Headache Platform

The use of opioids in the treatment of headache

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Introduction

Among the more difficult problems facing medical practitioners is the treatment of primary headache pain. Primary headache can present in a number of different patterns, predominantly tension headache, migraine, and the autonomic cephalgias, but one of the most debilitating forms is Chronic Daily Headache (CDH). Whereas some headaches respond to rescue medications such as the triptans, NSAIDs, opioids, or combinations thereof, CDH often proves refractory. As CDH affects as many as 4-5% of the population,[1-3] its management represents a significant challenge. Approximately 75% of individuals with CDH suffer from Medication Overuse Headache (MOH), formerly known as "rebound headache". MOH frequently develops after frequent and sustained use of analgesics for the suppression of mainly migraine pain. The nature of the pain slowly changes and eventually assumes the characteristics of chronic tension-type headache interspersed with episodes of migraine. Over time the headaches become more frequent and more intense, and more refractory to analgesic therapy. Paradoxically, the treatment with opioids for the original headache has the potential for causing more frequent and more severe headaches than the original complaint. On the contrary, patients with CDH but who had not undergone opioid therapy were more successfully treated than those with previous opioid treatment.[4]

Although the use of opioids in the abortive treatment of severe episodic primary headache is an important option, there are important limitations to their use in conditions such as CDH, which necessitate their more frequent use.[5]

Mechanism

It has been shown repeatedly that abnormal, opioid-induced pain is not limited to headache pain, which indicates the possible activation of a global pronociceptive mechanism by persistent analgesic exposure. Spontaneous pain, hyperaesthesia, and allodynia unrelated to the original pain have been produced by the long-term spinal administration of morphine.[6-9] Increased opioid-induced pain sensitivity has been shown to reduce 6 months after termination of the opioids, indicating that opioid-induced pain may be a reversible phenomenon.[10]

The mechanism by which opioids mediate abnormal pain involves descending facilitation, which promotes spinal sensitisation and consequent pain enhancement. The rostroventromedial medulla (RVM) is an important site for the processing of ascending nociceptive signals and of descending inhibitory and facilitatory pain modulatory circuits.[11] A number of studies have implicated the RVM as an important source of descending facilitation.[12-20]

Three types of neurons are involved

The RVM contains three types of neurons, distinguished by their responses to nociceptive stimuli, called the 'on' cells, 'off' cells, and 'neutral' cells. Activation of the off-cells produces inhibition of nociceptive input, whereas the on-cells activate descending facilitation of nociceptive processing.[21-23] Activation of the off cells leads to inhibition of nociceptive input and inhibition of nocifensive responses.[21-24] The on-cells, on the other hand, activate a descending facilitation of nociceptive processing through both local interactions within the RVM and descending systems projecting to the spinal cord.

The neutral cells show no electrophysiologic responses to nociception.[25] Knockdown of these on-cells resulted in a loss of the thermal and tactile hyperaesthesias induced by microinjection of cholecystokinin (CCK) into the RVM.[26] This observation taken with others provides compelling evidence that the activation of pain facilitatory systems from the RVM represents a critical component of opioid-induced abnormal pain, and that this pathway may be evoked by increased availability of CCK in the RVM.[25]

Enhanced release of exitatory transmittors

Further evidence indicates that activation of descending facilitation leads to enhanced release of excitatory transmitters in the spinal cord, which are possibly related to increased spinal dynorphin content.[27,28] (Dynorphin, an endogenous opioid Î-agonist, is strongly pronociceptive when raised to pathological levels in the spinal cord.)[29] Spinal injection of antiserum to dynorphin abolished opioid-induced enhanced pain and unmasked the antinociceptive action of the still-present opioid.[30] In addition, abolition of opioid-induced abnormal pain and upregulation of spinal dynorphin also abolish enhanced release of calcitonin gene related peptide (CGRP) from spinal cord sections obtained from morphine-exposed rats.[31] These observations explain a possible mechanism by which pathologically elevated levels of spinal dynorphin may promote spinal sensitization and enhanced pain.[27,28] An important consequence therefore of descending facilitation and enhanced release of neurotransmitters is the development of spinal sensitization.[32] This central sensitisation could underlie progressive worsening of headache in some patients. Significantly, refractoriness to treatment has been demonstrated in those patients who had previously used opioids as compared to those patients who had never been treated with opioids. This is true even in cases of intermittent use.[33] This finding confirms the clinical experience of many authorities that opioid treatment renders patients less responsive to standard treatment.[34]

Discussion

The safety and effectiveness of chronic opioid therapy in the treatment of headache remains controversial. While many practitioners remain convinced that opioid administration for headache is an important option, there is certainly no clear consensus among headache specialists as to when and how often they may be used.

When considering the use of opioids for headache pain, three fundamental questions must be asked:

- Can chronic opioid therapy effectively suppress otherwise intractable headache that is pervasive and detrimental to one's quality of life?
- If so, who is – or is not – an appropriate candidate?
- Does such treatment negatively impact long term headache prognosis?[35]

At this stage, these questions cannot be answered decisively. With regard to the first, long-term evaluation of the effectivity of short- and long-acting opioids administered on a daily scheduled basis, there were enduring treatment responses in 26% of patients.[36] Although this is not a particularly impressive response, it must be borne in mind that the subjects in the study were chronic headache patients who had not previously responded to conventional therapies, and were significantly disabled by their pain. Does one accept the relatively low response rate, or does one condemn those 26% to ongoing pain and suffering? The second question is just as difficult to answer, as it is impossible in most patients to pre-emptively determine who the responders and non-responders are likely to be. One group of patients that has however been identified who are unlikely to respond to long-term opioid treatment comprises patients with borderline personality disorder. They may exhibit psychobehavioural deterioration while taking opioids, and are frequently non-compliant with the required dosing regimen.[37] With regard to the third question – does chronic opioid therapy negatively impact long-term headache prognosis? – there are conflicting data.[38-40]

In practice, however, there are ominous signs that chronic opioid administration may have permanent deleterious effects on headache sufferers. Patients who have experienced an extended period of headache suppression with long-acting opioids, and who have had their doses tapered off, have almost without exception experienced rapid worsening of their headache as the dosage is reduced. When the long-acting opioids are resumed, their pain levels were again reduced.[41]

At this stage, the jury is still out as to whether chronic opioid therapy for intractable headache has an adverse effect on the long-term prognosis. It is clear however that there is a group of patients, albeit a minority, who enjoy a positive response over an extended period, so in certain cases it is of value. It is worth noting that approximately 2% of the population suffer from CDH, and as many as half of those will not respond to even the most aggressive conventional treatment.[42-45]

In conclusion, if chronic opioid therapy is to be considered in selected patients, careful medical, neurologic, and psychological evaluation must be made in each case. In patients considered eligible, there must be frequent follow-up and monitoring coupled with meticulous record keeping – and that most important caveat – *primum non nocere* – must constantly be borne in mind.

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