period leads to a reduction in perioperative myocardial ischemia episodes [26].

However, theoretical considerations against the use of α-2 adrenoceptor agonists have been the vasoconstrictive and hypotensive properties, which are potentially proischemic [10]. Laboratory investigations showed that large intravenous doses of dexmedetomidine caused moderate regional coronary vasoconstriction without metabolic signs of myocardial ischemia in young domestic pigs at the same time as a marked vasoconstrictive response in the systemic circulation [27]. At present, a reduction in myocardial ischemia and improved outcomes for patients at risk of cardiac events has only been documented for clonidine as a clinically available α-2 adrenoceptor agonist. The only available data for dexmedetomidine showed that perioperative infusion appeared to benefit the perioperative hemodynamic management of surgical patients undergoing vascular surgery [28]. Future studies will have to be focused on whether dexmedetomidine provides similar properties in reducing the incidence of myocardial ischemia and postoperative mortality compared with clonidine.

Neuroprotection

Dexmedetomidine possesses neuroprotective properties in various experimental models of cerebral ischemia, and attenuated hypoxic-ischemic brain injury in developing brains, highly susceptible to neuronal damage [29]. Moreover, a significant improvement in functional neurological outcomes after brain injury was demonstrated [29]. The exact mechanisms of neuroprotection are not clear, but catecholamine pathways play an important role. α-2 adrenoceptors modulate neurotransmitter release in the central and peripheral sympathetic nervous system, thus offering a possible explanation for the neuroprotective properties of dexmedetomidine.

Renoprotection

The effects of dexmedetomidine on renal function are complex. α-2 agonists exert a diuretic effect by inhibiting the antidiuretic action of vasopressin (AVP) at the collecting duct,

most likely through α-2a receptors, resulting in decreased expression of aquaporin-2 receptors and decreased salt and water reabsorption [30]. They also enhance osmolal clearance through non-AVP-dependent pathways, possibly mediated by the α-2b receptor. There is experimental evidence that dexmedetomidine attenuates murine radiocontrast nephropathy by preserving cortical blood flow [31]. This mechanism is supported by the observation that dexmedetomidine decreases the renal cortical release of norepinephrine. There is also evidence that it attenuates murine ischemia-reperfusion injury. However, prospective human studies establishing a benefit are not yet available.

TOXICOLOGY AND SIDE-EFFECTS

The teratogenic effects of dexmedetomidine have not been adequately studied at this time, but the drug does cross the placenta and should be used during pregnancy only if the benefits justify the risk to the fetus. No studies have been performed in children [4]. As expected from the pharmacological profile, bradycardia and hypotension are the most common side-effects of dexmedetomidine [28]. However, with the use of high concentrations there is also a potential for both pulmonary and systemic hypertension and direct or reflex bradycardia [19,32].

The incidence of postoperative bradycardia has been reported to be as high as 40% in healthy patients. These temporary effects have been managed with atropine, ephedrine, and volume infusion. Caution should be taken in those clinical situations where the sympatholytic actions of α-2 receptor agonists prove detrimental, such as in patients with left ventricular dysfunction and when administered to patients who are volume depleted, vasoconstricted, or have severe heart block [8]. Recently, severe bradycardia leading to cardiac arrest has been reported with the use of dexmedetomidine [33,34]. A closer look at these reports reveals several contributing factors that may have interacted, finally resulting in asystole. However, even if dexmedetomidine can probably not be held accountable as the only causative mechanism of these cardiac arrests, such case reports are important. They emphasize potentially deleterious effects that have significant implications for the safe use of these drugs in the critically ill, when multiple factors with negative chronotropic influences convene in a clinical setting, and underline the importance of adequate patient selection for the safe use of dexmedetomidine.

In summary, the adverse effects of dexmedetomidine include initial hypertension, hypotension, nausea, bradycardia, atrial fibrillation, and hypoxia [19,35]. Overdose may cause first-degree or second-degree atrioventricular block. Most of the adverse events associated with dexmedetomidine use occur during or shortly after loading dose.

CLINICAL APPLICATIONS

Anesthesia

Dexmedetomidine has been used as an adjunct to general anesthesia. When administered as a premedication at a dose range of 0.33-0.67 $\mu g.kg^{-1}$, given 15 min before surgery, it appears to be efficacious, while minimizing the cardiovascular side effects of hypotension and bradycardia. Within this dosage range, it reduces thiopental requirements (by around 30%) for short procedures and reduces the requirements of volatile anesthetics (by around 25%). Several prospective, randomized, pediatric studies have successfully documented the use of dexmedetomidine in preventing emergence delirium after general anesthesia and two adult studies have shown its efficacy in controlling delirium in the intensive care unit [36,37].

Neurosurgery

Some neurosurgical procedures have evolved toward minimally invasive, functional procedures including endoscopies, small-size craniotomies, stereotactic interventions, and intraoperative imaging [38,39]. Many neurosurgical procedures also require intraoperative active patient participation, including assessment of responses following initial deep brain stimulation for treatment of Parkinson's disease, electrode implantation, surgical management of epilepsy, and surgery near Broca's and Wernicke's speech areas [40]. Usually the anesthetic plan includes a deep stage of anesthesia during the highly stimulating craniotomy, and then awakens the patient in order to allow for neurocognitive testing. If the traditional method of general anesthesia with endotracheal intubation is followed, the patient will need to be extubated in order to allow speech and communication assessments, which is problematic for the anesthesiologist. Extubation can cause patients to reproduce valsalva manouver, which can increase intracranial pressure. Dexmedetomidine is a valuable aid in this situation as it can provide sedation during this phase of the awake craniotomy [41]: patients stay easily arousable with dexmedetomidine infusions.

Cardiac surgery

Several studies have shown that dexmedetomidine is a useful adjunct to cardiac anesthesia [17,42]. An infusion of dexmedetomidine at 0.4 $\mu g.kg^{-1}$ per hour during the procedure that is reduced to 0.2 $mg.kg^{-1}$ per hour in the ICU appears to reduce the time to extubation and decrease the length of stay in the ICU [17]. A 2003 metanalysis of 23 trials comprising 3395 patients concluded that the use of α-2 adrenergic agonists reduced mortality and myocardial infarction following vascular surgery and that during cardiac surgery, a reduction in ischemia was observed that may also have effects on myocardial infarction and mortality [43]. Dexmedetomidine can be successfully used to manage patients with pulmonary hypertension undergoing mitral valve replacement. In these cases, dexmedetomidine decreased fentanyl requirements, attenuated the increase in systemic vascular resistance index and pulmonary vascular resistance index at the poststernotomy period, and decreased mean arterial pressure, mean pulmonary arterial pressure, and pulmonary capillary wedge pressure, in comparison with the values in the placebo group [44].

Bariatric surgery

The rising incidence of obesity is increasing the need for bariatric surgery. Laparoscopic Roux-en-Y gastric bypass surgery, an effective surgical treatment of massive obesity, is one of the fastest growing surgical procedures in the United States [45]. Respiratory associate morbidities in morbid obesity may profoundly impact the anesthetic management of these patients. The ideal anesthetic would produce minimal respiratory depression while offering adequate pain relief. Dexmedetomidine has been used in general anesthesia to decrease opioid use and thereby decrease the incidence of respiratory depression. In one surgical center, over 2,000 bariatric procedures have been performed using perioperative infusion of dexmedetomidine, which has been shown to be cardioprotective and neuroprotective, while providing a hemodynamically stable course and reducing the need for opioids and volatile agents [46]. When compared with fentanyl, dexmedetomidine appeared to provide better postoperative analgesia and attenuated blood pressure changes [47]. In one case reporting the use of dexmedetomidine in a patient weighing 433 kg with obstructive sleep apnea and severe pulmonary hypertension, the authors chose to avoid opioids until required in the postoperative period [48]. The dexmedetomidine infusion was started preoperatively and continued through the first postoperative day. A significant reduction in the morphine dose requirements was observed on the first postoperative day when compared with the second postoperative day [48]. Dexmedetomidine can significantly attenuate postoperative pain and reduce opioid requirements, while not appearing to cause respiratory depression even in morbidly obese patients [48].

Awake fiber-optic intubation

Awake fiber-optic intubation in patients with a difficult airway is known to cause discomfort. This issue is problematic, as the anesthesiologist desires to maintain a patent airway with spontaneous ventilations to avoid the complications of respiratory depression and pulmonary aspiration. However, the patient must be sufficiently comfortable during the procedure. Many medications have been described to facilitate this process, including benzodiazepines, local anesthetic infusion, and opioid agonists. Dexmedetomidine provides an ideal solution to this problem in addition to creating a dry field for the anesthesiologist, as it is an antisialogouge [16]. In a recent investigation of seven patients who underwent intravenous sedation with dexmedetomidine and oropharyngeal topical anesthetic, no patient had saturation changes, all patients had successful fiber-optic intubation and no patients had any endtidal carbon dioxideevidence of respiratory depression [49].

Sedation/analgesia in the intensive care unit (ICU)

The importance of patient orientation and rousability is well established in ICU care [50]. Dexmedetomidine is well suited for use in the intensive care environment, allowing sedated patients to be quickly aroused and oriented upon demand [51]. Interestingly, this agent does not require discontinuation prior to weaning from mechanical ventilation [16]. Ongoing sedation can be maintained with the use of dexmedetomidine during and following extubation. As dexmedetomidine has the ability to potentiate opioids and other sedatives, this attribute suggests that these drugs can be administered in smaller doses [16,52]. To date, dexmedetomidine is approved by the FDA for sedation in initially intubated patients for a period of 24h [16]. This time limitation is probably due to lack of data concerning adverse events for its use for more than 24h.

In several studies dexmedetomidine has demonstrated advantages over propofol for sedation in mechanically ventilated postoperative adult patients. When both drugs were titrated to equal sedation, as assessed by the BIS index (approximately 50) and Ramsey sedation score (5), dexmedetomidine required significantly less alfentanil (2.5 *vs* 0.8 $mg.h^{-1}$). The time to extubation after discontinuation of the infusion was similar in both groups. Patients receiving dexmedetomidine appeared to have greater recall of their stay in the ICU, but all described it as pleasant overall [53,54]. Several other studies have confirmed the decreased requirement for opioids (over 50%) when dexmedetomidine is used for sedation *versus* propofol or benzodiazepines. Most studies also describe more stable hemodynamics during weaning from mechanical ventilation, when dexmedetomidine is used for sedation. This finding is of obvious benefit in patients at high risk of myocardial ischemia. One recent important double-blind study, the MENDS (Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction) study by Pandharipande et al. [37], compared the use of dexmedetomidine *vs* lorazepam in 106 adult mechanically ventilated medical and surgical ICU patients [37]. This study demonstrated that the use of dexmedetomidine infusion resulted in more days alive without delirium or coma and more time at the targeted level of sedation than with a lorazepam. It also demonstrated that dexmedetomidine-treated patients had a tendency towards lower incidence of postoperative mortality, 17 *versus* 27% ($p = 0.18$) and mortality at 1 year, 363 *versus* 188 days ($p = 0.48$).

In the pediatric population, one prospective and several retrospective studies have evaluated its usefulness in the intensive care unit [55]. Tobias et al. [56], in a prospective, randomized trial, found that dexmedetomidine at a dose of 0.5 $\mu g.kg^{-1}.h^{-1}$ provided more effective sedation than midazolam at 0.22 $mg.kg^{-1}.h^{-1}$ [56]. This was demonstrated by the need for fewer bolus doses of morphine, a decrease in the 24h requirements for supplemental morphine, as well as a decrease in the total number of assessment points with a Ramsey sedation score of 1 (inadequate sedation) and the number of patients who had a Ramsey score of 1. Chrysostomou et al. [57], in a retrospective study of 38 spontaneously breathing and mechanically ventilated children undergoing cardiothoracic surgery, found that dexmedetomidine provided adequate sedation 93% of the time and adequate analgesia 83% of the time. Side effects included hypotension (15%) and transient bradycardia in one patient [57]. Walker et al. [58] used dexmedetomidine in 65 burn patients who failed to be adequately sedated with opioi-

ds or benzodiazepines [58]. Dexmedetomidine was used as an adjunct and not as a replacement agent. The average duration of the infusion was 11 days (2-50), with an average dose of 0.5 $\mu g.kg^{-1}.h^{-1}$ (0.1-2 $\mu g.kg^{-1}.h^{-1}$). All patients were reported to be successfully sedated after dexmedetomidine was started.

OTHER CLINICAL USES

Pediatric procedural sedation

Several reports are now available of dexmedetomidine for both noninvasive and invasive procedural sedation in infants and children. It has been successfully used for diagnostic radiologic procedures, like MRI and CT scans, and for invasive procedures, like placement of central venous lines in infants, bronchoscopy and laryngoscopy, cardiac catheterization and others [59,60]. Dexmedetomidine has been also used to provide sedation in the postanesthesia care unit following sevoflurane anesthesia to decrease the incidence of agitation in the pediatric population, and to allow intubation in a sedated pediatric patient. Awake craniotomies have been performed on pediatric patients using dexmedetomidine [61].

An interesting future for dexmedetomidine is oral or nasal dexmedetomidine administration for pediatric sedation as oral absorption of dexmedetomidine is 82% when compared with intravenous administration [62]. Nasal dexmedetomidine administration has also been shown to be a well tolerated and effective route for sedation in adults [63], and has also been shown to be comparable with oral midazolam to decrease preoperative agitation [64].

Treatment of withdrawal

Prospective studies are lacking regarding the use of dexmedetomidine in treating withdrawal symptoms from either opioids or benzodiazepines. Nevertheless, a few retrospective case reports and series support its potential use [65,66], ameliorating the hemodynamic effects during withdrawal from illicit drugs and long-term sedation in the ICU. The two largest series are by Tobias [65] (7 patients) and Baddigam et al. [66] (3 patients). The infusion dose was in the range 0.25-0.7 $\mu g.kg^{-1}.h^{-1}$ and the duration of treatment was $\leq$ 3 days.

Perioperative and off-label use

Some innovative applications using the advantages of dexmedetomidine include administration as a total intravenous anesthetic (partly supplemented with local anesthesia) in patients with potential airway management problems [67]. Dexmedetomidine was administered until general anesthesia was achieved in doses up to 10 $mg.kg^{-1}$ per hour without hemodynamic compromise. No suppression of respiratory drive was observed, but one of three patients needed a chin lift and obstructive apnea might be a problem in predisposed deeply sedated patients. However, it is likely that the use of dexmedetomidine as a sole agent to induce an anesthetic state will be reserved for special clinical situations, and its use as an adjunct to anesthesia in the perioperative period will probably be more common.

Regional anesthesia, with dexmedetomidine used for moderate sedation and enhanced analgesic effect providing hemodynamic and respiratory stability, allowed ready interaction and arousal to facilitate the neurological evaluation of patients undergoing awake craniotomy [68] and awake carotid endarterectomy [69]. However, the effects of dexmedetomidine on cerebrovascular blood flow in this patient population need to be studied more thoroughly. In a recent preliminary, retrospective pediatric case series study, Chrysostomou et al. [70], found that dexmedetomidine was effective in controlling supraventricular and junctional tachyarrhythmias [70].

CONCLUSIONS

Dexmedetomidine is a potent, highly selective α-2 adrenoceptor agonist, with sedative, analgesic, anxiolytic, sympatholytic, and opioid-sparing properties. It provides a unique type of sedation, "conscious sedation", in which patients appear to be sleepy but are easily aroused, cooperative and communicative when stimulated. It has a quick onset and a relatively short duration of action, characteristics that render dexmedetomidine suitable for a critical care unit, for postoperative cardiac and noncardiac patients, and for invasive and noninvasive procedures, because it can be easily titrated. Short-term sedation has been shown to be safe in some studies, although hypotension and bradycardia are the most significant side effects. Furthermore, it appears to have minimal respiratory depression and, thus, it can be used safely in both mechanically ventilated and spontaneously breathing patients. These properties make dexmedetomidine a useful agent in the current era of early extubation and fast track of postoperative cardiac patients. Overall, dexmedetomidine has a unique constellation of properties that make it an attractive agent for both anesthesiologists and critical care physicians. It is an excellent sedative and analgesic agent, with opioid-sparing properties and minimal respiratory depression; does not decrease gut motility; prevents postoperative nausea, vomiting and shivering; and, at the same time, offers potential benefit towards neuroprotection, cardioprotection and renoprotection.

REFERÊNCIAS / REFERENCES

1. Carollo DS, Nossaman BD, Ramadhyani U – Dexmedetomidine: a review of clinical applications. Curr Opin Anaesthesiol 2008;21:457-461.
2. Venn RM, Bradshaw CJ, Spencer R et al. – Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. Anaesthesia 1999;54:1136-1142.
3. Panzer O, Moitra V, Sladen RN – Pharmacology of sedative-analgesic agents: dexmedetomidine, remifentanil, ketamine, volatile anesthetics, and the role of peripheral mu antagonists. Crit Care Clin 2009;25:451-469.
4. Gertler R, Brown HC, Mitchell DH et al. – Dexmedetomidine: a novel sedative-analgesic agent. Proc (Bayl Univ Med Cent) 2001;14:13-21.
5. Clarke KW, Hall LW – "Xylazine" – a new sedative for horses and cattle. Vet Rec 1969;85:512-517.
6. Coursin DB, Coursin DB, Maccioli GA – Dexmedetomidine. Curr Opin Crit Care 2001;7:221-226.
7. Paris A, Tonner PH – Dexmedetomidine in anaesthesia. Curr Opin Anaesthesiol 2005;18:412-418.
8. Haselman MA – Dexmedetomidine: a useful adjunct to consider in some high-risk situation. AANA J 2008;76:335-339.
9. Khan ZP, Ferguson CN, Jones RM – Alpha-2 and imidazoline receptor agonists: their pharmacology and therapeutic role. Anaesthesia 1999;54:146-165.
10. Kamibayashi T, Maze M – Clinical uses of alpha-2 adrenergic agonists. Anesthesiology 2000;93:1345-1349.
11. Nelson LE, You T, Maze M et al. – Evidence that the mechanism of hypnotic action in dexmedetomidine and muscimol-induced anesthesia converges on the endogenous sleep pathway. Anesthesiology 2001;95:A1368.
12. Chrysostomou C, Schmitt CG – Dexmedetomidine: sedation, analgesia and beyond. Expert Opin Drug Metab Toxicol 2008;4:619-627.
13. Dyck JB, Shafer SL – Dexmedetomidine: pharmacokinetics and pharmacodynamics. Anaesth Pharm Rev 1993;1:238-245.
14. Vilo S, Rautiainen P, Kaisti K et al. – Pharmacokinetics of intravenous dexmedetomidine in children under 11 yr of age. Br J Anaesth 2008;100:697-700.
15. De Wolf AM, Fragen RJ, Avram MJ et al. – The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment. Anesth Analg 2001;93:1205-1209.
16. Penttilä J, Helminen A, Anttila M et al. – Cardiovascular and parasympathetic effects of dexmedetomidine in healthy subjects. Can J Physiol Pharmacol 2004;82:359-362.
17. Ickeringill M, Shehabi Y, Adamson H et al. – Dexmedetomidine infusion without loading dose in surgical patients requiring mechanical ventilation: haemodynamic effects and efficacy. Anaesth Intensive Care 2004;32:741-745.
18. Scholz J, Tonner PH. – Alpha2-adrenoceptor agonists in anaesthesia: a new paradigm. Curr Opin Anaesthesiol 2000;13:437-442.
19. Ebert TJ, Hall JE, Barney JA et al. – The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000;93:382-394.
20. Nelson LE, Lu J, Guo T et al. – The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology 2003;98:428-436.
21. Al-Metwalli RR, Mowafi HA, Ismail SA et al. – Effect of intra-articular dexmedetomidine on postoperative analgesia after arthroscopic knee surgery. Br J Anaesth 2008;101:395-399.
22. Yoshitomi T, Kohjitani A, Maeda S et al. – Dexmedetomidine enhances the local anesthetic action of lidocaine via an alpha-2A adrenoceptor. Anesth Analg 2008;107:96-101.
23. Venn RM, Hell J, Grounds RM – Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. Crit Care 2000;4:302-308.
24. Elvan EG, Oç B, Uzun S et al. – Dexmedetomidine and postoperative shivering in patients undergoing elective abdominal hysterectomy. Eur J Anaesthesiol 2008;25:357-364.
25. Easley RB, Brady KM, Tobias JD – Dexmedetomidine for the treatment of postanesthesia shivering in children. Paediatr Anaesth 2007;17:341-346.
26. Wallace AW, Galindez D, Salahieh A et al. – Effect of clonidine on cardiovascular morbidity and mortality after noncardiac surgery. Anesthesiology 2004;101:284-293.
27. Jalonen J, Halkola L, Kuttila K et al. – Effects of dexmedetomidine on coronary hemodynamics and myocardial oxygen balance. J Cardiothorac Vasc Anesth 1995;9:519-524.

28. Talke P, Li J, Jain U et al. – Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. The Study of Perioperative Ischemia Research Group. Anesthesiology 1995;82:620-633.
29. Ma D, Hossain M, Rajakumaraswamy N et al. – Dexmedetomidine produces its neuroprotective effect via the alpha2A-adrenoceptor subtype. Eur J Pharmacol. 2004;502:87-97.
30. Rouch AJ, Kudo LH, Hébert C. – Dexmedetomidine inhibits osmotic water permeability in the rat cortical collecting duct. J Pharmacol Exp Ther 1997;281:62-69.
31. Billings FT 4th, Chen SW, Kim M et al. – Alpha 2-adrenergic agonists protect against radiocontrast-induced nephropathy in mice. Am J Physiol Renal Physiol 2008;295:F741-748.
32. Ebert T, Maze M. Dexmedetomidine: another arrow for the clinician's quiver. Anesthesiology 2004;101:568-570.
33. Ingersoll-Weng E, Manecke GR Jr, Thistlethwaite PA. – Dexmedetomidine and cardiac arrest. Anesthesiology. 2004;100:738-739.
34. Videira RL, Ferreira RM. – Dexmedetomidine and asystole. Anesthesiology 2004;101:1479.
35. Aho M, Erkola O, Kallio A et al. – Comparison of dexmedetomidine and midazolam sedation and antagonism of dexmedetomidine with atipamezole. J Clin Anesth 1993;5:194-203.
36. Kobayashi A, Okuda T, Kotani T et al. – Efficacy of dexmedetomidine for controlling delirium in intensive care unit patients. Masui. 2007;56:1155-1160.
37. Pandharipande PP, Pun BT, Herr DL et al. – Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298:2644-2653.
38. Sturaitis MK, Kroin JS, Swamidoss CP et al. – Effects of intraoperative dexmedetomidine infusion on hemodynamic stability during brain tumor resection. Anesthesiology 2002;97:A310.
39. Tanskanen PE, Kyttä JV, Randell TT et al. – Dexmedetomidine as an anaesthetic adjuvant in patients undergoing intracranial tumour surgery: a double-blind, randomized and placebo-controlled study. Br J Anaesth 2006;97:658-665.
40. Rozet I. – Anesthesia for functional neurosurgery: the role of dexmedetomidine. Curr Opin Anaesthesiol 2008;21:537-543.
41. Frost EA, Booij LH – Anesthesia in the patient for awake craniotomy. Curr Opin Anaesthesiol 2007;20:331-335.
42. Ruesch S, Levy JH – Treatment of persistent tachycardia with dexmedetomidine during off-pump cardiac surgery. Anesth Analg 2002;95:316-318.
43. Wijeysundera DN, Naik JS, Beattie WS – Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta-analysis. Am J Med 2003;114:742-752.
44. But AK, Ozgul U, Erdil F et al. – The effects of preoperative dexmedetomidine infusion on hemodynamics in patients with pulmonary hypertension undergoing mitral valve replacement surgery. Acta Anaesthesiol Scand 2006;50:1207-1212.
45. McCarty TM, Arnold DT, Lamont JP et al. – Optimizing outcomes in bariatric surgery: outpatient laparoscopic gastric bypass. Ann Surg 2005;242:494-498.
46. Ramsay MA, Saha D, Hebeler RF – Tracheal resection in the morbidly obese patient: the role of dexmedetomidine. J Clin Anesth 2006;18:452-454.
47. Feld JM, Hoffman WE, Stechert MM et al. – Fentanyl or dexmedetomidine combined with desflurane for bariatric surgery. J Clin Anesth 2006;18:24-28.
48. Hofer RE, Sprung J, Sarr MG et al. – Anesthesia for a patient with morbid obesity using dexmedetomidine without narcotics. Can J Anaesth 2005;52:176-180.
49. Cooper L, Samson R, Gallagher C et al. – Dexmedetomidine provides excellent sedation for elective, awake fiberoptic intubation. Anesthesiology 2005;103:A1449.
50. Jacobi J, Fraser GL, Coursin DB et al. – Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002;30:119-141.
51. Mantz J, Singer M – Importance of patient orientation and rousability as components of intensive care unit sedation, em: Maze M, Morrison P – Redefining sedation. London, UK, The Royal Society of Medicine Press Ltd, 1998;23-29.
52. Szumita PM, Baroletti SA, Anger KE et al. – Sedation and analgesia in the intensive care unit: evaluating the role of dexmedetomidine. Am J Health Syst Pharm 2007;64:37-44.
53. Venn RM, Grounds RM – Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. Br J Anaesth. 2001;87:684-690.
54. Triltsch AE, Welte M, von Homeyer P et al. – Bispectral index-guided sedation with dexmedetomidine in intensive care: a prospective, randomized, double blind, placebo-controlled phase II study. Crit Care Med 2002;30:1007-1014.
55. Tobias JD – Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. Pediatr Crit Care Med 2007;8:115-131.
56. Tobias JD, Berkenbosch JW – Sedation during mechanical ventilation in infants and children: dexmedetomidine versus midazolam. South Med J 2004;97:451-455.
57. Chrysostomou C, Di Filippo S, Manrique AM et al. – Use of dexmedetomidine in children after cardiac and thoracic surgery. Pediatr Crit Care Med 2006;7:126-131.
58. Walker J, Maccallum M, Fischer C et al. – Sedation using dexmedetomidine in pediatric burn patients. J Burn Care Res 2006;27:206-210.
59. Shukry M, Kennedy K – Dexmedetomidine as a total intravenous anesthetic in infants. Paediatr Anaesth 2007;17:581-583.
60. Munro HM, Tirotta CF, Felix DE et al. – Initial experience with dexmedetomidine for diagnostic and interventional cardiac catheterization in children. Paediatr Anaesth 2007;17:109-112.
61. Ard J, Doyle W, Bekker A – Awake craniotomy with dexmedetomidine in pediatric patients. J Neurosurg Anesthesiol 2003;15:263-266.
62. Anttila M, Penttilä J, Helminen A et al. – Bioavailability of dexmedetomidine after extravascular doses in healthy subjects. Br J Clin Pharmacol 2003;56:691-693.
63. Yuen VM, Irwin MG, Hui TW et al. – A double-blind crossover assessment of the sedative and analgesic effects of intranasal dexmedetomidine. Anesth Analg 2007;105:374-380.
64. Talon M, Woodson L, Sherwood E et al. – Nasal dexmedetomidine is comparable to midazolam as a perioperative sedation for children. Anesthesiology 2007;107:A1398.
65. Tobias JD – Dexmedetomidine to treat opioid withdrawal in infants following prolonged sedation in the pediatric ICU. J Opioid Manag 2006;2:201-205.
66. Baddigam K, Russo P, Russo J et al. – Dexmedetomidine in the treatment of withdrawal syndromes in cardiothoracic surgery patients. J Intensive Care Med 2005;20:118-123.
67. Ramsay MA, Luterman DL – Dexmedetomidine as a total intravenous anesthetic agent. Anesthesiology 2004;101:787-790.
68. Mack PF, Perrine K, Kobylarz E et al. – Dexmedetomidine and neurocognitive testing in awake craniotomy. J Neurosurg Anesthesiol 2004;16:20-25.
69. Bekker AY, Basile J, Gold M et al. – Dexmedetomidine for awake carotid endarterectomy: efficacy, hemodynamic profile, and side effects. J Neurosurg Anesthesiol 2004;16:126-135.
70. Chrysostomou C, Shiderly D, Berry D et al. – Dexmedetomidine, a novel agent for the acute treatment of supraventricular tachyarrhythmias after pediatric cardiac surgery. Crit Care Med 2007;8:A2.