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REVIEW

Analgesia for acute pain

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Abstract

Acute pain is known to every person universally, and the management of pain is one of the biggest industries in the world today. There are many and varied options to achieve analgesia, but if not used for the correct indication, if not initiated effectively, or if the intervention causes unacceptable side-effects, it can lead to suboptimal pain relief and potentially dire outcomes. Knowledge of the pathways involved in pain perception, and how these pathways can be targeted with various modalities is required to obtain adequate analgesia. This article provides an overview of the available evidence-based therapeutic options for acute pain management.

Keywords: analgesia, descending inhibition, management, neuropathic, nociceptive, pain

Introduction

Pain in its various forms is undoubtedly the most common ailment known to man, and acute pain is an experience familiar to all. Pain is defined as an unpleasant sensation associated with actual or potential tissue damage, mediated by specific nerve fibres to the brain, where its conscious appreciation may be modified by various factors.[1]

Pain in the acute setting generally manifests as three broad presentations; nociceptive, neuropathic and mixed pain. They have distinct aetiologies and pathways, and can be controlled at various action sites. Analgesia is seen as a fundamental human right, and therefore the aim of acute pain management is adequate pain control to achieve sufficient patient comfort in order to facilitate recovery, prevent chronic pain and accomplish this with minimal side-effects.[3,4] This may be achieved with single or combination analgesics. Successful mitigation depends on which type of pain is being treated, and where it is targeted.

Pain pathways

Acute nociceptive pain is initiated by local tissue injury which releases inflammatory mediators, such as prostaglandins, acetylcholine, serotonin and substance P. These mediators then stimulate the peripheral nociceptors, and impulses are propagated via the nerve fibres (A delta and C) to the dorsal horn of the spinal cord, to be further transmitted via the spinothalamic tract to the thalamus. The localisation and meaning of pain occurs in the somatosensory cortex, and inhibition or modulation of the same pain can occur via the descending pathways (Figure 1).[4]

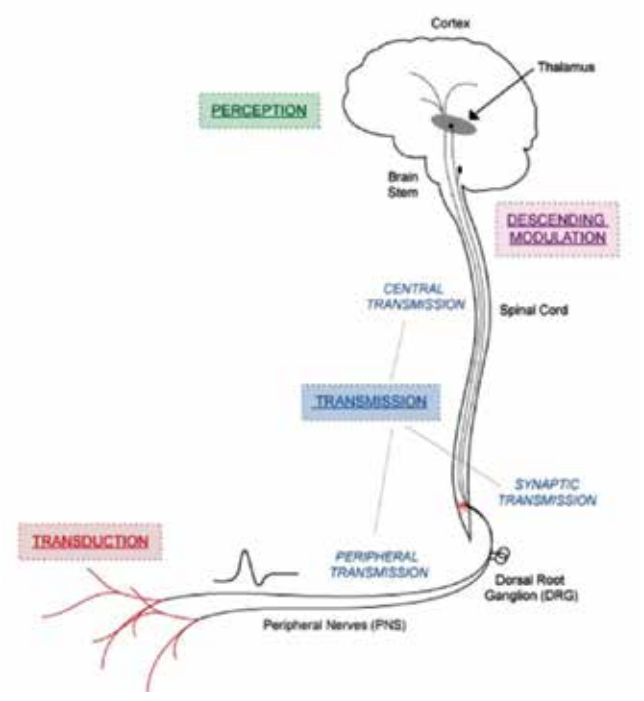

Figure 1: Pain pathways[5]

Neuropathic pain is a completely different entity, and is defined as pain caused by a lesion or disease of the somatosensory nervous system.[6] Usually, it has a more insidious onset than nociceptive pain, but may also appear suddenly as an acute presentation.[7] Therefore, acute pain cannot be treated with a standard drug or cocktail and a satisfactory patient response is based on targeting the correct pathways, although nociceptive and neuropathic pain do often co-occur, e.g. during surgery or traumatic nerve injury.

Management

The widely used and referenced World Health Organization's analgesia ladder has been the benchmark for general pain management since 1986, despite the fact that it was only designed for chronic cancer pain.[8] This stepwise approach has undergone some scrutiny. A multimodal, combination-analgesic approach starting with the highest justifiable level of pain control has since been proposed.[4,9–11] This is in accordance with the goals of acute pain management, and indicates that analgesia must be started promptly, adequately, and for the correct type of pain. It must also be noted that pain is not only a physical entity, but is also subject to psychological and social influences.[12] Therefore, pharmacological interventions may not be adequate to eliminate completely, and the goal of no pain at all is unrealistic.[3] Rather, patient comfort must be sought.

Pharmacological approaches and target action sites

Inhibiting local pain mediator production

Nonsteroidal anti-inflammatory drugs (NSAIDs) have analgesic, anti-inflammatory and antipyretic properties. These are exerted by the inhibition of cyclo-oxygenase (COX) enzymes responsible for prostaglandin synthesis, one of the main inflammatory mediators. The nonselective NSAIDs inhibit both COX-1 and COX-2, and the blockade of COX-1 (which produces the so-called "housekeeping" prostaglandins responsible for gastric mucosal integrity and platelet function) has been shown to cause unwanted side-effects, especially in the gastrointestinal, cardiovascular and renal systems.[13] The selective COX-2 inhibitors were developed to decrease these gastrointestinal side-effects (most notably peptic ulceration) by targeting the COX-2 enzyme with a minimal effect on COX-1, but these agents have been shown to lead to an increase in cardiovascular events, such as myocardial infarction, strokes and thrombosis.[14]

However, NSAIDs are a first-choice analgesic for pain,[15] and are very efficacious when used for the correct indication, i.e. stimuli leading to inflammatory mediator release. Different NSAIDs have very distinct side-effects. The US Food and Drug Administration (FDA) strengthened its existing "black box" warning in July 2015 to emphasise the increased risk of cardiovascular incidents or strokes with NSAID use.[16] Therefore, they should be used with caution, and if NSAIDs are indicated in a patient at high cardivascular risk, naproxen has been shown to result in the least increase in risk. Ketorolac, naproxen and indomethacin have the highest risk with regard to gastrointestinal side-effects. Therefore, they should only be used with a proton-pump inhibitor or misoprostol if another NSAID cannot be used or is unavailable.[14,17]

Interrupting neural impulses

Pain impulses can be directly blocked in the peripheral nerves by preventing depolarisation by means of physically plugging the sodium channels necessary for impulse propagation.[18] This is achieved with local anaesthetics. Lignocaine, bupivacaine and prilocaine are the most commonly used. Local anaesthetics can be applied topically, or infiltrated into the tissue or around the target nerves (nerve blocks). Nerve blocks and local infiltration are excellent for initial and sustained analgesia, and may decrease the dose of additional analgesics.[19] Local anaesthetics block impulses more readily through small pain-conducting nerve fibres (A delta and C) than through larger fibres. Therefore, touch, proprioception and motor function is relatively unaffected. The surrounding tissue pH strongly affects local anaesthetics. Thus, an acidic environment, e.g. an abscess or tissue necrosis, substantially decreases their efficacy. Tricyclic antidepressants (TCAs), such as amitriptyline, and anticonvulsants, such as pregabalin, gabapentin and carbamazepine, have central and peripheral effects, and act on the nerve fibres by inhibiting neurotransmitter release,[20] or diminishing impulse propagation via sodium-channel modulation.[21]

Myofascial trigger points are common sequelae from acute injures, such as whiplash injury, muscle sprains or even poor posture.[22] They are defined as "a hyperirritable spot, usually within a taut band of skeletal muscle or in the muscle fascia, which is painful on compression, and can give rise to characteristic referred pain, motor dysfunction and autonomic phenomena".[23] Local anaesthetics can be used to infiltrate these trigger points with notable patient relief and functional restoration.

Modulation of the central mechanisms

Of all prescriptions given in the USA in 2014, drugs which target the central mechanisms of pain perception were second on the list, and only by a small margin.[24] Modulation of these central mechanisms may be achieved by targeting nociceptive, neuropathic, descending or novel pathways.

Nociception can be modulated by various drugs. It is very effectively blocked by opioids mainly via μ-opioid receptors distributed in the brain and spinal cord.[25] Morphine derivatives, e.g. hydrocodone, oxycodone and fentanyl, are the most commonly prescribed. These drugs have very high addiction potential. Thus, they should be used with caution.[26] Analgesia should not be prescribed for ≥ 10 days without review, and possible side-effects need to be explained adequately to patients.[12] Parenteral morphine is the drug of choice in the emergency department, but careful monitoring of the patient needs to take place.

Codeine is the most commonly used opioid in the world. It is available over-the-counter in South Africa.[27] But despite it being used so widely, codeine has poor analgesic properties,[28,29] and carries a high risk of side-effects, especially in children. The European Medicines Agency has prohibited its use to treat coughs and colds in children aged ≤ 12 years, and the FDA is currently investigating its safety.[30]

Paracetamol not only has antinociceptive properties, but also has some COX inhibition. Also, although not fully understood, it appears to act on the opioid receptors as well.[31] Paracetamol, in combination with a NSAID, was more effective than paracetamol alone in a systematic review.[32] It is relatively safe if the maximum dose is adhered to.[33]

Neuropathic pain can be mitigated with various classes of drugs, most notably the anticonvulsants, TCAs and ketamine, which also has nociceptive effects. Dose-related adverse effects may diminish their use, but this can be attenuated by using a lower dose when they are used in combination with other analgesics.

The perception of pain is not a unidirectional process up the spinothalamic tract. Powerful input is received from higher central centres that terminate in the dorsal horn of the spinal cord, enabling the modulation of pain.

Descending inhibition of nociception is effected through the release of neurotransmitters, such as serotonin, noradrenaline and the endogenous opioids, although these processes are not fully understood.[34] This seems to be the reason why antidepressants such as TCAs, serotonin and noradrenaline reuptake inhibitors (SNRIs) and tramadol (all of which increase available serotonin and noradrenaline) enhance descending inhibition, although TCAs and SNRIs are not licenced for analgesic use. In contrast, opioids seem to act directly on this pathway.

Curiously, these modulatory processes can also increase the descending facilitation of nociception, and thus pain. Psychological factors, such as fear and anxiety, are able to modulate the descending tracts.

Exciting novel approaches to analgesia are currently being developed. Great promise is being shown by the melatonin 2-receptor antagonists,[35,36] cannabinoids[37] and magnesium.[38,39]

Nonpharmacological approaches

As stated, descending inhibition can have a marked effect on pain. Therefore, the higher centres involved in the pathway, such as the cerebral cortex, hypothalamus and brainstem, can modulate pain. Practically, this may mean that the way in which pain is perceived influences its potency,[33] and that sleep deprivation contributes to increased levels of pain.[31] Additionally, it was found in a systematic review that music therapy reduces anxiety and analgesia usage, further indicating the value and impact of descending inhibition.[40,41]

Pain pathway targets and interventions are highlighted in Table 1.

Table 1: Pain pathway targets and interventions

Target	Intervention
Inflammatory mediators	NSAIDs and coxibs
Nerve fibres	Local anaesthetics, anticonvulsants and TCAs
Central mechanisms	Opioids, paracetamol, ketamine, anticonvulsants and TCAs
Descending inhibitory pathways	TCAs, SNRIs, tramadol, opioids and cognitive therapy

NSAIDs: nonsteroidal anti-inflammatory drugs, SNRIs: serotonin and noradrenaline reuptake inhibitors, TCAs: tricyclic antidepressants

Conclusion

Many and varied mechanisms play a role in pain perception, and evidence-based therapeutic options should be utilised rationally, safely and with good indication in acute pain management. Combination analgesia initiated at an adequate dose, together with indicated nonpharmacological modalities and a cognitive understanding of a certain painful experience, can feasibly light the way to improved analgesia and patient satisfaction.

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