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REVIEW

Systemic non-opioid adjuvant analgesics: Their role in acute postoperative pain in adults

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SUMMARY

Non-opioid adjuvants can enhance analgesia when co-administered with a known analgesic, such as an opiate. This can be beneficial in patients in whom pain control with opioids is difficult or when it is preferable for opioid consumption to be minimised for enhanced recovery. Alpha-2 adrenoreceptor agonists (clonidine and dexmedetomidine), gabapentinoids (gabapentin and pregabalin), N-methyl-D-aspartate (NMDA) receptor antagonists (ketamine and magnesium), lidocaine and dexamethasone can all be systemically administered perioperatively to reduce pain intensity to differing degrees. Adjuvants can also reduce opioid related side effects, however, they may cause other side effects limiting their use. They have variable effects on pain scores and opioid consumption. The optimal regimens for systemic administration of these agents have yet to be determined as has the clinical significance of this reduction in pain intensity and reduced opioid consumption. Their routine use as a part of miultimodal analgesia is not yet widely established and their role in the perioperative outcome remains unclear.

1. Introduction

With a trend towards enhanced recovery programs for many types of surgery there is increasing pressure on anaesthetists and acute pain teams to provide effective postoperative pain relief, enabling early mobilisation and return to normal function without the postoperative nausea and vomiting (PONV), decreased gastrointestinal function, respiratory depression, urinary retention and sedation associated with opioid analgesics. The use of regional anaesthesia is one method, but another technique is through the use of adjuvant analgesics. An adjuvant analgesic is a medication that is not primarily an analgesic, although it may have an analgesic action. It can enhance analgesia when co-administered with a known analgesic, such as an opioid while decreasing the amount of opioids administered in the perioperative period. This can be of particular benefit where pain control with opioids may be difficult due to tolerance or side effects. Some of the adjuvants can be effective to manage opiate induced hyperalgesia, a phenomenon in which patients experience acute tolerance and a paradoxical increase in pain intensity with the use of an opioid.

This review outlines the physiology of acute pain and the current evidence regarding the perioperative use of systemic non-opioid adjuvants (NoA). We have mainly reviewed the findings of recent meta-analyses. We have focused on their effects on pain scores, morphine consumption and other risks and benefits. We have not included established drugs used for multimodal analgesia such as non-steroid anti-inflammatory drugs and paracetamol.

2. Physiology of acute pain

Multiple peripheral and central mechanisms interact to enable the detection of potentially damaging or noxious stimuli. This process of detection and processing is known as nociception and can be thought of in terms of four processes[1] transduction, transmission, perception and modulation. NoA may act on multiple processes (Fig. 1).

2.1. Transduction

Nociception begins with the transduction of a noxious stimulus into a nociceptive impulse via an action potential. This is achieved by free nerve endings called nociceptors. Nociceptors are distributed throughout the body and are comprised of small unmyelinated C fibres and larger myelinated A-δ fibres.

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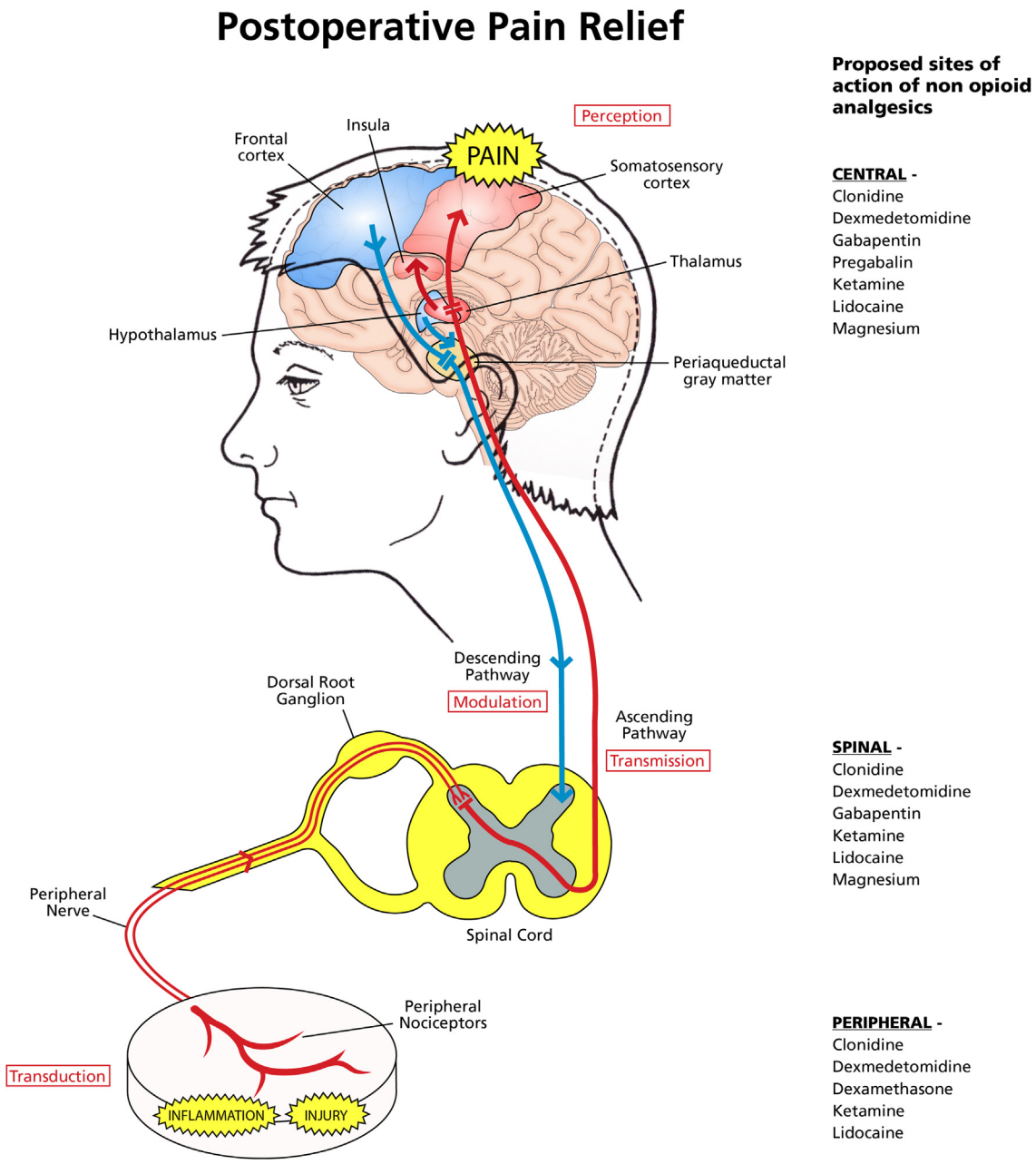

Fig. 1. Major factors involved in pain processing and proposed sites of action of non-opioid adjuvants.

C fibres are much more abundantly distributed when compared to A-δ fibres, and due to their being small in diameter and unmyelinated, they have a much slower conduction time. They are polymodal receptors and respond to mechanical, thermal and chemical stimuli via various receptors. They result in a pain that is described as dull, aching and often diffuse.

By comparison, A-δ fibres have a much faster conduction time. They are high threshold receptors that respond to mechanical or thermal stimuli. They result in sharp, well-localised pain.

Immune and inflammatory responses result in the release of several chemical substances that either act themselves as ligands or function as mediators to sensitise nociceptors. These modulators include cytokines (TNFα, IL-1, IL-6, IL-10), chemokines, neuropeptides, substance P and enzymes such as cyclo-oxygenase 2 (COX-2) and proteinases.

2.2. Transmission

This involves the transmission of the nociceptive impulse from the peripheral afferent neuron to the brain via the spinal cord. In order for an action potential to be propagated there must be movement of sodium at cell membranes.

The primary afferents from the head and neck are contained within the trigeminal nerve and pass to the trigeminal nucleus within the brainstem. The primary afferents that innervate the trunk, limbs and viscera synapse with nociceptive specific neurons within laminas I, II and V of the dorsal horn. These primary afferent terminals contain excitatory neurotransmitters, which are released to transmit the nociceptive impulse across the synaptic cleft to the nociceptive dorsal horn neuron. These neurotransmitters include glutamate, aspartate, bradykinin, adenosine triphosphate,