Brazilian Journal of Anesthesiology 2023;73(2): 128–131

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Is dexmedetomidine a lazy drug or do we have lazy anesthesiologists?

Dexmedetomidine is a highly selective α_2 adrenergic receptor agonist drug with unique sedative, anxiolytic and antinociceptive properties, inducing a sympatholytic effect with minimal respiratory depression.[1]

Dexmedetomidine activates central pre- and postsynaptic α_2 receptors in the *locus ceruleus* (LC) inducing a decrease in the release of noradrenaline, activation of inhibitory inputs to the midbrain, pons and hypothalamus, and a decrease of excitatory inputs from the LC to the forebrain and thalamus, impairing thalamocortical communication.[2] The net result of these actions is a state of depressed arousal like the natural sleep;[3] in addition, the antinociceptive effect of dexmedetomidine is mediated by activation of inhibitory neuronal networks synapsing in the dorsal horn of the spinal cord.[4] Dexmedetomidine may have significant cardiovascular effects including a biphasic, dose-dependent response in blood pressure, initially with temporary hypertension due to the activation of peripheral postsynaptic alpha-2_β adrenergic receptors and vasoconstriction followed by a decrease in the blood pressure and heart rate resulting from central alpha-2_α adrenergic receptors stimulated sympatholysis and baroreflex-mediated parasympathetic activation. Notably, dexmedetomidine has been associated with minimal respiratory effects[5] despite recent data showing the possibility to induce airway obstruction.[6] Other remarkable feature of dexmedetomidine is its neuroprotective effect,[7] particularly the association with a very low incidence of perioperative neurocognitive disorders.[8,9]

Unfortunately, the pharmacokinetic profile of dexmedetomidine is not so attractive. Noncompartmental kinetics calculated a distribution half-life of 6 minutes, a volume of distribution at steady state of 1.31–2.46 $L.kg^{-1}$ and an elimination half-time of 2.1–3.1 L in healthy volunteers.[10] In addition, there is a significant inter-individual variability for clearance and distribution volumes especially in critically ill patients.[11]

Different populational derived, multicompartmental, mammillary models have been developed to describe the pharmacokinetic-pharmacodynamics (PKPD) of intravenous administered dexmedetomidine, using different covariates.[10] Recently, Hannivoort et al.[12] and Colin et al.[13,14] developed a PKPD model with allometric scaling and hemodynamic and BIS predictive parameters, which supports the safe use of effect-site concentrations up to 2 ng. ml^{-1}.[15]

Nonoperating room anesthesia (NORA) obeys to very special conditions with patients undergoing uncomfortable and painful procedures outside the usual anesthetic environment inside operating rooms theaters. These includes diagnostic imaging, invasive radiological procedures, cardiac catheterization, endoscopy, and various surgical procedures including major blood vessels endovascular repair.[16] A vast majority of cases demands for moderate to deep sedation, has high turn-over and same day discharge from the hospital which challenges the anesthesiologist to choose anesthetic drugs with favorable pharmacological profile.

In the *Brazilian Journal of Anesthesiology*, Fonseca et al.[17] published a systematic review and meta-analysis studying the impact and safety of dexmedetomidine in different NORA settings among adult population. Ninety-seven randomized controlled trials with a total of 6706 participants were identified, including adult patients with more than 18 years old having procedures with dexmedetomidine only or dexmedetomidine in combination with other sedative agents. Ten endpoints were evaluated when dexmedetomidine had a comparator: time until full recovery, hemodynamic effects (hypotension and bradycardia), desaturation, nausea, pain/discomfort, amnesia and awareness of the procedure, physician satisfaction, patient satisfaction and grade of conscious sedation. The main findings were expectable: higher time until full recovery (average 2 min longer but no more than 4 min, with a low grade of evidence); high certainty of evidence of higher incidence of hypotension and bradycardia; moderate certainty of evidence for 55% lower risk of desaturation (< 90–92%); similar or better pain and discomfort control, similar or higher physician and patient satisfaction, similar or better sedation profile.

https://doi.org/10.1016/j.bjane.2023.01.001

The authors have highlighted the potentially dangerous hemodynamic effects of dexmedetomidine suggesting that its administration should be managed by dedicated professionals with cardiac life support training. In addition, they opened several pathways for future research including other fields where dexmedetomidine may be used (for example, labor, difficult airway management, endoscopic sinus surgery, pain medicine), concomitant use of ketamine and alternative routes of administration like nasal route to decrease the risk of hypotension.

Considering these findings, may we advocate the use of dexmedetomidine for NORA or shall we keep the old classical approach using variable combinations of midazolam, propofol and opioids? Sadly, the present systematic review and meta-analysis missed to discuss how to optimize the less favorable pharmacokinetics of dexmedetomidine and how to apply its unique pharmacodynamic properties in NORA setting.

Most of the studies used a bolus given in 10 min followed by an infusion with doses ranging from 0.4 to 1 $\mu g.kg^{-1}$ for the bolus and 0.1 to 0.5 $\mu g.kg^{-1}.h^{-1}$ as infusion rates. Using the allometric scaling PKPD model by Hannivoort et al.[12] and Colin et al.,[13,14] for a 40-year-old male with 70 kg and 170 cm, these dosing schemes correspond to effect-site concentrations between 0.3 and 0.9 $ng.ml^{-1}$ after an infusion of 60 min (Figs. 1 and 2), with the lowest predicted decrease in the heart rate after the initial loading bolus.

As mentioned before, the interindividual variability is significant and sedation occurs with blood concentrations between 0.2 and 2.5 $ng.ml^{-1}$.[18] Therefore, it is difficult to titrate and identify the optimal dose for a dynamic target level of sedation if such dosing schemes will be used and, possibly, in many moments, patients will be overdosed. Target Controlled Infusion (TCI) of intravenous anesthetic drugs, with stepwise, close titration of target concentrations, is the best approach to optimize limitations imposed by a slow onset and slow offset of a drug.[19,20] Fortunately, TCI of dexmedetomidine is now available in some commercial pumps and its implementation in the clinical practice with appropriate models[15] may overcome the hemodynamic consequences of the aforementioned approach. In the absence of such TCI pumps, clinicians may use current simulation apps like TivatrainerX (https://www.tivatrainerx.com) in the IV-Assist mode which has the unique capability of calculating the bolus and infusions required to obtain and maintain a specific effect-site concentration that can be changed at any point in time and that can be set to run real time the target concentration.

By other hand, electroencephalogram (EEG) monitoring during anesthesia/sedation, with proper knowledge of the raw signal and quantitative EEG parameters and spectral analysis, constitutes a unique tool to continuously *measure* the effect of anesthetic drugs on the brain.[21,22] The EEG signatures of dexmedetomidine are well known[23] and may be applied to titrate the effect-site target concentrations calculated by the TCI pump, aiming for the presence of a dominant alpha activity with short, regular spindles (Fig. 3) and avoiding dominant delta, slow oscillations. It should be remarked that dimensionless indices of consciousness derived from processed EEG have several limitations[24] and may not reflect the real effects of dexmedetomidine on the Central Nervous System.

The other cornerstone of optimal use of dexmedetomidine for NORA is its administration combined with other drugs, following the novel concept of multimodal general anesthesia or multimodal sedation.[3] The rationale supporting this anesthetic pharmacological approach is based on the use of different drugs acting by different mechanisms in different neuronal networks to promote depression of the arousal level, antinociception, immobilization/controlled movement and absence of reflexes, allowing to decrease their respective doses with lower incidence of side effects.

A plausible strategy could be to combine dexmedetomidine and propofol target-controlled infusions with ketamine and/or eventually opioids like remifentanil, with balanced dosing titrated to the intended endpoint of arousal depression and/or antinociception which are dynamic during the entire procedure. In the ideal world, this combination of

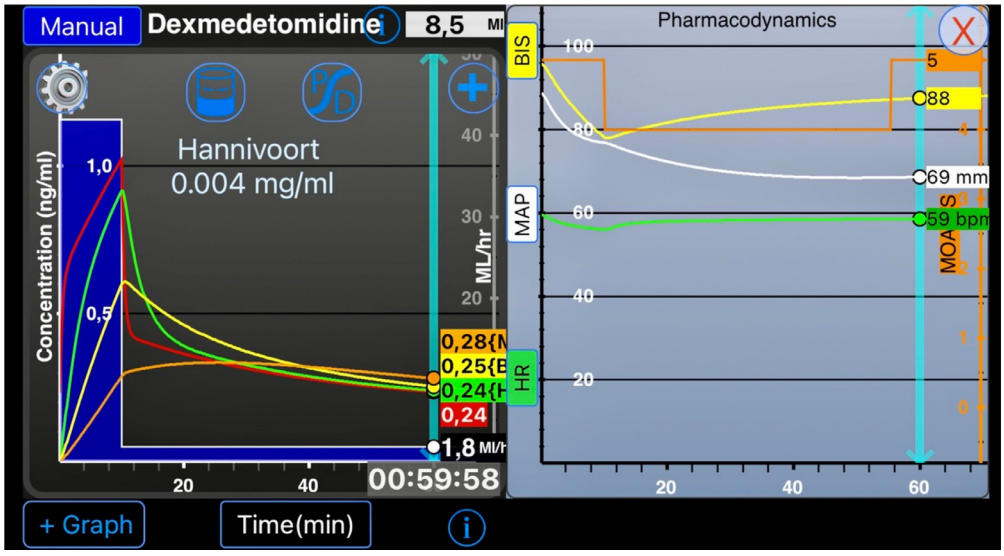

Figure 1 Simulation using TivatrainerX of a loading bolus of 0.4 $\mu g.kg^{-1}$ for 10 min followed by an infusion of 0.1 $\mu g.kg^{-1}.h^{-1}$ of dexmedetomidine. Male, 40 years old, 70 kg, 170 cm. Hannivoort/ Collins PKPD models.

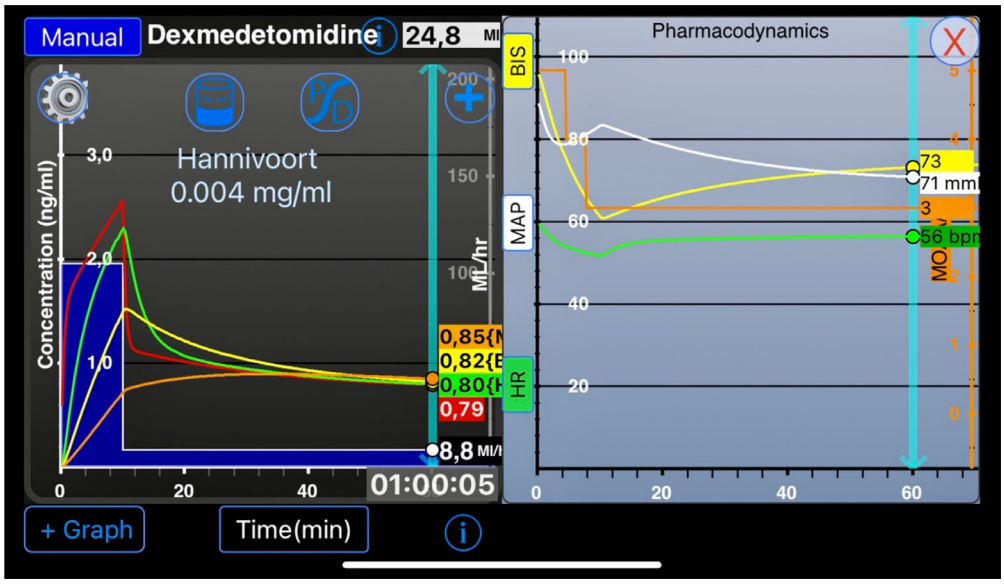

Figure 2 Simulation using TivatrainerX of a loading bolus of 1 μg.kg^{-1} for 10 min followed by an infusion of 0.5 μg.kg^{-1}.h^{-1} of dexmedetomidine. Male, 40 years old, 70 kg, 170 cm. Hannivoort/ Collins PKPD models.

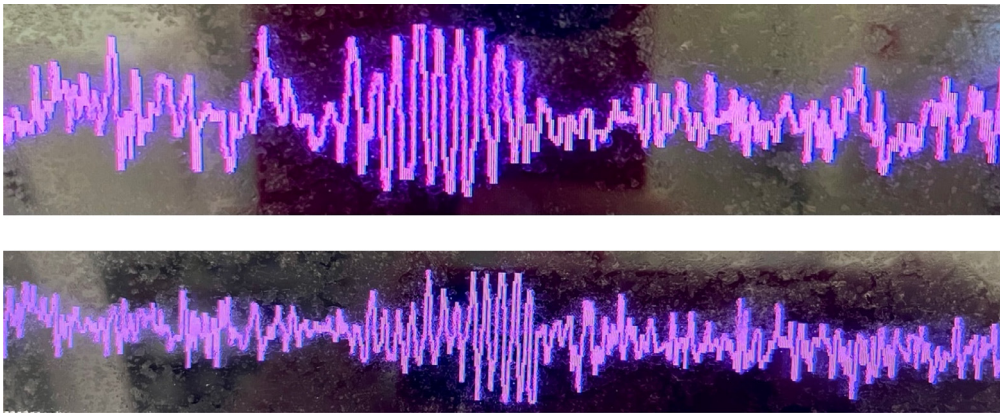

Figure 3 Electroencephalographic spindle induced by dexmedetomidine at effect-site concentration of 0.5 ng.ml^{-1} (on the top), resembling the sleep spindle, and the more asymmetrical spindle induced by propofol (on the bottom), with a typical "breaking" waxing and waning double oscillation. When combining propofol and dexmedetomidine, we may separate the respective effect by the predominant spindle activity.

different drugs would also require a multimodal monitoring approach with nociception-antinociception balance monitoring in addition to EEG, allowing to understand the equilibrium between anesthetic consciousness depression and antinociception, optimizing drug dosing schemes accordingly which component is being affected.[25]

Some skeptical, conservative and lazy voices may argue that this combined pharmacological and monitoring multimodal strategy is adding unnecessary complexity, workload and costs to cases that could *easily* be managed with fewer drugs and minimal monitoring; eventually, they are the same voices advocating mixtures of different drugs in the same syringe (dexmedetomidine + ketamine or propofol + ketamine, for example) running at magical infusion rates with no PKPD rationale behind and with an absolute impossibility to differentiate and separate effects of each drug. However, complexity in anesthesia is a relative concept[26] and most of the success in patient safety during anesthesia results from improved technology and pharmacology,[27] especially in NORA (https://www.apsf.org/article/safety-in-non-operating-room-anesthesia-nora/).

In conclusion, dexmedetomidine offers extraordinary benefits for NORA. Its unfavorable, *lazy* pharmacokinetics and the reported effects on blood pressure and heart rate may be optimized by smart delivery with TCI, in combination with other drugs and with tailored dosing guided by multimodal monitoring.

Conflicts of interest

The authors declare no conflicts of interest.

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Maryam Alshemeili , Francisco A. Lobo *
Anesthesiology Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates

* Corresponding author.
E-mail: francisco.lobo@me.com (F.A. Lobo).