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Use of dexmedetomidine for pain control

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Abstract

For many years, clonidine, an α2-adrenergic receptor (α2-AR) agonist, has been widely used as an analgesic adjuvant in perioperative conditions and pain therapy. Dexmedetomidine (DMET) is currently the most potent α2-AR agonist available and was first approved as a sedative agent for use in the intensive care unit. However, DMET has recently been investigated for its analgesic effects and has the potential to become an alternative to clonidine.

Introduction and context

Clonidine, an α2-adrenergic receptor (α2-AR) agonist, has been widely used and investigated as an analgesic adjuvant for anesthesia and pain therapy. Dexmedetomidine (DMET) belongs to the same family but presents with a different, more favorable pharmacokinetic profile (Table 1). DMET was first introduced into clinical practice as a short-term intravenous sedative in the intensive care unit. Because the drug also demonstrates analgesic properties related to α2-AR binding (DMET is 8–10-fold more selective for α2-AR than clonidine), several studies have investigated its use as a systemic analgesic adjuvant, mostly in the acute perioperative setting [1]. More recently, DMET has been investigated as an adjunct to local anesthetics in locoregional anesthesia and analgesia. However, neurotoxicity studies have not yet been performed [2] and the benefit of using DMET over clonidine has not yet been thoroughly assessed. Nevertheless, recent experimental studies seem to show that α1-AR activity counterbalances α2-AR-induced analgesia and, therefore, greater α2-AR selectivity may enhance the therapeutic window of α2-AR in the treatment of pain [3]. Furthermore, DMET demonstrates a synergistic analgesic effect with clonidine at the spinal level by a mechanism involving their different affinities for the three α2-AR subtypes. Neither clonidine or DMET is totally selective for any one of the α2-AR subtypes but DMET (besides demonstrating α2A-AR binding properties) seems to have higher α2C-AR affinity than clonidine [4].

Recent advances

Analgesic effects following systemic administration

α2-AR agonists and opioids act by different mechanisms and thus their combination produces a synergistic analgesic effect without increasing the respiratory depression that is often associated with opioid use. Furthermore, the opioid-sparing effect is generally associated with a reduction in adverse effects such as nausea and vomiting. Therefore, α2-AR agonists have been found to be particularly useful in perioperative conditions. Recent studies, not surprisingly, show that intraoperative DMET (bolus dose of 0.5–1 μg/kg, with or without continuous infusion of 0.5–2 μg/kg per hour) causes a significant reduction in the need for both intraoperative and postoperative analgesics in adults [5] and in children [6]. Even if the elimination half-life of DMET is short (i.e., 2–3 hours), the analgesic-sparing effect observed after a preoperative or an intraoperative administration usually lasts up to 24 hours, with the anxiolytic, sedative, and thymoanaleptic properties implicated as being partly responsible for this effect [6,7]. Self-administration of DMET by adding to intravenous patient-controlled analgesia morphine (5 μg DMET per 1 mg morphine dose) improves postoperative analgesia and decreases postoperative morphine consumption by 30%, as well as

Table 1. Major differences in the pharmacology of clonidine and dexmedetomidine

Clonidine	Dexmedetomidine*
Developed in the 1960s	Developed in the 1980s
Clinical practice: originally prescribed as a antihypertensive then as an analgesic in chronic pain (1983)	Clinical practice: tested in volunteers (1991) then used as a sedative in ICU (1999)
Ratio α2:α1 receptor binding is 200:1	Ratio α2:α1 receptor binding is 1600:1
Octanol/buffer partition coefficient: 0.8	Octanol/buffer partition coefficient: 2.8 More lipophilic (3.5-fold) than clonidine
Plasmatic half-life T½: 9–12 hours	Plasmatic half-life T½: 2–2.5 hours
Protein binding: 50%	Protein binding: 94%

*Detomidine, the racemic mixture, is widely used in veterinary medicine; dexmedetomidine is the active isomer of medetomidine. ICU, intensive care unit.

decreasing morphine-induced side effects like nausea, without additional sedation [8].

Besides the analgesic effect of α2-AR agonists being independent of the opioid system, the block of sympathetic over-activity is another benefit of using these agents for some patients. For example, perioperative management in patients chronically taking opioids (i.e., opioid addicts and chronic pain patients) is a challenge because of their higher pain levels, opioid tolerance, and risk of opioid withdrawal. Although poorly explored, DMET may have special value in these patients by helping to control pain and to alleviate opioid withdrawal symptoms [9].

Even at high doses, α2-AR agonists combine analgesic, sedative, and anxiolytic properties with preservation of respiratory function. Although typically-used sedative drugs (e.g., propofol), short-acting opioids, ketamine, and midazolam may provide successful sedation, they can also induce harmful respiratory depression in high-risk patients and unsuitable paradoxical effects with agitation in elderly patients. DMET, like other α2-AR agonists, does not affect respiratory function. Moreover, DMET seems to possess neuroprotective effects and attenuates neurocognitive impairment (mainly delirium and agitation) following anesthesia [10]. In children undergoing tonsillectomy, the use of an intraoperative infusion of DMET reduced the frequence of severe emergence agitation in comparison with an intraoperative infusion of fentanyl. [11]. In the intensive care unit, the choice of DMET infusion for sedation and analgesia has a favourable effect on the prevalence and the duration of delirium and confusion associated with the use of midazolam or morphine [12,13]. Therefore, systemic α2-AR agonists may be used as a perioperative supplement to improve locoregional analgesia, and the pharmacokinetic profile of DMET makes its use easier than clonidine for that indication. Additionally, pre- and intraoperative DMET prolongs the duration of the sensory block of local anesthetics during spinal anesthesia [14] and peripheral nerve block [15]. It is worth noting that DMET premedication can be provided by different noninvasive routes, such as buccal and intranasal routes, with a very good bioavailability [16]. Postoperatively, intravenous DMET infusion as an adjunct to epidural analgesia allows for better pain control and reduces epidural analgesic consumption after major surgery [17].

Finally, besides the perioperative administration, it is interesting to mention the recent (although anecdotal) report of DMET use in obstetric analgesia. The report asserts that, because of its high lipophilicity, DMET is retained in placental tissue and passes less readily than clonidine into the fetal circulation and thereby is less susceptible to cause harmful fetal bradycardia. Continuous intravenous DMET infusion has been successfully used as an adjunct to unsatisfactory analgesia by systemic opioids in laboring parturients who could not benefit from epidural analgesia [18,19]. Like clonidine, DMET demonstrates an antinociceptive effect in visceral pain conditions [20]. Furthermore, the drug also possesses attractive properties such as maternal hemodynamic stability, anxiolysis, and stimulation of uterine contractions.

Analgesic effects when used in locoregional analgesia

Because the analgesic effect of α2-AR agonists is mostly mediated at spinal level, neuraxial administration is the route of choice for DMET. Moreover, its high lipophilicity allows for rapid absorption into the cerebrospinal fluid and binding to the spinal cord α2-AR.

A few clinical studies have examined the epidural administration of DMET (usual dose 1–2 μg/kg) in thoracic and upper abdominal surgery. Unsurprisingly, epidural DMET potentiates neuraxial local anesthetics, decreases intraoperative anesthetic requirements, and improves postoperative analgesia hence reducing pulmonary complications associated with thoracotomy [21]. However, according to studies performed to date, DMET does not seem to offer any significant advantage over clonidine in this respect; DMET produces a similar prolongation in the duration of the motor and sensory blocks induced by local anesthetics, regardless of the neuraxial route of

administration (e.g., epidural [22], caudal [23], or spinal [24]). Incidence and magnitude of side effects like sedation and a decrease in systolic blood pressure (25–30%) following sympathetic block also do not differ. The lack of advantage resulting from DMET neuraxial use over clonidine should be taken into account seeing as regular neurotoxicity screening has not been performed for DMET. Although the drug has neuroprotective effects, demyelination in the white matter was observed after epidural administration of DMET in rabbits [25]. Consequently, advanced pathologic investigations are required before using DMET by neuraxial route.

Clonidine is currently used as an analgesic adjuvant in peripheral nerve blocks. Direct inhibitory effects of α2-AR agonists on the conduction of Aδ and C sensory fibers – inhibition of I_h (hyperpolarization-activated) currents and (perhaps) inhibition of tetrodotoxin-resistant Na^+ channels – accounts for the potentiation of the intensity and duration of perineural local anesthetics. Experimental studies show a DMET dose-dependent increase in the duration of the sensory block induced by long-acting local anesthetics such as bupivacaine and ropivacaine [26,27]. A first prospective study in pediatric patients undergoing cleft palate repair and receiving greater palatine nerve block with bupivacaine also demonstrated a 50% increase in the duration of postoperative analgesia [28]. Once again, although the experimental studies did not find neurotoxicity associated with perineural DMET injection, and have even found less perineural inflammation in the local anesthetic–DMET groups, caution remains before widespread clinical use [2]. Finally, peripheral analgesic effects of DMET that potentiate local anesthetics are mediated by α2A-AR binding [29]. Similar to the observations made with clonidine, addition of DMET to lidocaine for intravenous regional anesthesia improves the quality of intraoperative anesthesia and intra-articular administration of DMET decreases the need for postoperative analgesics after arthroscopic knee surgery [30].

Implications for clinical practice

Current perioperative applications for DMET rely on off-label uses of the drug. Systemic administration (pre-, intra- and postoperative) is associated with a useful potentiation of both systemic analgesics, particularly opioids, and local anesthetic sensory block in neuraxial and perineural routes. Furthermore, at moderate doses (bolus dose of <1 μg/kg; continuous infusion <2 μg/kg per hour), systemic DMET does not seem to induce unwanted hemodynamic side effects (e.g., hypotension and bradycardia). Consequently, systemic use as a supplement to general anesthesia and locoregional techniques seems the best and the safest indication for DMET use. However, neuraxial and perineural routes cannot be recommended before further neurotoxicity testing. In comparison with clonidine, currently, only the systemic route seems to show an advantage for DMET in accordance with the pharmacokinetic profile of the drug, while the neuraxial route does not seem to offer any advantage and the perineural route has not been assessed. Finally, potential applications for DMET outside of a perioperative context (i.e., in chronic pain therapy) certainly deserve further study.

Abbreviations

α2-AR, α2-adrenergic receptor; DMET, dexmedetomidine.

Competing interests

The authors declare that they have no competing interests.

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