Dexmedetomidine for acute postoperative pain

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Introduction
Acute pain can be defined as a normal physiological response to an adverse chemical, thermal or mechanical stimulus. It is generally associated with surgery, trauma or acute illness, but postoperative pain still remains the most common type of acute pain.

Dexmedetomidine is a relatively new alpha-2 agonist and like its predecessor, clonidine, has proven to have antihypertensive effects, sedative and anxiolytic properties, and most recently, analgesic qualities.

Pharmacokinetics of dexmedetomidine
Dexmedetomidine is a highly selective agonist of alpha-2 adrenergic receptors with an alpha-2 to alpha-1 ratio of 1620:1, which is approximately eight times more specific than clonidine for alpha-2 adrenergic receptors. It can be administered via intravenous, intramuscular, intranasal and transdermal routes. It does cross the blood-brain barrier and the CSF concentration approaches approximately 8% of the plasma concentration. This gives it the advantage of being able to stimulate alpha-2 receptors centrally.

Dexmedetomidine is primarily metabolised into methyl and glucuronide conjugates, which are excreted mainly by the kidneys (95%), while the metabolites are pharmacologically inactive.

Mechanisms leading to antinociception
The analgesic properties of dexmedetomidine are proposed to involve both peripheral and central mechanisms.

Evidence of the role of alpha-2 agonists in producing antinociception peripherally stems from the fact that clonidine and other alpha-2 adrenergic agonists produce analgesic effects, regardless of the ability to cross the blood-brain barrier.

The mechanism of action of alpha-2 agonists when administered peripherally remains unclear, although alpha-2 receptors have been isolated from the peripheral nerves of rats and several lines of evidence have been proposed for this effect:

- Clonidine at high concentrations causes blockade of peripheral nerve fibres, especially C-fibres;
- Clonidine causes local vasoconstriction, which may result in higher concentrations of local anesthetic near the nerves and lower concentrations within the plasma;
- The mu opioid receptor, the alpha-2 receptor and the A1-adenosine receptor exhibit properties of cross-tolerance and dependence. A few authors have suggested that alpha-2 receptor-mediated antinociception is closely related to that of opioid and adenosine receptors, and that the underlying molecular mechanism of this interaction is likely to be attributed to inhibitory G-proteins.

As for the central mechanism, alpha-2 adrenergic receptors are also located in the dorsal horn of the spinal cord, and it seems that alpha-2 agonists act on both pre- and postsynaptic mechanisms to produce antinociception.

Local neuraxial administration of clonidine:
- Reduces the excitability of the central terminal of primary afferent fibres;
• Inhibits release of substance P;
• Causes hyperpolarisation and a decrease in spontaneous activity of dorsal horn neurons.

However, the supraspinal role of alpha-2 adrenergic agonists remains unclear, although activation of central alpha-2 adrenoreceptors in the locus coeruleus seems to produce analgesia.

Whereas micro-injection studies in the nucleus raphe magnus can produce antinociception, a number of authors argue that there is no supraspinal mechanism of analgesia, as direct administration of alpha-2 adrenergic agonists into the brainstem conveys no antinociception.

Pharmacokinetic and pharmacodynamic studies support the spinal site of action as the primary location for antinociception of alpha-2 agonists, as lumbar injection of clonidine produces antinociception in the lower extremities, but not in the upper extremities of healthy volunteers, and the CSF level of clonidine corresponds to the degree of antinociception.

Therefore, while dexmedetomidine is known to be able to easily pass the blood-brain barrier, its central analgesic effect is most likely to be due to its effects at the level of the spinal cord, and not the brain.

**Postoperative analgesia**

**General anaesthesia**

Compared with clonidine, not many studies have investigated the use of dexmedetomidine in postoperative pain control as a primary outcome. Most of the literature concerning dexmedetomidine addresses the sedative properties of this alpha-2 agonist, particularly in the perioperative and intensive care unit setting. However, these studies have highlighted the opioid-sparing effect of dexmedetomidine.

Intravenous dexmedetomidine has a definite role in postoperative analgesia through reduction of opioid consumption, yet many of the reports are unable to show a significant decrease in pain scores despite this effect. The implication is that dexmedetomidine may not provide sufficient pain control when administered as a sole analgesic agent, but through synergistic mechanisms via the alpha-2 adrenergic pathways, it plays a part in multimodal analgesia and is able to reduce opioid consumption. This is particularly important in patients at risk of postoperative hypoventilation, such as those who have airway diseases and those who are obese.

**Regional anaesthesia**

Based on current evidence, it remains inconclusive as to whether or not systemic dexmedetomidine improves or augments the effects of epidural anaesthesia with local anaesthetics, and the utility of this alpha-2 agonist in multimodal analgesia remains in question.

Similarly, the use of dexmedetomidine as an adjunctive agent in spinal, epidural or regional anaesthesia has not been effectively validated. One reason for the paucity of evidence regarding this issue is the possible risk of the neurotoxicity of this drug when used epidurally.

However, dexmedetomidine has been shown to effectively improve analgesia when combined with lignocaine for intravenous regional anaesthesia.

Currently, in view of the paucity of evidence supporting the use of dexmedetomidine in regional anaesthesia, the role of this drug as part of a multimodal regional anaesthetic drug regime remains unclear.

**Conclusion**

Too few studies have been done to effectively evaluate the analgesic effect of dexmedetomidine in postoperative pain relief. The evidence mainly surrounds the intravenous administration of this alpha-2 agonist. When used as the sole analgesic agent, dexmedetomidine decreases morphine consumption. However, there is consensus internationally that it is not enough for analgesics to have only opioid-sparing effects without improvement in pain relief. Interestingly, many of the studies were unable to demonstrate a decrease in pain scores, despite the apparent morphine-sparing effect of this alpha-2 agonist.

As a class of drugs, the alpha-2 agonists seem to be promising with regard to postoperative analgesia, bearing in mind the potential adverse effects of sedation, hypotension and bradycardia. While the data supporting the use of clonidine in a postoperative analgesic regime are well established, evidence for the use of dexmedetomidine is still immature and further work is necessary to clarify its role in postoperative pain management.

References are available on request.