Ketamine hydrochloride – an adjunct for analgesia in dogs with burn wounds

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ABSTRACT
The management of pain in patients with burn wounds is complex and problematic. Burn-wound pain is severe, inconsistent and underestimated. Patients experience severe pain, especially during procedures, until wound healing has occurred. A multi-modality approach is needed for effective management of pain, which requires an understanding of the mechanisms of pain. Altered pharmacokinetics and pharmacodynamics in burn-wound patients makes drug actions unpredictable. Opioids alone are seldom sufficient for pain control. The multi-modality approach includes the use of opioids and non-steroidal anti-inflammatory, anxiolytic and alternative drugs. Ketamine has been found to be a useful agent for analgesia in burn-wound patients; a dose of 10 mg/kg qid per os was found to be an effective adjunct to pain therapy.

Key words: analgesia, burn wounds, dog, ketamine, pain management.

NIMRODUCTION
Management of patients with burn wounds is a long and tedious process. These patients experience intense pain, hyperalgesia and allodynia, which are difficult to assess and manage. Hyperalgesia and allodynia are part of a syndrome known as ‘winding up’ and hypersensitivity of the ascending sensory pathways. Hyperalgesia is increased sensitivity to painful stimuli, while allodynia is perception of pain from non-painful stimuli. ‘Winding up’ is a process characterised by a reduction in pain threshold and spontaneous depolarisation of ascending neurons. Hypersensitivity is the result of ‘winding up’ and is mediated by peripheral and central sensitisation.

Inflammation in burn wounds results in the production of inflammatory mediators, comprising potassium, serotonin, bradykinin, substance P, histamine and the products of the lipo-oxygenase and cyclo-oxygenase pathways. These chemicals sensitise the high threshold nociceptors, so that low intensity stimuli are perceived as painful, resulting in peripheral hypersensitivity. Silent nociceptors are activated by the inflammatory mediators. Drugs that reduce the activity of these inflammatory mediators help to prevent peripheral hypersensitivity, the rationale for the use of non-steroidal anti-inflammatory drugs in pain management.

Central hypersensitivity is mediated by a progressive increase in neuronal activity of the dorsal horn after stimulation by afferent C fibres, which renders these neurons more sensitive to impulses from peripheral nerves. Changes in the dorsal horn include increased receptive field size, increased magnitude and duration of response to stimuli, and reduced threshold potential. Several neurotransmitters and neuromodulators are involved in this process. The N-methyl-D-aspartate (NMDA) receptors in the dorsal horn synapse of the ascending sensory pathway have received considerable attention. They are activated by the removal of Mg²⁺ from the receptors. Binding of substance P to neurokinin receptors aids in the activation of the NMDA receptor but maintenance of sensitisation is not dependent on substance P. Increased neural conduction also activates NMDA receptors. In the activated state, the NMDA receptor site is easily occupied by the excitatory amino-acids, including glutamate and aspartate. The NMDA receptor causes opening of Na⁺ ion channels, an increase in intracellular Ca²⁺ and production of nitric oxide, resulting in reduction of the threshold potential and increased firing of the neuron.

The opioid receptor in the dorsal horn operates independently of the NMDA and substance P receptors. Opioid (Mu, Kappa and Sigma) receptors are bound to a G protein secondary messenger system, which causes a decrease in cyclic adenosine monophosphate, inhibition of Ca²⁺ channels and activation of K⁺ channels. Activation of opioid receptors results in hyperpolarisation of the neural plasmalemma while stimulation of NMDA receptors causes hypopolarisation. Opioids reduce initial responses to pain, particularly with respect to secondary pain, but do not prevent ‘winding up’ or hypersensitivity. As time progresses, the pain increases as more ion channels are opened through activation of the NMDA receptor until allodynia and hypersensitivity occur. NMDA antagonists do not prevent initial pain but do not prevent ‘winding up’. A combination of NMDA antagonists and opioids has great potential, especially for intrathecal use.

Pain is a constant problem in burn-wound patients until wound healing is complete. Undertreatment of pain results in anxiety. Anxiety, pain and depression form a vicious cycle whereby the magnitude of the pain is enhanced. Severe behavioural changes have been noted. Major depression and stress-induced analgesia may lead to the erroneous conclusion that analgesia is sufficient. Burn pain is severe, inconsistent and underestimated. The most painful part of burn-wound management occurs during the handling of the patient for dressing changes during which additional analgesia and sedation are required. Traditionally, opioids have been the mainstay of pain management. It is evident, however, that in spite of high doses of opioids, patients still experience pain during procedures. Opioid resistance is a well-recognised feature of neuropathic pain, which is the result of secondary central nervous system dysfunction caused by prolonged pain stimulation.

Common problems encountered with opioid analgesia are paralytic ileus, gastrointestinal irritation, and respiratory depression with resultant pneumonia and atelectasis.

There are a number of alternative drugs.
to opioids available for the management of pain in burn-wound patients. Ketamine hydrochloride is a cyclohexamine derivative related to phencyclidine with potent analgesic properties even at sub-anesthetic concentrations. It is a hypnotic, analgesic, amnesic and sedative that has been used in the treatment of burn wounds since 1975. Ketamine is a non-competitive NMDA receptor antagonist that has been shown to be very effective in the management of pain for dressing changes when given intravenously or intramuscularly prior to bandage changes. A dose of 2 mg/kg of ketamine combined with diazepam or midazolam has been used intravenously in human burn-wound patients. Ketamine has been used orally in the treatment and management of paediatric burn-wound patients at a dose of 10 mg/kg given 20 min before the procedure.

Based on the above review, ketamine was used for analgesia in the following 2 cases.

CASE HISTORY 1
A 5 kg, 7-month-old female dachshund was presented to the Outpatients Section of the Onderstepoort Veterinary Academic Hospital (OVAH) with burn wounds after having jumped into a bath of very hot water. The owner had immediately immersed the dog in cold water and then sought veterinary advice. The burns covered the chest, abdomen, axillae, vulva and lips. The burns were graded 1 with focal patches graded 2. Approximately 40% of the patient’s surface area was burnt. The initial treatment, on Day 0, comprised Ringers lactate (Intramed) at 100 ml/kg/day, intravenous amoxycillin (Amoxil, SmithKline Beecham) at 20 mg/kg every 12 h, and intravenous morphine sulphate (Intramed Morphine, Intramed) at 0.15 mg/kg every 2 h. The patient was admitted to the Department of Surgery, and remained in the Intensive Care Unit for 23 days. The day following admission, antibiotic therapy was changed to oral amoxycillin and clavulanic acid (Synulox, Pfizer Laboratories) (25 mg/kg po bid), resuscitation fluids (Balsol, Intramed) (100 ml/kg/day), morphine (0.1 mg/kg iv/qd) and lactulose (Lacson, Lennon) (2ml bid). Owing to pain, difficulty was encountered during clinical examination and while changing the bandages. The antibiotics were discontinued once the wounds were granulating. On Day 2 the morphine, lactulose and Balsol were discontinued and buprenorphine (Temgesic, R&G Pharmaceuticals) (0.02 mg/kg i/m tid) was used as an analgesic. Chloramphenicol eye drops (Chloromycetin Redi-drops 0.5 %, Warner-Lambert SA) were instilled into the right eye for 8 days to treat a large superficial corneal ulcer. During Days 2 and 3 the patient was observed to be in pain despite administration of buprenorphine. On Day 4, the pain had increased in intensity and the patient started to traumatised herself. She declined a commercial pelleted diet but continued to eat chicken. Day 5 represented a progression of the pain symptoms with the patient showing alldynia, dehydration and decreased water intake on Day 6. The patient was sedated with ketamine (Anaket, Centaur Labs, Premier Pharmaceutical Company) (5 mg/kg iv) and midazolam (Dormicum, Roche Products) (0.3 mg/kg iv) to facilitate handling, bandage changes and the placement of a phargostomy feeding tube. Analgesia was continued with oral ketamine at a dose of 10 mg/kg 4 times a day. This dose was based on published literature relating to human burn-wound patients and the pharmacokinetic data on ketamine in dogs. The following day her habitus had improved and no additional sedation or analgesia was required. The phargostomy tube remained in place until Day 15, during which time she was force-fed a high protein / high energy diet (Hill’s a/d prescription diet), and on day 10 the patient’s interest in food had returned. The ketamine was discontinued on Day 14. No adverse side-effects were noted during the entire time the ketamine was used. At this stage, acepromazine (Aceprom, Centaur Labs, Premier Pharmaceutical Company) (0.5 mg/kg) was given orally for sedation to reduce the patient’s movement. The acepromazine was discontinued on Day 20.

CASE HISTORY 2
A 4 kg, 4-year-old female Maltese poodle was referred to the Department of Surgery, 2 days after having been burnt with cooking oil. The burn wounds covered the dorsal thoracolumbar region with necrotic parched skin evident in some areas. Pain was intense and the patient cried when handled. Initial treatment on admission, Day 0, included topical acrilavlin and glycerine non-adherent dressings, buprenorphine (0.02 mg/kg tid), metronidazole (Triachole, Lennon) (25 mg/kg bid) and amoxycillin and clavulanic acid (Synulox, Pfizer Laboratories) (25 mg/kg bid). The animal displayed marked signs of pain at this time when injected intramuscularly and when handled. On Day 2, the patient was in extreme pain when handled, and was depressed. The buprenorphine was replaced with ketamine (1 mg/kg tid). This dose of ketamine was inadvertently low due to a misunderstanding. On Day 3, habitus had improved slightly but the patient was still in pain and required an adjustment of the ketamine dose to 12 mg/kg qid. By Day 4 pain control had improved and the patient was manageable during treatment and clinical examination, but remained depressed and had vomited during the night. Cimetidine (Tagamet Syrup, SmithKline Beecham) (10 mg/kg bid) and sucralfat (Ulsanic, Continental Ethicals) (30 mg/kg bid) were administered prophylactically for gastric ulceration. High protein / high energy diet (Hill’s a/d prescription diet) was fed and the metronidazole was discontinued. From Day 5 onwards pain management was viewed as adequate, although some pain remained. On Day 10, secondary closure of the remaining defect was performed under general anaesthesia. After premedication with morphine (0.1 mg/kg i/m), anaesthesia was induced with intravenous propofol (Diprivan 1 %, Zeneca SA) (6 mg/kg). General anaesthesia was maintained with 2 % halothane and oxygen and an uneventful recovery followed. Fluid balance was maintained intravenously with Ringers lactate (10 ml/kg/hour) and post-operatively with Balsol (80 ml/kg/day). Appetite remained good and metronidazole (25 mg/kg bid) was again added to the antibiotic regime. On Day 11, the ketamine dose was reduced to 3 times a day at a dose of 8 mg/kg. On Day 12, the ketamine and sucralfat were discontinued. On Day 13, the patient was discharged on a course of metronidazole and amoxycillin and clavulanic acid. No untoward side-effects due to ketamine were noted.

DISCUSSION
The development of alldynia and hypersensitivity followed a predictable pattern in these 2 cases. This was especially obvious when the case history of the 1st patient is reviewed. Pain was experienced during Days 1, 2 and 3. It was of a moderate intensity and considered clinically acceptable. However, it is during this period that the foundation for central and peripheral hypersensitivity and ‘winding up’ was laid. On Day 4, the pain intensity increased, food and water intake dropped and the patient became depressed. Day 5 represented a progression of these clinical signs to culminate in alldynia and hypersensitivity on Day 6. The dose of morphine was reduced from 96

Day 0 to Day 1 and then replaced by buprenorphine on Day 2. These opioids slowed the onset of allodynia but did not prevent it, as described in the introduction. The 2nd case was presented with allodynia. The other commonly noted signs of pain are poor appetite, reduced water intake and depression. It is worth noting that not all patients with severe pain will become anorexic. There was a reduction in appetite and a reluctance to eat in the 2nd case but at no time did the patient become anorexic. Anorexia is a warning sign of allodynia.

Morphine and buprenorphine are both effective opioid analgesics. Both patients were in pain, and the opioid analgesic protocol could be considered to be insufficient in these cases. Morphine is an agonist, while buprenorphine is a mixed agonist/antagonist synthetic opioid. Buprenorphine by its inherent nature has a ceiling effect after which the drug proceeds to act as an antagonist13, and has been used as a reversal agent for opioid-induced complications14. True agonist opioids are preferred, as the analgesia can be titrated to effect1. Unusually high doses of opioids are necessary due to altered pharmacokinetics in the burn-wound patient1. The pharmacokinetics and pharmacodynamics of drugs are altered in burn-wound patients owing to changes in fluid compartments, cardiac output, organ perfusion, renal and hepatic function and hypo- and dysproteinemias. The reaction of a patient to a particular drug is therefore not predictable and hence requires titration1.

Ketamine was used to provide analgesia in both cases. Even the low dose of ketamine originally used in the 2nd case had an effect on pain but was not sufficient to alleviate the pain adequately. At the higher dose of ketamine, pain control improved but the pain was never totally obliterated.

The dose of ketamine in these patients was determined empirically. The T elimination for ketamine in dogs is 122 min after a bolus dose of 10 mg/kg intravenously. The T ½ elimination for ketamine after an infusion of 300 μg/kg/min was 141 min after discontinuation of the infusion. The pharmacokinetics and pharmacodynamics for oral ketamine has not been determined in dogs. Low doses, in the order of 2 mg/kg, of ketamine are usually used for pain relief in man14.

Ketamine has been administered to human patients for as long as 32 days without any side-effects. No untoward side-effects were noted in the patients in this report. Transient stridor, random movements of limbs, increased salivation and increased intracranial pressure are common side-effects in man15. Hallucinations are common in man but can be avoided with the use of benzodiazepines. In human patients, hallucinations increase stress and anxiety16,17; however, it is not known whether dogs hallucinate. Respiratory depression and ileus are rare18. Ketamine stimulates the cardiovascular system, increasing heart rate and blood pressure1. The incidence of side-effects with orally administered ketamine are low19. In man, tolerance to ketamine has been reported20.

Ketamine is an anaesthetic agent but it did not overtly influence our anaesthetic regime in Case 2. It should always be remembered that oral administration of ketamine may reduce the induction requirements for anaesthesia and hence induction dose should be titrated to effect and not given as a bolus.

Total control of pain was not achieved because a multi-modal approach to analgesia was not used. In spite of the initial poor effect of opioids, the addition of opioids to the ketamine would have improved the analgesia in a synergistic or additive way. Benzodiazepines, barbiturates and propofol are useful for their anxiolytic and hypnotic effects. Non-steroidal anti-inflammatory drugs may be used but those with cyclo-oxygenase activity are preferred, such as ketorolac, ketoprofen and carprofen. Newer generation non-steroidal anti-inflammatory drugs have a reduced incidence of gastric ulceration and renal failure. A regional analgesia technique such as epidural analgesia is also a very useful adjunct.

CONCLUSION

The management of pain should be aggressive from the beginning to prevent changes in the peripheral and central pain pathways. The clinical endpoint of pain management should allow procedures to be performed on the patient with minimal discomfort, and food and water intake should remain acceptable. This requires that a multi-modality approach is used and that analgesia is titrated to effect. Ketamine offers a valuable tool to aid in the management of hypersensitivity and allodynia. Ketamine is not a panacea, but should be combined with opioids and sedatives. In this way, the synergistic effects of drugs can be utilised. Oral administration is easy, practical and can be combined with oral opioids and sedatives, reducing the requirement for injections. More work is necessary to evaluate oral ketamine as an adjunct to analgesia in canine and feline patients.

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REFERENCES


