Opioid is an ancient pain killer. The Greek philosopher Theophrastus was first used an opioid as a pain killer in the third century. Till now it is randomly used in acute, chronic and cancer pain management. There are various opioids (eg- fentanyl, ramifentanyl etc.) continue to be manufactured those share the same basic properties as morphine and pethidine, but at much greater cost. Because of prolong use of opioid, some adverse situation inevitably developed, among them tolerance and hyperalgesia are really a problematic. Opioid induced hyperalgesia (OIH) is a clinical challenge now. OIH is a paradoxical response to an opioid agonist, whereby instead of an analgesic or antinociceptive effect occurring, there is an increased in pain perception. This may occur in the area of the pain being treated or may be a more generalized increased in pain, often with features associated with neuroapthic pain such as hyperalgesia or allodynia. Though, clinically OIH and tolerance are overlapped with each other but in case of OIH, pain will increase with doses paradoxically and in case of tolerance is not.

Basic science studies are beginning to clarify some of the contributory mechanisms, many of which are similar to those that underlie the development of tolerance. From laboratory models of OIH, it is clear that as with many chronic pain states, there are both peripheral and central changes in nociceptive processing. Alteration in the spinal cord are important, with some form of central sensitization occurring. This is likely to involve the ionotropic glutamate receptor, the N-methyl-D-asparate (NMDA) receptor, known to play a key role in central sensitization. C-fibre potentiation has been demonstrated similar to that seen with central sensitization in chronic opioid administration. This presented with NMDA receptor block and a range of studies have demonstrated the efficacy of NMDA receptor antagonist in preventing OIH. Spinal removes in culture show increased NMDA receptor activity after chronic morphine administration, also seen acutely with remifentanyl or a dymorphin agonist. Further evidence for the involvement of glutamate comes from work using gabapentin, which has a presynaptic effect on glutamate release and dose dependently decrease OIH from repeat fentanyl in rats.

Modulation of spinal input by descending pathways from the brainstem is also implicated in the development of OIH, with a shift in the balance between descending inhibitory control towards pronociceptive system. These pronociceptive system may be more active in certain chronic pain states and also seems to play a role in OIH, acting via 5 HT3 and possibly 5-HT2 receptors. Ondansetron a widely used 5-HT3 antagonist blocks signs of OIH.

Peripheral receptors also play a role in OIH, with evidence that the transient receptor potential (TRP)-V1 is important in the development of hyperalgesia. A TRPV1 antagonist was found to reverse OIH, with an associated increased in TRPV1 in the dorsal root ganglia and an increased response to capsaicin. TRPV1 knockout mice did not develop either tactile or thermal hypersensitivity to chronic morphine administration. Alteration in cytokine levels has also been detected in the periphery in mice with OIH, where higher levels of IL-1beta, IL-6, G-CSF, KC, and TNF-alpha were found along with increased mechanical sensitivity.

Intracullar mechanism share some similarities with opioid tolerance. In that blocking L-type calcium channels or using PKC antagonist prevent or reduce OIH. Nitric oxide synthase (NOS) knockout mice show much reduced development of OIH and NOS inhibitors preventing development of OIH.

Genetic factors are also likely to paly a role in susceptibility to OIH. A clinical study of 43 healthy volunteers using a painful thermal stimulus found that individuals homozygous for the met (158) polymorphism of catechol O-methyl transferase gene had greater pain sensitivity after a potent parenteral opioid.

Editorial

Beware of randomly used opioid!

Opioid is an ancient pain killer. The Greek philosopher Theophrastus was first used an opioid as a pain killer in the third century. Till now it is randomly used in acute, chronic and cancer pain management. There are various opioids (eg- fentanyl, ramifentanyl etc.) continue to be manufactured those share the same basic properties as morphine and pethidine, but at much greater cost. Because of prolong use of opioid, some adverse situation inevitably developed, among them tolerance and hyperalgesia are really a problematic. Opioid induced hyperalgesia (OIH) is a clinical challenge now. OIH is a paradoxical response to an opioid agonist, whereby instead of an analgesic or antinociceptive effect occurring, there is an increased in pain perception. This may occur in the area of the pain being treated or may be a more generalized increased in pain, often with features associated with neuroapthic pain such as hyperalgesia or allodynia. Though, clinically OIH and tolerance are overlapped with each other but in case of OIH, pain will increase with doses paradoxically and in case of tolerance is not.

Basic science studies are beginning to clarify some of the contributory mechanisms, many of which are similar to those that underlie the development of tolerance. From laboratory models of OIH, it is clear that as with many chronic pain states, there are both peripheral and central changes in nociceptive processing. Alteration in the spinal cord are important, with some form of central sensitization occurring. This is likely to involve the ionotropic glutamate receptor, the N-methyl-D-asparate (NMDA) receptor, known to play a key role in central sensitization. C-fibre potentiation has been demonstrated similar to that seen with central sensitization in chronic opioid administration. This presented with NMDA receptor block and a range of studies have demonstrated the efficacy of NMDA receptor antagonist in preventing OIH. Spinal removes in culture show increased NMDA receptor activity after chronic morphine administration, also seen acutely with remifentanyl or a dymorphin agonist. Further evidence for the involvement of glutamate comes from work using gabapentin, which has a presynaptic effect on glutamate release and dose dependently decrease OIH from repeat fentanyl in rats.

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Genetic factors are also likely to paly a role in susceptibility to OIH. A clinical study of 43 healthy volunteers using a painful thermal stimulus found that individuals homozygous for the met (158) polymorphism of catechol O-methyl transferase gene had greater pain sensitivity after a potent parenteral opioid.
Reviewing studies of the clinical syndrome of OIH has highlighted the lack of good quality clinical research in this area, despite the fairly extensive basic science evidence.

Further research is needed to define the clinical problem, in order to develop clinical strategies to reduce OIH. Likely targets would include agents that act on glutaminergic system, such as NMDA receptors antagonists or gabapentin, and also using agents to target peripheral effects, such as non steroidal anti-inflammatory drugs, or more novel agents, such as TRPV1 antagonists. Given the complex nature of the problem and the multiple factors likely to be involved, including genetic influences, dose, duration, type and route of administration of opioid, along with the effect of the type of pain being treated, clinical research will need to be appropriately targeted to produce meaningful results.

A small number of studies have looked at the clinical characteristics of OIH patients with chronic pain on strong opioids. Both opioid dose and duration of treatment seem to be important factors affecting descending inhibitory control and also pain and unpleasantness to a defined noxious stimulus particularly in females.9,10

In summary, it is simply defined that a paradoxical increase in pain as a result of opioid administration in OIH but in practiced the situation is much more complex either clinically or neurobiologically. Though there are many evidences in basic science studies in favour of OIH but in clinical studies still to small. Besides, studies need to be desinged to differentiate between acute tolerance and OIH. Now a days, we are anxious due to misuse and abuse of opioid in our country. As an anaesthesiologist we faced some problem in perioperative management of patient specially in anaesthetic requirement.

References:

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