The maintenance of natural sleep during sedation might speed recovery time in the ICU (Maze and Bonnet, 2008). Dexmedetomidine is considered a near ideal agent for sedation in the ICU. It has no respiratory depressant effect; it also induces sedation by initiating a process similar to that found during natural sleep (Nelson et al., 2003). The use of dexmedetomidine in clinical anesthesia and intensive care, while discussing the controversial issue of its harmful effect on cerebral blood flow.

**Neuroprotective Effects of Dexmedetomidine**

Dexmedetomidine exerts its neuroprotective effects via several mechanisms which make the usage of this drug a promising tool during cerebral ischemia. Dexmedetomidine decreases the peripheral catecholamine levels thus balancing the ratio between cerebral oxygen supplies, reducing excitotoxicity, and improving the perfusion in the ischemic penumbra (Engelhard et al., 2002). Dexmedetomidine stimulates astrocytic α-2 adrenergic receptors, raising astrocytic calcium concentrations, which in turn stimulate the glutaminase enzyme activity and the ability of astrocytes to dispose the glutamine by oxidative metabolism (Huang et al., 2000). The peculiar feature for dexmedetomidine neuroprotection is its ability to inhibit the pro-apoptotic mitochondrial signaling via α-2 adrenergic receptor stimulation (Wheeler et al., 2001). Dexmedetomidine increases the concentration of BCL-2 in the mitochondrial membrane during the time of ischemia thereby decreases the mitochondrial membrane permeability. The decreased mitochondrial membrane permeability during ischemia is crucial to avoid the release of proapoptotic protease activity such as cytochrome C or the apoptosis-inducing factor from the mitochondria into the cytosol (Engelhard et al., 2003; Wheeler et al., 2003). Dexmedetomidine also inhibits isoflurane induced caspase-3 expression in hippocampal slice cultures suggesting that dexmedetomidine may be an important adjunct to prevent isoflurane-induced neurotoxicity in the growing brain (Sanders et al., 2009).

**The Use of Dexmedetomidine in Clinical Anesthesia and Intensive Care (ICU)**

Dexmedetomidine is mainly used as a sedative agent in ICU or as an adjunct agent during general anesthesia. Dexmedetomidine reduces minimal alveolar concentration (MAC) by 99% (Segal et al., 1988; Aho et al., 1992). The use of dexmedetomidine infusion as an anesthetic adjunct up to 0.6 ng/ml plasma concentration did not change the ability to record the evoked potentials during complex spine surgery by any clinically significant amount (Bala et al., 2008). During the awake craniotomy procedures, dexmedetomidine provides sedation, amnesia, and anxiolysis with minimal effect on respiratory function (Ard et al., 2003). Deep brain stimulation (DBS) is considered the final therapy for Parkinson disease and other chronic neurological disorders such as dystonia, depression, and chronic pain syndromes when medical therapies fail. The DBS procedure requires fixation of the patient’s head to the stereotactic apparatus for accurate electrode placement. This can lead to substantive patient discomfort. Dexmedetomidine properties make it well suited for sedation during DBS procedures. It has little effect on the patient’s motor symptoms, maintains respiratory status, and yet creates an environment in which the patient feels comfortable and relaxed during the procedure (Khaibul et al., 2008; Ronet et al., 2006). Dexmedetomidine is considered a near ideal agent for sedation in the ICU. It has no respiratory depressant effect; it also induces sedation by initiating a process similar to that found during natural sleep (Nelson et al., 2003). The maintenance of natural sleep during sedation might speed recovery time in the ICU (Maze and Bonnet, 2004). In a recent study using dexmedetomidine as a sedative agent in the ICU, the patients who received dexmedetomidine had less delirium and less tachycardia and hypertension in comparison to those who received midazolam (Riker et al., 2009).

**The Effect of Dexmedetomidine on Cerebral Blood Flow**

Early studies in animals raised concern over the potential of α-2 agonists to reduce cerebral blood flow (CBF) out of proportion to their effect on CMRO2 (cerebral metabolic rate of oxygen).

For example, Karlsson et al. (1990) measured canine global CBF and CMRO2 during 1 MAC (minimal alveolar concentration) halothane anesthesia. At a dose of 10 µg/kg, dexmedetomidine caused a significant reduction in CBF without influencing CMRO2. Decreasing the halothane concentration to 0.1% caused no changes in CBF reduction, but instead increased the CMRO2 by 19%.

Asano et al. (1997) in their elegant study compared the effects of locally applied dexmedetomidine with systemically administered dexmedetomidine on pial arterioles with and without local application of the specific α2-antagonist atipamezole. Six groups of male rats were anesthetized with isoflurane. Local application of dexmedetomidine caused significant dose-dependent constriction, starting at 10-5 M for small and medium sized arterioles and 10-7 M for large arterioles. Intravenous dexmedetomidine at 1 µg/kg caused modest constriction which resolved after eight minutes. However, the dose of 10 µg/kg constricted the arterioles of all sizes. The constriction started to resolve after 10 minutes. The major finding in this study was the ability of atipamezole to completely abolish the vasoconstrictor effect of locally applied dexmedetomidine. However, it partially abolished the vasoconstrictor effect of systemically administered dexmedetomidine. The vasoconstrictor response to...
systemically administered dexmedetomidine might be due to its direct vasoconstrictive actions via α2-receptors.

McPherson et al. (1997) studied the effect of intraventricular dexmedetomidine on CBF during normoxia and hypoxic-hypoxia in dogs anesthetized by 1.4% isoflurane. Dexmedetomidine decreased normoxic flow in the cerebral hemispheres from 76 ± 6 to 44 ± 4 ml min⁻¹ 100 g⁻¹, with similar decreases in other regions. After dexmedetomidine, regional blood flow in all regions during hypoxia was halved by dexmedetomidine (P < 0.05). However, the percent increase in flow during hypoxia was similar before and after dexmedetomidine. In other words, the absolute change in flow resulting from hypoxia is unaltered by dexmedetomidine, suggesting that dexmedetomidine does not alter the underlying mechanism for cerebrovascular response to hypoxia.

CMRO₂ was maintained at control values during normoxia despite the reduction in CBF during hypoxia. However, the reduction in CMRO₂ during hypoxia in dexmedetomidine treated dogs was mainly due to the reduction of oxygen delivery rather than the observed reduction in CBF during hypoxia. The other interesting finding of the study was that when the cerebral cortex was approximately 1% of the concentration in the ipsilateral caudate nucleus as evidenced by H₃-clonidine distribution in the brain. This interesting finding led the authors to speculate that if the mechanism of blood flow reduction was mediated by direct vascular effect, it would have a greater effect on blood flow in the regions with the highest concentration of α₂ receptors. However, in this study the blood flow effect was similar among the different brain regions. The authors speculated that the reduction in CBF by dexmedetomidine was mainly due to its inhibitory effect on the locus coeruleus.

Iida et al. (1999) compared the constrictive effects of topically applied dexmedetomidine, clonidine, phenylephrine, and epinephrine in three different concentrations of spinal and cerebral pial vessels in pentobarbital-anesthetized dogs. In cerebral arterioles, greater constrictions were induced by dexmedetomidine and clonidine than those induced by phenylephrine and epinephrine. Ogawa et al. (2008) studied the effect of low dose of dexmedetomidine (loading 3 µg/kg per minute, maintained at 0.2 µg/kg per minute for 60 minutes) and a high dose dexmedetomidine (loading 6 µg/kg per minute for 10 minutes, maintenance at 0.4 µg·kg⁻¹·h⁻¹ for 60 minutes) on the dynamic cerebral auto regulation assessed by using the transfer function and analyzed using the thigh cuff method in 14 healthy male volunteers. The finding of this study was very interesting as the authors demonstrated that dexmedetomidine weakens dynamic cerebral auto regulation and delays restoration in CBF velocity during temporary decreases in arterial pressure. The authors cautioned that dexmedetomidine may lead to further sustained reductions in CBF when arterial pressure decreases temporarily with postural changes or release of the tourniquet. Dexmedetomidine was shown to decrease cerebrovascular CO₂ reactivity more than propranolol sedation in patients with septic shock. This finding is important as maintaining CBF is crucial to avoid septic encephalopathy (Kadi et al., 2008).

In an elegant study by Iida et al. (2006), the authors evaluated pial vessel diameters, cerebral oxygen extraction, and systemic hemodynamics in pentobarbital anesthetized, mechanically ventilated dogs before and after cardiac arrest (5 minutes) and resuscitation in the presence or absence of dexmedetomidine. The use of dexmedetomidine during CPR did not alter the changes in cerebral arterial 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 phenylephrine used to maintain blood pressure during CPR, and it also reduced the number of ventricular ectopic beats observed after CPR. The authors suggested that dexmedetomidine-induced stabilization of the systemic circulation and maintenance of optimal cerebral perfusion pressure after CPR may lead to a good outcome after CPR.

Drummond et al. (2008) investigated the relationship between middle cerebral artery velocity (CBFv) and cerebral metabolic rate equivalent (CMRe) in six volunteers under dexmedetomidine sedation. Dexmedetomidine was found to cause a dose-related reduction in both CBF and CMR in healthy subjects. Dexmedetomidine caused the CMR-CBF coupling with no decrease in CBFv/CMRe ratio. However, the authors cautioned that the results of their study do not give assurance that dexmedetomidine will not cause adverse effects on the CBF/CMR ratio in patients with neurologic injuries. Bekker et al. (2006) demonstrated the safety of using dexmedetomidine sedation during awake carotid endarterectomy with no increase in the incidence of intracranial shunting. The contradiction in the findings from different studies especially in animal studies can be attributed to the following factors:

1. Bigger doses of dexmedetomidine were used in animal studies compared to human studies.

2. Dexmedetomidine causes a greater reduction in CBF in isoflurane and halothane anesthetized dogs than in pentobarbital-anesthetized dogs (Fale et al., 1994) which could explain the contradicting results in dog model studies.

3. Species difference in α₂-receptors and their concentration in cerebral arteries. Dogs have higher concentration than humans (Toda, 1983).

Randomized control studies are still needed to prove the safety of using dexmedetomidine in patients with neurological disorders where maintaining normal CBF is crucial.

References


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