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DEXMEDETOMIDINE: A NEW AGENT IN ANAESTHESIA & CRITICAL CARE PRACTICE

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Alpha 2-adrenoceptor agonists are being increasingly used in anaesthesia and critical care as they not only decrease sympathetic tone and attenuate the stress responses to anaesthesia and surgery; but also cause sedation and analgesia. They are also used as adjuvant during regional anaesthesia. Clonidine, which was initially introduced as antihypertensive, is the most commonly used alpha 2 agonist by anaesthesiologists. Dexmedetomidine is the most recent agent in this group approved by FDA in 1999 for use in humans for analgesia and sedation.

MECHANISM OF ACTION

Alpha 2 receptors are found in the peripheral and central nervous systems, platelets, and many other organs, including the liver, pancreas, kidney, and eye. Stimulation of the receptors in the brain and spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation, and analgesia. The responses from other organs include decreased salivation, decreased secretion, and decreased bowel motility, inhibition of renin release, increased glomerular filtration, and increased secretion of sodium and water in the kidney; decreased intraocular pressure; and decreased insulin release from the pancreas (1).

The mechanism of action of dexmedetomidine differs from clonidine as it possesses selective alpha 2-adrenoceptor agonism especially for the 2A subtype of this receptor, which causes it to be a much more effective sedative and analgesic agent than clonidine.

PHARMACODYNAMICS AND PHARMACOKINETICS

The majority of patients receiving dexmedetomidine were effectively sedated yet were easily arousable, a unique feature not observed with other sedatives (2).

Dexmedetomidine does not appear to have any direct effects on the heart (3). A biphasic cardiovascular response has been described after the administration of dexmedetomidine (1,4-6). The bolus of 1 mcg/kg dexmedetomidine initially results in a transient increase of the blood pressure and a reflex fall in heart rate, especially in younger, healthy patients (5). Stimulation of alpha B-2-adrenoceptor in vascular smooth muscle seems to be responsible for the initial rise in the blood pressure, which can be attenuated by a slow infusion. However, even at slower infusion rates, the increase in mean arterial pressure over the first 10 minutes was shown to be in the range of 7%, with a decrease in heart rate between 16% and 18%(6). The initial response lasts for 5 to 10 minutes and is followed by a slight decrease in blood pressure due to the inhibition of the central sympathetic outflow. The presynaptic alpha 2-adrenoceptors are also stimulated decreasing the

norepinephrine release resulting in fall in blood pressure & heart rate (7). These effects may also be observed in the postoperative period, and can be easily managed with atropine, ephedrine and volume infusion (8). However, these effects may be deleterious in hypovolemic patients or patients with fixed stroke volume.

The respiratory depression caused by dexmedetomidine has been reported to be much less than with other sedatives (9).

Pharmacokinetics

Dexmedetomidine undergoes almost complete hydroxylation through direct glucuronidation and cytochrome P450 metabolism in liver. Metabolites are excreted in the urine (about 95%) and in the feces (4%). It is unknown whether they possess intrinsic activity. The elimination half-life is approximately 2 hours (1). It may be necessary to decrease the dose in patients with hepatic failure, since they will have lower rates of metabolism of the active drug. In cases of renal failure, the metabolites may accumulate the effects of which have not yet been studied.

The average protein binding of dexmedetomidine is 94%, with negligible protein binding displacement by fentanyl, ketorolac, theophylline, digoxin, and lidocaine, drugs commonly used during anesthesia and in the ICU (1).

SIDE EFFECTS

Dexmedetomidine crosses the placenta and its safety is not established in pregnancy and in children. The common adverse effects of dexmedetomidine include hypotension, hypertension, nausea, bradycardia, atrial fibrillation, hypoxia (10) and various atrioventricular blocks. Most of these adverse effects occur during or briefly after bolus dose of the drug. Omitting or reducing the loading dose can reduce adverse effects.

USE DURING ANAESTHESIA

Dexmedetomidine possesses anxiolytic, sedative, analgesic, and sympatholytic properties, it might be used for premedication, especially for patients in whom preoperative stress is undesirable. Dexmedetomidine has also been found to be an effective drug for premedication before i.v regional anesthesia (11) as it reduces patient anxiety, sympathoadrenal responses, and opioid analgesic requirements

For the intraoperative period, it is used in the dose 0.2 to 0.7 mcg/kg/hr. Dexmedetomidine, like clonidine attenuates the stress-induced sympathoadrenal responses to laryngoscopy, intubation and surgery and provides increased hemodynamic stability. It potentiates the anaesthetic effects of all intraoperative anesthetics, regardless of method of administration (intravenous, volatile, or even regional block). Aho MS (12) demonstrated the analgesic properties of dexmedetomidine using it as a single agent after minor surgery. Talke PO et al (13) studied the effects of dexmedetomidine on neuromuscular blockade in human volunteers using rocuronium infusion. The authors showed that increasing plasma concentrations of dexmedetomidine resulted in further decreased muscle force using mechanomyography. Although these changes were statistically significant, the investigators concluded that they were not clinically relevant. The use of dexmedetomidine is not advised in patients with intracranial pathologies until further studies have proven its safety in this group.

Overall, dexmedetomidine administration during anaesthesia maintains hemodynamic stability, allows lower doses of anesthetics and opiates to be used, resulting in more rapid recovery from anesthesia and a reduced need for pain medication in the PACU, thereby reducing the length of stay.

Dexmedetomidine also provides intense analgesia during the postoperative period. In one study, by Venn RM et al, (2) the postoperative analgesic requirements were reduced by 50% in cardiac patients and the need for rescue midazolam for sedation was diminished by 80%. However, dexmedetomidine may lack amnesic properties, as a small number of patients during the study were able to recall their ICU stay and found the experience very stressful. Dexmedetomidine seems to have few respiratory side effects and it can be continued safely in the extubated, spontaneously breathing patient. The postoperative hemodynamic effects of dexmedetomidine are due to bradycardia, alpha 2-adrenergic stimulation, and a decrease in oxygen requirement. Like clonidine, dexmedetomidine is associated with a lower rate of shivering.

Use in regional anaesthesia and analgesia

While clonidine has been in use as an adjuvant in regional anaesthesia and analgesia, there are only a few studies available on such effects of dexmedetomidine. Epidural/subarachnoid administrations of alpha 2-adrenergic agonists produce analgesia partly by causing spinal acetylcholine and nitric oxide (NO) release since clonidine-induced analgesia is enhanced by subarachnoid neostigmine and inhibited by N-methyl-L-arginine (NMLA), a blocker of NO synthesis. Bouaziz H et al (14) in a study administered clonidine and dexmedetomidine in subarachnoid space to ewes, and found that both clonidine and dexmedetomidine produced dose-dependent analgesia with similar potency. Clonidine was potentiated more than dexmedetomidine by neostigmine pretreatment and NMLA did not affect the dexmedetomidine-induced analgesia. They concluded that it may reflect the lower intrinsic efficacy of clonidine and that analgesia from dexmedetomidine is less dependent on acetylcholine-NO mechanisms than clonidine. In another study, Sabbe MB et al (15) concluded that dexmedetomidine produces a powerful antinociceptive effect, mediated at the spinal level, while systemic redistribution of the drug leads to a hypnotic state with significant cardiorespiratory effects.

USE IN CRITICAL CARE

Dexmedetomidine has been used in the intensive care for its sedative, anxiolytic, and analgesic properties and does not produce respiratory depression due to its non-opioid mechanism of analgesia. The doses should be titrated to the desired clinical effect. For adult patients, dexmedetomidine is generally initiated with a loading infusion of 1 mcg/kg over 10 minutes, followed by a maintenance infusion of between 0.2 to 0.7 mcg/kg/hr. Dexmedetomidine must be diluted in 0.9% saline for infusion. The bolus dose is not used as it can cause paradoxical increases in blood pressure.

Patients who received dexmedetomidine in the intensive care unit were observed to be arousable and alert when stimulated from sedation and quickly return to their sleep-like state (16). Dexmedetomidine has been tried in postsurgical patients requiring intensive care management. It is recommended for infusion lasting up to 24 hours only as the safety and effectiveness of dexmedetomidine has not been studied by infusion over 24 hours. It is not necessary to discontinue dexmedetomidine prior to extubation. Dexmedetomidine has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and postextubation.

Dexmedetomidine should be used cautiously in patients with pre-existent severe bradycardia and conduction problems, in patients with reduced ventricular functions (ejection fraction <30%), and in patients who are hypovolemic or hypotensive. Dexmedetomidine reduces sympathetic activity, resulting in lower blood pressure and reduced heart rate. These hemodynamic values return to baseline when the infusion is discontinued. Alternatively, treatment may include increasing the rate of IV fluid administration, elevation of the lower extremities or the use of presser agents.

FUTURE

Alpha 2-adrenoceptor agonists may be used as an adjunct to anaesthetic agents because of their sedative, analgesic and hemodynamic-stabilizing effects. Dexmedetomidine provides a sedated patient in the preoperative period, reduced need for analgesics and anaesthetic drugs in the intraoperative period. It attenuates the stress response thus providing the hemodynamic stability and protection from ischemia. In future, if the safety of long term infusion of dexmedetomidine is established, it may be used more frequently for the post-operative pain relief and for the ICU sedation. All effects of dexmedetomidine could be antagonized easily by administering the alpha 2-adrenoceptor antagonist atipamezole(A-17), which, like dexmedetomidine, reverses sedation and sympatholysis and has a half-life of 1.5 to 2 hours. The combination of dexmedetomidine and atipamezole might be the basis for a reversible intravenous anesthetic technique that could provide timely independent recovery from anesthesia and sedation in the future (13).

REFERENCES:

1. Ralph Gertler, H. Cleighton Brown, Donald H. Mitchell, and Erin N. Silvius. Dexmedetomidine: a novel sedative-analgesic agent. BUMC Proceedings 2001; 14:13-21 www.baylorhealth.com
2. Venn RM, Bradshaw CJ, Spencer R, Brealey D, Caudwell E, Naughton C, Vedio A, Singer M, Feneck R, Treacher D, Willatts SM, Grounds RM. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. *Anaesthesia* 1999;54:1136-1142.
3. Housmans PR. Effects of dexmedetomidine on contractility, relaxation, and intracellular calcium transients of isolated ventricular myocardium. *Anesthesiology* 1990;73:919-922.
4. Dyck JB, Maze M, Haack C, Vuorilehto L, Shafer SL. The pharmacokinetics and hemodynamic effects of intravenous and intramuscular dexmedetomidine hydrochloride in adult human volunteers. *Anesthesiology* 1993;78:813-820.
5. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology* 1992;77:1134-1142.
6. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. *Anesth Analg* 2000;90:699-705.
7. Aantaa R, Kanto J, Scheinin M, Kallio A, Scheinin H. Dexmedetomidine, an alpha 2-adrenoceptor agonist, reduces anesthetic requirements for patients undergoing minor gynecologic surgery. *Anesthesiology* 1990;73:230-235.
8. Jalonen J, Hynynen M, Kuitunen A, Heikkila H, Perttila J, Salmenpera M, Valtonen M, Aantaa R, Kallio A. Dexmedetomidine as an anesthetic adjunct in coronary artery bypass grafting. *Anesthesiology* 1997;86:331-345.
9. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. *Anesthesiology* 1992;77:1125-1133.
10. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology* 2000;93:382-394.

11. Jaakola ML. Dexmedetomidine premedication before intravenous regional anesthesia in minor outpatient hand surgery. *J Clin Anesth* 1994 May-Jun;6(3):204-11
12. Aho MS, Erkola OA, Scheinin H, Lehtinen AM, Korttila KT. Effect of intravenously administered dexmedetomidine on pain after laparoscopic tubal ligation. *Anesth Analg* 1991;73:112-118.
13. Talke PO, Caldwell JE, Richardson CA, Kirkegaard-Nielsen H, Stafford M. The effects of dexmedetomidine on neuromuscular blockade in human volunteers. *Anesth Analg* 1999;88:633-639.
14. Bouaziz H, Hewitt C, Eisenach JC. Subarachnoid neostigmine potentiation of alpha 2-adrenergic agonist analgesia. Dexmedetomidine versus Clonidine. *Reg Anesth* 1995 Mar-Apr;20(2):121-7
15. Sabbe MB, Penning JP, Ozaki GT, Yaksh TL. Spinal and systemic action of the alpha 2 receptor agonist dexmedetomidine in dogs. Antinociception and carbon dioxide response. *Anesthesiology* 1994 May;80(5):1057-72
16. <http://dexmedetomidine.com>
17. (A)Scheinin H, Aantaa R, Anttila M, Hakola P, Helminen A, Karhuvaara S. Reversal of the sedative and sympatholytic effects of dexmedetomidine with a specific alpha2 adrenoreceptor antagonist atipamezole: a pharmacodynamic and kinetic study in healthy volunteers. *Anesthesiology* 1998;89:574-584

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