Sedation outside the operation room
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Citation for published version (APA):
Eberl, S. (2017). Sedation outside the operation room
DEXMEDITOMIDINE.
A SUMMARY

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SUMMARY

Dexmedetomidine is a selective $\alpha_2$-agonist, which since June 2011 has been approved for ICU sedation of adult patients in the Netherlands. Dexmedetomidine provides sedation, analgesia, and anxiolysis. Patients are sedated, but remain arousable to verbal stimulation. Dexmedetomidine is with its half-life of 2 hours suitable for perioperative use and even procedural sedation. In contrast to other sedatives, dexmedetomidine shows less respiratory depression. It increases the activity of opiates, benzodiazepines and other sedatives, and could therefore impair side effects. Recent studies have shown that dexmedetomidine even has neuroprotective properties. Dexmedetomidine in children is used off-label but with good results.
INTRODUCTION

The interest in the role of $\alpha_2$-agonists in anaesthesia and intensive care has grown continuously over the past few years. $\alpha_2$-agonists show a wide range of effects including sedative, anaesthetic-sparing, analgesic, and sympatholytic properties.

In Europe clonidine is often used as pure $\alpha_2$-agonist. In America, Asia, the Middle East, Japan, and Australia dexmedetomidine has been used since 1999 as $\alpha_2$-agonist for sedation of adults in the ICU and during procedural sedations and intraoperative procedures. In June 2011, dexmedetomidine (as Dexdor) was also approved by the European Medicine Agency (EMA) for sedation of adult ICU patients where it is necessary that sedated patients respond purposefully to verbal commands.1-4

$\alpha_2$-agonists

The first $\alpha_2$-agonists were sold in the early sixties as spray for nasal congestion. However, this preparation was quickly taken off the market due to its adverse side effects (hypotension and prolonged sedation). In 1966, the same agent, now known as clonidine, had a revival as antihypertensive agent. Over the years, more and more new indications were added, e.g., treatment of alcohol and drugs withdrawal, adjuvant medication in myocardial ischaemia, pain treatment, and intrathecal applications. Dexmedetomidine had been extensively used in veterinary medicine for sedation and analgesia, before it was registered in 1999 for sedation in humans.

Pharmacodynamics

A long time, clonidine has been the only $\alpha_2$-agonist used in clinical practice. The application field of $\alpha_2$-agonists significantly expanded with the arrival of dexmedetomidine (Table 1). The elimination half-life ($T_{1/2}$) of only 2 hours in contrast to clonidine ($T_{1/2} = 8$ hours) contributes to this development. Dexmedetomidine has a $\alpha_1$: $\alpha_2$ selectivity of 1:1620 compared with 1:220 for clonidine. It is more selective for $\alpha_2$A-receptors and has less affinity with the imidazoline receptor.3 Bradycardia and hypotension remain - even with dexmedetomidine - the major side effects. After a bolus of 1 μg/kg dexmedetomidine, blood pressure will initially rise by activation of the peripheral $\alpha_2$B-receptors in the vascular wall. Heart rate will decline as a reflex. This is more pronounced in younger patients. This first response lasts 5-10 minutes, then blood pressure and heart rate will stabilise 10-20% below the baseline values. Hypotension and bradycardia seldom require intervention. In patients with a precarious haemodynamic balance, it is wise to avoid a bolus of dexmedetomidine and to treat the expected hypotension preventively. For patients with uncontrolled hypotension or advanced AV-block (grade 2 or 3), dexmedetomidine is contraindicated. Compared with clonidine, the rebound hypertension after abrupt withdrawal of dexmedetomidine is not seen.
Table 1. Pharmacology of dexmedetomidine and clonidine

<table>
<thead>
<tr>
<th></th>
<th>Dexmedetomidine</th>
<th>Clonidine</th>
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<tbody>
<tr>
<td><strong>α₂:α₁</strong></td>
<td>1620:1</td>
<td>220:1</td>
</tr>
<tr>
<td><strong>α₂-A-receptor</strong></td>
<td></td>
<td>Imidazole-receptor</td>
</tr>
<tr>
<td><strong>T₁/₂</strong></td>
<td>2 h</td>
<td>8 h</td>
</tr>
<tr>
<td><strong>Intravenous, intramuscular</strong></td>
<td></td>
<td>Intravenous, intrathecal, oral</td>
</tr>
<tr>
<td><strong>No rebound effect</strong></td>
<td></td>
<td>Rebound effect</td>
</tr>
</tbody>
</table>

**Pharmacokinetics**

Dexmedetomidine has a distribution half-life of 6 minutes and an elimination half-life of approximately 2 hours. Even with prolonged treatment, no accumulation is seen. Dexmedetomidine is for 94% bound to plasma proteins and is almost completely degraded by the liver. The various metabolites have negligible pharmacological activity and are excreted by the kidneys for 95% and for 4% via faeces. Less than 1% is eliminated unmetabolised in the urine. It should be considered to reduce the starting dose for patients with hepatic impairment. Patients with renal impairment do not show altered pharmacokinetics compared to healthy subjects. No significant pharmacokinetic differences are observed based on age or gender.

**Receptors**

A₂-receptors are located pre-, extra-, and postsynaptic (Figure 1). They are found in the peripheral and central nervous system, on platelets and various organs such as the liver, pancreas, kidneys, and eyes. The presynaptic α₂-receptors appear clinically more relevant. They regulate the release of norepinephrine and ATP via a negative feedback mechanism. A₂-receptors are G-protein coupled: stimulation of the receptor leads to activation of various G-proteins. These proteins initiate an enzyme cascade that finally leads to the inhibition of the calcium-entry into the nerve endings with a reduced release of norepinephrine. Aside, G-proteins adapt via a second-messenger system ion channels, thereby inducing an efflux of potassium ions. This allows for a hyperpolarisation of the cell membrane. In summary, activation of α₂-receptors diminishes the release of noradrenaline and inhibits neuronal activity.5

**Mechanism of action**

The desired effects of α₂-agonists are sedation, anxiolysis, and analgesia. These effects are mediated via different receptors. There are also (unwanted) central and peripheral side effects. The receptors are divided into α₂-A-, α₂-B- and α₂-C-receptors triggering analgesic, vasoconstrictive, and anxiolytic effects mainly due to the location of the different receptors in the body.
Sedation

One of the highest concentrations of α₂A-receptors is found in the locus coeruleus (Figure 2). This core is located bilaterally in the upper part of the brain stem. Here lies a major centre for the natural sleeping patron. Inhibition of noradrenergic activity in the locus coeruleus creates an increase of the GABA and galanin in the brain. These inhibitory neurotransmitters provide a central decrease of histamine secretion. Less occupation of histamine receptors in subcortical areas leads to the state of hypnosis.\(^6\)

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**Figure 1.** α₂-receptor (picture by courtesy of Ron Slagter)

\(\alpha_2\)-receptors are located pre-, extra-, and postsynaptic. Presynaptic \(\alpha_2\)-receptors inhibits noradrenaline release, postsynaptic \(\alpha_2\)-receptors influence effects on target tissue.

**Figure 2.** Locus coeruleus (picture by courtesy of Ron Slagter)
**Analgesia**

$\alpha_2$-agonists have spinal and supraspinal analgesic effects. Spinal effects stimulate receptors in the dorsal horn, which results in inhibition of the firing of nociceptive neurons and reduces the secretion of the nociceptive neurotransmitter substance P. Supraspinal effects are located in the locus coeruleus. Here, the $\alpha_2$-noradrenergic and the opioid system have the same effector systems. But if only mild to moderate sedation is desired, dexmedetomidine will not provide adequate analgesia counteracting strong and acute pain stimuli. That means that another analgesic must to be added.

**Anxiolysis**

$\alpha_2$-agonists can achieve a comparable anxiolysis with benzodiazepines without respiratory depression.

**Central nervous system**

Dexmedetomidine has a minor effect on the intracranial pressure. It lowers cerebral blood flow during anaesthesia in combination with isoflurane in animal models without inducing global ischaemia. Recent studies could even show neuroprotective properties of dexmedetomidine. In neonatal rat models, dexmedetomidine reduces neurotoxicity induced by isoflurane. This effect is attributed to a mechanism that is not mediated via $\alpha_2$-receptors. The assumption is that dexmedetomidine increases the expression of growth factors such as epidermal growth factor (EGF) and brain-derived neurotropic factors (BDNF), which on their part cause the neuroprotective effect. At the moment, there are no evidenced based data that dexmedetomidine should be used in acute cerebrovascular threatening situations.
Systemic effects (Figure 3)

Figure 3. Physiology of target organs of dexmedetomidine (picture by courtesy of Ron Slagter)

Dexmedetomidine decreases tachycardic and increases bradycardic episodes in the heart, induces vasoconstriction and vasodilatation, and has an anti-shivering and diuretic effect.

Cardiovascular

The period of hypertension, directly after the bolus administration of an α2-agonist, is due to the activation of peripheral α2B-receptors and α1-receptors in the vascular wall. Subsequently, injection of a α2-agonist is followed by a longer lasting period of hypotension and bradycardia - due to the central inhibition of the sympathetic activity and at the same time an increase in parasympathetic activity. The exact mechanism behind these haemodynamic changes is not known yet. Probably, the imidazole ring – part of both molecules, dexmedetomidine and clonidine - is an important factor. Imidazoline receptors in the brain receive signals from baroreceptors in the carotid artery and the aorta. Their activation causes a centrally induced hypotension and anti-arrhythmic effect.

α2-agonists do not have direct myocardial effects. Due to the reduced sympathicotonus and activation of the parasympathetic nervous system, reduction of heart rate, metabolism, contractility, and systemic vascular resistance is induced and thus myocardial O2-requirements reduced. This explains the role of clonidine in the treatment of angina pectoris. Theoretically, activation of α2-receptors could induce coronary vasoconstriction, but due to
the simultaneous release of NO from the coronary endothelium after α₂-stimulation, this effect is not clinically relevant.

**Respiratory**
Dexmedetomidine shows no significant effect on hypercapnic or hypoxic respiratory drive and displays less respiratory depression than other sedatives. However, administration of opiates, hypnotics, and other sedatives can intensify the positive effects of dexmedetomidine but also induce negative side effects such as respiratory depression.

**Renal**
Dexmedetomidine inhibits the release of renin, increases glomerular filtration rate and excretion of sodium and water, and induces an increased diuresis. It seems that dexmedetomidine has the potential to reduce perioperatively ischaemia-reperfusion injury.

**Gastrointestinal**
α₂-agonists inhibit the secretion of water and increase the net absorption in the large intestine. Due to this characteristic, clonidine has even been used in the treatment of diarrhoea. Production of saliva is also reduced. This can clinically lead to a dry mouth.

**Platelets**
α₂-agonists can – comparable with adrenaline - stimulate the activation of platelets. For that purpose, a high dose of dexmedetomidine is needed. However, since the normal dosage of dexmedetomidine decreases the plasma concentration of adrenaline and activates nitric oxide release, finally a decrease of platelet aggregation is induced.

**Applications**

**ICU**
Sedation for ICU patients was the first approved application of dexmedetomidine. Especially for patients in whom a RASS score of 0 to -3 (mild to moderate sedation) is pursued, dexmedetomidine has an attractive sedation profile. It provides an adequate level of sedation, where patients remain arousable to verbal stimulation without respiratory depression. This enables an easier weaning process and a significantly shorter period of time to extubation compared with midazolam (3.7 vs. 5.6 days). This was demonstrated in the SEDCOM study. Patients were treated with a loading dose of 1 μg/kg dexmedetomidine within 10 min and a continuous maintenance infusion of 1.4 μg/kg/h (EMA approved dosage) of dexmedetomidine compared with a continuous infusion of midazolam for up
to two weeks. The researchers found no significant difference between both groups in the achieved RASS score (between +1 and -2), length of stay on the ICU, and 30-day mortality. In contrast, the incidence of delirium in the dexmedetomidine group was 54%, and compared with 77% in the midazolam treated patients significantly lower.

The number of tachycardic and hypertensive episodes decreased during treatment with dexmedetomidine, however with increased number of bradycardic events.

An open-label study of Maldonado et al. showed a significant decrease in the incidence of post-operative delirium in ICU patients after heart valve surgery. Patients sedated with propofol or midazolam showed in 50% a delirium compared with 3% in the dexmedetomidine group. This can be explained either due to the specific sedation profile of dexmedetomidine or its characteristic to enable the reduction of other drugs that can potentially trigger delirium. In the MENDS trial, 106 intubated and ventilated patients were sedated with dexmedetomidine or lorazepam. Patients in the dexmedetomidine group had significantly more days without delirium or coma than those in the lorazepam group. Coma was defined as a RASS of -4 or -5 (Table 2). In addition, the total percentage of the time with an adequate RASS was higher in the dexmedetomidine group. To treat pain, both groups could be given fentanyl. The incidence of fentanyl injections was significantly lower in the lorazepam group. The authors discuss as a possible explanation that patients sedated with dexmedetomidine can specify pain more appropriately. Important to know: both trials (SEDCOM and MENDS) were sponsored by industry.

Table 2. Richmond Agitation and Sedation Scale (RASS)

<table>
<thead>
<tr>
<th>Score</th>
<th>Rating</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>+4</td>
<td>Combative</td>
<td>Violent, immediate danger to self and staff</td>
</tr>
<tr>
<td>+3</td>
<td>Very agitated</td>
<td>Aggressive, removes devices, tubes, catheters</td>
</tr>
<tr>
<td>+2</td>
<td>Agitated</td>
<td>Ventilator dys-synchrony, frequent non-purposeful movement</td>
</tr>
<tr>
<td>+1</td>
<td>Restless</td>
<td>Anxious but no aggressive movements</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy</td>
<td>Sustained eye opening and eye contact to voice (&gt; 10 s) but not fully alert</td>
</tr>
<tr>
<td>-2</td>
<td>Light sedation</td>
<td>Brief eye opening and eye contact to voice (&lt; 10 s)</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate sedation</td>
<td>Movement or eye opening to voice but no eye contact</td>
</tr>
<tr>
<td>-4</td>
<td>Deep sedation</td>
<td>No response to voice, but movement or eye opening in response to physical stimulation</td>
</tr>
<tr>
<td>-5</td>
<td>Un-arousable</td>
<td>No response to voice or physical stimulation</td>
</tr>
</tbody>
</table>
Perioperative use

Dexmedetomidine has the potential to gain a place in the perioperative setting. Its sedative, analgesic, and anxiolytic effects make it a suitable agent for premedication. An anticipated difficult airway necessitates an awake fiberoptic intubation. To minimise stressful moments for the patient, sedation offers a most welcome support. However, it is important to keep the patient cooperative and spontaneously breathing. Dexmedetomidine can meet this requirement in contrast to other sedatives and additionally provide a reduction of salivation. During awake craniotomies an active participation of the patient in surgery is necessary and expected. Tanskanen et al.\textsuperscript{10} showed that awakening, extubation, and obtaining of adequate spontaneous breathing is reached more quickly with dexmedetomidine in comparison with fentanyl. Patients indeed were sedated but respond adequately. During the postoperative phase, dexmedetomidine can reduce the necessary amount of opioids. Especially with patients at risk for a compromised airway, dexmedetomidine may play an important role.

Procedural Sedation

The demand for sedation support during minimal invasive procedures is continuously growing. Most hospitals have specific protocols for sedation during colonoscopies, gastroscopies, and ERCP’s. Medication varies from midazolam to propofol, often combined with an opiate; sedation is often administered by specially trained anaesthesia nurses for procedural sedation (PSA). The on-going question is whether dexmedetomidine also could play a role in procedural sedation. Till now, a number of small studies had been performed studying endoscopist’s and patients satisfaction. For sedation during procedures that are unpleasant but not painful, dexmedetomidine certainly has a value. Patients are more cooperative, less retching, and afterwards just as satisfied as patients who received midazolam. Also, the endoscopist is more satisfied with patients of the dexmedetomidine group.\textsuperscript{11} Painful procedures such as colonoscopies often necessitate opiates as rescue medication and longer recovery times due to hypotension and bradycardia. In addition, for the acute colic pain during ERCP’s, dexmedetomidine has not sufficient analgesic effect. The same is shown in healthy volunteers: dexmedetomidine has no effect on experimental acute pain.\textsuperscript{12}

Future

For paediatric sedation, dexmedetomidine is still used off-label. Nevertheless, it seems to be a welcome addition to standard used sedatives. During MRI, children sedated with dexmedetomidine remained calmer compared to midazolam, and recovered faster in
There is not sufficient experience in the paediatric population to ensure safety and efficacy, but dexmedetomidine appears to have a similar pharmacological profile in children as in adults. Currently, only one dexmedetomidine solution for intravenous usage is available, but the future could be nasal or buccal administration. A further look into the future could be the introduction of an α₂-antagonist in daily practice. Atipamezole is a selective α₂-antagonist with a half-life of about 2 hours. It has been used in veterinary medicine already for a long time to antagonise the central effects of dexmedetomidine, but is still in phase 1 trials in humans.
REFERENCES

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