



Course n°:

Alfa-2 agonistii. Farmacologie si implicatii clinice

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Definitii; generalitati

- ❑ α - agonistii = clasa de subst simpatomimetice cu actiune exclusiva asupra receptorilor α .
- ❑ receptorii α sunt de tip α 1 si α 2
- ❑ α - agonistii sunt la randul lor α -1 si α -2
- ❑ Exista in total 9 tipuri de receptori adrenergici
 - α -1a, α -1b si α -1d
 - beta-1, beta-2, beta-3
 - α -2a, α -2b, α -2c (si α -2d dupa unii autori)

Ruffolo Jr RR, Stadel JM, Hieble JP. α -Adrenoceptors: recent developments. Med Res Rev 1994;14:229–270

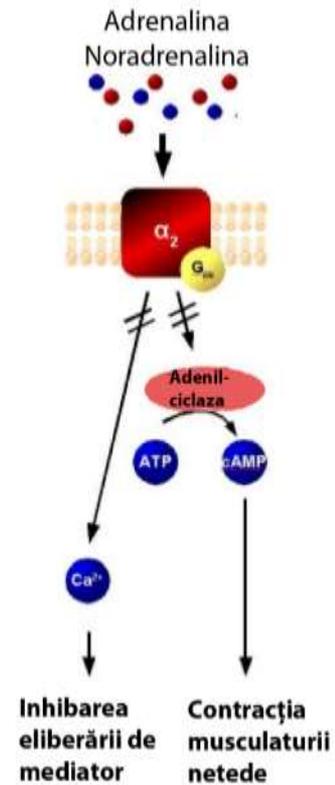
Scheinin M, Lomasney JW, Hayden-Hixson DM. Distribution of α_2 -adrenergic receptor subtype gene expression in rat brain. Mol Brain Res 1994;21:133–149

- Receptorii de importanta clinica includ:
- α_{2A} , care regleaza starea de veghe, awareness, trezirea si vigilentia la nivelul trunchiului cerebral,
- α_{2B} regleaza efectele vasoconstrictoare periferice
- $\alpha-1$ care regleaza starea de veghe, trezire, determina cresterea tonusului locomotor si vigilentia

- Efectele clinice depind de doza, distributia si densitatea receptorilor, afinitatea acestora pentru agonist.

Fiziologie; fiziopatologie

- ❑ α_2 este un receptor cuplat cu proteina G
- ❑ Activarea receptorului si cuplarea cu proteina G \rightarrow \downarrow c-AMP intracel (det contractia musc netede inervate din teritoriul aferent, si alte efecte)
- ❑ Mediatori la nivelul recept adrenergici α_2 : adrenalina si noradrenalina atat la nivelul SNC, cat si la nivelul SNP
- ❑ Receptorii α_{2A} , α_{2B} , and α_{2C} -adrenergici sunt localizati:
 - la nivelul sistemului nervos central si periferic,
 - presinaptic si postsinaptic,
 - extrasinaptic, in teritoriul vascular,
 - la nivelul altor organe: ficatul, pancreasul, rinichii, ochii, trombocitele.



Efectele comune ale stimulării α -2- recept:

- - suprimarea eliberării de NA prin feedback negativ
- - hTA după un răspuns inițial hipertensiv
- - vasoconstricția unor anumite teritorii arteriale
- - venoconstricție
- - vasoconstricția unor mușchi netezi vasculari
- - vasoconstricția coronarelor, care este însă moderată și poate fi anulată de efectele vasodilatatoare ale β_2 receptorilor
- - ↓ motilității musculare netede de la nivelul tractului gastrointestinal
- - inh lipolizei

Sun D, Huang A, Mital S, Kichuk MR, et al. Norepinephrine elicits beta2-receptor-mediated dilation of isolated human coronary arterioles. *Circulation* 2002;106 (5): 550–555.

Rang HP. *Pharmacology*. Edinburgh, Churchill Livingstone, 2003: 163.

Stoelting RK, Hillier SC. Antihypertensive drugs. In Stoelting RK, Hillier SC. *Pharmacology and physiology in anesthetic practice*. Lippincott Williams & Wilkins, Philadelphia 2206: 338- 369.

Efectele individuale ale stimulării α -2- recept din diverse teritorii :

- - medierea transmisiei pre- si postsinaptice, cu \downarrow elib de Ach si NA
- - inh elib de insulina la nivel pancreatic si a lipolizei la nivelul tes adipos
- - stim secretiei de glucagon
- - contractia sfincterelor gastrointestinale cu relaxarea tractului GI
- - \downarrow secretiei salivare
- - agregare plachetara
- - \downarrow productiei de umoare apoasa la nivelul globului ocular.

Sun D, Huang A, Mital S, Kichuk MR, et al. Norepinephrine elicits beta2-receptor-mediated dilation of isolated human coronary arterioles. *Circulation* 2002;106 (5): 550–555.

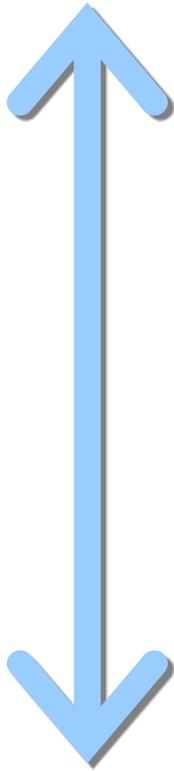
Rang HP. Pharmacology. Edinburgh, Churchill Livingstone, 2003: 163.

Stoelting RK, Hillier SC. Antihypertensive drugs. In Stoelting RK, Hillier SC. Pharmacology and physiology in anesthetic practice. Lippincott William & Wilkins, Philadelphia 2206: 338- 369.

Agonistii alfa-adrenoreceptorilor.

Afinitatea pentru receptori

Alfa-1



Alfa-2

- Norepinefrina (noradrenalina) (α , β 1)
- Epinefrina (adrenalina) (α , β 1+2)
- Dopamina (α , β 1+2)
- Tizanidina
- **Clonidina (α -2/ α -1 200/1, I1)**
- Guanfacina (predom α -2)
- Guanabenz
- Medetomidina
- **Dexmedetomidina (α -2/ α -1 600/1)**

- **Efecte cardiovasculare**
- α_2 – agonistii produc atat HTA cat si hTA. La doze mici efectul dominant este simpaticoliza mediata de α_2A - receptori.
- Mecanismele implicate in producerea acestui efect includ :
 - **\downarrow activit SNCS (alpha-2A) si a descarcarii de la nivelul locus coeruleus**
 - \downarrow elib NA la nivelul sinapselor neuroefectoare (α_2 -A si C)
 - stim elib presinaptice de NA din musc neteda vasc (α_2 -B)
 - stim endoteliului
 - stim receptorilor imidazolici centrali (I-2)
 - o oarecare activitate vagomimetica.

Efecte cardiovasculare

Rezultatele clinice ale adm α_2 – agonistilor includ:

- bradicardia si o incidenta mai mare a reactiilor vagale
- hTA sau chiar HTA, in functie de doza, contextul anesteziac, afectiuni asociate si administrarea altor substante.
-

De cele mai multe ori efectul clinic rezultat este hTA produsa prin mecanism central.

- **sedare, anxioliza si analgezie**
- **Sedarea** este minima, similara somnului natural, pacientul este usor trezibil.
- Mec sedarii includ hiperpolarizarea neuronilor de la nivelul locus coeruleus si implicarea $\alpha 2A$ - receptorilor.
- Obs! Nu este pe deplin cunoscut pana in prezent daca sedarea produsa de $\alpha 2$ – agonisti este insotita de amnezie, dar studii pe animale afirma acest lucru. La subiectii umani se pare ca amnezia este incompleta

Galeotti N, Bartolini A, Ghelardini C. Alpha-2 agonists induce amnesia through activation of the Gi-protein signalling pathway. *Neuroscience*. 2004;126(2):451-60.
Wajida G, Kelly JS. Sedation in intensive care settings. In Urman RD, Kaye AD. *Moderate and Deep Sedation in Clinical Practice* Cambridge University Press, Cambridge, 2012: 218-228.

- **Efectul analgetic** se manifesta atat de sine statator, cat mai ales prin reducerea necesarului de opioide cu pana la 40% in cazul clonidinei si al dexmedetomidinei.
- Un alt efect la nivelul SNC este **modularea memoriei spatiale** cu ajutorul α_{2A} -receptorilor ceea ce presupune ca α_2 – agonistii sunt prima clasa de sedative care cresc de fapt performanta cognitiva.
- sedarea cu α_2 – agonisti, in special cu dexmedetomidina, reduce semnificativ incidenta delirului si a disfunctiilor cognitive in TI.

Scahill L. Alpha-2 adrenergic agonists in children with inattention, hyperactivity and impulsiveness. *CNS Drugs*. 2009;23 Suppl 1:43-9.

Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, *et al*. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: The MENDS randomized controlled trial. *JAMA* 2007;298:2644-53.

Shehabi Y, Botha JA, Ernest D, Freebairn RC, Reade M, Roberts BL, *et al*. Clinical application, the use of dexmedetomidine in intensive care sedation. *Crit Care Shock* 2010;13:40-50.

Kaur M, Singh PM. Current role of dexmedetomidine in clinical anesthesia and intensive care. *Anesthesia Essays and Researches* 2011; 5(2):128-133

Efecte respiratorii

- depresie respiratorie minima
- Exista insa posibilitatea obstructiei caii aeriene
- Depresia respiratorie minima= unul dintre principalele avantaje ale folosirii α_2 – agonistilor pentru sedare in TI

- **Alte efecte:**
 - ↓ presiunii intraoculare
 - ↓ metab si a consumului de oxigen
 - ↑ duratei anestezicelor locale
 - protectie cardiaca/neurologica fata de ischemie si perioperatorie
 - preven rigiditatea indusa de opioide
 - ↓ motilitatii tubului digestiv
 - ↓ secretiilor digestive
 - ↓ reactiei la stress
 - amelioreaza raspunsul imun si ↓ incidenta infectiilor nosocomiale prin absenta depresiei imune induse la adm prelungita

- **Premedicatia**
- Clonidina si dexmedetomidina au in premedicatie urm efecte :
 - - ↓ consumului de oxygen
 - - sedare asociata tehnicilor regionale
 - - sedare si anxioliza preoperatorie
 - - ↓ necesarului de opioide si anestezice intraoperator
 - - cardio- si neuroprotectie perianestezica
- Administrarea se poate face i.m. in doze de 2- 4mcg/kg si respectiv 1- 2, 5 mcg/kg (pt Dex)

Taittonen MT, Kirvelä OA, Aantaa R, Kanto JH. Effect of clonidine and dexmedetomidine premedication on perioperative oxygen consumption and haemodynamic state. Br J Anaesth 1997;78(4):400-6.

Virkkilä M, Ali-Melkkilä T, Kanto J, Turunen J, Scheinin H. Dexmedetomidine as intramuscular premedication for day-case cataract surgery. A comparative study of dexmedetomidine, midazolam and placebo. Anaesthesia 1994;49(10):853-8.

Spellman A. Clonidine premedication and anesthetic effects. Available at: http://anesthesia.slu.edu/pdf/CLONIDINE_PREMEDICATION.pdf

- **Intraanestezic**

- Adm intraanestezica a alfa-2 agonistilor are urmatoarele efecte :
 - ↓ raspunsul simpatic la intubatie si detubare, dar si la alte stimuli
 - ↓ consumul intraoperator de opioide si anestezice inhalatorii
 - analgezie chirurgicala suficienta in interventiile chirurgicale minore, in asociere sau nu, cu anestezice inhalatorii (dex)
 - ↓ consumul de opioide in camera de trezire
- Clonidina se poate adm si pe cale peridurala sau rahidiana (unic agent, sau adjuvant la anestezicele locale sau opioide).
- Asocierea clonidinei ↑ durata blocului si ↓ cantit de anestezic local si/sau opioid adm si ↓ incidenta pruritului, a GV si retentia de urina consecutive adm opioidelor

Aho M, Lehtinen AM, Erkola O, Kallio A, Korttila K. The effect of intravenously administered dexmedetomidine on perioperative hemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. *Anesthesiology* 1991;74:997–1002.

Khan ZP, Munday IT, Jones RM, Thornton C, Mant TG, Amin D. Effects of dexmedetomidine on isoflurane requirements in healthy volunteers. 1: Pharmacodynamic and pharmacokinetic interactions. *Br J Anaesth* 1999;83:372–380.

Fragen RJ, Fitzgerald PC. Effect of dexmedetomidine on the minimum alveolar concentration (MAC) of sevoflurane in adults age 55 to 70 years. *J Clin Anesth* 1999;11:466–470.

Postoperator

- In perioada postoperatorie se manifesta atat efectele intraop, cat si cele postop:
- - ↓ incidentei frisonului
- - ↓ incidentei delirului postoperator
- - recuperarea mai rapida a functiilor psihocognitive
- - analgezia postoperatorie
- - cardioprotectie fata de ischemia miocardica, efect dem in special pentru clonidina la adm perioperatorie timp de 4 zile a acesteia.
- Efectul clonidinei + aspirina asupra incidentei ischemiei miocardice perioperatorii este in studiu

Sedarea in terapie intensiva

- Clonidina si mai ales dex = sedarea pacientilor din TI
- Dex (recent aprobata atat de catre FDA si UE pentru sedarea i.v. in TI pentru maxim 24 h),
- numeroase studii raporteaza utilizarea pentru perioade mai lungi
- Avantajele sedarii :
 - depresia respiratorie minima, (sevratul de ventilator este facilitat), se pot face ferestre de sedare zilnic in perioada sevrajului
 - efectul analgetic det ↓ dozelor de opioide.

Obs! Sunt foarte rare cazurile in care Dex se va folosi ca unic sedativ; in majoritatea cazurilor se vor asocia opioide si/sau alte sedative

- nu da dependenta si poate contribui la profilaxia si/sau sevrajul de opioide si/sau alte substante (de ex. alcool) atat in TI cat si la trezirea din anestezie

Sedarea in terapie intensiva

- ↓ semnificativ incidenta delirului in TI
- efecte imune. Desi efectele α_2 – agonistilor sunt combinate pro-inflam (mecanismele periferice), si antiinflam (efectele centrale),
- in prezenta inflamatiei, efectele rezultante ale α_2 – agonistilor sunt anti-inflamatorii.
- Dex are ca efecte: 1) efecte anti-inflamatorii superioare altor agenti, 2) activitate antiapoptotica si 3) amelioreaza functia macrofagelor.
- trialuri recente au dem ameliorarea outcome-ului pacientilor septic sedati cu Dex comparativ cu benzodiazepinele si la reducerea numarului de zile de ventilatie mecanica
- efecte neuroprotective
- Efectele sec: hTA si mai ales bradicardia, care poate ajunge chiar la asistolie (manopere vagale si la doze mari de Dex).

von Dossow V, Baehr N, Moshirzadeh M, et al. Clonidine attenuated early proinflammatory response in T-cell subsets after cardiac surgery. *Anesth Analg* 2006; 103(4):809–14.

Ma D, Hossain M, Rajakumaraswamy N, et al. Dexmedetomidine produces its neuroprotective effect via the α_2A -adrenoceptor subtype. *Eur J Pharmacol* 2004;502:87–97.

Riker RR, Shehabi Y, Bokesch PM, et al. SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA* 2009; 301:489–99.

Pandharipande PP, Sanders RD, Girard TD, et al. and the MENDS investigators. Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an *a priori* designed analysis of the MENDS randomized controlled trial. *Critical Care* 2010, 14:R38

Role of Dexmedetomidine for the Prevention and Treatment of Delirium in Intensive Care Unit Patients

Yoonsun Mo, Anthony E Zimmermann

CONCLUSIONS: Currently available evidence suggests that dexmedetomidine is a promising agent, not only for prevention but also for treatment of ICU-associated delirium. However, larger, well-designed trials are warranted to define the role of dexmedetomidine in preventing and treating delirium in the ICU.

Ann Pharmacother 2013;47:xxx.

Ahmed and Murugan *Critical Care* 2013, 17:320
<http://ccforum.com/content/17/3/320>



JOURNAL CLUB CRITIQUE

Dexmedetomidine use in the ICU: Are we there yet?

Shakeel Ahmed¹ and Raghavan Murugan^{*1,2}

Conclusions

Among ICU patients receiving prolonged mechanical ventilation, dexmedetomidine was not inferior to midazolam and propofol in maintaining light to moderate sedation. Dexmedetomidine reduced duration of mechanical ventilation compared with midazolam and improved the ability of patients to communicate pain compared with midazolam and propofol. Greater numbers of adverse effects were associated with dexmedetomidine.

Dexmedetomidine vs Midazolam or Propofol for Sedation During Prolonged Mechanical Ventilation

Two Randomized Controlled Trials

Stephan M. Jakob, MD, PhD

Esko Ruokonen, MD, PhD

R. Michael Grounds, MBBS, FRCA, MD

Toni Sarapohja, MSc

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for the Dexmedetomidine for Long-Term
Sedation Investigators

Conclusions Among ICU patients receiving prolonged mechanical ventilation, dexmedetomidine was not inferior to midazolam and propofol in maintaining light to moderate sedation. Dexmedetomidine reduced duration of mechanical ventilation compared with midazolam and improved patients' ability to communicate pain compared with midazolam and propofol. More adverse effects were associated with dexmedetomidine.

Trial Registration clinicaltrials.gov Identifiers: NCT00481312, NCT00479661

JAMA. 2012;307(11):1151-1160

www.jama.com

Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an *a priori*-designed analysis of the MENDS randomized controlled trial

Pratik P Pandharipande^{1,2}, Robert D Sanders^{*3}, Timothy D Girard^{4,5,6}, Stuart McGrane^{1,2}, Jennifer L Thompson⁷, Ayumi K Shintani⁷, Daniel L Herr⁸, Mervyn Maze⁹, E Wesley Ely^{4,5,6} for the MENDS investigators

Conclusions: In this subgroup analysis, septic patients receiving dexmedetomidine had more days free of brain dysfunction and mechanical ventilation and were less likely to die than those that received a lorazepam-based sedation regimen. These results were more pronounced in septic patients than in non-septic patients. Prospective clinical studies and further preclinical mechanistic studies are needed to confirm these results.

[53]. In the animal studies, the improved hemodynamic stability correlated with reduced inflammation following DEX administration [38-40]. Indeed in two recent studies, DEX sedation has been associated with a reduction in pro-inflammatory cytokines in patients with sepsis relative to midazolam [54] and propofol [55]. It is plausible that hemodynamic-stabilizing and anti-inflammatory effects of DEX are linked by central sympatholysis [27,38,39]; although appearing counter-intuitive, we consider that a reduction in pro-inflammatory cytokines would outweigh any direct hypotensive effect of DEX [27,38,39], the net effect being improved hemodynamic stability.

Interestingly, although we observed significant benefits of α_2 adrenoceptor agonist based sedation compared with GABAergic sedation in septic patients, we did not observe all the benefit in the non-septic group. DEX-treated patients did have lower odds of development of delirium, whether septic or non septic; however, the improvements in duration of brain dysfunction were predominantly seen in the septic patients on DEX. This may be because the non-septic group was smaller than the septic group and thus had limited statistical power to identify any beneficial or detrimental effect of either treatment. Additionally differences in pathogenesis of delirium may account for the greater benefit seen in septic patients. Furthermore septic shock is associated with neuronal apoptosis in the brain, including the locus ceruleus [57], where there is an abundance of α_2 adrenoceptors. Given that DEX prevents central neuroapoptosis via activation of α_2 adrenoceptors [42], these neuroprotective effects may have contributed to the benefits



National Guideline Clearinghouse

Guideline Summary NGC-9692

Guideline Title

Management/Treatment

1. Treatment of pain
 - Preemptive analgesia and/or nonpharmacologic interventions (e.g., relaxation)
 - Nonopioid analgesics to decrease opioid use and side effects
 - Intravenous (IV) opioids
 - Enterally administered gabapentin or carbamazepine plus IV opioids
 - Thoracic epidural anesthesia/analgesia
2. Treatment of agitation and sedation
 - Titration of sedative medications to target lightest level of sedation or daily sedation interruption (DSI)
 - Monitoring depth of sedation and brain function (RASS and SAS)
 - Objective measures of brain function (e.g., auditory evoked potentials, Bispectral Index, Narcotrend Index, Patient State Index, or state entropy as indicated)
 - Electroencephalogram monitoring (EEG)
 - Sedation strategies using nonbenzodiazepine sedatives (propofol or dexmedetomidine)
3. Treatment of delirium
 - Early mobilization of adult intensive care unit (ICU) patients
 - Consideration of delirium risk factors
 - Routine monitoring of delirium
 - IV dexmedetomidine, if sedation is required
4. Strategies for managing pain, agitation, and delirium
 - Routine daily sedation interruption or a light target level of sedation in mechanically ventilated adult ICU patients
 - Analgesia-first sedation
 - Promoting sleep in adult ICU patients (optimizing patients' environments, strategies to control light and noise, clustering patient care activities, and decreasing stimuli at night)
 - Interdisciplinary ICU team approach (provider education, preprinted and/or computerized protocols and order forms, and quality ICU rounds checklists)

Clonidina

- α_2 – agonist partial selectiv, cu actiune centrala, initial utilizat pt trat HTA severe, in special acelei renin-dependente
- **T_{1/2} 6-12 h**, ceea ce reprezinta un potential dezavantaj al utilizarii sale in ATI in adm continua din cauza riscului de cumulare.
- Doza recomandata pentru adm in spatiul subdural/peridural: (75)150-450 μg (solutia fara conservant).
- se poate adm si in blocul Bier, asociata anestezicelor locale (prelungirea duratei blocului), in doza de 1 $\mu\text{g}/\text{kg}$.
- In premedicatie se poate adm pe cale orala (doza de pana la 5 $\mu\text{g}/\text{kg}$ (150-350 μg)) cu 40-60 min inaintea anesteziei sau pe cale i.m., i.v.
- In adm orala, doza zilnica variaza intre 0,2-0,3 (0,4) mg/zi. Doze mai mari pot fi necesare in tratamentul sevrajului de alcool.

Clonidina

- se mai poate adm si sub forma de patch (in UE Catapres-TTS) si pe cale i.m sau i.v. In cazul adm transdermice doza este de 0,1-0,2 mg/zi absorbtie transcutanata.
- Oprirea brusca a tratamentului poate det HTA rebound cu debut dupa 8-36 h de la ultima doza si apare la doze mai mari de 1,5 mg/zi. Acesta este det de cresterea cu 100% a cantitatii de catecolamine si o intensa vasoconstrictie.
- Tabloul clinic al fen rebound: HTA, tahicardie, transpiratii, dureri abdominale si cefalee severa. Tratamentul consta in reluarea tratamentului sau administrarea de vasodilatatoare.
- Antagonistul selectiv al clonidinei, ca si al dexmedetomidinei este atipamezolul.

Dexmedetomidina

- α_2 – agonist inalt selectiv, dextroizomerul medetomidinei.
- **T1/2** de eliminare 2-3 h, iar cel de distributie 6 min.
- Circula legata in mare parte de proteinele plasmaticice, iar metabolismul este predominant hepatic
- T1/2 mai scurt permite administrarea Dex in perfuzie continua in TI.
- Potenta Dex este mult mai mare decat a clonidinei, fapt este demonstrat de reducerea cu pana la 90% a MAC-ului pentru agenti inhalatori, (comparativ cu clonidina, unde reducerea este de 40%).
- Din punct de vedere cardiovascular, Dex determina un raspuns initial de tip hipertensiv mediat de receptorii α_2B , urmat de un raspuns de tip hipotensiv mediat de subtipul α_2A

Dexmedetomidina

- La nivelul SNC, Dex are efect neuroprotectiv prin ↓ nivelului de catecolamine la nivel cerebral si pe cea a nivelului de glutamat
- Ca premedicatie, administrarea se poate face i.m., iv sau intranazal, aceasta din urma, in cazul premedicatiei la copii.
- Dozele de premedicatie raportate variaza intre 1-2,5 µg/kg
- Dex se adm in special i.v. intraanestezic, ca adjuvant sau singur analgetic asociat anesteziei inhalatorii
- Dex se adm i.v. continuu pentru sedarea pacientilor in TI, durata aprobata fiind de maxim 24 h, iar dozele recomandate sunt de 0.2 to 0.7 µg/ kg/ hr.

Short J. Use of Dexmedetomidine for primary sedation in a general intensive care unit. Crit Care Nurse 2010; 30 (1): 29-38.

Lin YY, He B, Chen J, Zhi Nong Wang ZN. Can dexmedetomidine be a safe and efficacious sedative agent in post-cardiac surgery patients? a meta-analysis. Critical Care 2012;16:R169.

Concluzii

- Substantele $\alpha 2$ – agoniste, cele mai interesante pentru ATI: clonidina si dex.
- numeroase efecte favorabile in ATI si asupra evolutiei postop a pacientilor:
 - \downarrow semnificativa a necesarului de opioide,
 - \downarrow numarului de zile de ventilatie mecanica si a incidentei delirului in TI
 - Neuro- si cardio-protectia perioperatorie
 - Efecte imune modulatorii, manifeste la pacientii cu pattern inflamator sau la septici, (necesita studii viitoare).
- va trebui stabilit exact locul si rolul $\alpha 2$ – agonistilor in protocoalele de sedare in TI si in managementul perioperator.

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Va multumesc pentru atentie