CONTROL OF ORAL PAIN : A DISCUSSION

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SUMMARY: To be totally effective in dealing with both the peripheral and central components of oral pain, one must make an informed selection of the drugs used. Unless there is specific contra-indication, the anti-inflammatory analgesics should be considered a part of any regimen for the control of oral pain. The "para-aminophenol" drugs considered for use only as a substitute. If stronger oral analgesics are required, careful consideration should be taken to include those narcotics which have low oral/parenteral dose ratios.

Introduction

Pain, in its totality, has both a peripheral and a central component. The peripheral component involves the initiation of a message, *via* the peripheral nervous system, that tissue damage has occurred. The central component adds the effect, motivational approach or understanding that our particular cultural background gives to pain. The two components together produce the total perception, per individual, for a particular stimulus. The clinician must take into account both elements if he is to be effective in the pharmacologic management of pain. This dual approach is particularly important in the management of fifth (V) nerve pain.

V nerve pathways

Unlike most somatic pain, V nerve pain is primarily mediated through small-diameter, relatively slow-conduction A delta and C fibres. There is little or no contribution from the large diameter, rapid-conduction A Alpha somato-sensory fibres which usually contribute a spatiotemporal discriminative capacity to a pain stimulus in a peripheral nerve. This may be the reason why V nerve pain shows very little stereognostic localization on the cerebral cortex.

Prior to reaching the cerebral cortex, V nerve stimuli transverse the hypothalamus, thalamus and limbic forebrain structures. The forebrain structures, in particular, are intimately involved in subserving the motivational-affective dimension of pain perception. Fifth nerve pain also tends to radiate throughout the brain stem proper, providing stimuli to the nuclei of the III, IV, VI, VII, VIII, IX, X and XII nerves through their anatomic association with the sensory nucleus of V. This radiation effect is very disruptive, affecting more body processes than stimuli arising from any other peripheral source.

Pain control

Pain control may be achieved by pharmacologic intervention at any one of three locations in the nervous system: (a) At the source of the stimulus; (b) Along the route of transmission of the stimulus; (c) At the central nervous system (C.N.S.).

Control at the source

Removal of the source, be it mechanical, chemical or thermal, will usually terminate a painful stimulus unless sufficient local tissue damage has occurred to liberate intracellular hydrolytic proteinases at the site of injury. The release of the lysosomal proteinases is, at least, modulated by the synthesis of a hydroxycarboxylic acid, prostaglandin E_1 at the site. Following release, the proteinases are thought to act on a class of body plasma proteins, the alpha 2 globulins, breaking them down into 9 or 10 amino acid polypeptide chains collectively referred to as "kinins". Even in extremely low doses the plasma kinins can produce painful stimuli by their direct effect on peripheral nerve endings. Prostaglandin E_1 may mediate this effect of the kinins by its ability to alter the threshold of the affected nerve endings. The kinins also appear to be associated with vasodilation and increased capillary permeability which result in the formation of local oedema.

The local tissue effects of a pain producing stimulus can be pharmacologically antagonized by the anti-inflammatory analgesics. The antagonism occurs peripherally and is in addition to any central, thalamic, analgesic effects of the drugs. This peripheral effect is not seen with the "para-aminophenol" drugs, phenacetin and acetaminophen, or with the narcotic analgesics (Table I).

Table I
Primary therapeutic effect of common analgesic drugs

Analgesic drug	C.N.S. analgesia	Antipyresis	Peripheral analgesia
Aspirin	+	+	+
Phenacetin	+	+	—
Acetaminophen	+	+	—
Phenylbutazone	—	—	+
Narcotic derivatives	+	+	—

The anti-inflammatory analgesics appear to manifest their peripheral pain control through their ability to prevent the release of lysosomes from injured cells, probably through their antagonism of the prostaglandin E_1 synthesis mechanism. The "salicylate" and the "pyrazolon" drugs are the most widely used anti-inflammatory analgesics for the control of pain at its source, that is, at the tissue level.

Control along the route of transmission

The next step, intervention into the transmission of a painful stimulus, involves the injection of a chemical in close proximity to a peripheral nerve to create a conduction block. This usually takes place somewhere between the site of injury and the C.N.S. We will limit our discussion to the actions of those local anaesthetics typically used to control oral pain.

Basically, the local anaesthetic drugs operate by interfering with the generation of an action potential. They accomplish this by blocking large transient increases in the permeability of the axolemma to sodium ions normally produced by a threshold stimulus to a nerve. The exact mechanism of this blocking action is not thoroughly understood.

Chemically, the local anaesthetic drugs are structurally active as secondary or tertiary amines existing as positively charged substitution ammonium ions or as uncharged molecules depending on the pH of their environment. It is generally stated that the free base or un-ionized form of an anaesthetic drug, which is lipid soluble, allows it to pass through the tissues surrounding a peripheral nerve. Because the pKa (dissociation constant) of most local anaesthetics lies between 8.0 and 9.0, only 10 to 20 per cent of an anaesthetic solution will be in the base form if injected into normal, healthy tissue with the slightly basic pH of 7.4 (Table II).

Table II
Dissociation constants of local anaesthetics at pH 7.4

Anaesthetic	pKa	Percentage un-ionized at pH 7.4
Lidocaine	7.86	26
Tetracaine	8.49	10
Dibucaine	8.54	7
Cocaine	8.80	4
Procaine	8.92	3

This is important because these drugs often have to diffuse through inflamed connective tissue and cellular membranes to reach their site of action. Clinicians are aware of the problems of achieving good anaesthesia in an inflamed, low pH environment which tends to push the equilibrium of the local anaesthetic away from the free base form toward the ionized, slow diffusing form.

Again, although the exact mechanism of action is not known, once the anaesthetic solution arrives at the axolemma, it is generally believed to be the ionized form rather than the free base that is involved in the actual blockage of the nerve action potential. Oral pain control by means of a local anaesthetic is usually applicable only to those painful stimuli which are relatively short in duration and do not cause extensive tissue damage.

Control at the C.N.S.

Pharmacologically speaking, the analgesic drugs exert their greatest influence on the control of pain at the C.N.S. level. We will first discuss the action of the non-narcotic analgesics as they affect the C.N.S.

The drugs of this group include "salicylates", the "para-aminophenol derivatives" and the "pyrazolon derivatives". At the C.N.S. level they all have, to some degree, both antipyretic and analgesic effects. Their antipyretic activity is aimed at the hypothalamic nuclei through which they lower body temperature by "resetting" the body thermostat. Their C.N.S. analgesic activity, through supraspinal, is thought to be subcortical because, in analgesic doses, they do not normally cause mental clouding, hypnosis or sedation. Since most painful stimuli appear to be integrated in the thalamus, it is believed that the non-narcotic analgesics exert their pain control mainly through the pain centres in this area. As a group, they are an effective control of mild to moderate

oral pain. In normal therapeutic doses they do not alter the appreciation or affect component of oral pain or mitigate its disruptive effect on the C.N.S. Only the narcotic analgesics are able to accomplish this.

Depending on the dose the narcotic analgesics produce C.N.S. analgesia, euphoria, mental clouding, sedation and sleep. Yet, if narcotics are used in pain-free individuals they sometimes produce dysphoria. All drugs of this class are variably addicting. Unlike the barbiturates, narcotics do not cause motor inco-ordination. Usually, they are more effective in controlling continuous dull pain than sharp intermittent pain. At the same time, the perception of pain is not always decreased even in those patients who obtain satisfactory pain relief with therapeutic doses of a narcotic analgesic. There appears to be an altered reaction to the stimulus. The patient feels the pain but does not seem to mind it. (Physiologic pain *v.s.* pain as a component of suffering. Appreciation of a sensation *v.s.* reaction to that sensation).

As stated previously, narcotics do not have a peripheral analgesic effect and thus do not alter the threshold or responsivity of nerve ending to noxious stimuli. In contrast to the non-narcotics, they do seem to have an effect on multisynaptic pathways at the spinal level as well as their well-known subcortical effects. Like the non-narcotics they have a body temperature decreasing effect on the hypothalamus.

All narcotics produce equal amounts of respiratory depression in equal analgesic doses. There appears to be an increased threshold in the respiratory centre for the CO₂ drive mechanism. All narcotics cause nausea and vomiting by their direct action on the chemoreceptor trigger zone (C.T.Z.) in the medulla. This stimulation occurs at low drug concentrations, while at high concentration the C.T.Z. is obtunded. Thus, nausea and vomiting is usually seen soon after the administration of a narcotic or as a late effect of the drug. By their direct action on smooth muscle, narcotic analgesics tend to produce cramping and decreased intestinal peristalsis resulting in an increased incidence of constipation. At the same time, a therapeutic dose of morphine tends to dilate cutaneous vessels, causing flushing in the mantle area which frequently results in pruritis and sweating.

It has been determined that an optimal narcotic dose is that subcutaneous dose which will control moderate to severe pain in 70 per cent of the population. This works out to be 10 mg/70 kg of body weight for morphine and serves as a standard by which the potency of all analgesics are measured (Table III).

Narcotic addiction has been defined by the World Health Organization as that stage of drug dependence where the patient becomes useless to society. Dependence can be divided into physiologic dependence and psychologic dependence. Physiologic dependence indicates there have been cellular alterations such as changes in cell metabolism. Psychologic dependence is usually manifest by a mental drive or need. Addiction is usually caused by a continued use of a drug which produces tolerance and in turn produces a need for an increased dose to receive the continued desired effect.

The addicted patient, who has been taking morphine or pethidine type drugs is driven to request his next dose by a desire to maintain what to him is physiologic and psychologic normalcy. As previously stated, in therapeutic doses, these drugs can produce both excitatory and depressive effects. Usually the depressive effects or euphoric state masks any excitatory effects in the non-addicted patient. In the addicted patient the

Table III
Analgesic efficiency of narcotic derivatives

Narcotic derivative	Equal analgesic dose to M.S.	Oral/parenteral analgesic dose
Morphine	10 mg	6/1
Pethidine	65 mg	7/1
Pentazocine	30— 40 mg	3/1
Codeine	120 mg	2/1
Alphaprodine	30 mg	4/1
Proladone	14 mg	2/1
Dextropropoxyphene	150 mg	2/1

opposite is true. After repeated doses the excitatory effects tend to last longer than the depressive or euphoric effects. Thus, the addicted patient tends to request additional drug to overcome his flushing, sweating, cramping, itching, chills and hallucinatory symptoms. But again, the euphoric and depressive effects will wear off first and he will seek another dose of the drug to mask the longer lasting stimulatory effects. The cycle continues.

Conclusion

It has not been our intent to present a comprehensive pharmacologic description of the analgesic and local anaesthetic drugs. We have touched on the site of action and relative dosages only to help elucidate the concept of total pain control. Other factors such as potency, absorption, metabolism, excretion, side effects and toxicity, to mention a few, have to be considered if one is to accurately compare the efficacy of using any one drug over another. Nevertheless, at least three generalizations can be made. The concept of total pain control dictates the use of drugs which antagonize *both* the peripheral and central components of pain. Secondly, when selecting a local anaesthetic, an attempt should be made to pick a drug with a *low* pKa value and thus provide for a rapid diffusion to the site of action. Finally, if oral narcotics are used, preference should be shown to those drugs with *low* oral/parenteral analgesic dose ratios.