Review article

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USE OF DEXMEDETOMIDINE IN AN INTENSIVE CARE UNIT

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A critical disease requiring intensive treatment represents a very stressful event. The factors preceding the admission to an intensive care unit (ICU) are life-threatening conditions, trauma or a very complex surgery, which by themselves induce a strong physiological reaction. Sedatives and analgesics are among the drugs most frequently used in ICUs. Their use aims at increasing comfort, reducing stress response and facilitation of diagnostic and therapeutic procedures. It has been confirmed that pain, oversedation and delirium are significant causes of distress in patients in ICUs and are associated with increased morbidity and mortality. The term "ICU triad" describes the close association of pain, agitation and delirium, as well as the approach to their management. The 2013 and 2018 guidelines for analgesia and sedation in the critically ill recommended the use of midazolam only for short-term sedation, lorazepam for long-term sedation, and propofol for patients in whom intermittent waking up is planned. A new version of the guidelines has given precedence to non-benzodiazepine sedatives such as dexmedetomidine. Dexmedetomidine produces a unique sedation pattern, markedly different in comparison to all other sedative drugs. The patients sedated with this drug easily establish contact, respond to verbal stimulation, communicate and cooperate with ICU staff, and after the contact is established they achieve good results at attention tests.

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Introduction

A critical disease requiring intensive treatment represents a very stressful event. The factors preceding the admission to an intensive care unit (ICU) are life-threatening conditions, trauma or a very complex surgery, which by themselves induce a strong physiological reaction. Therapeutic interventions, especially mechanical, accompanied by environmental factors in intensive care units, act as a powerful cause of discomfort in critically ill patients. As part of the efforts to control their hemodynamic status, many of these patients receive inotrope and vasopressor support with adrenaline, noradrenaline and dopamine, which, being stress hormones, may increase the intensity of stress reaction.

Sedatives and analgesics are among the drugs most frequently used in ICUs. Their use aims at increasing comfort, reducing stress response and facilitation of diagnostic and therapeutic procedures (1).

It has been confirmed that pain, oversedation and delirium are significant causes of distress in patients in ICUs and are associated with increased morbidity and mortality. The term "ICU triad" describes the close association of pain, agitation and delirium, as well as the approach to their management (2). Consequently, sedatives should be administered only when specific pharmacological and nonpharmacological strategies aimed at pain and delirium management are employed.

Although there have been many randomized studies comparing different effects of sedatives, it could not be concluded that any of the agents is superior to any of the other agents. The choice of a sedative depends on the sedation indication in each individual patient. Essential is a thorough knowledge of pharmacodynamic and pharmacokinetic properties of sedative drugs, such as context-sensitive

half-time, metabolic pathways and presence of active metabolites and adverse effects. The choice should be guided by the patient's clinical condition, possible comorbidities and chronic therapy, as well as the presence of organic dysfunctions.

The 2013 and 2018 guidelines for analgesia and sedation in the critically ill recommended the use of midazolam only for short-term sedation, lorazepam for long-term sedation, and propofol for patients in whom intermittent waking up is planned (3).

The ABCDEF bundle (assess, prevent, and manage pain; both spontaneous awakening and breathing trials: choice of analgesia and sedation; delirium assess, prevent, and manage; early mobility and exercise; family engagement/empowerment) aims to promote practice where patients are more awake, cognitively engaged, and physically active (4).

A new version of the guidelines has given precedence to non-benzodiasepine sedatives such as dexmedetomidine.

Dexmedetomidine

While the agonists of γ-aminobutyric acid receptors are the most frequently used sedative agents in ICUs, the development of novel agents increased the number of alternative drugs. Dexmedetomidine is a selective α2-receptor agonist with sedative, analgesic and sympatholytic properties. It is a more potent, more selective and more specific α2-agonist than clonidine, with minor effects on α1-sreceptors. Dexmedetomidine induces a unique sedation pattern, considerably different from all other sedation agents. The patients sedated with this drug easily establish contact, respond to verbal stimuli, communicate and cooperate with ICU personnel, and after establishing contact, they accomplish well at attention tests (5). The recommended sedation depth ranges from 0 to -3 on the RASS scale (mild to moderate sedation) (Table 1). Experimental and clinical studies have indicated that dexmedetomine-induced sedation resembles natural non-REM sleep (6).

Table 1. Richmond agitation-sedation scale

Richmond agitation-sedation scale (RASS)		
+4	Combative	Violent, danger for staff
+3	Very agitated	Pulls or removes tubes and catheters; aggressive
+2	Agitated	Frequent unpurposed movements; intolerant for ventilator
+1	Restless	Anxious, but without aggressive or violent movements
0	Alert and calm	
-1	Drowsy	Not fully alert; having sustained awakening (eye opening/eye contact > 10 s)
-2	Light sedation	Being briefly awake (with eye contact to voice <10 s)
-3	Moderate sedation	Movement and eye opening to voice (without eye contact)
-4	Deep sedation	No response to voice, but movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

The usual dosage range is 0.2-0.7 mcg/kg/h, but the safety of higher doses (1.0-1.5 mcg/kg/h) has been demonstrated as well, with careful titration until the desired effect has been achieved. Sedation usually occurs after 15 minutes since the infusion is started, and the maximum effect should be expected within an hour.

Pharmacodynamic properties

Dexmedetomidine is a selective α2-receptor agonist with a broad range of pharmacological actions. It exerts a sympatholytic effect by reducing noradrenaline release in sympathetic nerve endings. Sedative action of dexmedetomidine is mediated by neuronal transmission inhibition in the locus coeruleus in the brain stem, as an important center for the maintenance and modulation of awakeness and attention. Dexmedetomidine has an analgesic effect and also provides the use of smaller amounts of anesthetics/analgesics. Its cardiovascular effects depend on the dosage, and at slower infusion rates the effects on the central nervous system tend to predominate, lowering heart rate frequency and reducing blood pressure. With higher doses, peripheral vasoconstrictive effects predominate, leading to increased systemic vascular resistance and blood pressure, additionally increasing the bradycardic effect. Dexmedetomidine is virtually without depressive effects on the respiratory system when used as a monotherapy in healthy examinees (7).

In postoperative patients in ICUs, who were earlier intubated and sedated with midazolam or propofol, dexmedetomidine significantly reduces the need for additional sedatives (midazolam or propofol) and opioids during sedation in the period up to 24 hours. Most patients receiving dexmedetomidine do not require additional sedative agents. The patients can be successfully extubated without interrupting dexmedetomidine infusion. The studies of individuals who have not been in ICUs confirmed that dexmedetomidine could be safely administered

in patients without endotracheal intubation, provided that they are under appropriate medical surveillance. Dexmedetomidine has shown results similar to midazolam within the targeted sedation extent in mostly nonsurgical patients requiring prolonged mild to moderate sedation (RASS from 0 to -3) in ICUs up to 14 days, with shortened duration of mechanical ventilation compared to midazolam and shortened time to extubation compared to midazolam and propofol. Compared to both propofol and midazolam, the patients are easier to wake up and they are more cooperative and better to communicate with, regardless of the presence of pain.

There have been studies which measured the severity of delirium using the CAM-ICU scale; delirium was reduced in patients receiving dexmedetomidine in comparison to those receiving midazolam, and delirium-associated side effects were more unlikely to occur with dexmedetomidine compared to propofol (8).

Pharmacokinetic properties

Pharmacokinetic properties of dexmedetomidine have been assessed during a short-term IV administration in healthy volunteers and during a long-term infusion in ICU patients. Dexmedetomidine distribution demonstrated a two-compartment model. In healthy volunteers, it demonstrates a rapid distribution phase with the central estimated distribution half-time ($t1/2\alpha$) of about 6 minutes. The mean estimated half-time final elimination value (t1/2) was 1.9 to 2.5 h (min 1.35; max 3.68 h), and the mean estimated value of the volume of distribution in the dynamic equilibrium (Vss) was approximately 1.16 to 2.16 l/kg (90 to 151 l). The clearance (Cl) had a mean value of 0.46 to 0.73 l/h/kg (35.7 to 51.1 l/h). The mean value of body mass related to these Vss and Cl estimates was 69 kg. The plasmatic pharmacokinetics of dexmedeto-midine is similar in ICU patients after an infusion > 24 h. Dexmedetomidine is bound to plasma proteins in 94%. Binding to plasma proteins is constant in the concentration range from 0.85 to 85 ng/ml. Dexmedetomidine binds to serum albumins and alpha-1-acid glycoprotein, with serum albumin being the principal binding protein for dexmedetomidine in the plasma (9).

Biotransformation and elimination

Dexmedetomidine is transformed by hepatic metabolism. There are three types of initial metabolic reactions: N-glucuronidation, N-methylation and cytochrome P450 catalyzed oxidation. Two most prevalent dexmedetomidine metabolites are two N-glucuronide isomers. By way of cytochrome P450 catalyzation two less prevalent metabolites are created. After IV administration of radiolabeled dexmedetomidine, 95% of radioactivity has been found in the urine after nine days, and 4% in the feces, supporting the notion that elimination occurs via the kidney (9).

There were no significant pharmacokinetic differences related to age and gender. Compared to the healthy, binding of dexmedetomidine to plasma proteins is reduced in individuals with hepatic function disorders, necessitating dosage adjustments in such patients. Dosage modification is required as well in patients with kidney failure, since the main route of dexmedetomidine elimination is by renal excretion.

Therapeutic indications

In ICUs, dexmedetomidine is used to sedate adult patients requiring the degree of sedation in which the patient can be woken up by verbal stimulation (RASS values 0 to -3). In those in whom an appropriate degree of sedation cannot be achieved by dexmedetomidine at the maximum dose, another sedation agent should be administered. There have been no clear data about the use of this drug in the periods longer than 14 days.

During dexmedetomidine administration, continuous hemodynamic monitoring is required in all patients. In non-intubated patients, respiratory monitoring is necessary since there is a risk of respiratory depression and, in some cases, apnea.

There have been studies suggesting that bradycardia occurred in relatively healthy non-ICU examinees who received dexmedetomidine. The symptoms receded after leg lifting and anticholinergic therapy such as atropine or glycopyrrolate. In isolated cases, in patients with pre-existing bradycardia, it developed up to the asystolica level. Hypertension was associated with the use of a loading dose, and that reaction could be mitigated by avoiding administering loading doses or by reduced infusion rates or the loading dose level (10).

In the data from clinical studies and data collected after the drug has been made commercially available, there have been several instances of dexmedetomidine overdosing. In these cases, the highest recorded dexmedetomidine infusion rate was up to 60 μg/kg/h for 36 minutes and 30 μg/kg/h for 15 minutes in a 20 months old child and in an adult. The most common reported side effects associated with overdosing in these cases involved bradycardia, hypotension, oversedation, drowsiness and cardiac arrest. In the cases of overdosing with clinical symptoms, dexmedetomidine infusion should be slowed down or stopped. With higher concentrations, hypertension can be more severe than hypotension (11). In clinical studies, bradycardia tended to resolve spontaneously and slowly or it responded to atropine and glycopyrrolate use. Reanimation was necessary in isolated cases of severe overdosing resulting in cardiac arrest.

Since dexmedetomidine must not be used in leading or bolus doses, a physician should be ready to use some other sedative against acute agitation, especially in the first several hours of treatment. Dexmedetomidine should not be used as an induction for intubation or for sedation with the use of muscle relaxants (12).

Dexmedetomidine does not have anticonvulsive effects as some other sedatives and it will not prevent epileptic activity. Caution should be exercised when combining dexmedetomidine with other drugs with sedative or cardiovascular effects, since synergistic action may occur. Dexmedetomidine re-

duces heart frequency and blood pressure by its sympatholytic action, but at higher concentrations, it causes peripheral vasoconstriction leading to hypertension (13). Normally, dexmedetomidine does not produce deep sedation and patients are easily woken up. Dexmedetomidine is therefore unsuitable for patients requiring deep sedation or those with a very unstable cardiovascular system (14).

The use of dexmedetomidine together with anesthetics, sedatives, hypnotics and opioids will probably boost up its action, including sedative, anesthetic and cardiorespiratory effects. Some studies have confirmed increased effects for isoflurane, propofol, alfentanil and midazolam (15). Due to possible pharmacodynamic interactions when anesthetics, sedatives, hypnotics and opioids are combined with dexmedetomidine, it is necessary to reduce their or the dose of dexmedetomidine.

Conclusion

In ICUs, critically ill patients are usually exposed to different therapeutic and diagnostic interventions and environmental stress. Sedatives and analgesics are among the most frequently used drugs aimed to improve the comfort and tolerability of various procedures in ICUs. It has been demonstrated that inadequately treated pain and agitation, and also oversedation, are associated with increased morbidity and mortality rates. Routine monitoring, using reliable scales, enables early detection of agitation and pain, avoiding thus oversedation and severe consequences of delirium. The latest guidelines have advised the use of non-benzodiazepine sedation with dexmedetomidine whenever possible with an aim to improve the outcome in mechanically ventilated critically ill patients. Dexmedetomidine produces a unique sedation pattern, markedly different in comparison to all other sedative drugs. The patients sedated with this drug easily establish contact, respond to verbal stimulation, communicate and cooperate with ICU staff, and after the contact is established they achieve good results at attention tests.

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UPOTREBA DEKSMEDETOMIDINA U JEDINICI INTENZIVNOG LEČENJA

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Kritična bolest koja zahteva intenzivan tretman predstavlja veoma stresan događaj. Faktori koji prethode prijemu u jedinicu intenzivne nege su životno urožavajuća stanja, trauma ili veoma složena operacija, koji sami po sebi izazivaju snažnu fiziološku reakciju. Sedativi i analgetici su među lekovima koji se najčešće koriste u intenzivnoj nezi. Njihova upotreba ima za cilj povećanje udobnosti, smanjenje odgovora na stres i olakšavanje dijagnostičkih i terapijskih procedura. Potvrđeno je da su bol, prekomerna sedacija i delirijum značajni uzročnici stresa kod bolesnika u intenzivnoj nezi i povezani sa povećanim morbiditetom i mortalitetom. Termin „trijada intenzivne nege" opisuje blisku povezanost bola, uznemirenosti i delirijuma, kao i pristup njihovom lečenju. U smernicama iz 2013. i 2018. godine za analgeziju i sedaciju kod kritično bolesnih preporučena je upotreba midazolama, samo za kratkotrajnu sedaciju, lorazepama, za dugotrajnu sedaciju, a propofola za bolesnike kod kojih je planirano povremeno buđenje. U novim verzijama smernica data je prednost sedativima koji nisu benzodiazepin, kao što je deksmedetomidin. Deksmedetomidin proizvodi jedinstveni obrazac sedacije, koji se značajno razlikuje u poređenju sa svim drugim sedativnim lekovima. Bolesnici sedirani ovim lekom lako uspostavljaju kontakt, reaguju na verbalnu stimulaciju, komuniciraju i sarađuju sa osobljem intenzivne nege, a nakon uspostavljanja kontakta, postižu dobre rezultate na testovima pažnje.

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Ključne reči: *deksmedetomidin, sedacija, jedinica intenzivne nege, delirijum*