The rationale for combining local anaesthetics with adjuvant drugs is to use lower doses of each agent, maintaining analgesic efficacy whilst reducing the incidence and severity of side effects.

MODULATION OF NOCICEPTION

Acute postoperative pain is the result of a complex physiological reaction to tissue injury. A full discussion of this process is beyond the scope of this lecture, knowledge of nociception in the dorsal horn of the spinal cord is important to understand the mechanism of action of adjuvants drugs for regional anaesthesia.

The dorsal horn is the site of termination of primary afferents and there is a complex interaction between afferent fibres, local intrinsic spinal neurons and descending fibres from the brain. (fig 1) A number of peptides, catecholamines and indoleamines are implicated as neurotransmitters at the dorsal horn. These substances, including substance P, serotonin, norepinephrine, acetylcholine, adenosine, glutamate are released in the dorsal horn and modulate peripheral nociceptive input. [1]. Reflex activity also modulates peripheral nociception.

FIGURE 1

![Diagram](image)

Figure 1. Schematic representation of the organisation of dorsal horn systems processing nociceptive information. [1]

Adjuvant drugs used with local anaesthetics may interact with one or more of these neurotransmitters exerting an antinociceptive effect. The most widely used are alpha 2-adrenergic drugs (clonidine) and epinephrine. Anti-cholinergic agents (neostigmine), NMDA receptor antagonists (ketamine) and N-specific calcium-channel blockers (ziconotide) are also used. As might be anticipated all these drugs produce a variety of side effects in addition to their anti-nociceptive effects.
INTERACTION OF DRUGS

A pharmacodynamic interaction occurs when the actions of one drug are altered by the concurrent administration of another. If the effect of the combination is greater than the sum of the effects of the individual agents, the interaction is said to be synergistic. Synergistic interaction can occur when drugs affect different critical points along a common pathway. Isobolographic analysis is commonly used to analyse drug interactions. This method can be applied to test the effect of combination of drugs after individual dose-response curves have been established for individual drugs and drug combinations.[2]

LOCAL ANAESTHETICS

Local anaesthetics are classified as either esters or amides, depending on the chemical link between the aromatic moiety and the hydrocarbon chain. Local anaesthetics block the generation and propagation of action potentials in excitable nerve tissues primarily by impairing the function of sodium (Na⁺) channels in the axonal membrane. [3] The sodium channel is a specific receptor for local anaesthetic molecules. At low concentrations local anaesthetics may produce differential blockade of small fibers. Varying sensitivities of nerves to local anaesthetics may result in clinically important differential blockade of somatic sensory fibers and pre-ganglionic sympathetic fibers. The clinically important properties of local anaesthetic agents include speed of onset, potency, duration of action and differential blockade of sensory and motor nerves.

CLONIDINE

Clonidine is a selective α₂ adrenergic agonist with some α₁ agonist activity.

Alpha 2- adrenergic drugs produce analgesia by activating the descending noradrenergic inhibitory system and by inhibiting synaptic transmission within the dorsal horn of the spinal cord via an activation of spinal cholinergic neurons.[4] Activating the α₂ adrenoceptor triggers an inwardly rectifying potassium conductance in dorsal horn neurons that causes hyperpolarization, reduced excitability and analgesia. Spinal clonidine produces analgesia by mimicking the effect of norepinephrine on wide dynamic range neurons. This inhibiting effect is also seen in the intermediolateral cell column where sympathetic vasoactive neurones originate and causes a decrease in sympathetic outflow.

CENTRAL NEURAL BLOCKADE

Clonidine acts synergistically with local anaesthetics because of its action of opening potassium channels. The duration of both sensory and motor blockade from spinal and epidural block is prolonged.[5,6] This is a dose dependent phenomenon with a maximum effect after 75-100 µg. The type of local anaesthetic does not seem to be important. The antinociceptive interaction of intrathecal clonidine and lidocaine was demonstrated in a rat model[7]. Isobolographic analysis showed that this combination synergistically enhanced analgesia.

Arterial hypotension is the most commonly reported side effect of neuraxial clonidine. Hypotension is mostly due to direct inhibition of sympathetic outflow from preganglionic neurons in the spinal cord. Other side effects include sedation and a reduction in heart rate.

PERIPHERAL BLOCKADE

Clonidine has been found to prolong the action of local anaesthetics in peripheral blocks in the post-operative period[8]. The effect of clonidine is dose-related. After brachial plexus block with mepivacaine the minimum doses which significantly prolong analgesia and anaesthesia are 0.1 and 0.5 mcg/kg respectively.[8] Clonidine may complement the action of local anaesthetics on sodium channels by opening the potassium channels resulting in membrane hyperpolarization, a state in which the cell is unresponsive to excitatory input.[9]

KETAMINE

Ketamine is a phencyclidine derivate and is commercially available as a racemic mixture of the two enantiomers S(+) ketamine and R(-) ketamine. It is a N-methyl-D-aspartate (NMDA) receptor antagonist. The NMDA receptor is believed to play an important role in the development of neuropathic pain by activation by excitatory amino acids (glutamate) in the dorsal horn. [10] Ketamine is a non-competitive antagonist at the NMDA receptor calcium channel and in this way ketamine inhibits excitatory transmission by decreasing depolarisation.
It therefore modulates the development of or attenuates established neuropathic pain arising from dorsal horn wind-up phenomenon. S(+)-ketamine, the left-handed optical isomer of racemic ketamine, has a fourfold higher affinity for NMDA receptors than right-handed R(-)-ketamine.[11] Ketamine is also known to produce both sensory and motor block, but the mechanism of action is not clear.

CENTRAL NEURAL BLOCKADE

There is concern about neurotoxicity after neuraxial use of ketamine and spinal myelopathy has been reported with intrathecal injection of large doses. However in animals and humans there is no evidence for neurological injury after repeated intrathecal injection of preservative-free ketamine.[12]

In clinical practice conflicting results have been reported when epidural ketamine is for pain management. One study found a reduction in the onset time of sensory block with epidural bupivacaine following epidural administration of 25 mg ketamine with bupivacaine.[13] Postoperative analgesic duration was comparable to bupivacaine alone. Others found that the combination of S(+)-ketamine and ropivacaine epidurally improved postoperative pain relief when compared with ropivacaine.[14] Intrathecal ketamine added to a small dose of intrathecal bupivacaine did not provide extended postoperative analgesia or decrease the postoperative analgesic requirements. [15] In addition, neuraxial ketamine is associated with side effects like sedation, dizziness, nystagmus, ‘strange feelings’, and nausea and vomiting both as sole agent and as an adjuvant to bupivacaine. It seems likely that the use of neuraxial ketamine as an adjuvant to local anaesthetics will be limited.

NEOSTIGMINE

The cholinergic system is thought to modulate pain transmission by a spinal mechanism. [16] Acetylcholine is one of more than 25 neurotransmitters involved in spinal cord modulation of pain signaling. Intrathecal neostigmine provides antinociception by inhibiting breakdown of acetylcholine, which acts on cholinergic neurones within the spinal cord. Increased concentration of acetylcholine in the spinal fluid stimulates spinal muscarinic and nicotinic receptors. Muscarinic receptors play a part in producing analgesia. The analgesia produced by neostigmine is not associated with respiratory depression but there is a significant incidence of nausea, vomiting and more rarely anxiety.

CENTRAL NEURAL BLOCKADE

Epidural neostigmine 1 to 4 µg added to a local anaesthetic solution produced a dose-independent analgesic effect in patients after minor orthopaedic procedures. [17] Addition of 50 µg neostigmine to intrathecal bupivacaine prolonged the duration of sensory and motor block. [18] Smaller doses of neostigmine (6.25 and 12.5 µg) did not significantly enhance sensory or motor block but did increase the incidence of nausea and vomiting. The high incidence of these side effects will limit the clinical usefulness of intrathecal neostigmine.

ADENOSINE

Adenosine receptors are expressed on the surface of most cells. Five classes of adenosine receptors have been identified. The A1 and A2 receptors are present centrally and peripherally, with agonists of the A1 receptor being antinociceptive and agonists of the A2 receptor algogenic (i.e., activation results in pain). [19]

CENTRAL NEURAL BLOCKADE

In volunteers, reduction in areas of experimental hypersensitivity was the same following an intrathecal dose of 0.5 or 2 mg adenosine, however side effects are more common with the larger dose.[20] The diagnostic and therapeutic role for intrathecal adenosine in acute and chronic pain states is under investigation by several research groups. Intrathecal adenosine decreased the spontaneous and evoked pain intensity in patients with neuropathic pain involving hyperalgesia / dysesthesia / allodynia. [21] Its interaction with spinal local anaesthetics is just beginning to be studied.

EPINEPHRINE

Vasoconstrictor drugs, in particular epinephrine, are commonly used as adjuvants in solutions of local anaesthetics to slow systemic absorption leading to increased neuronal uptake of local anaesthetics.[22] As a consequence the depth and duration of neural blockade are increased. In clinical practice, local anaesthetic solutions usually contain epinephrine at a concentration of 5 µg/ml (1:200,000). The ability of epinephrine to prolong the duration of action of neural blockade varies with each local anaesthetic and its concentration.
CENTRAL NEURAL BLOCKADE

Prolongation of sensory analgesia has been shown to be more pronounced with epidurally administered shorter acting local anaesthetic agents like lidocaine and prilocaine.[23] On the other hand, addition of epinephrine to either bupivacaine or etidocaine solutions appears to increase the intensity of motor blockade. The effect of adding epinephrine is more important when the concentration of the local anaesthetic is low than when it is high.

With spinal anaesthesia the prolongation of neural blockade might be related to vasoconstriction of the vessels supplying the dura mater and spinal cord, leading to slower vascular absorption and increased neuronal uptake of the local anaesthetic, or to a direct $\alpha$-adrenergic effect of the vasoconstrictor on the spinal cord. The greatest increase in duration is seen when epinephrine is added to amethocaine solutions. Addition of epinephrine to lidocaine and bupivacaine will have much less, if any, effect on the duration.[23] The most profound effect of adding epinephrine to the spinal solution occurs in the lumbosacral region.

OPIOIDS

Neuraxially administered opioids produce significant dose-dependent analgesia through opioid receptors in the substantia gelatinosa. Opioids have two well established actions on neurons. [24] First, they inhibit a voltage-sensitive calcium channel on presynaptic nerve terminals. This action inhibits release of neurotransmitters, including substance P and glutamate that are active in spinal nociceptive transmission. Second, opioids can hyperpolarize, and thus inhibit, postsynaptic neurons by opening potassium channels.

The analgesic effects of epidural or intrathecal opioids are based on the interference at different opioid receptors (principally mu receptors) in the spinal cord. Since the dura mater is not a lipid membrane, the rate of diffusion from epidural into intrathecal space is inversely proportional to molecular size, and high lipophilicity actually increases the uptake into epidural fat and blood vessels. Analgesia is dose related, equianalgesic epidural dose is 5 to 10 times the subarachnoid dose.

In animal studies, isobolographic analysis reveals synergistic antinociception with co administration of morphine and local anaesthetics. [25]

CENTRAL NEURAL BLOCKADE

The primary differences between opioids relate to their onset of action, duration of action and propensity to produce side-effects. For analgesia, fentanyl and sufentanil are the most popular opioids. Combination therapy is mostly used for postoperative and labour pain. Although the interaction between epidural local anaesthetics and opioids is highly synergistic in animals, a clear benefit from this interaction in humans has been surprisingly difficult to demonstrate. Studies strongly suggest that the mode of action for epidurally administered lipid-soluble opioids is uptake into the systemic circulation with subsequent distribution to receptors in the brain. There is no evidence of a selective spinal site of action.[26, 27] In contrast the potent analgesia produced by modest doses of the hydrophilic drug morphine is largely the result of redistribution from the epidural space to spinal cord opioid receptors.

The dose required for intrathecal administration of opioids is about 5-10 times smaller than that required for epidural administration. Combination therapy reduces dose requirements for either class of drug.[28] Using a local anaesthetic with a spinal opioid improves the control of incident (movement-related) pain. Compared to epidural administration there is a greater risk of adverse effects, including late-onset respiratory depression.

CONCLUSION

Antinociceptive drugs have been combined with local anaesthetics in several settings in an attempt to reduce side effects or to intensify or prolong their effect. Different groups of drugs, each acting by a unique mechanism, have been shown to block nociceptive transmission in the spinal cord. These compounds interfere with receptor systems that do not only transmit pain. Local anaesthetic drugs act by inhibiting the generation and propagation of action potentials in excitable nerve tissue primarily by impairing the function of voltage gated sodium (Na$^+$) channels in the axonal membrane.

Neuraxially administration of local anaesthetics and antinociceptive drugs produce analgesia, but not without side effects. Balanced neuraxial analgesia using a combination of low doses of drugs, with separate but synergistic mechanisms of analgesia may produce the best results.
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