The use of ketamine in cancer palliation

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ABSTRACT

Cancer pain is caused by continuous tissue injury, which may be due to surgery, infiltration of the surrounding organs including nerves, as well as from mucositis after chemo- or radiotherapy. Nerve involvement, chronic opioid therapy and continuous nociceptive input cause hyperalgesia. Chronic stimulation of the dorsal root neurons leads to hyperalgesia and resistance (tolerance) to μ opioid analgesics (hyperalgesia-tolerance). The NMDA receptor antagonist ketamine reverses tolerance to morphine. Ketamine aggravates the sedative effect of opioids and other drugs used for neuropathic pain, such as sodium valproate and amitriptyline. The pain experienced by cancer patients needs a multimodal approach, including ketamine. Although ketamine appears to be a useful analgesic, the literature dealing with ketamine as an analgesic lacks randomised controlled trials.

Introduction

Cancer patients receiving palliative treatment often experience pain. Cancer pain is caused by continuous tissue injury, which may be due to multiple surgical procedures, pressure on or destruction of the surrounding organs, (including nerves), and also mucositis after chemo- or radiotherapy.

Cancer patients are often treated with opioids. These patients may also suffer from painful co-existing degenerative diseases. Tolerance has been defined as the need for higher doses of a drug to achieve the same effect. The long-term administration of opioids causes functional tolerance and dependence. Tolerance does not lead to morphine-induced miosis and constipation.

The spinal cord and brain stem are bombarded with nociceptive stimuli from the primary efferent neurons innervating injured tissue. The unabated stimulation by primary afferent neurons is complicated by the sensitisation of spinal (spinal wind-up) and brain stem neurons distorting afferent impulses. Painful stimuli may then be more painful than would be expected and are experienced over a larger area than the original pathology (hyperalgesia). In addition, stimuli that are not painful, like touch and pressure, may become painful (allodynia), or the patient may experience pain after the original lesion has healed. Pain following nerve involvement causes neuropathic pain, which is often characterised by intractable hyperalgesia and allodynia.

The relationship between tolerance and hyperalgesia

Chronic exposure to opioids gives rise to tolerance, while continuous nociceptive input causes hyperalgesia. The larger doses of opioids needed to treat pain effectively may therefore result from tolerance or exaggerated nociception, i.e. hyperalgesia. Consequently, both tolerance and hyperalgesia necessitate increasing the opioid dose, often to very large doses.

Apart from tolerance, opioids themselves can also produce hyperalgesia and allodynia.[1] Opioid tolerance presents with symptoms similar to opioid abstinence syndrome and hyperalgesia. Accordingly, opioid tolerance and hyperalgesia are regarded as two sides of the same coin, as they share the same pathogenesis and therapeutic approach.

The relationship between neuropathic pain and morphine tolerance has been reviewed by Mayer et al.[2] Tissue destruction gives rise to the release of intracellular substances and an inflammatory reaction, exposing the afferent nerve endings to several nociceptive substances. Both chronic tissue injury and nerve involvement (neuropathy) give rise to continuous nociceptive input to primary afferent cell bodies, neurons in the superficial layers of the dorsal horn of the spinal cord, the sympathetic nervous system, as well as supraspinal structures involved in pain perception.

Neuropathic pain syndromes and opioid tolerance may present as hyperexcitability (hyperalgesia) and/or disinhibition (spontaneous pain, allodynia). Mayer *et al.* have proposed the following model: chronic bombardment of neurons in the dorsal horn gives rise to the activation of glutamate receptors, N-methyl-D-aspartate (NMDA) receptors and non-NMDA receptors.[2]

The excessive stimulation of NMDA receptors and the subsequent calcium influx occur directly or indirectly: directly by glutamate released from the primary afferent neuron, or indirectly by repetitive μ receptor stimulation in the dorsal horn neurons. Activation of the μ receptor activates the second messenger protein kinase (PK) C_1. PKC_1 activates NMDA receptors by the removal of Mg^{2+} ions from ligand (glutamate) and voltage-gated Ca^{2+} channels. The increased intracellular calcium stimulates several processes, which eventually lead to hyperalgesia and resistance (tolerance) to the effects of opioid analgesics. Hence the term "hyperalgesic tolerance".

The directly and indirectly augmented calcium influx initiates three processes, namely activation of other protein kinases (PKC_2 and PKC_3) and larger amounts of PKC_1, activation of nitric oxide (NO) synthase (NOS), and an increase in the production of superoxide from mitochondria.

PKC_2 activates non-NMDA glutamate receptors, resulting in the influx of Na^+ and the efflux of K^+, which hypopolarises the cell membrane. PKC_2 may function as a transcription factor, resulting in the synthesis of another PKC, namely PKC_3. PKC_3 decreases μ opioid receptor responsiveness by uncoupling the receptor from its associated G protein and the subsequent decreased efflux of K^+, which prevents hyperpolarisation.

NOS increases the production of NO. NO and superoxide combine

to form peroxynitrite ($ONOO^-$). $ONOO^-$ initiates DNA strand fragmentation, which stimulates the nuclear repair enzyme poly(ADP ribose) synthase (PARS). Pronounced activation of PARS results in the inhibition of mitochondrial respiration, the depletion of energy stores and programmed cell death (so-called dark neurons). Similar processes may occur in primary afferent neurons.

NMDA receptor antagonists can at least partially reverse hyperexcitability (hyperalgesia) that results from PKC-mediated alterations of the NMDA receptors, while events like allodynia are not improved by NMDA antagonists,[3] but by the inhibition of the NO/PARS pathway.[4]

Another mechanism of tolerance to μ agonists is their effect on the re-uptake of glutamate from the synaptic cleft. In the central nervous system, extracellular glutamate is regulated by the glutamate transporter system (GT).[5] Different GTs are present on neuronal and glial cells.[5,6] Mao *et al*. demonstrated that chronic exposure to morphine induces down-regulation of GTs in the spinal cord.[7] Increased synaptic glutamate stimulates the NMDA receptor despite an inhibitory effect of opioids. The non-competitive NMDA receptor blocker MK-801 blocks this effect.

Apart from central modes of analgesia, morphine also demonstrates a peripheral location of action and target of morphine tolerance.[8] Kolesnikov and Pasternak demonstrated that both systemically and peripherally (but not intrathecally) applied NMDA receptor antagonists (MK-801 and ketamine) block topical morphine tolerance.[9,10] According to Kolesnikov and Pasternak, these observations are consistent with the possibility that peripheral tolerance is mediated through peripheral NMDA receptors, possibly on the same dorsal root ganglia neurons containing the opioid receptors.

Mayer *et al*. focussed mainly on the role of the NMDA receptor in the pathogenesis of neuropathic pain and opioid tolerance, but pointed out that several other non-NMDA factors or receptors may play a role, including Ca^{2+}/calmodulin, cyclic AMP and other second messengers, and cholecytokinin.[11] This may explain, at least partially, why NMDA receptor blockade does not always reverse opioid tolerance.

Although tolerance to opioids is associated with long-term opioid treatment, tolerance may also develop rapidly after exposure to opioids.[12,13] Tolerance and hyperalgesia have been reported after a single administration of high doses of μ-opioid agonists.[14,15,16]

The analgesic effect of ketamine may be influenced by its effect on peripheral inflammation.[17,18] Ketamine does not reduce the inflammatory effect of endothelium, but reduces the chemotactic activation of neutrophils.[17]

Management of hyperalgesic opioid tolerance

Protracted tissue destruction, afferent neuron stimulation and exposure to μ receptor agonists give rise to hyperalgesia. The approach to the treatment of pain in this scenario is multimodal and includes the prevention of tissue destruction, inhibition of peripheral nociceptive substances, blockade of peripheral nociceptors, nerve block, and the inhibition of the NMDA/NO-mediated cascades in the dorsal root neurons as well as neurons in the dorsal horn.

In animals, ketamine almost completely reverses tolerance to morphine.[19] Although ketamine appears to be a useful analgesic, the human literature dealing with ketamine as an analgesic, especially in cancer patients, is characterised by numerous case reports, small numbers and very few randomised controlled trials.

Célèrier *et al*. found that hyperalgesia lasting for days following the acute administration of fentanyl can be prevented by pre-treatment with ketamine.[14] Eilers *et al*. reported a case where severe tolerance to mega-doses of fentanyl (7000 μg/h) was reversed by low dose intravenous ketamine (0.1 mg/kg/h). They suggest the early use of small-dose ketamine.[20]

Laulin *et al*. demonstrated a preventive, long-lasting effect of ketamine on, what they termed, the dual phenomenon of immediate fentanyl-induced hyperalgesia and related acute tolerance to the analgesic effect of morphine. The hyperalgesia effect of fentanyl was immediate and dose-dependent. They suggest that opioids do not only activate antinociceptive systems, but also longer-acting pronociceptive systems. According to these authors, the NMDA receptor antagonist, Ketamine, potentiates the analgesic effect of fentanyl by preventing early hyperalgesia and by reversing acute tolerance. Secondly, they state that both hyperalgesia and acute tolerance stem from a common NMDA-receptor-dependent mechanism.[21] Thirdly they suggest that ketamine should not only be administered preventively, but should also be co-administered with a long-acting drug such as morphine, in order to sustain NMDA receptor blockade. These observations may explain the lack of benefit from ketamine-morphine combinations when ketamine is limited to the postoperative period.

In a literature review, McQueen and Baroletti found available data to suggest that the supplementation of morphine with subanaesthetic doses of ketamine improves analgesia in cancer patients. It reduced opioid requirements and related side effects and was well tolerated.[22]

Neuropathic pain is characterised by its resistance to standard pharmacological therapies. In an uncontrolled open-label study, Kannan *et al.* administered ketamine orally as adjuvant to oral morphine in cancer patients with intractable neuropathic pain. Non-recurrence of pain after discontinuation of oral ketamine was reported in two out of three patients.[23]

Anghelescu and Oakes reported a case of end-stage abdominal neuroblastoma in a five-year-old child with severe opioid tolerance. Before initiating ketamine, the child needed astronomical doses of fentanyl and sufentanil. After ketamine 0.11 mg/kg/h IVI was started, it was possible to titrate opioid doses down by 45%. It was not necessary to increase the opioid dose until the child died seven days later. Sedation scores were acceptably low, allowing the child to interact with relatives.[24]

Bell reported three cases of terminally ill morphine-tolerant cancer patients who benefited substantially from low-dose (1 mg/kg/24 hours) subcutaneous ketamine.[25]

Kotlińska-Lemieszek and Łuczak have used morphine for the treatment

of cancer pain for more than 16 years.[26] The indications were moderate to severe pain (especially of neuropathic origin), despite opioid dose escalation and rotation, and a high incidence of breakthrough pain requiring intravenous rescue doses of potent opioid and midazolam. They administered ketamine orally, subcutaneously, intravenously or epidurally. Complete pain relief was possible in 62% of cases, there was partial relief in 23% of cases and none in 15% of cases. Despite the use of midazolam from 5 mg/day and/or haloperidol from 2 mg/day, dreams, confusion, and hallucinations occurred in 18% of the patients, and drowsiness developed in 56.5% of the patients. Although the addition of ketamine improves the analgesic effect of morphine, it was possible to decrease the dose of morphine in only 17% of the patients. It also seems that tolerance to ketamine develops, necessitating an increase in the doses of both the opioid and ketamine – but still providing better pain relief.

"Burst" ketamine therapy was offered to terminally ill cancer patients.[27] They received ketamine 100 to 500 mg/day IV for three to five days (working on an average body mass of about 60 kg, this amounts to about 0,2 mg/kg/hour – which is the normal known analgesic dose). The response was 88% for somatic pain and 61% for neuropathic pain. After the cessation of ketamine, 24/29 (83%) of the patients maintained good pain control for up to eight weeks; the other five (17%) needed ketamine again 24 hours after it was stopped. With increasing doses, psychotomimetic side effects occurred in 12/29 (41%) of the patients; four of these patients were non-responders and eight were responders. Psychotomimetic side effects subsided with dose reduction in three patients after the dose of ketamine was reduced; the other five rejected dose-reduction.

According to Kannan *et al*. all patients suffering from head and neck cancer benefited from oral ketamine. They suggest that ketamine might control pain transmission via the trigeminal system (more modulated/attenuated) more effectively than impulses via lower spinal levels.[23] Neuropathic pain in the distribution of the trigeminal nerve is more susceptible to treatment with carbamazepine and baclofen than other neuropathic pain conditions.[28] More studies are required to verify this observation.

Radiotherapy in patients with head and neck cancer, and chemotherapy, are often complicated by moderate to severe mucositis. These patients invariably suffer from pain and hyperalgesia. The latter causes severe pain of the mucosa during mastication and swallowing. Systemic opioids are of little help for mechanical and chemical hyperalgesia that occurs during eating. Slatkin and Rhiner addressed the problem of mucositis in patients who received chemo- and radiotherapy for a tongue carcinoma.[29] The patient used ketamine mouthwash and experienced substantial pain relief, eventually using the solution for several months. The authors ascribed the efficacy of topical ketamine to its sodium channel blocking effect or a mild anti-inflammatory effect.

Some agents, like methadone and pethidine, act as μ agonists as well as NMDA receptor antagonists.[30] Both the non-competitive NMDA receptor blockers, ketamine and dextromethorphan, reduced abstinence symptoms in heroin addicts.[31]

Is ketamine always effective?

Jackson *et al*. found ketamine to be ineffective in the treatment of pure visceral pain.[27] Haines and Gaines[32] and Enarson *et al*.[33] did not find oral ketamine beneficial for chronic neuropathic pain.

Does pre-emptive administration of ketamine make a difference to morphine consumption after surgery? As has been pointed out above, the mechanism underlying reduced pain and analgesic consumption after the pre-emptive administration of local anaesthetics and opioids is the prevention of NMDA-mediated sensitisation of the spinal cord dorsal horn neurons. Katz et al. studied the effect of pre-emptive ketamine in patients undergoing radical prostatectomy. They administered low-dose ketamine intraoperatively, starting with 0.2 mg/kg before incision, followed by an infusion of 0.15 mg/kg/h for 80 min, or starting 70 min after incision for 80 min. They could not demonstrate a significant difference ($0.05 < p \leq 0.08$), in either pain scores or in morphine consumption during the first 48 postoperative hours. However, after 48 hours until the end of the study 24 hours later, the group receiving pre-incision ketamine needed significantly less morphine. At follow-up two weeks and then six months later, no difference was detectable between the groups. They pointed out that a bigger difference might have been evident had larger doses of ketamine been used and if *ketamine had been continued into the postoperative period*, when inflammation contributes to nociception and central sensitisation. Furthermore, early intraoperative noxious events contribute more to central sensitisation than late intraoperative or postoperative events.[34] This means that analgesia must outlast noxious stimuli – both before the noxious stimuli start and until noxious stimuli end.

Side effects

Ketamine aggravates the sedative effect of opioids,[35] and the sedation caused by other drugs used for neuropathic pain, such as sodium valproate and amitriptyline. There appears to be tolerance to ketamine-induced sedation.[23]

Randomised controlled trials are needed to test the occurrence of nausea and vomiting in patients taking ketamine. In our experience with morphine/ketamine patient-controlled intravenous analgesia, ketamine does not seem to increase nausea and vomiting. These symptoms are part of the cancer disease process and not necessarily ascribable to the drugs being taken by the patients.

Psychotomimetic effects are unlikely at ketamine doses of 2.5 μg/kg/min or around 200 to 350 mg/day.[36] Although psychotomimetic side effects do occur with the use of ketamine, no patients in the trial by Jackson and Goodchild had the ketamine stopped because of this.

Intrathecal ketamine has been used for the treatment of acute postoperative pain and to provide analgesia in neuropathic pain syndromes.[37] Sator-Katzenschlager *et al*. report the long term (24 days) antinociceptive effect of intrathecal S(+)-ketamine in a patient with established morphine tolerance.[38] Vranken et al. address the question of the possible neurotoxicity of ketamine. They found evidence of severe neuropathological changes following 28 days of intrathecal administration of preservative-free S(+)-ketamine to a terminally ill patient with cancer of the cervix, suffering from intractable neuropathic pain. They point out that the safety of intrathecal ketamine has not been proven in animals and that this mode of ketamine administration should be reserved as a last resort in terminally ill patients.[39] Neither

the patient of Vranken *et al*. nor of Sator-Katzenschlager showed any clinical signs of neurotoxicity. However, it should be borne in mind that both these patients had peripheral nerve involvement, which might have clouded the signs of neurological deficit. However, weakness was not reported in these patients. Incidentally, the duration of intrathecal S(+)-ketamine in both these cases was approximately the same (24 and 28 days). Cognisance should therefore be given to the findings of Vranken *et al*.

How much ketamine is necessary?

Analgesic requirements may vary enormously. These are determined by both pharmacodynamic and kinetic factors, including tolerance and route of administration.

Rectal ketamine suppositories have been used in children. The dose is 10 mg/kg. It supplies good postoperative analgesia and is well tolerated. Peak concentrations are between 30 and 60 min. The $t_{1/2}$ of ketamine and norketamine was about three hours (the range is approximately 1,5 to 5 hours).[40] The dosage interval is therefore four hours (two to seven hours) ($t_{1/2}$ x 1.4).

Intravenous ketamine is used widely. Łuczak *et al* start with ketamine 5 mg to 10 mg IVI, which provides analgesia and sedation for up to 15 minutes. A dose of 20 to 40 mg of ketamine, preceded by midazolam 2 mg, is sufficient in the majority of patients.[41] In a randomised, controlled, cross-over study, bolus infusion of 0.25 or 0.5 mg/kg ketamine over 30 minutes significantly reduced pain in almost all cancer patients receiving morphine.[42] As discussed previously, the "burst" ketamine therapy of Jackson *et al* consisted of 100 to 500 mg/day IV for three to five days (working on an average body mass of about 60 kg, this amounts to about 0,2 mg/kg/hour – which is the normal known analgesic dose).[27] Ivani *et al*. of the Regina Margherita Children's Hospital in Turin, Italy, reviewed the use of ketamine. They use one to two mg/kg IV for short painful procedures. For pain and sedation in ICU they use 0,5 to 1,5 mg/kg/h.[43]

In their patient with mucositis after chemo- and radiotherapy for a tongue carcinoma, Slatkin and Rhiner used 5 ml of a 20 mg/ml ketamine mouth wash. The patient rinsed the mouth for approximately one minute, after which the solution was expectorated.[29]

Kotlińska-Lemieszek and Łuczak have used morphine in the treatment of cancer pain.[26] They administered ketamine orally, subcutaneously, intravenously or epidurally. The median ketamine dose was about 200 mg/day (range 13 mg/day to 1400 mg/day). The morphine dose in their patients ranged from 60 to 11500 mg/day. They recommend the following regimen: 1. Start with a ketamine test dose of 20 mg PO, or 2.5 to 5 mg IVI or SC. Add midazolam 1 mg IVI if vivid or threatening dreams occur. 2. Continue with ketamine 0.6 to 0.8 mg/kg/day PO or SC. 3. Order midazolam concomitantly. 4. Increase the ketamine dose by 25% as permitted by side effects. 5. For breakthrough pain (dressing changes, movement), give 1/10 to 1/6 of the total oral or SC dose, or 5 mg to 10 mg IVI. 6. Adjust the midazolam or haloperidol doses if side effects occur. 7. Ketamine should be introduced on an inpatient basis. Patients may be discharged once pain control has been achieved.

Ketamine is biotransformed in the liver and its major metabolite is norketamine.[44] Norketamine has analgesic properties and is excreted by the kidneys.[45] Liver and kidney function must therefore be taken into account when calculating dosages.

Has the adjuvant use of ketamine for cancer pain been proven?

Numerous case reports and small studies have been published, addressing the use of ketamine in cancer patients. In a systematic study to determine the effectiveness and side effects of ketamine, Bell *et al*. found only two randomised controlled trials suitable for inclusion in the study. Both studies concluded that ketamine improves the effectiveness of morphine in the treatment of cancer pain. However, they concluded that high-quality randomised controlled trials with larger numbers, with standardised, clinically relevant routes are needed to confirm the value of ketamine as adjuvant in cancer pain.[46] Jackson and Goodchild criticised meta-analyses of the use of ketamine in the palliative scenario.[47] They pointed out that the palliative care patient population does not lend itself to randomised controlled trials, with standardised routes of administration.

Good *et al*. have also recently criticised the WHO's incremental additive approach of strong opioid dose escalation for analgesia in cancer patients, as this does not take into account the mechanism of pain, and valuable time is lost with the ladder approach (from weak to strong opioids), which contributes to the development of intractable pain. They suggest the initiation of pain therapy by a short-term, intensive *'triple agent' regimen*, namely an opioid (morphine), an NSIAD or steroid or both, and ketamine. The short-term intensive treatment is deployed to block nociceptive input and to prevent central sensitisation. A low-toxicity regimen consisting of an anti-inflammatory drug in combination with an oral or transdermal opioid can follow this. This is analogous to the modern multi-agent chemotherapy of cancer. After remission has been induced, a less toxic regimen is chosen for maintenance if necessary.[48]

Tolerance to opioids can be partially overcome by *opioid rotation*. This has been demonstrated with methadone and hydromorphone. In an opioid-tolerant cancer patient, the dose of hydromorphone could be reduced dramatically, with the alternative use of methadone.[49] This may be ascribed to the NMDA-blocking effect of methadone.[30]

Recommendations

The following dosages (averages) are recommended:

1. For short painful procedures: 1 – 2 mg/kg IV.
2. For pain and sedation in ICU: 0,1 – 0.3 mg/kg/h IVI.
3. For "burst" therapy: 1.5 to 8 mg/kg/day or 0.04 to 0.2 mg/kg/h IVI for 3 – 5 days.
4. Mouth wash 5 ml of a 20 mg/ml. Rinse for about 1 min and expectorate.
5. Rectal suppositories: the dose is 10 mg/kg every 4 hours.
6. As adjuvant in opioid tolerance: start with a test dose of 0.3 to 0.5 mg/kg PO or 0.05 to 0.1 mg/kg IVI or SC. Continue with 0.15 to 0.2 mg/kg 4-hourly PO or SC. Increase the ketamine dose by 25 % as permitted by side effects. For breakthrough pain, 1/10 to 1/6 of the daily oral or SC dose, or 0.1 mg/kg IVI. Order midazolam 0.015 mg/kg IVI if dreams occur.

Conclusion

The pain experienced by cancer patients needs a multimodal approach in which ketamine may have a role to play. It is recommended that patients be made pain free from the onset – even starting preoperatively if appropriate. This analgesia should include at least two different modalities, chosen from the following "penta-analgesia" armamentarium: an opioid, ketamine, an anti-inflammatory, a nerve block, and a tricyclic antidepressant or similar agent. The primary aim in palliation should be the alleviation of suffering and the management of specific side effects of the analgesics, which may cause discomfort.

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