

Opioid Induced Hyperalgesia

M Mudely

Commentator: L Naidoo

Moderator: U Singh



UNIVERSITY OF
KWAZULU-NATAL

INYUVESI
YAKWAZULU-NATALI

Department of Anaesthetics

CONTENTS

INTRODUCTION	3
DEFINITIONS	3
Hyperalgesia	3
Opioid Induced Hyperalgesia	3
Tolerance	4
OPIOID REGIMENS AND OIH	7
Dose and Concentration	7
Route of Administration	8
Categories of Opioids	8
Duration of Usage	11
MECHANISMS	12
CLINICAL IMPLICATIONS	19
MANAGEMENT	20
Perioperative Setting	20
Chronic Opioid Users	22
CONCLUSION	25
REFERENCES	26

INTRODUCTION

There is an increasing body of literature from both clinical and basic science studies regarding opioid induced hyperalgesia (OIH). Although there has been debate about its clinical relevance, it is becoming clear that OIH presents a clinical challenge in acute, chronic and cancer pain settings.

Evidence so far suggests that OIH does develop in humans and may have important clinical implications. Data supporting this notion has been collected in three distinct experimental settings:

- in former opioid addicts maintained on methadone
- in patients undergoing surgery
- in human volunteers tested in experimental pain paradigms.

DEFINITIONS

Hyperalgesia

The International Association of the Study of Pain defines hyperalgesia as an increased response to a stimulus which is normally painful.

Opioid Induced Hyperalgesia

Opioid induced hyperalgesia (OIH) is defined as a state of nociceptive sensitization caused by exposure to opioids. It is characterised by a paradoxical response whereby a patient receiving opioids for the treatment of pain could actually become more sensitive to certain painful stimuli.

The type of pain may be the same as the underlying pain or might be different from the original underlying pain. OIH appears to be a distinct definable and characteristic phenomenon that could explain the loss of opioid efficacy in some patients ⁽¹⁾.

Tolerance

Opioid tolerance is a phenomenon in which repeated exposure to an opioid results in decreased therapeutic effect of the drug or need for a higher dose to maintain the same effect ⁽²⁾.

There are several aspects of tolerance relevant to this issue:

Innate Tolerance

This is the genetically determined sensitivity or lack thereof, to an opioid that is observed during the first administration.

Acquired Tolerance

This can be divided into pharmacodynamic, pharmacokinetic and learned tolerance.

- *Pharmacodynamic tolerance*

This refers to adaptive changes that occur within systems affected by the opioid, such as opioid induced changes in receptor density or desensitisation of opioid receptors. The response to a given concentration of a drug is reduced. This type of tolerance may involve the NMDA receptor.

- *Pharmacokinetic tolerance*

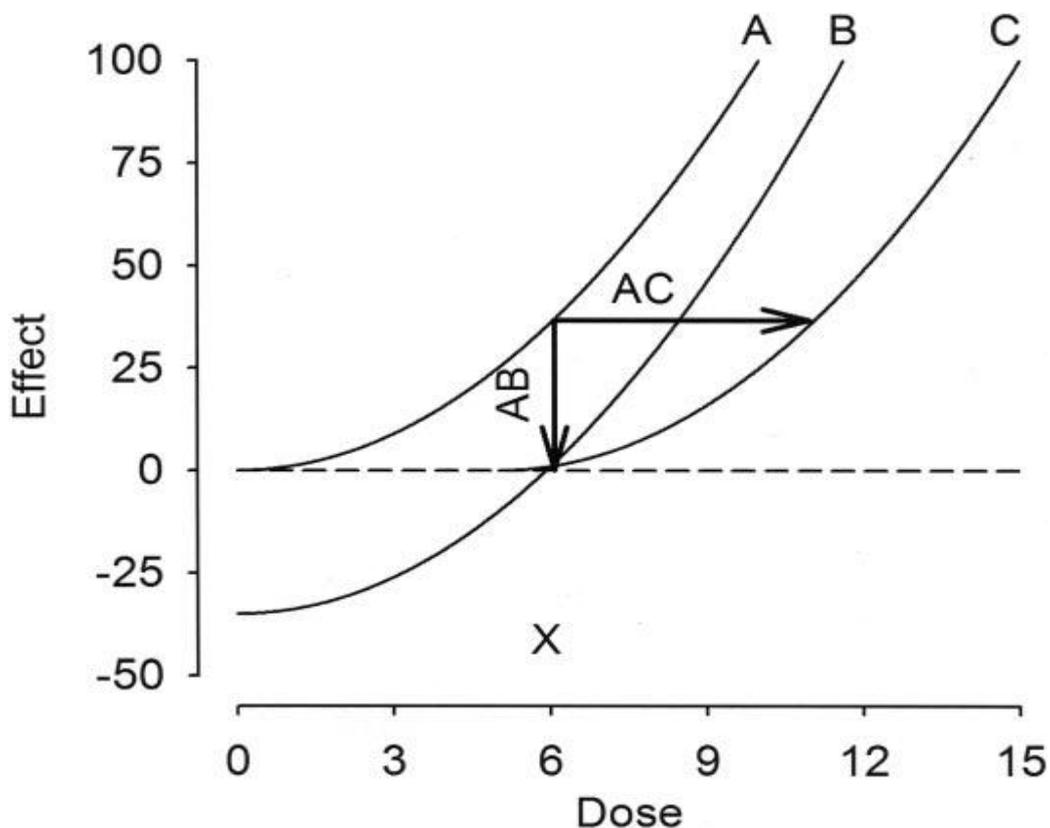
After repeated drug administration there is a reduced concentration of the opioid in the blood or at the site of drug action. The most common mechanism of this phenomenon is an increase in the rate of the metabolism of the opioid.

- *Learned tolerance*

This type of tolerance develops when environmental cues are consistently paired with the administration of the drug.

Differentiation between OIH and tolerance requires a method directly assessing pain sensitivity. Implementation of such a method into a clinical trial is difficult and has not yet been attempted ⁽³⁾.

TOLERANCE VS OIH



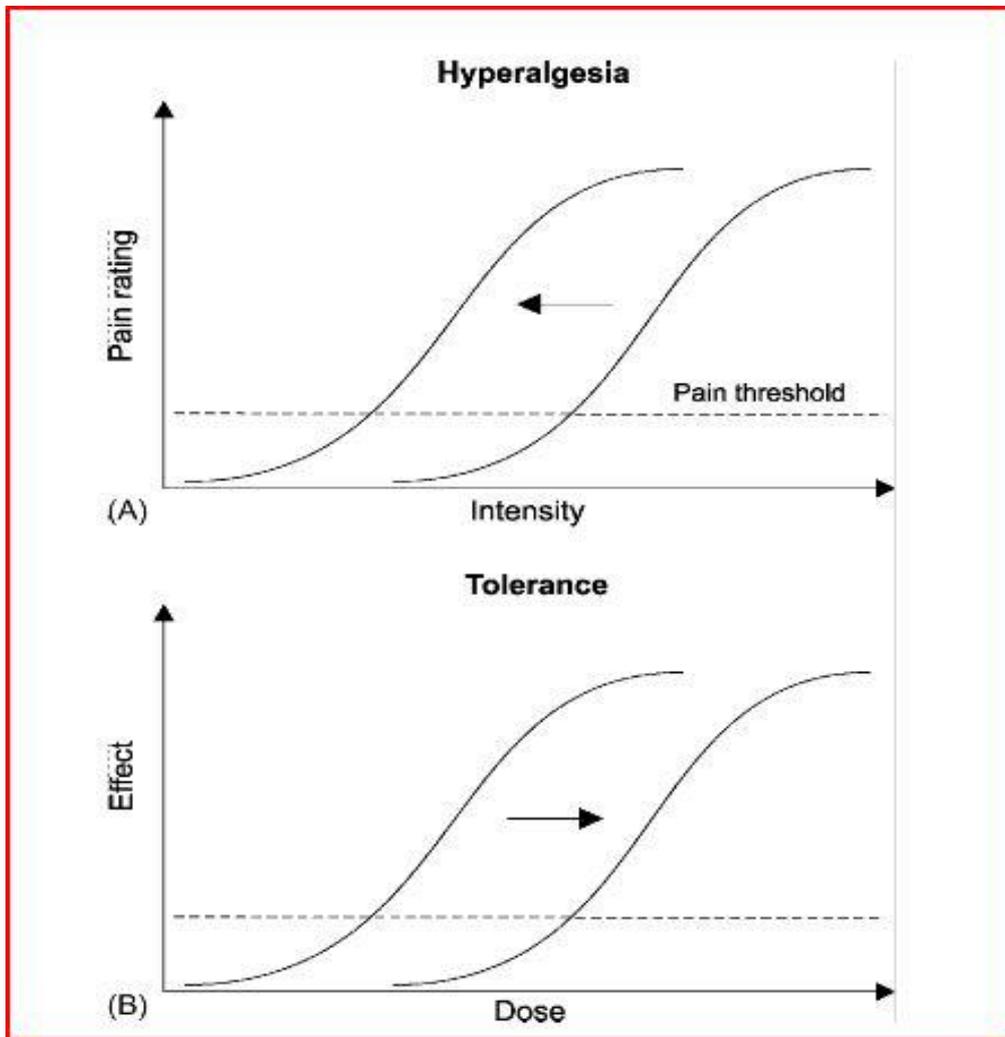
If tolerance is expressed, decreased drug potency is reflected by a right-shift of the dose versus effect relationship (AC).

If OIH is expressed, increased pain sensitivity is reflected by a downward shift of the dose versus effect relationship (AB).

Both, tolerance, or OIH result in a decreased effectiveness of a given drug dose (X).

Both tolerance and OIH are pharmacologically distinct phenomena. This can be demonstrated by the dose vs effect curve. If tolerance is expressed, decreased drug potency or decreased sensitisation of the antinociceptive pathway to opioids, is reflected by a right shift of the dose vs effect relationship. If OIH is expressed, increased pain sensitivity or sensitisation of the nociceptive pathways, is reflected by a downward shift of the same relationship. Both tolerance and OIH result in a decreased effectiveness of a given drug dose.

Alternatively hyperalgesia is characterised by a leftward shift of the stimulus intensity –pain curve ie a normally non painful stimulus becomes subsequently noxious ie allodynnia, while a normally painful stimulus increases in intensity.



- (A) Hyperalgesia is characterised by a leftwardshift of the stimulus—pain curve, i.e. a normally non-painful stimulus becomes subsequently noxious (=Allodynia), while a normally painful stimulus increases in intensity.
- (B) A rightward shift of the dose—effect curve can be observed for the tolerance development i.e. the drug loses its potency.

Since tolerance is characterised by decreasing efficacy of a drug, it can be overcome by increasing the dose. OIH cannot be overcome by increasing the dose since it is a form of pain sensitisation induced by the drug. Pain is worsened with increased opioid dosing and is improved by reducing or eliminating the opioid ⁽⁴⁾.

Further complicating matters, the phenomena of tolerance and hyperalgesia can coexist, at least theoretically. Prospective studies in humans are needed to clarify whether both phenomena develop simultaneously and to determine how they are interrelated ⁽⁵⁾.

OPIOID REGIMENS AND OIH

Several factors regarding an opioid regimen may influence the development of OIH.

Dose and Concentration

It is still unclear as to what opioid dose ranges lead to OIH.

The data available from human studies investigating dosing schedules in terms of OIH development are limited and conflicting. Prospective controlled clinical studies have reported increased postoperative pain despite increased postoperative-opioid use.

A study investigating the effects of cumulative-morphine consumption in patients undergoing surgery found that a large dose of intraoperative remifentanyl increased postoperative pain and morphine consumption. In contrast, no increased pain or postoperative-opioid consumption in patients receiving intraoperative remifentanyl during elective gynaecological surgery has also been reported, offering mixed support for the evidence of OIH development after acute-perioperative opioid exposure. The contradictory reports could have arisen due to differences in opioid dosing, suggesting that the development of OIH could be dose dependent.

In a study by Zhao, electrophysiologic recordings of NMDA current were made from cultured rat dorsal horn neurons treated with remifentanyl at various concentrations for 60 min. The remifentanyl-induced enhancement of NMDA-evoked peak current amplitude was shown to be concentration dependent and occurred at clinically relevant concentrations.

Spinal fluid concentrations of remifentanyl required for the enhancement of NMDA receptor responses were achieved with intravenous infusions of relatively low doses of remifentanyl ranging from 0.1 to 0.2 ug/kg/min

The time-dependent enhancement of NMDA current by remifentanyl is relevant to the acute development of OIH or tolerance. This correlation of *in vitro* and *in vivo* effects suggests that the remifentanyl-induced changes are due to the recruitment of intracellular processes that operate on relatively rapid time scales, within 36 min. These processes may include NMDA receptor phosphorylation, e.g., by PKC or transport of subsynaptic NMDA receptors to the cell surface.

Opioid receptor phosphorylation, arrestin binding, and uncoupling of G-protein activation resulting in receptor desensitization have been shown to occur within 10 min in some instances. Others, such as gene induction, superactivation of adenylyl cyclase, and accumulation of cyclic adenosine monophosphate may play less of a role.⁽⁷⁾

Route of Administration

Opioid given through neuraxial or systemic routes in animal studies are comparable to moderate opioid doses in clinical settings and have been shown to induce OIH.

Categories of Opioids

There may be a difference between different categories of opioid medications in terms of their ability to induce hyperalgesia.

Fentanyl

In animal experiments, after repeated application of fentanyl, a dose-dependent reduction of pain thresholds can be observed after fading of the analgesic effect. With application of 80ug/kg, this effect lasts only 1 day, while an application of 400ug/kg produces a heightened pain sensitivity that can still be observed after 5 days.

Similarly, the painfulness of an experimentally produced inflammation is further increased after cessation of fentanyl therapy. Since this hyperalgesia can be alleviated, in all cases, by the NMDA-receptor antagonist ketamine, fentanyl is supposed to already have caused a significant activation of NMDA-receptor systems after short term application.

This could also explain the partial loss of analgesic effect of morphine when applied immediately after the fading fentanyl analgesia. It has also been demonstrated that the combination of fentanyl with ketamine or N₂O restores the analgesic strength following morphine application. In line with these results, patients receiving high intraoperative fentanyl doses (15ug/kg), as opposed to low fentanyl doses (1ug/kg), have significantly higher postoperative morphine consumption.

Alfentanil

In animal experiments, a reduction of analgesic effect can already be observed during the first hour after alfentanil application. In addition to PKC-mediated coupling of G-proteins, activation of NMDA-receptor systems can underlie this effect. The clinical relevance of these findings is, however, questionable. In postoperative pain therapy, no significant dose increase of alfentanil has been found for a 6-h infusion indicating the absence of relevant tolerance development.

Remifentanil

Similar observations have been made with the fast acting opioid remifentanil. One study reports that continuous infusion of remifentanil in healthy volunteers leads to a rapid decrease of its analgesic effect to a quarter of its maximal effect. The lack of a control group as well as the exclusion of many volunteers, however, confounds these results. In other studies, a clear dose-dependent effect has been

demonstrated for remifentanil; also, during a 3-h infusion, no loss of effect of the opioid was observed.

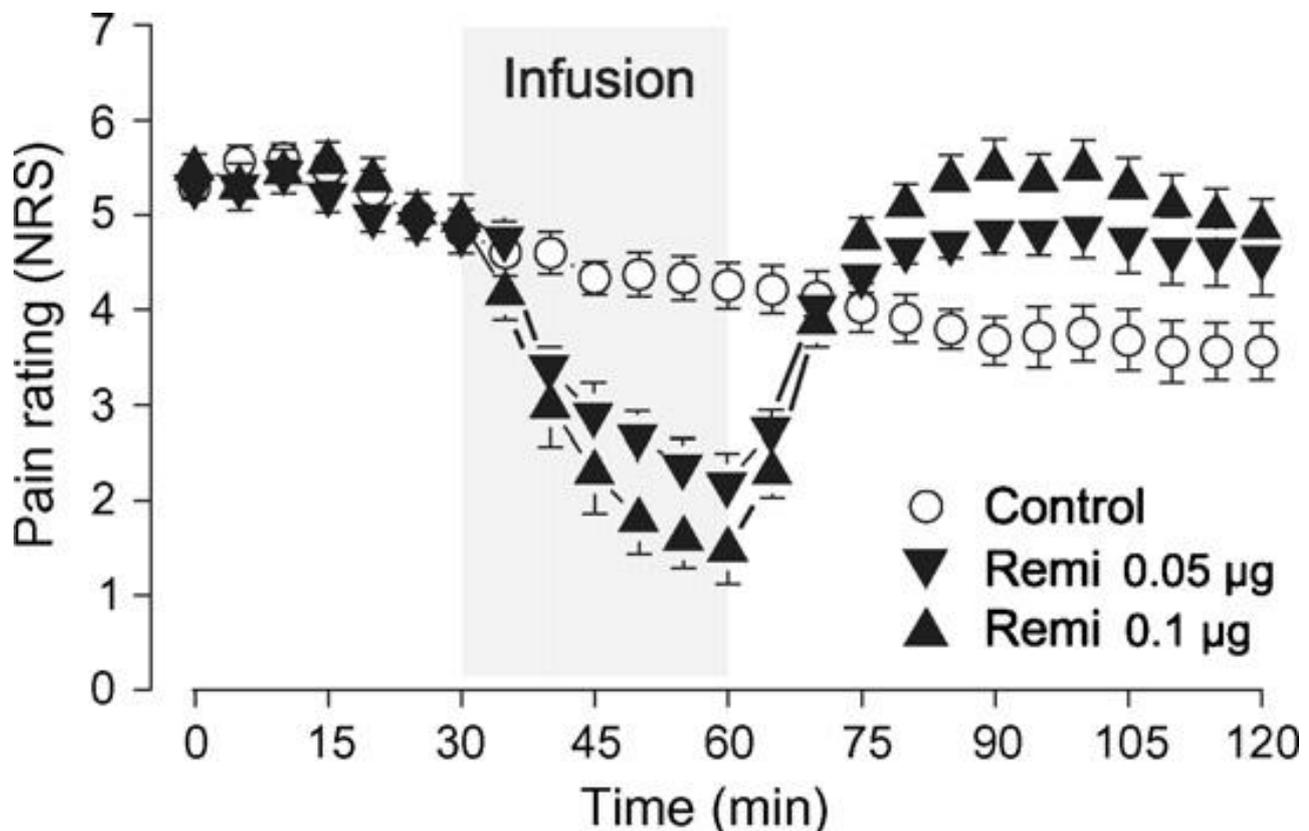
These findings were verified by clinical observations in postoperative pain therapy. Nevertheless, there is evidence that remifentanil, even after a short period, causes a clinically relevant activation of pronociceptive systems leading to increased pain responsiveness after the discontinuation of the opioid.

Patients who underwent abdominal surgery, and received high intraoperative remifentanil dose (0.3ug/kg/min) had a significantly higher postoperative morphine consumption than the patient groups that received a low intraoperative dose (0.1ug/kg/min) of remifentanil.

However, if remifentanil is administered for a shorter period and at a lower dose, no clinically significant difference can be observed in postoperative pain medication. These results imply that the activation of pronociceptive systems is time and dose related. Experimental investigations support these ideas. In several studies with healthy volunteers, a dose-dependent increase in pain sensation and a threshold decline for mechanical stimuli have both been observed after the discontinuation of opioids.

The combination of remifentanil with ketamine also causes an inhibition of central sensitisation processes. These results are in line with clinical observation according to which intraoperative application of ketamine (Bolus 0.15 mg/kg, followed by a long-term infusion of 2ug/kg min) in addition to remifentanil, caused a significant reduction of postoperative morphine consumption.

In a human volunteer model using electrically evoked pain, remifentanil increases this electrically evoked pain sensation upon cessation. This increase of pain has been attributed to remifentanil induced opioid receptor internalisation and consecutively reduced analgesia by endogenous opioids, similar to an acute withdrawal.



Time course of pain ratings during continuous electric stimulation in humans. The current was delivered by a stainless-steel needle which was inserted intradermally over a length of 1 cm at the central volar forearm of the subjects. A skin surface electrode (1.0 cm×0.5 cm) was attached directly above the needle serving as anode. The infusion of remifentanyl causes an initial, dose dependent decrease in pain intensity. After completion of the infusion, a significant pain increase can be observed. (B) During the infusion of remifentanyl, the observed antihyperalgesic effects are associated with a significant increase in the area of secondary mechanical hyperalgesia after completion of infusion. Shown are averages and standard error (n = 13).

Morphine

In contrast to the observations in the perioperative setting, hyperalgesic pain conditions already emerge *during* administration in a long term (days to weeks) application of this opioid. It can be shown experimentally that both, systemic and intrathecal applications of morphine activate the NMDA-receptor system. Specific (MK-801) and unspecific NMDA receptor antagonists (ketamine, dextromethorphan) cause a significant reduction of hyperalgesia.

These findings are supported by clinical observations, in which a combination of morphine with ketamine or dextromethorphan reduces analgesic consumption and prevents the occurrence of paradoxical pain, particularly in chronic use. Additionally, dose-dependent excitatory effects can be observed under morphine therapy and are usually attributed to accumulation of M-3-G in plasma. In addition to pain increase and the occurrence of new pain qualities, myoclonia and seizures can indicate an accumulation of M-3-G.

Methadone

Unlike morphine, methadone functions antagonistically with the NMDA-receptor. It can be shown that this antinociceptive interaction contributes to an improvement of analgesia. Although a cross-tolerance with morphine is assumed, the tolerance development and resulting hyperalgesia under morphine can be prevented by methadone.

In addition to the blocking of NMDA-receptors, higher receptor specificity of methadone is also crucial for these effects. However, a decrease of pain thresholds can also be observed under therapy with methadone. These findings can be traced, in part, back to the study design and the pharmacokinetic properties of the opioid: methadone possesses a very long half-life and, therefore, was administered only once per day. Thus, the findings might indicate a brief withdrawal with clinically relevant activation of pronociceptive systems ⁽⁸⁾.

Duration of Usage

The temporal correlation between opioid therapy and the development of OIH remains unknown, although it has been demonstrated in acute, chronic and cancer pain settings ^(2,6).

Two fundamental patterns characterizing the onset and resolution of OIH can be distinguished.

The first is observed after the acute administration of an opioid, that is, the systemic administration of one to four relatively high opioid doses within 1 h. Morphine, heroin, and fentanyl have been administered acutely to mice and rats and evoked a consistent, biphasic, and dose dependent response.

Intense antinociceptive effects were followed by a 2- to 3-h period of mechanical hyperalgesia. However, one of these studies demonstrated prolonged hyperalgesia that lasted up to 5 days after a very high dose of fentanyl. Thus acute opioid administration typically evoked a transient hyperalgesic response lasting for hours, except for some instances of prolonged hyperalgesia lasting for days. The duration of acute OIH clearly is related to the opioid dose.

More commonly investigators have exposed animals to opioids on a more chronic time course (3–12 days). Animals given repeated systemic or intrathecal boluses of opioids developed progressive hyperalgesia to thermal or mechanical stimuli over the course of several days. The time course of resolution of OIH was similar to the time course of its development.

Of particular interest is a study by Celerier *et al.* documenting that animals with normal noxious sensitivity after recovering from OIH expressed recurrent and

robust hyperalgesia if challenged with a single bolus of either drug, an opioid agonist or antagonist. These findings have two important implications.

First, animals that apparently recovered from OIH remained sensitized to the hyperalgesic effects of opioids.

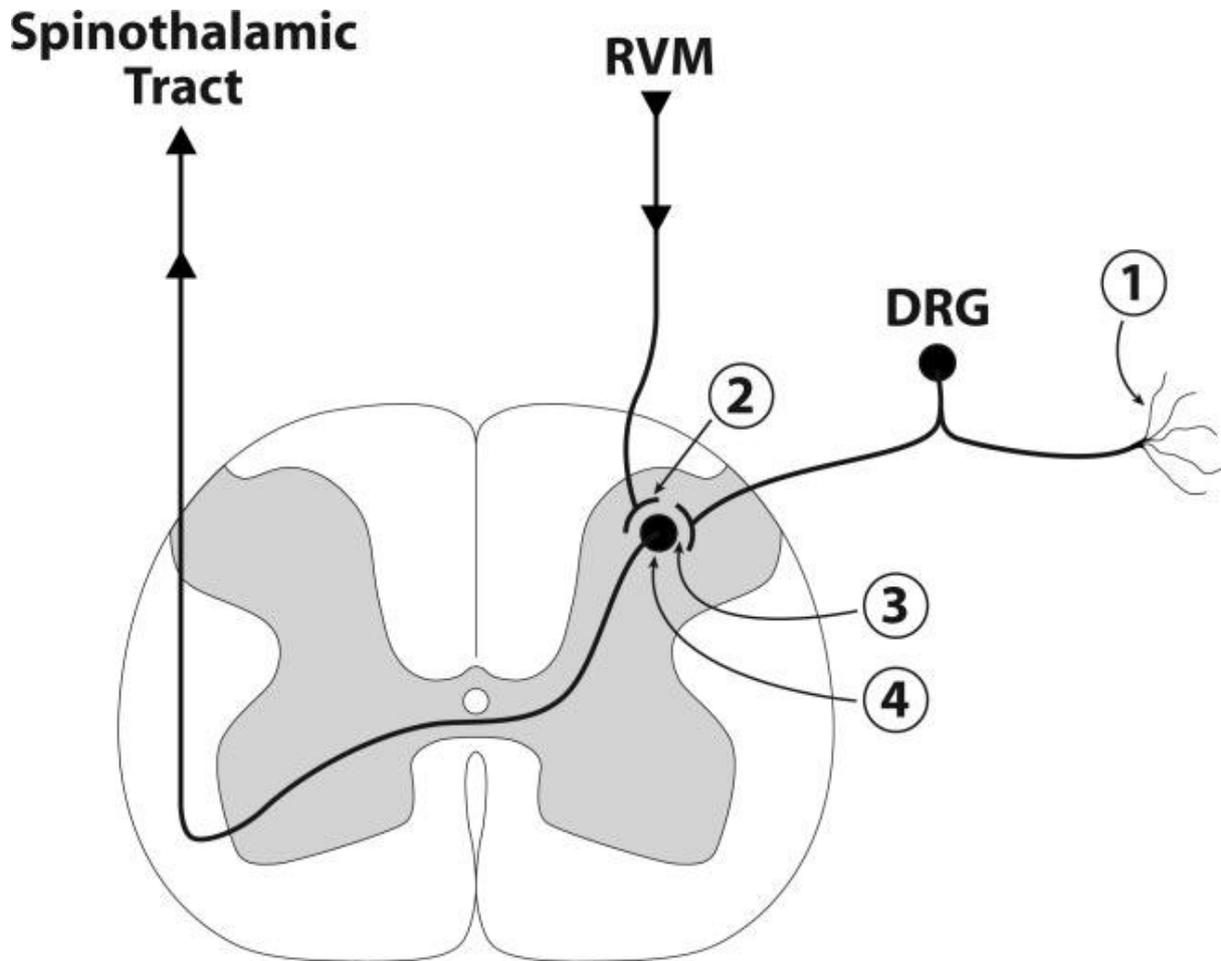
Second, this sensitization most likely was opposed by an endogenous opioidergic system, because the injection of an opioid antagonist unmasked hyperalgesia. This implies that OIH resolved because of upregulated inhibitory pathways opposing activity of sensitized excitatory pathways rather than the desensitization of excitatory pathways. According to this concept, resolution of OIH occurred at a new equilibrium of high neuronal activity between excitatory and inhibitory pathways (see later).

It is conceivable that an equilibrium achieved at a high level of neuronal activity is prone to derangements, which in a clinical context may translate into increased vulnerability to pain ⁽¹⁾.

MECHANISMS

The neurobiology of OIH is complex, and likely to involve more than one system, with probable differences between acute and chronic settings at both pre and post synaptic levels, affecting NMDA receptor activity, G proteins and intracellular systems ⁽⁹⁾.

Existing data suggest that peripheral, spinal cord and higher central nervous system structures may be involved in OIH, but many specifics are missing from our understanding. These involve the central glutaminergic system, spinal dynorphins, descending facilitation, genetic mechanisms and decreased reuptake and enhanced nociceptive responses ^(3,4).



Neuroanatomical sites and mechanisms implicated in the development of opioid-induced hyperalgesia during maintenance therapy and withdrawal. ⁽¹⁾ Sensitization of peripheral nerve endings. ⁽²⁾

Enhanced descending facilitation of nociceptive signal transmission. ⁽³⁾

Enhanced production and release as well as diminished reuptake of nociceptive neurotransmitters. ⁽⁴⁾

Sensitization of second-order neurons to nociceptive neurotransmitters.

This figure does not illustrate all potential mechanisms underlying opioid-induced hyperalgesia, but rather depicts those that have been more commonly studied.

DRG -dorsal root ganglion; RVM - rostral ventral medulla.

Mechanisms described for this clinical entity include:

- (1) Sensitization of peripheral nerve endings.
- (2) Enhanced descending facilitation of nociceptive signal transmission.
- (3) Enhanced production and release as well as diminished reuptake of nociceptive neurotransmitters.
- (4) Sensitization of second-order neurons to nociceptive neurotransmitters.
- (5) Genetic Influences
- (6) Balancing of the pronociceptive and antinociceptive systems

(1) SENSITIZATION OF PERIPHERAL NERVE ENDINGS

It has been suggested that opioid-induced and injury-induced hyperalgesia share common underlying mechanisms. A synaptic model of injury-induced hyperalgesia is the long term potentiation (LTP) at synapses between nociceptive C fibers and neurons in superficial spinal dorsal horn. Opioids may not only modify but also induce synaptic plasticity⁽¹⁰⁾.

In neuroscience, *plasticity* is the term used to denote the dynamic functional and/or anatomical changes occurring in the nervous system as a result of an injury or disease. Plasticity occurs not only in the neural pathways damaged directly, but also in undamaged pathways in the peripheral and central nervous systems as part of a compensatory reorganization.

With regard to postoperative pain, the relevant mechanisms are processes whereby tissue injury increases the responsiveness of the sensory system so that subsequent stimuli have an enhanced effect—a phenomenon termed *sensitization*⁽¹¹⁾

Correctly defining the cellular origin of opioid-induced LTP is critical because it impacts whether we should focus on primary sensory neurons or spinal second-order neurons in our future research to uncover the mechanisms of opioid-induced hyperalgesia and tolerance.

There is new evidence that opioid-induced LTP in the spinal cord results from increased presynaptic glutamate release from TRPV1-expressing primary afferents.

The critical role of TRPV1-expressing primary afferents in opioid-induced LTP has not been recognized previously, and this subpopulation of sensory neurons could be targeted to prevent or minimize opioid-induced hyperalgesia and tolerance⁽¹²⁾.

(2) ENHANCED DESCENDING FACILITATION OF NOCICEPTIVE SIGNAL TRANSMISSION

Descending inhibition originates in the periaqueductal gray matter of the midbrain (PAG) and the rostral ventromedial medulla oblongata (RVM). In the RVM there are three classes of cells: Off-cells are inhibited by painful stimuli, On-cells increases their firing rate upon painful stimulation, and neutral cells do not respond to painful stimuli.

Off and On cells project onto dorsal horn neurons to inhibit and facilitate, respectively, the synaptic transmission of nociceptive inputs. The central analgesic effect of μ agonists is attributed to an inhibition of On-cells and an activation of Off-cells.

It is presumed that long-term application of opioids causes a reversal of activation patterns of ON cells in the RVM and thus results in the development of hyperalgesia. This suggests that time-related RVM plasticity serves to initiate descending facilitation, opioid-induced abnormal pain and subsequent decreased spinal anti-nociceptive potency of opioids. In addition, lesioning of the descending pathway to the spinal cord prevents the increase seen in excitatory neuropeptides ^(1,8,14).

A study by Vishvarani Wanigasekera et al provides the first clear evidence from humans that the brainstem MPRF plays a key role in the expression of hyperalgesia without peripheral injury induced by opioid withdrawal; i.e., an injury-free model of central sensitisation in humans ⁽¹⁵⁾.

(3) ENHANCED PRODUCTION AND RELEASE AS WELL AS DIMINISHED REUPTAKE OF NOCICEPTIVE NEUROTRANSMITTERS

Increased levels of spinal dynorphins with continuous infusions of mu receptor agonists lead to the release of spinal excitatory neuropeptides such as calcitonin gene-related peptide from primary afferents. OIH is therefore a pro-nociceptive process facilitated by increasing the synthesis of excitatory neuropeptides and release upon peripheral nociceptive stimulation ^(1,4).

The decreased reuptake of neurotransmitters from the primary afferent fibres has been considered as the common mechanism, along with enhanced responsiveness of spinal neurons to nociceptive neurotransmitters like substance P and glutamate ⁽¹³⁾.

(4) SENSITISATION OF SECOND ORDER NEURONS TO NOCICEPTIVE NEUROTRANSMITTERS

Persistent activation of the NMDA receptor by excitatory amino acids released from primary afferent terminals results in sensitization of spinal (second order) neurons of the spinal dorsal horns to noxious stimuli ⁽¹⁴⁾.

The excitatory neurotransmitter NMDA plays a central role in the development of OIH. The current data suggest that pharmacological tolerance and OIH, while distinct processes may share common cellular mechanisms partly mediated through activation of the central glutaminergic system ⁽⁴⁾.

Pain signalling propagates through the spinal cord by glutamatergic neurotransmission involving the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors. These receptors are activated by the presynaptic release of glutamate from nerve terminals of dorsal root ganglia cells depolarized by pain-provoking mechanical or chemical stimuli ⁽⁷⁾.

An anatomical and molecular link between the NMDA and mu receptors has been demonstrated. In the spinal cord, mu and delta opioid receptors like NMDA receptors are primarily located postsynaptically in some DH neurons, specifically excitatory interneurons. This suggests that NMDA receptors may promote enhanced neurotransmitter output as opposed to opioid receptors which inhibit the same ⁽⁷⁾.

At a molecular level, mu opioid receptor stimulation increases the NMDA receptor-mediated glutamate response by intracellular protein kinase c-mediated removal of the magnesium blockade of the NMDA receptor channel. Subsequent increase of intracellular Ca concentration further stimulates protein kinase C activity, causing lasting enhancement of glutamate synaptic efficiency, creating a positive feedback loop ⁽¹⁴⁾.

This results in the propagation of the pain signal from neuron to neuron through the spinal cord to the brain. At many points in this pathway, the pain signal can be pathologically augmented. In particular, the enhancement of NMDA receptor function in DH neurons may underlie increased pain states in chronic pain and OIH.

(5) GENETICS

A substantial and growing body of literature supports the conclusion that genetics influence pain sensitivity and analgesic responses and consequently also OIH ⁽⁴⁾.

Emerging evidence from preclinical studies suggest a role for genetics in opioid-induced hyperalgesia. Hyperalgesia, which could be partly due to opioid withdrawal, can be influenced by the common functional polymorphism (val 158met) of the *COMT* (*catechol-O-methyltransferase*) gene.

In a study by Vishvarani Wanigasekera et al patients with the met/met polymorphism reported the highest pain intensity ratings, while subjects with the val/val polymorphism reported the lowest pain intensity ratings during the opioid withdrawal period. These observations support the presence of OIH only in a subset of participants. ⁽¹⁵⁾.

(6) BALANCING OF ANTINOCICEPTIVE AND PRONOCICEPTIVE SYSTEMS

A model of the neuroadaptive changes underlying expression and recovery of OIH has been proposed by Celerier et al. Antinociceptive and pronociceptive systems are in balance at a low level of neuronal activity before the exposure to opioids. Pronociceptive systems become upregulated as a result of opioid exposure, which is reflected by the development of OIH.

Upregulation of antinociceptive systems is associated with the discontinuation of opioid exposure, which results in the offset of OIH. However, recovery from OIH is the result of a new equilibrium between pronociceptive and antinociceptive systems that occur at high level of neuronal activity. The high level balance between pronociceptive and antinociceptive systems may be prone to derangements, which in a clinical context may build the basis for a long term vulnerability to pain ⁽³⁾.

(i) **Antinociceptive Systems**

Opioids activate peripheral, spinal and supraspinal opioid receptors. To date four different opioid receptors have been identified – mu, delta, kappa, ORL-1. The opioid receptors mediate their effects via G proteins. Opioid receptor initiated effects include:

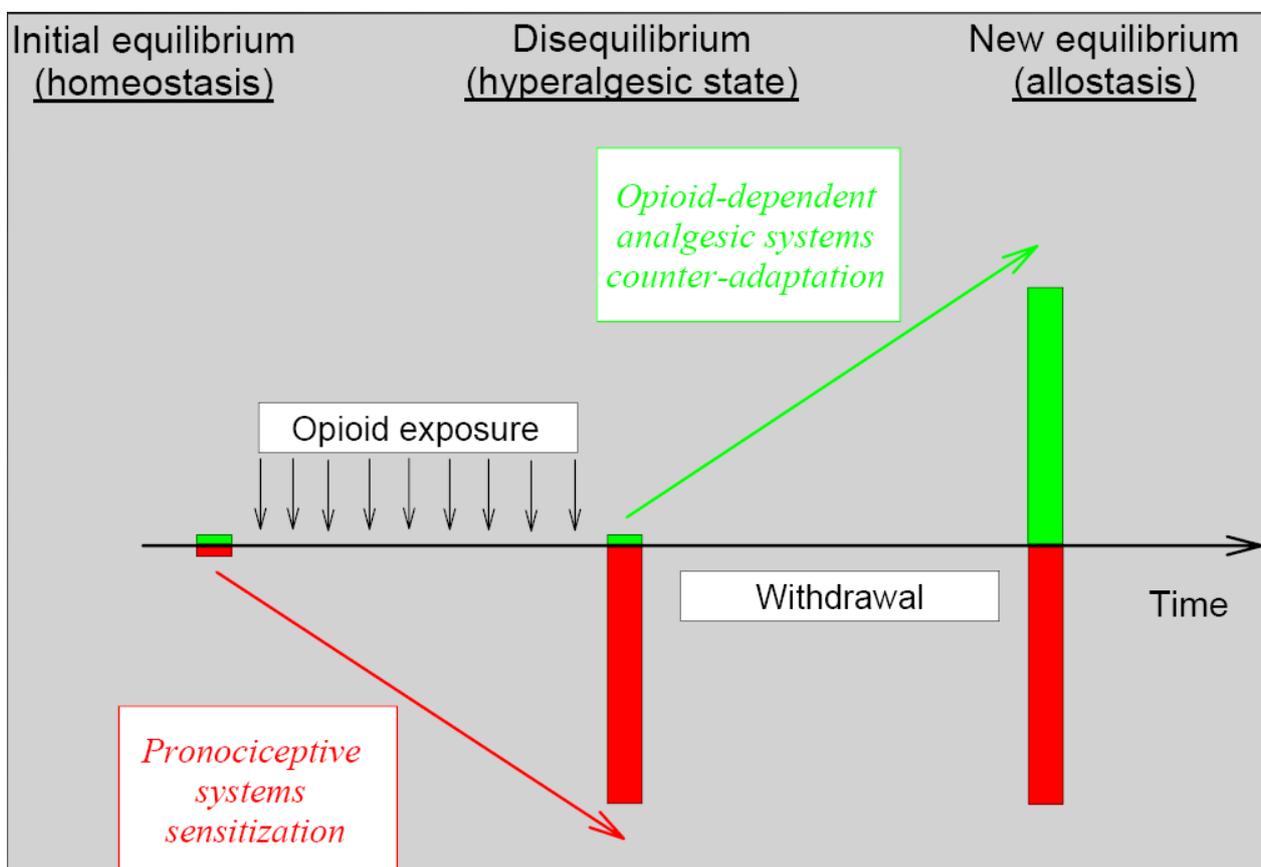
- Modulation of membrane potential
Activation of G proteins leads to a K⁺ efflux and to the closing of voltage-gated Ca⁺⁺ channels leading to hyperpolarization and reduced neuronal excitability.
- Deactivation of adenyl cyclase
G protein mediated activation of opioid receptors inhibits adenylate cyclase and consequently causes a decrease in cAMP, which can lead to hyperpolarisation and inhibition of neurotransmitter release such as glutamate and substance P at spinal and supraspinal levels.
- Receptor trafficking
After activation, the opioid receptor becomes phosphorylated and is separated from the G protein. As a result the receptor increases its affinity for the cellular protein arrestin which initiates endocytosis. Following internalization, the receptor is either recycled and will re-express at the cell surface or it will be degraded.
- Descending inhibition
This has been described earlier.

(ii) **Pronociceptive Systems**

Possible mechanisms of opioid induced pronociceptive effects are summarized as follows:

- Receptor Desensitisation
Opioid receptors show a rapid onset desensitisation despite continuous availability of ligands. This process can be attributed primarily to protein kinase C mediated phosphorylation and internalisation of opioid receptors. Currently desensitisation can be demonstrated for all opioids in clinical use.

- Activation of Adenyl Cyclase
Long term application of u agonists can cause up regulation of adenyl cyclase activity resulting in increased cAMP levels which in turn causes an increase in the release of excitatory neurotransmitters at a spinal level.
- NMDA Receptor Activation
This has been described in detail earlier in the text.
- Release of Anti Opioid Peptides
Long term application of opioids can induce peptides with pronociceptive properties. The most important of these peptides are cholecystokinin(CCK), neuropeptide FF(NPFF) and nociceptin. Recent studies have shown that Dynorphin A possesses relevant pronociceptive properties which may result in the activation of the NMDA-receptor system.
- Descending Facilitation
A facilitation of synaptic transmission in dorsal horn neurons can be observed with continuous application of u agonists. Long term application of opioids can cause a reversal of activation patterns of On-cells in the RVM and thus result in development of hyperalgesia. CCK and nociceptin also facilitate these pronociceptive effects, while they inhibit u-agonist induced activation of Off-cells. ⁽¹³⁾.



CLINICAL IMPLICATIONS

A diminishing opioid analgesic efficacy during opioid treatment is often considered a sign of pharmacological tolerance, assuming there is no apparent disease progression. Escalation of opioid doses has been a common approach to improve analgesia. However, this conventional practice of dose escalation needs to be revisited in light of both animal and human study evidence of paradoxical OIH ⁽²⁾.

The major dilemma facing the clinician is distinguishing between tolerance and OIH since the treatment of each is quite different. Tolerance requires a dose escalation as opposed to OIH which responds favourably to a decrease in the dose of opioid.

Differentiation between OIH and tolerance requires a method directly assessing pain sensitivity. Implementation of such a method into a clinical trial is difficult and has not yet been attempted ⁽³⁾.

In addition the clinician must be able to distinguish between OIH and clinical exacerbation of pre-existing pain.

Several features of OIH may be helpful in differentiating between it and increases in pre-existing pain:

- OIH will exacerbate a pre-existing painful condition and therefore will increase pain intensity above the pre-existent pain following opioid treatment. Further disease progression needs to be ruled out which would increase pain.
- OIH typically produces diffuse pain, less well defined in quality, which extends beyond the areas of distribution from the pre-existing pain state, given that the underlying mechanisms of OIH involve neural circuits and extensive cellular changes.
- Quantitative sensory testing may reveal changes in pain threshold, tolerability and distribution patterns associated with the development of hyperalgesia. These parameters may also help make distinctions between the exacerbation of pre-existing pain and opioid-induced pain.
- Under treatment of a pre-existing pain or the development of pharmacologic tolerance may be overcome by a trial of opioid dose escalation. Opioid – induced pain will be worsened following an increase in opioid dose ^(2,4).

There are two other categories that can also contribute to declining analgesia

- **Increased activity in nociceptive pathways**
Mechanical factors (tumour growth), biochemical changes (inflammation) and peripheral neuropathic processes (neuroma formation) may explain causes of increased peripheral nociceptive receptor activation. Centrally, increased activity in nociceptive pathways may occur because of central neuropathic processes (sensitisation, shift in receptor fields, or changes in modulatory processes).
- **Psychological processes**
These can include anxiety, depression, change in the cognitive state leading to altered pain perception or reporting (delirium) and conditioned pain behaviour that is independent of the drug⁽²⁾.

MANAGEMENT

I have divided this section into the perioperative and chronic pain settings.

Perioperative Setting

Opioid Receptor Agonists

The effect of pre-emptive opioids in preventing opioid-induced hyperalgesia has not been studied so far using formal sensory testing methods. However, the application of a long-acting opioid before the start of a remifentanyl infusion has not been shown to improve postoperative pain outcomes. Pre-treatment with 150ug/kg morphine did not decrease the initial 24hour morphine consumption in adolescents who received remifentanyl by infusion for surgical correction of idiopathic scoliosis⁽¹⁶⁾.

Ketamine

The NMDA receptor is composed of several different subunits (NR1, NR2A-D, and sometimes NR3A/B) that are differentially expressed in various regions of the brain and during development. Further, the subunit expression of individual NMDA receptors can affect their binding sensitivity to neuromodulators and function. However, multiple drugs available have variable and undetermined effectiveness. The first generation NMDARAs, such as ketamine and dextromethorphan, have limited clinical utility in some patients precisely because of these reasons.

Even though ketamine binds to many different receptor sites, it is known to be an uncompetitive antagonist of the phencyclidine binding site of NMDA receptor, where its primary anaesthetic effects are thought to occur. While its role as a clinical anaesthetic has been limited, its role as NMDA receptor antagonist in chronic neuropathic pain has been expanding. Meta-analyses of studies examining perioperative low-dose ketamine in conjunction with opioid administration yielded opposing results.

Further, a systematic review failed to show any significant evidence that ketamine improves the effectiveness of opioid therapy in cancer pain. However, ketamine has been shown to be significantly beneficial in patients who require large amounts of opioid medications or exhibit some degree of opioid tolerance. Human experimental pain studies have shown that administration of S-ketamine abolishes remifentanyl-induced aggravation of hyperalgesia induced by intradermal electrical stimulation. In addition, the findings were corroborated in the post-surgical patient population⁽¹⁾.

The anti-hyperalgesic effects of ketamine on the development of postoperative pain has been observed in a low-dose regimen consisting of an initial intravenous application of 0.5—1 mg/kg followed by a continuous infusion of 10—20Ug/kg/min. With application of S-ketamine, this dosage should be reduced by 50%⁽¹³⁾.

Joly et al demonstrated in a clinical study in patients undergoing major abdominal surgery that the large postoperative areas of secondary peri-incisional hyperalgesia associated with high-dose intraoperative remifentanyl infusion could be significantly reduced by the concomitant use of small-dose ketamine.

These data are supported by studies documenting effects of ketamine on opioid-induced hyperalgesia using acute clinical postoperative pain outcomes⁽¹⁷⁾.

In summary, there is some evidence to show that perioperative administration of low-dose ketamine might modulate the expression of OIH or analgesic tolerance and that it reduces postoperative wound hyperalgesia after acute intraoperative opioid exposure. However, the clinical significance of these benefits still needs to be demonstrated in larger prospective studies and in chronic pain populations⁽¹⁾.

Alpha 2 Agonists

Some studies have examined the role of α_2 receptor agonists in modulating OIH. Koppert et al. showed that the α_2 agonist clonidine attenuated opioid-induced post-infusion antianalgesia and abolished opioid-induced post-infusion secondary hyperalgesia. These data suggest a possible role for α_2 agonists in OIH modulation.

In contrast, Davies et al. failed to report hyperalgesia after cessation of chronic administration of the α_2 agonist dexmedetomidine in mice. Overall, animal studies provide contradictory evidence for the role of α_2 agonists. α_2 agonist might or might not directly cause hyperalgesia. However, human studies provide direct evidence in support of the ability for these drugs to attenuate expression of OIH in human experimental pain models after acute opioid exposure ⁽⁴⁾.

Regional Anaesthesia

Regional anaesthesia blunts the central sensitization feedback loop. This modality therefore plays an integral role in preventing and treating OIH.

Currently ketamine and regional anesthesia remain the most common preventive modalities clinically available perioperatively ⁽¹⁴⁾.

The South African Acute Pain Guidelines 2009 does not factor in OIH as an entity and a suggested approach to this condition is therefore not included in its guidelines.

Chronic Opioid Users

While the pain practitioner has several options when confronted with a demonstrated lack of opioid efficacy and the diagnosis of OIH is established, the treatment can be time-consuming and, at times, impractical.

In managing these patients, weaning from high doses of opioids usually requires time and patience, along with understanding on the part of the patient and the family. While reducing the opioid dose, patients might experience transient increases in pain or mild withdrawal which can exacerbate the already exacerbated pain.

Further, the hyperalgesic effect might not be mitigated until a certain critical dose of opioid is reached. During this process, patients and physicians become frustrated and develop differences in philosophy, which could require multiple visits or could even sever the relationship between the patient and physician. These patients often seek opioid treatment elsewhere.

The treatment includes rational polypharmacy with non-opioid medications, minimizing opioid usage and reducing the adverse events of withdrawal and OIH. However, certain pain conditions, including neuropathic pain, tend to preferentially respond to non-opioid medications such as antidepressants and anticonvulsants. Rotation to a different class of opioid might yield improvement in analgesia. Interventional pain management can reduce the need for pharmacotherapy or

eliminate it altogether. Behavioural management can accomplish some or all of the goals. The medical options available include methadone, buprenorphine and dextromethorphan.

Methadone

Methadone, although a pure μ -receptor agonist, has properties that might prevent or reduce OIH. It is a racemic mixture in which the d-isomer is an NMDA receptor antagonist. Methadone also displays incomplete cross-tolerance properties unique from other μ -receptor agonists which might create a niche role for it in the treatment of OIH and other forms of intractable pain, especially neuropathic pain.

Multiple published reports in the literature have shown that opioid rotation to methadone significantly improved or resolved suspected OIH. However, methadone is also associated with multiple disadvantages of complex conversion and toxicity, including Torsades de Points, when high doses are administered.

Further, methadone exposure has been linked to increased pain states in studies of former opioid addicts maintained on methadone. Thus, methadone might activate pronociceptive pathways, despite its NMDARA properties.

Buprenorphine

Buprenorphine has been used to treat chronic pain. It is a partial opioid agonist with antagonist properties which has been used for decades in anaesthesia and for the treatment of pain. The intravenous/ intramuscular (IV/IM) formulation (Buprenex) is available in the United States for the treatment of pain and in Europe is available as a transdermal preparation.

Most recently, it has been used for the treatment of opioid dependence in its sublingual form (Suboxone, Subutex). Buprenorphine has been shown to be intermediate in its ability to induce pain sensitivity in patients maintained on methadone and control patients not taking opioids. Buprenorphine showed an enhanced ability to treat hyperalgesia experimentally induced in volunteers compared to fentanyl.

In addition, spinal dynorphin, a known kappa receptor agonist, increases during opioid administration, thus contributing to OIH. Buprenorphine is a kappa receptor antagonist. For these reasons, buprenorphine might be unique in its ability to treat chronic pain and possibly OIH ⁽¹⁾.

Dextromethorphan

Dextromethorphan is a non-competitive NMDARA typically used as a cough suppressant. There have been a number of studies indirectly examining the ability of dextromethorphan to attenuate or prevent expression of OIH or analgesic tolerance in patients on opioid therapy.

Galer et al, in 3 large randomized, double-blinded, placebo-controlled multicentre trials of MorphiDex (morphine and dextromethorphan mixture in a 1:1 ratio) in chronic non-cancer patients, were unable to find any significant difference between MorphiDex and morphine alone in the outcome measures. The study showed analgesic superiority for MorphiDex.

Cox Inhibitors and Paracetamol

Cyclooxygenase (COX)-inhibitors and paracetamol also exhibit preventive effects on the development of postoperative pain and increased demand for opioids. The prostaglandins have been shown to modulate nociceptive processing, and are able to stimulate the release of the excitatory amino acid glutamate in spinal cord dorsal horn. COX inhibitors have been shown to antagonize NMDA receptor function in the CNS. They have also been shown to attenuate development of opioid tolerance in animals.

Thus, it has been hypothesized that inhibition of prostaglandin synthesis in the spinal cord might attenuate or inhibit expression of OIH by modulating NMDA receptor function. Evidence suggests a role for COX-2 inhibitors in the modulation of OIH in humans. Thus, it is suggested that there is a possible role for prostaglandins in sensitizing the nociceptive system before pathologic activation, and that although OIH is modulated by Cox-2 activity, it probably has a less important role than the NMDA receptor system, at least in human experimental pain models after acute opioid exposure⁽¹⁾.

Opioid Rotation

The majority of clinically used opioids are characterised by intrinsic activity at the u-receptor. However, as compared to k-agonists, u-agonists exhibit clear, pronounced pronociceptive properties. It can be shown that both the synthetic k-agonist U-50,488H and also the combined k-agonist/u-antagonist nalbuphine can delay or inhibit morphine tolerance.

Interestingly, early studies with transdermal application of buprenorphine, a partial u-agonist/k-antagonist, have shown similar results. After the rotation of buprenorphine, a sustained reduction of opioid consumption can be observed in many patients.

Furthermore, buprenorphine was found to exert lasting antihyperalgesic effects in an experimental pain model. These antihyperalgesic effects showed a significantly longer half time as compared to its analgesic effects and contrasts the delayed increase of hyperalgesia observed following administration of pure μ -receptor agonists. It is yet unclear as to whether these effects of buprenorphine also translate into improved treatment of pain states dominated by central sensitisation.

However, opioids with solely μ -agonistic properties are recommended for opioid rotation also. The rationale of this opioid rotation is based on incomplete and the clinically often very difficult to predict cross-tolerance between the μ -agonists. Morphine is, therefore, often rotated with transdermal fentanyl, hydromorphone, oxycodone or methadone.

An improvement of analgesic quality and a reduction of undesirable side-effects can be achieved in two out of three patients. Methadone in particular seems to exhibit advantages due to its greater affinity to the μ -receptor, as well as an antagonistic effect at the NMDA-receptor.

The recommended dosage after opioid rotation is 50% of the calculated equivalent dose and, if necessary, a brief high titration, since the individual strength of equivalent doses can vary due to the activation of pronociceptive systems. However, there is not yet clinical evidence for one opioid being more effective in opioid rotation than another one ⁽¹³⁾.

CONCLUSION

The key unanswered questions are where and how opioids initiate plasticity in the nervous system, which leads to opioid-induced hyperalgesia and tolerance. This problem has not been adequately studied in the nociceptive circuitry where native opioid receptors are expressed and, thus, the specific cellular sites and signalling mechanisms involved in the initiation of opioid-induced hyperalgesia and tolerance are not fully known ⁽¹²⁾.

Challenges in the pain field include translation from animal models to identification of novel targets for drug development for humans and developing strategies that lead to improvements in patient care ⁽¹¹⁾

REFERENCES

1. Lee M, Silverman SM. A comprehensive review of Opioid – induced Hyperalgesia. *Pain Physician* 2011; 14:145-161.
2. Chang G, Chen L. Opioid Tolerance and Hyperalgesia. *Medical Clinics of North America* 2007; 91:199-211
3. Angst MS, Clark JD. Opioid Induce Hyperalgesia. *Anesthesiology* 2006; 104:570-587.
4. Silverman SM. Opioid Induce Hyperalgesia; Clinical Implications for the Pain Practitioner. *Pain Physician* 2009; 12: 679-684.
5. Carroll, Angst, Clark et al Management of Perioperative Pain in Patients Chronically Consuming Opioids. *Regional Anesthesia and Pain Medicine* Vol. 29 No. 6 November–December 2004.
6. Bannister K, Dickenson AH. Opioid Hyperalgesia. *Current Opinion in Supportive and Palliative Care* 2010; 4:1-5.
7. Min Zhao *Enhancement of Spinal N-Methyl-D-aspartate Receptor Function by Remifentanil Action at delta Opioid Receptors as a Mechanism for Acute Opioid-induced Hyperalgesia or Tolerance.* *Anesthesiology* 2008; 109:308–17
8. Koppert W. Opioid-induced hyperalgesia—Pathophysiology and clinical relevance. *Acute Pain* (2007) 9, 21—34
9. Colvin LA. Opioid –induced hyperalgesia: a clinical challenge. *British Journal of Anaesthesia* 2010; 104:125-127
10. Drdla R, et al. Induction of Synaptic Long-Term Potentiation After Opioid Withdrawal. *SCIENCE* 2009 VOL 325: 207-210.
11. Raja S.N, et al. *Anesthesiology* 2006; 104:397–8
12. Zhou et al. Opioid-Induced Primary Afferent Stimulation *J. Neurosci.*, March 24, 2010 • 30(12):4460–4466.
13. Koppert W, Schmelz M. The impact of opioid-induced hyperalgesia for postoperative pain. *Best Practice and Research Clinical Anaesthesiology* 2007; 21: 65-83.
14. Bekhit MH. Opioid – Induced Hyperalgesia and Tolerance. *American Journal of Therapeutics* 2010; 17: 498-510.
15. Vishvarani Wanigasekera et al. Neural Correlates of an Injury-Free Model of Central Sensitization Induced by Opioid Withdrawal in Humans. *The Journal of Neuroscience*, February 23, 2011 • 31(8):2835–2842).
16. McDonnell C. et al. Pre-treatment with morphine does not prevent the development of remifentanil-induced hyperalgesia. *Canadian Journal of Anesthesiologists* 55:12, 813-818.
17. Ruscheweyh et al. Long-term potentiation in spinal nociceptive pathways as a novel target for pain therapy. *Molecular Pain* 2011, 7:20)

18. Guignard B, Bossard AE, Coste C, et al. Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. *Anesthesiology* 2000; 93:409–417.
19. Cortinez LI, Brandes V, Munoz HR, et al. No clinical evidence of acute opioid tolerance after remifentanil-based anaesthesia. *Br J Anaesth* 2001; 87:866–869.
20. Doherty M, White JM, Somogyi AA, Bochner F, Ali R, Ling W. Hyperalgesic responses in methadone maintenance patients. *Pain* 2001;90:91–6.
21. Compton P, Charuvastra VC, Ling W. Pain intolerance in opioid-maintained former opiate addicts: effect of long-acting maintenance agent. *Drug Alcohol Depend* 2001;63:139–46.