

Dexmedetomidine in sedation

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Introduction

Dexmedetomidine (Precedex®) is a selective alpha-2-receptor agonist that has been available for clinical use since 1999. Dexmedetomidine is currently registered in South Africa for post-operative sedation, after cardiac surgery, for 24 hours. The off label use of dexmedetomidine, for indications and duration of use other than registered, is widely published and accepted.

Pharmacokinetics

Dexmedetomidine contains an imidazole ring and is up to eight times more selective for the alpha-2 receptor than clonidine, with a alpha-1:alpha-2 ratio of 1:1620. Dexmedetomidine is 95% protein-bound, with a small volume of distribution. Complete biotransformation occurs in the liver via glucuronidase- and cytochrome P450-mediated metabolism. Metabolites with no known clinical effect are excreted mainly via the kidneys (95%), but reduced dosing is necessary only with a creatinine clearance less than 30 ml/min. Decreased doses (up to 50%) are necessary for those with hepatic impairment.

The distribution $t_{1/2}$ is 6 minutes, and the elimination $t_{1/2}$ is 120 minutes. Although the context-sensitive $t_{1/2}$ is currently unknown, accumulation does not seem to occur, even with infusions longer than 24 hours. Therapeutic plasma levels will be at 0,3 – 0,6 ng/ml. No pharmacokinetic differences have been described for the age range of 18 to 75 years.

Alpha receptors

Alpha-1 receptors are widely distributed, and are mainly involved with the regulation of vascular tone.

Alpha-2 receptors are pre- and postsynaptic receptors which are found within the central and peripheral nervous system.

Alpha-2A receptors are located in the locus coeruleus and are responsible for the sedation, anxiolysis and sympatholysis mediated by G-protein inhibition of L-type calcium channels in the post-synaptic receptors. Stimulation of pre-synaptic alpha-2A receptors here will also decrease the release of norepinephrine with sedation. The effects of dexmedetomidine are noncortical and subcortical, and do not cause impairment or disinhibition of cognitive function. This is in contrast with propofol and the barbiturates, which cause diffuse neuronal hyperpolarisation via opening of chloride channels. None of the effects of dexmedetomidine are mediated through GABA receptors.

Both **alpha-2B** and -2C receptors are mostly post-synaptic. These receptors are located mainly in the dorsal horn of the spinal cord, and activation will inhibit nociception. Stimulation of alpha-2B receptors post-synaptically will mediate vasoconstriction in the arterial and venous systems.

Characteristics of sedation with dexmedetomidine

The unique characteristics of sedation with dexmedetomidine include the following:

- Sedation is not mediated by GABA, resulting in decreased delirium;
- Sedation and anxiolysis are similar to that achieved with the benzodiazepines;
- No respiratory depression;
- Analgesic effect;
- Decreased shivering;
- Minimal and unpredictable amnesia;
- Tolerance and rebound phenomena are not seen;
- No withdrawal has been described, even with prolonged infusion;
- No weaning is necessary, and infusion can be terminated abruptly;
- No risk for physical dependence.

The most important aspect of sedation with dexmedetomidine is the quality of the cooperative sedation. Patients display a unique arousability. This means that the patient can be in a deep sleep when not stimulated, but communication and detailed neurophysiologic evaluation is possible when stimulated. When BIS monitoring is applied, the values return to awake baseline values when spoken to, even though patients are deemed to be moderately, even deeply, sedated. Sedation with dexmedetomidine is similar to natural sleep and does, in fact, promote REM sleep.

Respiratory effects

The main advantage of sedation with dexmedetomidine is the positive respiratory profile. The maintenance of spontaneous respiration and patency of the airway is unrivaled by the other available drugs for sedation. The ventilatory response to hypoxia and hypercarbia is maintained. No effect on the respiratory mechanics, airway resistance or pattern of breathing has been described. Some authors have reported a slight increase in respiratory rate; this can complicate the evaluation of adequacy of analgesia and anxiolysis.

Respiratory depression and apnoea can occur if a bolus is given too quickly, e.g. in less than 10 minutes.

Analgesia

The analgesic effect of dexmedetomidine is an important advantage during anaesthesia and sedation. The MAC-lowering effects of dexmedetomidine, between 50 and 90%, have been well-described. An opioid sparing effect of up to 66% has been noted. This is mainly in the post-operative period, with a reduction in opioids-related side-effects, especially respiratory depression and nausea. Intra-operative synergistic effects with opioids do exist, with the decrease in supplemental analgesia during procedures being clear.

Dexmedetomidine alone is definitely not sufficient for intra- or post-operative analgesia, and must be supplemented. Most studies have also shown a synergistic analgesic effect with neuraxial and peripheral nerve blocks. Administration of dexmedetomidine has been shown to decrease the discomfort associated with tourniquet ischaemia.

DEX will have limited effect on surgical/procedural pain, but excellent effect on post-operative analgesic requirements. Pain to the cold pressor test is reduced by only 30% when DEX is used as solitary agent

Haemodynamic effects

The biphasic haemodynamic effects of dexmedetomidine are dose dependent and occur mainly during administration of the bolus dose. The initial hypertensive response (in 12% of patients) is due to peripheral post-synaptic α -2-B stimulation with vasoconstriction, and can be observed during the initial 10 - 30 minutes. This is seen despite persistent lowering of the central norepinephrine concentration, and can be avoided by elimination or slow administration of the bolus dose.

Central pre-synaptic α -2-A stimulation, with decreased norepinephrine, will lead to hypotension (due to peripheral vasodilatation) and bradycardia. Haemodynamic parameters will decrease by 20 - 30% during the first 4 hours of infusion, and after this a further 5 - 10% reduction in the blood pressure and heart rate may occur. These effects may persist for 6 hours after cessation of infusion.

The bradycardia is a baroreceptor mediated response in the initial pressor phase, while the decreased sympathetic outflow in the latter phase will slow the heart rate.

The haemodynamic effects can be eliminated by simply not administering a bolus dose or by giving a smaller bolus dose over a longer period (30 minutes). The hypotension usually will respond to a fluid bolus.

Sympatholytic effects

The predictable sympatholysis caused by dexmedetomidine may be advantageous (with less hypertension and tachycardia), or less desirable (with hypotension and bradycardia).

The beneficial effect on myocardial oxygen balance has been shown to decrease peri-operative myocardial ischaemia and infarction in cardiac, as well as non-cardiac, surgery. Decreased mortality in these studies has also been shown.

Patients with hypovolaemia, septic shock and cardiogenic shock (with high adrenergic tone) will show exaggerated haemodynamic effects with. Asystole, episodic sinus arrest and heart block has being described. Dexmedetomidine should be used with caution in patients with heart blocks and existing bradycardia, and procedures during which vagal responses may occur e.g. ophthalmic procedures. The paediatric population will show a higher incidence and degree of bradycardia, but usually with less hypotension than the adult population. The bradycardia is usually responsive to anti-cholinergic treatment.

Amnesia

Amnesia with dexmedetomidine is not predictable, particularly at lower doses. Despite this, anterograde, and even retrograde, amnesia has being described in several studies. The standard dosage will cause impairment of memory in about 50% of patients. Many patients will describe recall during sedation with , but mostly with a level of comfort and calmness acceptable to them. If amnesia is a requirement during sedation, combination with a benzodiazepine may be indicated.

Nausea

Nausea has been described in up to 11% of patients receiving dexmedetomidine, and prophylaxis may be required. This effect is overshadowed by the reduction in opioids-related nausea and vomiting, due to lowered analgesic requirements.

Gastrointestinal effects

A reduction in vagus-mediated effects on the gastrointestinal system does occur, with concomitant decreased gastric acid secretion and decreased gastric and duodenal motility. Despite this, the administration of dexmedetomidine may result in a reduction in the incidence and severity of post-operative ileus, due to associated lower opioid use. Decreased lower oesophageal sphincter tone, similar to that seen with propofol administration, has been described.

Oversedation

Oversedation may occur, and is usually related to relative excessive doses of concomitant drugs used. This usually clears within one hour of cessation of the infusion. Elderly patients (> 65 years) are more susceptible to the sedative effects of dexmedetomidine.

Excitatory effects of concomitant anaesthetic agents

Dexmedetomidine administration led to a reduction in the excitatory phenomena observed during emergence from sevoflurane in paediatric anaesthesia (26 vs. 60%). Reduction in the sympathetically mediated effects of ketamine and desflurane were also demonstrated.

Other systemic effects

Other systemic effects described include the following:

- Intrinsic diuretic effect;
- Decreased intra-ocular pressure with mydriasis;
- Increased growth hormone;
- Decreased plasma insulin and prolactin;
- Antisialogogue;
- Inhibition of cortisol synthesis in animal studies.

Recommended dose of dexmedetomidine

The manufacturer of dexmedetomidine recommends a loading dose of up to 1 µg/kg over 20 minutes, followed by an infusion rate of 0,1 – 0,7 µg/kg/hour. The loading dose can be omitted when combined with other anaesthetic techniques.

When used for procedural sedation, an age-related bolus dose of between 0,2 and 1 µg/kg can be administered over 20 - 30 minutes. Loading doses up to 3 µg/kg have been described, but with more haemodynamic side-effects. Infusion rates up to 2 µg/kg/hour have been used. Effective sedation usually occurs at infusion rates of 0,2 – 0,4 µg/kg/hour, and it is uncertain if a rate greater than 0,7 µg/kg/hour is more efficacious. This may only increase the incidence of side-effects.

Dexmedetomidine is currently only registered for administration for 24 hours. Several studies were published with usage of up to 7 days, and case studies beyond 3 weeks, without any side-effects.

Although intravenous administration of dexmedetomidine is standard practice, intramuscular, subcutaneous, intranasal and epidural administration has been described. The intranasal route is effective (with 82% absorption) and well tolerated. The nasal route has recently been explored, with dexmedetomidine being used as a premedication in children at a dose of 1 - 2 µg/kg.

As with all new drugs, the direct cost seems to be high. It is difficult to quantify the cost of sedation with DEXMEDETOMIDINE, as many savings induced by its usage are indirect. Studies have shown increased pharmacy cost with those receiving DEXMEDETOMIDINE, but significant savings were noted on the total hospital cost for these patients. This was related to more ventilator free days and shorter ICU stay, earlier return to delirium free cognitive state and earlier discharge.

Monitoring of sedation

Monitoring of sedation in the patient receiving dexmedetomidine may be problematic. The Ramsey and other sedation scores may not be able to accurately quantify the unique sedation provided by dexmedetomidine.

Uses of dexmedetomidine

Sedation with dexmedetomidine in the ICU setting is very promising with increased patient satisfaction, maintenance of natural sleep cycle and better tolerance of general procedures, including turning

and suctioning. The decreased incidence and severity of delirium, as well as shorter ventilation and quicker discharge, are major advantages. Preliminary evidence suggests improved outcome in patients with sepsis. This is probably due to the anti-inflammatory properties of dexmedetomidine, supported by improved macrophage function and anti-apoptotic effects.

Withdrawal syndromes carry high morbidity and mortality. Sedation offered by, and the haemodynamic profile of, dexmedetomidine will facilitate the management of withdrawal from ethanol, benzodiazepines and opioids.

The benefits of using dexmedetomidine during functional neurosurgery are clear. Dexmedetomidine has little effect on electrophysiologic monitoring, and facilitates comprehensive cognitive and psychomotor evaluation during awake surgery. Improved haemodynamic control has been described in this setting. Maintenance of spontaneous respiration and airway patency is crucial during these procedures.

The use of dexmedetomidine during awake fibre-optic intubation is associated with improved patient satisfaction, better haemodynamic control and decreased usage of supplemental drugs. Airway patency and maintenance of spontaneous ventilation, complemented by decreased secretions, are essential during this procedure.

The benefits for morbidly obese patients, especially those presenting for bariatric surgery, are obvious. Suggestions that all patients undergoing major open pleural and peritoneal procedures should receive dexmedetomidine, as part of a multimodal analgesic approach, have been mentioned. Dexmedetomidine may eventually make the epidural obsolete in these cases.

Dexmedetomidine can be used for sedation during dental, cosmetic and gynaecologic procedures, cardiac catheterisation and radiologic interventions. Its use has been reported during almost all procedures. Reports from the closed claims studies indicate that adverse events are most commonly associated with respiratory depression and airway related problems. Hopefully, the use of dexmedetomidine will improve this situation.

Another concern during office-or outpatient-based procedural sedation might be slower onset and recovery, and longer discharge times, particularly when compared to propofol. Psychomotor performance was impaired for at least one hour after cessation of infusion, but all returned to baseline within 4 hours.

Conclusion

The unique characteristics of dexmedetomidine may eventually lead to it becoming the basis of all sedation techniques. With the current approach of analgo-sedation, dexmedetomidine may go a long way to fulfilling this ideal. Even if other drugs were to be added, the dose-sparing effect of dexmedetomidine will enhance the already superior safety profile of this drug. Dexmedetomidine has the ability to unlock the full potential of other sedative drugs, even at lower doses. With the potential for organ protection and improved outcomes, dexmedetomidine certainly is a drug to be considered.