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Preemptive analgesia

Throughout this meeting the definition of pain will have been given several times but it is still worth repeating again as understanding of this definition is the cornerstone in the philosophy of analgesia, pre-emptive of otherwise.

What is Pain?
An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.
The inability to communicate in no way negates the possibility that an individual is experiencing pain and is in need of appropriate pain relieving treatment. (IASP 1994)

The important concepts in this definition are that there is an emotional component to pain; it is not just a sensation described by the term 'nocioception'. This leads to the question 'do animals have emotions?' and if not can they experience pain? Until the second part of the definition was added in 1994, there was an argument as to whether animals experience pain and so required pain relief. However with the addition of the second paragraph, the implication is that if appropriate neural pathways are present, in the face of potential or actual tissue damage it must be assumed that an organism is experiencing pain and so requires treatment.

"Pleasure is nothing but the intermission of pain"
John Selding

Cartesian Model of Pain
The Cartesian Pain model was the primary theory of pain perception until Melzack and Wall proposed their new theory of pain, the Gate Theory of Pain, in 1965. The Cartesian Model presumed simple linear wiring from the sensory endings at the site of tissue damage to the spinal cord and up to the brain, with an equally simple effecter system from the brain to motor function. However the Gate Theory of Pain introduced the idea of modulation of the information and proposed that this modulation could be relatively local within the spinal cord or from the brain. Subsequently although the basic theory still remains good, there have been tremendous advances in the understanding of pain and nocioception and consequent additions to the theory.

Physiological Pain
Physiological pain is generally accepted to be the experience of immediate acute tissue damage. It results from high intensity stimuli activating A delta and C peripheral sensory nerve fibres, while low intensity stimuli activate A beta fibres and an innocuous sensation is felt. The nocioceptors involved in this initial reaction are unsophisticated, small bare nerve endings that respond to temperatures greater than $45^{O}C$, severe mechanical stimuli and acute inflammatory mediators. The spinal and central transmitters involved in the initial processing of the information are relatively simple peptides and / or purines acting via sodium channels.
If the damaging stimulus is applied for a long period of time or sets up an inflammatory process which is not controlled, a cascade of events is initiated which may result in long lasting changes in the central nervous system. If these changes are allowed to become established chronic pain, hyperalgesia (increased response to painful stimuli) and or allodynia (painful response to normally unconscious stimulus) may ensue, even after the initiating injury has ceased.

The Role of Pre-emptive analgesia
The concept of that pain is more difficult to treat once it has become established due to changes at the site of injury and more centrally in the spinal cord was first proposed in the early 1980's, when Woolf and others showed changes within the spinal cord after distant injury. Subsequently the improved effectiveness of analgesic treatment provided before the application of a noxious stimulus was demonstrated in experimental animals. This has lead to the controversial term ' Pre-emptive Analgesia'. The pre-requisites of this are that analgesic treatment is provided before and during noxious stimulation that is capable of modifying central excitatory responses. The result of this treatment is that there is decreased delayed nocioception to injury, which outlasts the duration of drug action.

Chronic Pain
There are peripheral and central changes that occur in response to lasting stimuli, in particular chronic inflammatory states. These changes are termed peripheral and central sensitisation.

Peripheral Sensitisation
At the site of tissue damage several influences e.g. cell membrane damage, involvement of local blood vessels, local sympathetic nerve terminals, presence of immune cells and activity of primary afferent neurones, result in the production of a nocioceptor sensitising 'soup'. Substances that have been implicated are hydrogen ions, noradrenalin, kinins, histamine, potassium, prostaglandins, cytokines, serotonin, leukotrienes, nerve growth factors and neuropeptides. The exposure of the nocioceptors to these chemical s results in lowering of the threshold of high threshold receptors, increasing receptor field and conversion of low threshold receptors into high threshold receptors. One of the central substances in these processes is nerve growth factor (NGF)

Nerve Growth Factor (NGF)
In foetus NGF is responsible for the survival and phenotypic development of small diameter afferent and efferent neurons. However in adult, NGF is major

modulating factor in hyperalgesia and allodynia, requiring the functional presence of sympathetic efferent neurons. Via the action of interleukin -1betą and tumour necrosing factor - alfa, NGF is released from inflammatory calls and connective tissue. It then binds to tyrosine kinase A sites on primary nocioceptors that changes the threshold of these cells. NGF also binds to similar site to silent nocioceptors or low threshold receptors and effects the conversion of the role of these receptors to high threshold responders. NGF also feeds back to inflammatory cells causing further release of the substance and a multiplying cascade is formed. The braking system on this peripheral cascade is thought to be the endocannabinoid system. With increased nocioceptor activity, there is increased input to the dorsal horn cells of the spinal cord. The responsiveness of the DHCs is activity related. This is mediated by NGF and modified by N-methyl –D- aspartamate (NMDA), neurokinins and neurotrophins, with nitric oxide and prostaglandins acting as second messengers within the cells. Thus within the spinal cord NGF up regulates the synthesis of peptide neurotransmitters, receptor expression and ion channel density and modulates NMDA receptor expression.

NMDA Receptors

These receptors are fundamental in central sensitisation rather than the perception of pain itself. Stimulation of the receptors increases neurotransmitter release, increases receptive field size, increase magnitude and duration of response and changes response threshold. They also promote new nerve growth.

Pre-emptive Analgesia (PEA)

From the above it can be seen that the experience of the nervous system can and does cause major changes in its structure and function resulting in altered responsiveness. The aim of pre-emptive analgesia is not to prevent pain but to prevent the plastic changes in the CNS resulting from the initial painful experience and so to try to prevent the development of chronic pain syndromes. To be effective drugs must be applied before and during the sensitising stimulus.

Pre-emptive analgesic techniques

These may be divided into traditional application of analgesics, multimodal analgesia, the novel application of traditional analgesics, novel analgesics

1. Traditional Drugs and Techniques

These drugs are given prior to injury to prevent the initial nocioceptive response. This technique has several limitations. Unless high doses are used, opioids are not particularly effective in completely blocking the response. Unfortunately high doses are also associated with the undesirable side effects of respiratory depression and bradycardia. Whilst these effects may be treated intraoperative when the anaesthetist has more control over the animal, the effects limit the high dose drug use as premedication.

Pre-operative nonsteroidal anti-inflammatory drugs may be again have a role, particularly in blocking the inflammatory component of the response, mixed cyclo-oxygenase inhibitors are associated with gastric ulceration and acute renal failure in the presence of hypotension. These side effects have limited their use pre-operative until the development of more specific COX-2 inhibitors e.g. carprofen, meloxicam, which are purported to have increased safety profiles. However although they may have a major role in pre-emptive analgesia, as straight analgesic agents they are not very effective for severe pain and are generally given as adjunctive therapy to opioids. Because their action is through the inflammatory pathways, ideally they should be administered prior to injury for maximum effect.

Local anaesthesics applied topically or as local blocks have been shown to be most effective as pre-emptive analgesics, experimentally. However implicit in the technique of PEA, is that the drugs are acting throughout the period of sensitising stimuli. Most local analgesics are relatively short acting and until very recently continued administration of these drugs post-operatively has not been common. The other disadvantage is that not only is the sensory component blocked but there is often motor blockade as well. In veterinary patients this may cause distress to the animals and result in management problems. In recent years local analgesics have been developed which are more selective for sensory nerves e.g. rocuronium, but as yet there are in common use in veterinary medicine

2. Multimodalanalgesia

As with multimodal anaesthesia, the aim of this technique is to block nocioception at multiple sites to enable the use of low doses of each drug for a more complete block. This will probably prove the most effective technique for PEA. Each drug must still be applied prior to sensitisation and continue for the whole period. Thus an animal may be premedicated with an opiate and a non-steroidal anti-inflammatory agent and then have intra and post-operative opioids combined with a local technique. The use of low doses will reduce the incidence of undesirable side effects. This technique is probably the technique of choice at present for veterinary clinicians.

3. Novel applications of traditional analgesics

Whilst not a technique as such, the central effects of NSAIDs and the effect of opioids at the sites of inflammation should also be considered. Likewise, lignocaine is generally thought of as a local anaesthetic but increasingly this drug is recognised to have major analgesic effects when given at low doses by continuous intravenous infusion.

In veterinary medicine, perioperative analgesics are generally administered parentally, however with the development of fast melt tablet technology (Zydis), there is the possibility tat in the future premedication may be by the oral route. Likewise the rectal route has been under utilized.

Increasingly slow release transdermal forms of fentanyl are being used in veterinary medicine. These should be applied prior to surgery as the effective plasma concentrations only occur after about 12-18 hours. There is an effective duration of action of approximately 72 hours in the dog and 5 days in the cat. Thus this

formulation provides good postoperative analgesia without the need for repeated dosing.

Continuous rate infusions (CRI) of opioids, alpha-2 agonists and low dose ketamine are all being used clinically intra-operatively and post-operatively. Whilst the techniques and dose rates are well described their effectiveness in PEA is not. Theoretically CRI's should be very effective, giving effective plasma levels and so blockade throughout the sensitisation period.

Likewise the epidural application of opioids, alpha-2 agonists and ketamine should be investigated further .

4. Novel analgesics

With the increasing information on the mechanisms of peripheral and central sensitisation, more specific blocking agents have been developed and are commonly used in the experimental setting, There is interest in taking some of these compounds into the clinical setting.

a) Potential Mechanisms to Reduce NGF-induced hyperalgesia

The development of specific antagonists to nerve growth factor so far has proved unsuccessful. However attempts at enhancing the physiological antagonistic control by the use of cannabinoids, for NGF-induced hyperalgesia have been very successful in animal experiments. The endocannabinoid system has been shown to suppress trk-A expression. If cannabinoid antagonists are given experimentally a hyperalgesic state is produced. The evidence for the effectiveness of this approach is so convincing that Type 2 Clinical trials are underway and cannabis has been licensed for medical use in several countries.

b) Although ketamine is a very potent NMDA antagonist, the psychotropic effects are sufficiently marked that is use is limited in man. However very low doses may be useful and have not been full investigated for use in animals. Other NMDA antagonists are under development. The NMDA activity of methadone has historically been overlooked but may account for some of its analgesic effect. Likewise magnesium has been shown to have similar activity.

c) Several anticonvulsants are now in common use in chronic pain states in man, blocking release of neuro-excitatory transmitters or acting on voltage controlled sodium or calcium channels (egg. Gabapentin, Lamotrigine)

This is a rapidly changing field and more drugs for chronic pain control are being proposed each year, which indicates that the existing treatments are not effective in all cases.

Problems with Pre-emptive Analgesia

Although pre-emptive analgesic effects have been clearly demonstrated experimentally, the effects have been less convincing in the clinical setting. There are several possible explanations for this. There is much confusion over what is meant by pre-emptive analgesia and without definition, comparison between studies may be difficult on this point alone. As already suggested in this paper, if analgesia is incomplete, sensitisation will still take place and so the effect of the analgesia will be reduced. Some studies have used relatively minor surgical models, which may be insufficient to stimulate central sensitisation . Other studies have used pain states that have been established prior to the administration of the analgesic and so sensitisation has already taken place. Other reasons may be that the duration of analgesia is shorter that the stimulus duration or that the analgesia is inappropriate for the stimulus. The final point is that in clinical trials it is unethical to have and analgesia-free control group so that all subjects are subject to some form of analgesia and this may decrease the power of the study.

In Conclusion

Understanding processes allows logical therapy in any area of medicine but particularly in the field of pre-emptive analgesia. The aim of the therapy is to pre-empt and block central excitatory changes in the CNS in response to nocioceptive inputs and so to prevent longer lasting structural and functional changes in the system. In future this may be achieved by specific antagonists to compounds involved in this process, but at present multimodal analgesia with a long duration is probably the most effective means we have of blocking the primary and secondary phases of injury.