a subcutaneous infusion of sufentanil with doses of up to 850 μg/24 h, in addition to the transdermal fentanyl, in an attempt to deliver opioid more quickly following dialysis, but continued to suffer severe pain consistently, during and following each dialysis session. On many occasions, pain control was only just achieved by the time his next dialysis session was due. The patient was subsequently commenced on methadone and referred for placement of an intrathecal opioid delivery system, but continued to deteriorate and died within 5 days of electing to discontinue dialysis.

Serum fentanyl levels were not measured at any stage, but we present this case as anecdotal evidence to suggest that, contrary to the published literature, lipophilic opioids may be removed by dialysis and hence may not provide effective pain relief. This may have been the result of the particular dialyzer membrane used, as fentanyl has been shown to be dialyzable with some membranes but not others. As it takes a finite period of time for serum and central nervous system opioid levels to reach an efficacious level following dialysis, the only appropriate drug to use in chronic pain is one that is not removed by dialysis. Methadone may have been a more appropriate opioid to use earlier in this case. There is some evidence to suggest that it is poorly removed by dialysis.

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doi:10.1016/j.jpainsymman.2006.09.003

References

Successful Use of Ketamine Infusion in the Treatment of Intractable Cancer Pain in an Outpatient

To the Editor:

Pain is the most devastating complication that occurs in cancer patients. Over 90% of patients in the advanced stage of their disease report uncontrolled pain. Cancer pain may be managed by following the World Health Organization “analgesic ladder” approach, which, when followed, can provide adequate pain relief in greater than 80% of the cases. The incidence of intractable cancer pain that cannot be controlled by traditional methods is estimated to be around 2% in those with advanced disease. Inadequate pain control could be due to opioid tolerance, dose-limiting side effects, and progression of disease.

Several studies in recent years have demonstrated ketamine as a coanalgesic for intractable cancer pain. Subanesthetic doses of ketamine have been shown to be effective as an adjuvant analgesic in decreasing opioid requirements. An advantage of using a subanesthetic dose of ketamine is the lower risk of side effects, including delirium, hallucinations, nightmares, and dysphoria. We report a case in which an intravenous ketamine infusion was used successfully to obtain adequate pain relief in an outpatient with intractable cancer pain.

Case Report

The patient was a 31-year-old, 55 kg female with a medical history of adenocarcinoma of the colon. At age 28, she underwent colon resection and several courses of chemotherapy. Two years later, she underwent exploratory laparotomy with sigmoid resection and bilateral salpingo-oophorectomy secondary to metastasis. She was admitted for pain management
due to extensive metastases to the liver, pelvis, lungs, and bone. Despite escalating doses of intravenous opioids, her pain remained 10/10 on the visual analog scale (VAS). Two weeks prior to her last admission to our hospital, she sustained a fracture to her left mid-femoral diaphysis and underwent placement of an intramedullary rod. She complained of pain in the left hip with left sciatic pain distribution, as well as pain over the quadriceps femoris. A consultation was requested from the Chronic Pain Service for management of pain and reduction of sedation to allow discharge to home.

After admission, the patient was treated with morphine patient-controlled analgesia (PCA) infusion therapy (basal 0.36 mg/kg/h, 10 mg every 5 min bolus, maximum 12 doses per hour), extended-release oxycodone 240 mg twice daily, and gabapentin 300 mg four times daily. Rapid titration of morphine to 0.91 mg/kg/h failed to provide adequate relief and resulted in excessive sedation. Neuraxial analgesia was contraindicated secondary to the anticoagulant therapy for her cancer-associated hypercoagulable state.

An intravenous infusion of ketamine was initiated after the patient was transferred to the intensive care unit. Ketamine infusion was started at 0.2 mg/kg/h and slowly titrated to 0.3–0.4 mg/kg/h over the next 4 hours in conjunction with the morphine PCA (basal 0.36 mg/kg/h, 10 mg every 5 min bolus). In the next couple of days, ketamine was further increased to 0.6 mg/kg/h and the morphine basal infusion was decreased to 0.2 mg/kg/h to obtain a VAS of 2/10 before hospital discharge. Other pain medications to be continued at home included extended-release oxycodone 80 mg three times daily, hydromorphone 8 mg twice daily, and gabapentin 300 mg four times daily. Our goal was to titrate the morphine dose down while concurrently increasing the ketamine dose. The infusion rates for ketamine and morphine were adjusted based on daily clinical assessment for pain and side effects by a visiting nurse and consultation with the Chronic Pain Management Service.

Fig. 1 shows a decreasing morphine infusion rate as the ketamine dosage was increased in an outpatient setting beginning on Day 4. Throughout the month-long infusion, the patient denied any side effects (hallucinations, evoked nystagmus, vertigo, dizziness, speech difficulties, and altered mental status) that could be induced by ketamine administration. Within 8 days of the start of ketamine infusion, we were able to decrease the morphine by half while keeping ketamine at 0.62 mg/kg/h. During the next 21 days, morphine was kept at approximately 0.09 mg/kg/h as ketamine was...

![Fig. 1. Daily infusion rates (mg/kg/h) of (■) morphine and (◆) ketamine required by the patient in an outpatient setting.](image-url)
titrated down from a maximum of 0.65 mg/kg/h. As the patient’s pain was getting under control with ketamine and morphine, she received another round of chemotherapy with mitomycin and 5FU/leucovorin on Days 20 and 23. Intravenous access became a concern due to the need for continuous infusion of chemotherapy. It was decided to stop the ketamine infusion in the hope that the N-methyl-D-aspartate (NMDA) receptors had been reset to allow the antinociceptive effects to persist. On Day 27, ketamine was eventually titrated off for 5 days, with a constant basal morphine infusion of 0.09 mg/kg/h. The patient experienced excruciating pain secondary to tumor progression on Day 32, requiring rapid escalation of the morphine basal infusion to 21.8 mg/kg/h (not shown in Fig. 1). Chemotherapy was discontinued and palliative care reinstated, with ketamine infusion restarted at 0.29 mg/kg/h. The patient expired on Day 33.

Comment
Ketamine is commercially available as a racemic mixture of R(−) and S(+) enantiomers. It has a relatively short half-life. The alpha-elimination phase lasts a few minutes and its beta-elimination half-life is 2–3 hours. It is metabolized by the hepatic cytochrome p450 system. Ketamine interacts with numerous receptors, including NMDA and non-NMDA glutamate receptors, nicotinic and muscarinic cholinergic receptors, and monoaminergic and opioid receptors.6 Ketamine is a noncompetitive NMDA receptor antagonist that can inhibit the “wind up” phenomenon in spinal cord neurons.7 It is this antagonistic effect that accounts for most of the analgesic, amnestic, psychotomimetic, and neuroprotective effects.9 Woolf and Mannion (1999)8 demonstrated that blocking central sensitization with NMDA antagonists can abolish pain hypersensitivity in patients with neuropathic pain. Our patient received a ketamine infusion varying between 0.09 mg/kg/h to 0.65 mg/kg/h. The subanesthetic ketamine doses were effective in controlling pain without inducing significant side effects. The possible side effects of ketamine include somnolence, vertigo, hallucinations, increased salivation, evoked nystagmus, and altered mental status. Satisfactory analgesia was achieved without exceeding 0.65 mg/kg/h ketamine. Progressive reduction in morphine dose was not associated with opioid withdrawal. Eventually ketamine was titrated off on Day 27, which was the 10th day on a constant morphine PCA rate of 0.09 mg/kg/h. The discontinuation of ketamine was short-lived, lasting only 5 days before it was restarted at 0.29 mg/kg/h on Day 32 when the basal morphine PCA infusion reached 21.8 mg/kg/h. The increased pain one day prior to her death may have been related to tumor progression or to the possibility that ketamine had an additive or a synergistic effect on morphine. As shown in Fig. 1, morphine had to be increased from 0.09 mg/kg/h to 0.18 mg/kg/h, then to 0.36 mg/kg/h when ketamine was terminated on Days 26 through 31. Animal studies have shown that the concomitant administration of an NMDA antagonist and an opioid may result in a synergistic or additive analgesic effect.9

With the use of ketamine <0.65 mg/kg/h, morphine was decreased by fourfold. We believe this decrease was attributed to the reduction in opioid tolerance. A study by Tiseo and Inturri10 demonstrated that mu opioid tolerance is mediated by NMDA receptors and the nitric oxide system. The NMDA receptor also plays a role in chronic pain development via central sensitization. A persistent noxious stimulus to the dorsal horn can lead to activation of NMDA receptors as well as activation of wide dynamic range neurons, resulting in the expansion of receptive fields and an increase in the magnitude and duration of response.11 Lossignol et al.12 reported the successful use of ketamine in the treatment of intractable cancer pain, but their patient required escalating doses of morphine despite the coadministration of ketamine. Walker et al.13 reported a case in which a continuous low dose intravenous ketamine infusion was successful in producing a rapid reduction in intrathecal morphine dosage and hyperalgesia.

We report a case of successful use of ketamine infusion for the treatment of intractable cancer pain in an outpatient for greater than 30 days. Our patient was able to spend quality time with her son, husband, and other family members without sedation and other side effects, which limited opioid dosage, and remain in the comfort of her home. A reliable visiting nurse service, with the involvement of a chronic pain specialist, was critical in the success of this
treatment option for our patient, who did not wish to be placed in a hospice. She underwent chemotherapy on Days 20 and 23, as her pain was getting under control with ketamine, in the hope for a chance of longer survival.

In conclusion, patients with intractable cancer pain may benefit from the use of intravenous ketamine infusion to obtain adequate pain relief. Our patient was effectively managed as an outpatient with both ketamine and morphine via continuous infusion. This technique of outpatient infusion therapy hopefully will allow palliative treatment of the dying in the dignity of the home.

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doi:10.1016/j.jpainsymman.2006.09.004

References

Failure of Pain Control Using Transdermal Fentanyl During Rifampicin Treatment

To the Editor:

Transdermal fentanyl (TDF) is a rational fentanyl delivery system for relieving moderate-to-severe chronic cancer pain, but Takane et al.1 have reported that the analgesic effect of TDF can be attenuated by combined use of rifampicin. This paper describes a similar case of pain control failure in TDF therapy, possibly due to drug interaction with rifampicin.

Case Report

A 64-year-old man with colon cancer was admitted to our hospital to receive anticancer chemotherapy. At another medical facility before admission to our institute, the patient had been prescribed rifampicin 450 mg/day, isoniazid 300 mg/day, and ethambutol 750 mg/day for three months to treat pulmonary tuberculosis. Although loxoprofen 180 mg/day was also administered for pain control, the patient began to complain of increasing pain. Application of TDF patch was commenced at a dose of 0.6 mg/day according to a request from the patient. Under careful observation, the daily TDF dose was gradually increased to 2.5 mg/day, but a significant improvement of pain could not be achieved despite the administration of rescue medication. Thus, TDF 2.5 mg/day was...