

Adverse Effects of Opioids on the Central Nervous Systems of Palliative Care Patients

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ABSTRACT. Opioids, defined as drugs that stimulate opioid receptors, are primarily used in the treatment of moderate to severe pain. They induce central nervous system (CNS) adverse effects which can be divided into three groups. The first group includes effects that lower the level of consciousness—sedation, drowsiness and sleep disturbance. The second group affects the thinking process and the ability to react—cognitive impairment, psychomotor impairment, delirium, hallucinations, dreams and nightmares. The third group is of the direct toxic effects of opioids on neurons and includes myoclonus (perhaps), hyperalgesia and tolerance.

This review addresses the incidence, possible mechanisms, and treatment of each of these groups of opioid-induced adverse effects. doi:10.1300/J354v21n01_05 [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <<http://www.HaworthPress.com>> © 2007 by The Haworth Press, Inc. All rights reserved.]

KEYWORDS. Opioids, adverse effects, central nervous system, palliative care

INTRODUCTION

Each year cancer-related pain affects around nine million people world-wide.¹ The prevalence of pain in patients with malignancies is around 50% at some stage of the disease and 80% or greater in the advanced or terminal stages.¹⁻³ The severity of pain in patients with advanced cancer is reported to be mild in around 24%, moderate to severe in 30 to 50%, severe in 21% and very severe/excruciating in 25 to 30%.^{2,4}

Opioids are defined as drugs that interact with the mu, kappa, and delta opioid receptors which are found in the brain, spinal cord and peripheral nervous system.^{3,5} The mix of recep-

tors or sub-type of receptors stimulated by each opioid is unique. In addition each individual patient may have differing opioid-receptor profiles and genetic expression of any enzymes responsible for the metabolism of opioids. These factors determine the overall analgesia and adverse effects produced by opioids.^{2,3,5-7}

There are other non-opioid receptor mechanisms by which opioids produce analgesia. Opioids, to varying degrees, antagonize N-METHYL-D-ASPARTATE (NMDA) receptors and activate the descending serotonin and noradrenaline pain pathways from the brain stem, all of which inhibit nociceptive transmission and result in analgesia.⁸ The extent to which each mechanism contributes to analge-

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Journal of Pain & Palliative Care Pharmacotherapy, Vol. 21(1) 2007

Available online at <http://jppcp.haworthpress.com>

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doi:10.1300/J354v21n01_05

sia varies between individual opioids. Conversely agonism of NMDA receptors may result in chronic, neuropathic or paradoxical pain and the development of tolerance.⁹

Pure mu opioids agonists do not exhibit a dose-ceiling effect, per se; doses are only limited by adverse effects or toxicities. Kappa agonists and partial mu agonists do have a dose-ceiling. The prolonged use of high dose opioids is associated with a high incidence of adverse effects.^{10,11} All opioids have predictable and manageable adverse effects and none of them causes irreversible organ damage although neuron apoptosis does occur. Systematic comparison and quantification of adverse effects between opioids, however is lacking.¹²

ADVERSE EFFECTS OF OPIOIDS ON THE CENTRAL NERVOUS SYSTEM

The adverse effects of opioids on the central nervous system (CNS) are complex but all share common mechanisms.^{2,5,10-19} These effects can be divided into three groups:

- Those that result in a decrease in the level of consciousness—sedation, drowsiness and sleep disturbance.
- Those that affect the thinking process and the ability to react—cognitive impairment, psychomotor impairment, delirium, hallucinations, dreams and nightmares.
- Direct toxic effects of opioids on neurons—myoclonus (perhaps), seizures, hyperalgesia and tolerance.

LOWERING THE LEVEL OF CONSCIOUSNESS

Sedation/Drowsiness

Opioids commonly cause sedation on initiation but tolerance to this adverse effect normally develops quickly. Because these drugs have multiple inhibitory effects on cerebral activity, and on cholinergic activity in particular,²⁰ central anticholinergic effects of opioids may produce sedation and drowsiness as discussed below. Rapidly escalating doses of mor-

phine have resulted in sedation, sometimes with no enhancement of analgesia.²¹

Sedation caused by opioids may be reduced by decreasing the dose,^{5,15} adding a psychostimulant such as methylphenidate,¹⁵ or by rotation to an alternative opioid. Opioids vary in their propensity to cause sedation⁵ and in a randomized cross-over study, rotation to fentanyl was associated with less daytime drowsiness than morphine.⁴ These effects may relate to the effects on non-opioid receptors.

Communication Impairment

The presence of sedation or drowsiness may affect a patient's ability to communicate. The use of high doses of opioids has been shown to be linked to impaired communication capacity but, as for opioid-induced CNS adverse effects in general, it is often difficult to differentiate the effects of opioids from the effects of disease on the ability to communicate.²²

Sleep Disturbance

Sleep disturbance is common in cancer patients.²³ It is usually attributed to insomnia or pain, but there is little evidence to support this. Arousal from sleep or disturbed sleep from pain has been reported but there is some evidence that patients in pain do not suffer from disturbed sleep as much as those not in pain. In addition, no correlation has been found between pain severity and sleep disturbance.²³ The effect of opioids on sleep in palliative care patients has not been well studied. Opioids are generally believed to enhance sleep but there is little evidence to support this belief.

Both cortical arousal and the sleep-wake cycle are regulated by converging inputs from the brainstem biogenic amine nuclei and pontine cholinergic projections.²⁰ Sleep and waking is regulated by many neurotransmitters including noradrenaline, serotonin, acetylcholine, dopamine, histamine, gamma-aminobutyric acid, the pituitary hormones and the neurohormone melatonin.²⁴ Any drugs that alter the balance of these neurotransmitters, as opioids do, can potentially affect sleep. The same is true of diseases that affect the central nervous system. Although the exact mechanism by which opioids disrupt sleep is unclear, morphine has been

shown to reduce REM sleep via inhibition of acetylcholine release in the medial pontine reticular formation. The resultant disruption of sleep architecture affects the states of arousal during wakefulness.²⁰ In animals REM suppression is associated with mu but not kappa or delta opioid receptor agonists.²³

Studies into the effect of opioids on sleep have been carried out largely in healthy or addicted volunteers. Of eight studies discussed in one article, six were in opioid addicted prisoners.²³ These studies show that opioids fragment sleep, and suppress both rapid eye movement (REM) sleep and non rapid eye movement (NREM) sleep during both stage 2 and perhaps slow wave sleep.²³⁻²⁵ In addition to the healthy volunteer studies, anecdotally patients given opioids are reported to be awake more often at night and find it hard to get to sleep, which reduces sleep time and sleep efficiency.²³

It is difficult to differentiate the sleep disruption caused by the disease process from that caused by opioids. In chronic pain patients, sleep recordings show alpha-EEG anomalies normally only seen during wakefulness (inappropriate intrusion of alpha waves into deep NREM stages 3 and 4).²³ In healthy volunteers, stage 2 NREM sleep is the stage most often disturbed by acute pain while deeper NREM stages 3 and 4 (slow wave sleep) are less affected.²³

Effective treatment of opioid-induced sleep disruption is not well established. It may be that psychostimulants, such as methylphenidate, improve opioid-induced disruption of normal sleep architecture. In one inconclusive study methylphenidate improved nocturnal sleep patterns and reduced day-time drowsiness.⁴

DISTURBANCE OF THINKING AND ABILITY TO REACT

Cognitive Impairment

Cognitive functioning is the acquisition, processing, storage and retrieval of information by the brain.^{26,27} Impairment may lead to decreased attention span, disorientation to time, restlessness, agitation, hallucinations and delirium which have a significant effect on the quality of life of both the patients and their

carers.^{26,28} The incidence of cognitive impairment in cancer patients has been reported to be 14 to 29%.²⁷ Among hospitalized cancer patients receiving opioids, 77% experience trouble with thinking, as do 20 to 44% of patients on admission to a palliative care unit.²⁷ This has been reported to increase to 80 to 90% immediately before death (in a palliative care unit).²⁷ Because cognitive impairment occurs in the terminally ill even in the absence of opioids, it is difficult to determine how much of the impairment is due to opioids and how much to the disease process, organ failure or pain itself.^{23,26,27} Consequently there are few studies into the effects of opioids on cognitive function in palliative care patients.

However, several studies have investigated the cognitive effects of opioids in healthy volunteers.^{26,27} These have shown that while parenteral opioids have been associated with significant dose-related cognitive impairment, oral opioids have been associated only with insignificant and mild impairment.²⁶ Indeed some studies report that morphine is associated with improved cognition, while others report more cognitive impairment from lorazepam than opioids.²⁶ In other healthy volunteer studies morphine administration was associated with increased reaction times, but not with decreased accuracy of reactions.²⁷

Opioids differ in their ability to cause both cognitive and psychomotor impairment. In healthy, opioid naïve volunteers, psychomotor and cognitive impairment was greatest with pethidine (meperidine), less with hydromorphone and less again with morphine.²⁷

Observations made in healthy volunteers cannot, of course, be extrapolated to patients with chronic pain or advanced cancer. The effects of opioids on cognition in patients suffering from chronic nonmalignant pain (four papers) have not been established.²⁷ Lorenz showed improvement in perceptual-cognitive status in six opioid naïve patients given oral morphine (30 to 150 mg) for pain relief,²⁹ while Moulin reported no decrease in cognitive scores of patients with nonmalignant pain treated for the first time with strong opioids who had previously been given weak opioids.³⁰ Haythornthwaite studied 19 patients with chronic non-malignant pain before and after stabilization on long-acting opioids and ob-

served no decrease in cognitive function,³¹ while Sjorgen studied 40 patients with chronic non-malignant pain and found significantly more cognitive and psychomotor impairment in those receiving opioids compared with controls.³²

In patients with advanced cancer, opioid-induced cognitive and psychomotor impairment have not been well studied. The studies that do exist are contradictory. In one study by Bruera, the cognitive function of 20 hospitalized cancer patients receiving stable doses of morphine were compared with 20 patients receiving escalating doses. Those on stable doses showed no cognitive impairment while those on escalating doses exhibited some impairment of memory, reasoning and reaction times, suggesting that tolerance to cognitive effects occurs once a stable dose has been reached.^{15,26} Clemon compared cognitive function in 16 healthy volunteers, six cancer patients not taking opioids, and seven advanced cancer patients receiving stable doses of opioids. Impairment of reaction times and attention capacity in the cancer patients was evident when compared with healthy volunteers, but there was no difference in the level of impairment observed between the two cancer patient groups.²⁶ In addition, a case series by Wood compared 18 clinically alert cancer hospice patients receiving stable doses of morphine with published norms using several neuropsychological measures. The patients demonstrated marked impairment in information processing, recall ability and conceptual tracking.²⁶

Anecdotally, patients have reported a sense of mental dullness, fuzziness, confusion, dreaminess or "spaceyness" while taking opioids, along with being more accident prone, being more forgetful, having concentration lapses, making more mistakes, having slowed reactions, having poor problem solving abilities and having difficulty with thinking.²⁶

Several review articles on the effect of opioids on cognitive function and psychomotor abilities have reached contradictory conclusions. Payne found that the majority of studies indicated that chronic exposure to opioid analgesics had few effects on cognitive and motor functioning.³³ Of 23 reports into the effects of opioids on cognitive function only seven demonstrated that patients taking stable doses of

opioids exhibited some impairment of psychomotor abilities.³³ Some authors have reported that there were only minimal effects of opioids on psychomotor or cognitive function.³⁴ O'Neill, however concluded that opioids do cause cognitive and psychomotor impairment during initiation and dose escalation but that this impairment decreases (although not back to baseline) once a stable dose of opioid is reached.³³

Treatment of opioid-induced cognitive impairment includes the administration of psychostimulants such as methylphenidate, opioid rotation, hydration (to increase morphine metabolite clearance), the use of adjuvants,²² and the reduction of opioid dose.⁵ There is a lack of evidence of efficacy of psychostimulants although they are not uncommonly used in the United States. Opioid rotation has been found to be effective in minimizing cognitive impairment. In one study rotation from morphine or hydromorphone to hydromorphone or methadone resulted in some improvement in cognitive failure,^{35,36} and reduction in myoclonus and hallucinations although these were not significant.⁴ In addition, mental state and clouding of consciousness have been reported to improve on rotation from morphine to oxycodone.⁴

In summary, there certainly appears to be cognitive impairment associated with the initiation or dose escalation of opioids.^{4,5} The studies in cancer patients suggest opioid use may result in mild cognitive impairment compared with healthy controls but there is not enough evidence to support the claim that opioids cause marked deficits in measurable cognition particularly at stable doses during chronic use.²⁶

Psychomotor Impairment

The evidence for an adverse effect of opioids on psychomotor abilities such as driving is also conflicting. Long-term stable dose opioids have not been associated with impairment of psychomotor ability even immediately after a dose of opioids has been administered.³³ Opioids have, however, been associated with central cerebral sedation which can have an effect on ability to drive or operate machinery.⁴ In addition, it has been found that cancer patients receiving stable doses of oral morphine had im-

paired reaction times compared with healthy volunteer controls.²⁶

As the extent of opioid-induced psychomotor impairment is unknown, the treatment of it is not well established. It has been proposed that psychostimulants may have a place in therapy. One placebo controlled trial of methylphenidate in patients administered continuous morphine demonstrated an improvement in objective psychomotor performance scores and in subjective drowsiness.⁴

Delirium

Delirium is described as a disturbance in consciousness and cognition. It develops abruptly and has been reported as an adverse effect of opioids.^{26,27} It may, however, also be a sign of severe illness and of imminent death unrelated to opioid use.²⁷

The incidence of delirium in the terminally ill has been reported to be 28-88% and is most prevalent in the last few days of life.²⁶ The incidence of opioid-induced delirium varies from opioid to opioid. It is difficult to define how much of the deliria seen at the end of life can be attributed to opioids (or other medicines) and how much to the disease itself. Cognitive impairment is a recognized part of delirium, and opioid-induced cognitive impairment, as discussed above, may represent subsyndromal delirium.²⁷

The causes of delirium in patients with advanced cancer are often multiple. In one study aimed at determining the etiology of delirium, opioids were regarded as a precipitating factor in 21% of cases.³⁷ In addition, published case reports suggest that rapidly escalating doses of opioids are associated with excitatory adverse effects such as agitated delirium.^{14,20}

An imbalance in the cholinergic/dopaminergic systems in the CNS occurs in delirium and this is thought to be the mechanism by which opioids induce delirium. It is known from electrophysiological and behavioral studies that morphine and other opioids inhibit central cholinergic activity in multiple cortical and subcortical regions of the brain.²⁰ These central anticholinergic effects may therefore be responsible for opioid-induced deliria. Morphine-induced delirium via anticholinergic effects may be related to an accumulation of the metabolites

formed by the glucuronidation of morphine—morphine-3-glucuronate (M3G) and morphine-6-glucuronate (M6G). M6G is excreted mainly by the kidneys and has been implicated in CNS adverse effects of morphine including delirium, particularly in patients with renal impairment.

The suggestion that opioid-induced CNS adverse effects are related to the anticholinergic actions of opioids is supported by the involvement of the cholinergic system in consciousness. Acetylcholine is known to be involved in modulating cortical arousal and information processing.²⁰ In addition, conscious awareness and attention are maintained by cholinergic projections from the basal forebrain to the thalamus and cortex.²⁰ Hallucinations and other disturbances may be due to disruption of the basal forebrain cholinergic pathways or acetylcholine deficiency in these areas. Other drugs with anticholinergic properties such as hyoscine have also been associated with impairment in vigilance and in memory function.

The pharmacological gold standard for the treatment of delirium of any etiology is the antipsychotic haloperidol.³⁸ This rebalances the cholinergic/dopamine imbalance mainly via an anti-dopaminergic action. Other treatments, including rotation to an alternative opioid,^{4,20,37,39} discontinuation of anticholinergic adjuvants, and hydration²⁰ aim to reduce the anti-cholinergic load on the patients or to remove active, potentially toxic metabolites. Pro-cholinergic agents, such as acetylcholinesterase inhibitors, have also been tried.²⁰ In one case report of opioid-induced hypoactive delirium with myoclonus caused by rapidly escalating fentanyl doses combined with morphine for breakthrough pain, the delirium was reversed by the administration of the pro-cholinergic drug physostigmine.²⁰ The patient was then maintained in remission with the oral acetylcholinesterase inhibitor donepezil, after rotation to an alternative opioid had been unsuccessful. The improvement was reported as being rapid—within 5 minutes of administration of the physostigmine the myoclonus ceased and the patient became responsive.²⁰

In summary, opioids undoubtedly have the ability to cause delirium probably through inhibition of the cholinergic system. There are sev-

eral alternatives available for the treatment of this adverse effect.

Hallucinations, Dreams, and Nightmares

There are numerous case reports of hallucinations and nightmares associated with opioid use, but these are mainly in the post-operative rather than the palliative care setting.¹⁶ In the terminally ill, nightmares, particularly about death, have been associated with opioid use, but once again disentangling this from the disease process is difficult.²⁸ There is little evidence to suggest that opioid-induced dreams, nightmares or hallucinations occur in palliative care patients, other than as part of a delirium, perhaps as prodromal symptoms.

TOXIC EFFECTS ON NEURONS

Neurotoxicity, defined as damage to nerve cells, is a major adverse effect opioid analgesics.¹⁴ Opioid-induced neurotoxicity is increasingly being reported as prolonged use of high doses becomes more common.^{7,17}

The mechanism by which opioids exert their neurotoxic effects is complicated and involves several different pathways including endocytosis of opioid receptors,¹⁴ and the activation of NMDA receptors.⁴⁰ In animals (morphine-tolerant rats) opioid-induced neurotoxic effects were shown to be regulated by the NMDA receptor-caspase pathway. Glutamate is the neurotransmitter which activates NMDA receptors and opioid-induced neurotoxicity is thought to be regulated, at least in part, by spinal glutaminergic activity and NMDA receptors.⁴⁰

The treatment of the neurotoxic effects of opioids is not well established. Blocking NMDA receptors with antagonists such as ketamine may be helpful in both prevention and treatment.⁴⁰ Modulating glutamate transporter activity in the spinal cord may also help prevent the development of opioid-induced neurotoxic changes. Opioid rotation is another method used in the alleviation of neurotoxicity. In one case report of a patient who had a poor analgesic response to morphine and morphine-induced neurotoxicity, rotation to methadone, an opioid with known NMDA antagonistic properties, aided analgesia and alleviated the neurotox-

icity.⁴¹ It may be that both the lack of analgesia and the neurotoxic adverse effects were due to the accumulation of the active metabolites of morphine.¹⁷

MYOCLONUS

Myoclonus or uncontrollable twitching and jerking of the extremities is a centrally mediated symptom mainly arising from the cortex and the brain stem.⁴² The reported incidence in cancer patients is 3% to 87% and it has been commonly associated with chronic opioid use, particularly high doses.^{43, 44} The risk of developing myoclonus is increased in the presence of spinal cord lesions.⁴² Although the precise mechanism of induction of myoclonus related to opioid use is unclear it may be mediated by an inhibition of glycine in dorsal horn neurons resulting in a decrease in the inhibitory effects of this neurotransmitter and so myoclonus and hyperalgesia.^{42, 43} There is also some evidence that myoclonus may be indirectly mediated through glutamate activation of NMDA receptors, or perhaps through serotonergic and GABA aminergic pathways in the brain stem.^{42, 43} Dopamine antagonism in the basal ganglia is another mechanism by which opioids may induce myoclonus through extrapyramidal pathways.⁴³ There is some evidence that myoclonus associated with morphine use may be induced by the accumulation of the active metabolite morphine-6-glucuronide and the toxic metabolite morphine-3-glucuronide.⁴²

Treatment is similar to that of other CNS adverse effects ie opioid rotation or dose reduction. In addition, the introduction of benzodiazepines,⁴⁴ or baclofen may also alleviate myoclonus.⁴²

HYPERALGESIA

Hyperalgesia is a gradual increase in neuronal response to repeated stimulation.⁴⁵ It can develop in conjunction with opioid tolerance and may be a result of opioid-induced apoptosis of certain cells. A large number of these cells are GABAminergic within the superficial spinal cord dorsal horn. The loss of GABA neurons to apoptosis may result in changes in spinal

neuronal circuits involved in pain and pain modulation. Sensitivity to pain may be increased resulting in hyperalgesia.⁴⁰ NMDA receptor agonism also has a major role in the development of hyperalgesia,¹⁹ as does glycine, an inhibitory neurotransmitter that mediates the post synaptic inhibition of spinal neurons.¹⁴ Glycine is inhibited by morphine, perhaps via its metabolites.^{14,46} This antiglycinergic action of morphine results in a reduction of post-synaptic inhibition at the spinal cord level and an increase in pain.¹⁴

The treatment of hyperalgesia is not well established. As the NMDA receptor has some involvement in this process NMDA antagonists may alleviate it. In rats ketamine prevented fentanyl-induced hyperalgesia.⁴⁶

TOLERANCE

The development of tolerance to opioid analgesia (where the same dose results in less analgesia or an increase in dose fails to increase analgesia)^{5,15,18,45} is a common physiological effect of opioids but its existence remains controversial. It is characterized by a shortened duration of action and decreased extent of analgesia, euphoria, sedation and other effects caused by CNS depression, as well as by marked elevation of the average lethal dose.¹⁵ Although rapidly escalating dose of opioids may be indicative of pharmacological tolerance, it may also reflect escalating pain from disease progression.^{15,18} Tolerance to analgesic effects has been reported in cancer patients but it is rarely clinically important as there is no ceiling to the dose of opioid that can be given, provided it is increased gradually.⁷ Many studies in patients with cancer pain have shown that opioid doses can remain stable for weeks, months or years, suggesting that tolerance is not a major problem clinically.¹⁵ Indeed, some authors suggest that loss of analgesic effects cannot be attributed to tolerance unless an alternative explanation for increasing pain cannot be found.¹⁵ The incidence of tolerance in patients receiving parenteral opioids has been reported by Bruera to be 15%.¹⁸

Tolerance can in fact develop to any opioid effect, including analgesia, sedation, cognitive changes, respiratory depression and nausea.¹⁸

It has been classed as a neurotoxic adverse effect, shares some of the mechanisms of other opioid-induced neurotoxicity, and closely resembles hyperalgesia. It has been reported to develop early in therapy⁴⁶ which prevents many patients and clinicians from starting opioids early amid fears that the opioid analgesic effects may wane.¹²

There are two different types of tolerance—innate tolerance (which is genetically determined and will be present from the initial dose of drug) and acquired tolerance.¹⁵ Acquired tolerance can be further divided into pharmacokinetic (or dispositional), pharmacodynamic and learned tolerance. Pharmacokinetic tolerance results from changes in disposition or metabolism of a drug on repeat dosing, resulting in decreased drug concentrations. Pharmacodynamic tolerance results from drug-induced changes to body systems on prolonged drug use so that response decreases. Learned tolerance results in a decrease in efficacy as a result of compensatory mechanisms that are learned.¹⁵

Opioid tolerance has been demonstrated in animal studies to be largely of the pharmacodynamic type, to be time and dose, receptor specific and reversible on discontinuation.¹⁵ In mice, both competitive and non-competitive NMDA receptor antagonists block the development of tolerance to morphine but not to fentanyl or a pure delta opioid receptor agonist.¹⁵ Few studies have, however, been carried out in humans in pain.

Acute tolerance may also exist. In one study of patients with mucositis, one group self administered morphine while another were administered continuous infusions of morphine.¹⁵ All patients experienced morphine dose increases over several days, which then plateaued. Those self administering used less morphine, and dose escalation was less than for the group who received nurse-administered continuous infusions.

The exact mechanism by which tolerance to opioid analgesia develops is unclear but it is thought to be multifactorial and include changes to opioid receptors, activation of NMDA receptors and movement of calcium and magnesium ions.^{3,7,10,40,47} During the development of tolerance there is functional uncoupling of the opioid receptor-G proteins complex and increased activity in the anti-opioid systems such

as the NMDA receptor system.⁷ The diminished response to opioids, seen as tolerance, may also be due to compensatory responses that counteract the analgesic opioid effects leading to enhanced nociceptive signaling, probably via NMDA receptor agonism.^{19,40,46} In addition there is evidence of cross-talk between opioid and NMDA receptors.¹⁴ NMDA and mu opioid receptors exist on the same neuron throughout the CNS including the spinal cord.⁴⁰ Prolonged sensory afferent (c fiber) activation is associated with spinal release of peptides which, together with glutamate, activate NMDA receptors leading to tolerance and hyperalgesia via neuronal excitation.⁴⁸ The NMDA receptors are also involved in the pathophysiology of neuropathic pain and in other chronic pain conditions.³

In a placebo-controlled study conducted to establish the cellular mechanism of morphine tolerance, opioid tolerance was induced in rats by administering morphine to one group for seven days while other groups received either placebo or a single dose of morphine.⁴⁰ The presence of tolerance was established using several behavioral tests. On day eight, apoptotic cells were found in the spinal cord dorsal horns of the rats treated with morphine continuously for seven days, but not in those of the placebo treated rats or those of the rats administered a single dose of morphine. This demonstrates that apoptosis is not an effect of acute or single doses of morphine. The extent of apoptosis observed in the morphine tolerant rats was dose dependent and many of the apoptotic neuronal cells were GABAergic inhibitory neurons. The induction of neuronal apoptosis was accompanied by an increase in sensitivity to noxious heat stimulation in the affected rats.⁴⁰

Prolonged opioid use therefore leads to tolerance and neuronal excitotoxicity via apoptotic cell death regulated by spinal glutamate transporters. Glutamate is an excitatory neurotransmitter and an NMDA receptor agonist whose physiological purpose is to regulate the memory process of neural pain pathways.³ Changes in glutamate transporter activity regulate synaptic glutamate availability.⁴⁰ Opioids, particularly mu opioid receptor agonists, enhance NMDA receptor excitability and increase synaptic glutamate in the spinal cord

dorsal horn, especially on prolonged use.^{17,40} Tolerance (and hyperalgesia as discussed earlier) involves the activation of excitatory glutamate receptors of the NMDA type in the CNS.¹⁴ NMDA receptor stimulation initiates an intracellular cascade involving an increase in intracellular calcium concentrations, activation of protein kinase C (PKC) and the calcium-calmodulin-mediated production of nitrous oxide.^{5,14,18} PKC activation leads to phosphorylation of NMDA receptors which activates a further series of cascades leading to opioid receptor down regulation (opioid tolerance) and hyper-responsiveness (hyperalgesia).¹⁴

The enhanced NMDA receptor excitability and increased synaptic glutamate may lead to the activation of NMDA receptors even in the presence of an overwhelming inhibitory opioid effect.⁴⁰ This activation of NMDA receptors initiates apoptotic cell death. There is a link between morphine-induced apoptosis, morphine tolerance and tolerance related abnormal nociceptive sensitivity. If neuronal apoptosis is a part of the mechanism of opioid tolerance, tolerance would be less likely to get better and more likely to get worse with subsequent opioid therapy. Opioid induced apoptosis would be of particular concern in cancer and chronic non-malignant pains requiring prolonged opioids.

Other suggested mechanisms of tolerance involve complex changes to the opioid receptors themselves. Neurotransmitters found in pain neuronal pathways include substance P, neurokinin, bradykinin, adenosine, nitrous oxide, serotonin and cholecystokinin.³ The prolonged activation of supersensitized excitatory opioid receptor functions leads to tolerance at a cellular level.¹⁴ Opioid receptors are thought to exist in differing states depending on the concentrations of various substances around them. These differing states are G_s , G_i or G_o coupled states and interconversion can occur. Activation of G_s coupled opioid receptors on sensory neurons results in excitation, a reduction of inhibitory G_i/G_o coupled effects and thus tolerance and hyperalgesia.¹⁴ The change of an opioid receptor from a G_s to G_i/G_o coupled state is controlled by the concentrations of glycolipid GM1 ganglioside on neuronal cell membranes. In opioid tolerance there is an

upregulation of the G_s coupled state messenger system and an elevation of GM1.¹⁴ GM1 is elevated by sustained activation of G_s coupled opioid receptor functions which may increase the conversion of opioid receptor states from inhibitory (G_i/G_o coupled) to excitatory (G_s) resulting in supersensitized excitatory state receptors and so tolerance and hyperalgesia.¹⁴

In addition to the mechanisms outlined above, tolerance to morphine appears to be contributed to by the metabolites, morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G).^{14,18} These metabolites also have a role in morphine-induced hyperalgesia, myoclonus and agitated delirium. As M6G is itself a potent analgesic and as M3G may antagonize M6G, any analgesic response to morphine may depend on the M6G/M3G ratio in the body.¹⁸ The normal ratio at which analgesia is seen is 5 M6G:1 M3G and any change in this ratio might result in paradoxical pain or hyperalgesia.¹⁸ The ratio of these metabolites shows inter-individual variation. In one study of 11 patients administered morphine systemically for cancer pain, however, the range of the ratios of M6G to M3G was not predictive of response to pain.¹⁸

Tolerance from prolonged use of opioids results from persistent changes in the neural circuits involved in pain modulation.⁴⁰ This is manifested as escalating doses and an intractable chronic pain state refractory to opioid therapy. Neuropathic pain may also result through CNS neurotoxic changes.

The treatment or prevention of opioid tolerance revolves around NMDA receptor antagonism and nitrous oxide synthetase inhibition. NMDA receptor antagonists such as ketamine have the ability to prevent and reverse tolerance and abolish hyperalgesia.^{18,45,46,48} The mechanism is not an effect of the initial fast synaptic transmission in dorsal horn neurons but rather inhibition of an increase in neural responses to successive stimuli, suggesting that NMDA antagonists affect central hyperexcitability and inhibit 'wind up' in dorsal horn neurons.⁴⁵ There is also a suggestion that NMDA antagonism is specific for morphine and not other opioids,¹⁵ although NMDA antagonists reverse tolerance of other opioids in animals.¹⁷ In addition the NMDA antagonist, ketamine, at the low doses used in palliative care, may also have

opioid receptor antagonist properties which is selective to opioid receptors in an excitatory (G_s coupled) state in dorsal root ganglion neurons.¹⁴

Methadone, an opioid thought to have some NMDA antagonistic activity, may decrease the development of tolerance by antagonizing NMDA receptors.¹⁰ As for many of the adverse effects discussed in this paper tolerance may be minimized by opioid rotation.¹² Rotation to methadone from other opioids may decrease tolerance,⁴⁵ although the literature is not conclusive about his observation. Tolerance to methadone has also been demonstrated, although less commonly than other opioid-tolerance, and some studies have, reported no development of tolerance.^{17,45,47} Methadone exists as two isomers—S and R-methadone. The S-methadone isomer has weak NMDA antagonist properties while R-methadone acts at mu and delta receptors.⁴⁷ It has been suggested that S-methadone blocks morphine tolerance and NMDA-induced hyperalgesia,³ but there is not good evidence to support that position. It may be that S-methadone could be used with morphine to increase analgesia, treat the hyperalgesic aspect of neuropathic pain, and minimize tolerance. In rats, methadone is less likely to induce tolerance than morphine.⁴⁷

CONCLUSION

Opioids have the potential to cause serious adverse effects in the CNS of palliative care patients. Many of these effects have complex mechanisms and are sometimes difficult to differentiate from disease progression or other pathological causes. Treatment or prevention is often with NMDA receptor antagonists or rotation to an alternative opioid.

Tolerance to opioids does develop but the clinical relevance is unclear. Hyperalgesia shares a common mechanism with tolerance and it may be that hyperalgesia is a manifestation of tolerance itself. The majority of required opioid dose escalations in cancer patients are due to progressive pathology.⁴⁹

Knowledge of these cerebral side effects of opioids is essential in the care of palliative patients.

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RECEIVED: 05/13/06

REVISED: 08/10/06

ACCEPTED: 08/20/06

doi:10.1300/J354v21n01_05

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