• 技術和方法 •

Pain Management with Oral Ketamine in Patients with Advanced Cancer

YUNG Wai Tan, SHAM Mau Kwong*

【**Abstract**】 The use of oral ketamine in the pain management of seven advanced cancer patients is reported. The starting dosage of oral ketamine was 45 to 160 mg/day. The causes of pain were different in these patients. Pain was controlled satisfactorily in five of the patients, at a dosage of 30 to 40 mg tid to qid. Pain was controlled in another patient after conversion to continuous subcutaneous infusion of ketamine, as the patient could not tolerate oral drugs because of intestinal obstruction. Other analgesics were used in addition to ketamine. In one patient, the dosage of morphine decreased from an equivalent oral dosage of 144 mg/day to 80 mg/day. Of the six patients maintained on oral ketamine, pain was controlled within five days in five. The remaining patient had significant improvement of his pain three days after starting oral ketamine, but died on the sixth days before his pain could be controlled. Oral ketamine was maintained in these seven patients for three to 43 days. One patient had nightmares, controlled with droperidol; another had palpitation not requiring treatment. Two patients had ketamine withdrawn because they were unable to tolerate oral drugs shortly before death. In one patient, ketamine 100 mg/day by subcutaneous infusion was substituted with oral ketamine 30 mg qid. The conversion ratio was approximately 1:1, as recommended in the literature.

【**Key words**】 Oral ketamine; Pain; Advanced cancer

以口服氯胺酮治療末期癌症病人的疼痛

容慧丹, 沈茂光. 鏡湖醫院, 內科, 澳門特別行政區, 中國; Tel : (+853)-2951608; E-mail : tammyyung@hotmail.com ;* 鏡湖醫院, 康寧中心, 澳門特別行政區, 中國.*

【**摘要**】本文報告7例末期癌症病人，以口服氯胺酮治療疼痛的臨床資料。口服氯胺酮起始的劑量為45至160毫克/日。雖然7例病人的疼痛的起因不同，其中5例病人在接受口服氯胺酮每天3-4次，每次30至40毫克的治療後，疼痛可以控制至病人滿意的程度；另外1例則因為腸梗阻，須由口服改為持續皮下輸注氯胺酮，疼痛才受到控制。除了氯胺酮外，也同時使用其他鎮痛藥物。1例接受口服氯胺酮後，嗎啡的劑量由相等於每天口服嗎啡144毫克減至80毫克；其中5例，疼痛在5天之內受到控制；餘下的1例，接受口服氯胺酮治療3天後，疼痛雖已顯著改善，但在第6天，疼痛還未受到控制時去世。口服氯胺酮治療在這7例病人維持了3至43天。1例病人服用氯胺酮後有噩夢，以氟哌利多控制；另1例有短暫心悸，不需任何治療。兩例病人在瀕臨死亡時不能接受口服藥物，而需停用氯胺酮。1例病人由持續皮下輸注氯胺酮100毫克/日，改為口服氯胺酮每天120毫克，皮下輸注對口服氯胺酮的比例，和文獻記載的1:1比例差不多。

【**關鍵詞**】 口服氯胺酮; 疼痛; 末期癌症

INTRODUCTION

Ketamine is an anaesthetic agent which has been in use for more than 30 years. With its N-methyl-D-aspartate (NMDA) receptor antagonist action, it has been used, in low dosages, as an analgesic drug. Its effectiveness in alleviating allodynia and spontaneous pain has been confirmed, though only in few randomized controlled trials[1]. Opioid sparing effect has also been demonstrated, which might result from reversal of opioid tolerance[2].

Authors address : Internal Medicine, Kiang Wu Hospital, Macau SAR, China; Tel : (+853)-2951608; E-mail : tammyyung@hotmail.com; *Hospice and Palliative Care Center, Kiang Wu Hospital, Macau SAR, China.

Ketamine can be administered by various routes, including oral, rectal, intramuscular, intravenous, subcutaneous, transdermal, nasal, epidural or intrathecal routes[3]. Among these, the oral route has the advantage of convenience, without the requirement of carrying and refilling the pump, and also avoids the risk of inflammation at the site of injection.

It has been suggested that low dosages of ketamine are effective with the oral route, and adverse effects are less frequent than parenteral ketamine. Orally administered ketamine undergoes extensive first-pass metabolism, resulting in low concentrations of ketamine but high concentrations of norketamine in blood and tissue[3]. As norketamine is also an NMDA receptor antagonist, the first-

pass metabolism does not affect the potency of the drug significantly. The parenteral to oral dose ratio has indeed been demonstrated to be approximately 1:1[4]. Some workers recommended a starting dose of oral ketamine 0. 3-0.5 mg/Kg one to three times a day, titrating to a maximum of 500 mg/day. Other workers, however, used lower dosages, even as low as 2 mg three times daily.

Adverse effects of oral ketamine include nausea, vomiting, anorexia, tiredness, dizziness, nervousness, headache, numbness or tingling sensation, taste changes and feeling 'unreal', which may necessitate withdrawal of the drug. Higher dosages of ketamine may result in dysphoria, confusion and depression, which may not be controlled with the addition of benzodiazepines. It is known that ketamine may affect the heart, with increase in heart rate and blood pressure. A case of angina pectoris has been reported with use of subcutaneous ketamine, which subsided after its withdrawal[5].

CASE PRESENTATION

During the six-month period from May to October 2003, seven patients were treated in the Hospice and Palliative Care Center of Kiang Wu Hospital with oral ketamine as an analgesic agent. These seven cases are presented.

1 Case 1

Mr WLW was a 48-year-old man suffering from carcinoma of colon with metastases to kidney and the third and fifth lumbar vertebrae. He was admitted with severe distending pain in both lower limbs with numbness, not controlled with diclofenac. The next day he was started on oral ketamine 15 mg tid. After two days, his pain was controlled with oral ketamine 30 mg tid, amitriptyline 10 mg bd and sodium valproate 200 mg bd. He was given ketamine orally for a week, and then because of vomiting, switched to continuous subcutaneous infusion until death 26 days after admission.

2 Case 2

Mr NCP was another 48-year-old man with hepatocellular carcinoma and metastasis to the eighth thoracic vertebra. He complained of moderate right lower chest pain and severe stabbing right shoulder pain, not controlled with naproxen 250 mg tid, carbamazepine 100 mg tid and morphine 45 mg/day. He was then started on oral ketamine 40 mg qid. Pain was controlled after 5 days with the same dosages of naproxen and oral ketamine, while the dosage of morphine was gradually increased to 220 mg/day. He did not suffer from psychotomimetic or cardiovascular adverse effects of ketamine, which was maintained for 27 days until death.

3 Case 3

Mr LWY was a 65-year-old man with carcinoma of oesophagus. He had metastases to mediastinal lymph nodes, liver and the first and second lumbar vertebrae. He complained of moderate to severe stabbing pain in the lumbar spine, not controlled with imipramine 10 mg nocte and morphine 25 mg/day. The next day after admission, he was prescribed oral ketamine 30 mg qid. Two days later, his pain was controlled with oral ketamine 40 mg qid while maintaining on the same dosages of imipramine and morphine. He once complained of palpitation, which subsided spontaneously. Ketamine was maintained for 43 days until four days before his death, when he was unable to take oral drugs. His pain was then managed with subcutaneous infusion of morphine 45 mg/day.

4 Case 4

Mr KTY was a 65-year-old man suffering from disseminated carcinoma of hard palate. He complained of overwhelming low back pain, stretching in character. Investigation revealed degenerative changes in the lumbar spine with no evidence of metastases. His pain was not controlled with morphine 144 mg/day, naproxen 250 mg tid, sodium valproate 400 mg bd and amitriptyline 25 mg nocte. He was then given oral ketamine 15 mg tid. Ten days later, he developed intestinal obstruction. Ketamine and morphine were then given by continuous subcutaneous infusion. Fourteen days later, his pain was eventually controlled with subcutaneous ketamine 250 mg/day. Moreover, it was possible to reduce the dosage of morphine to 40 mg/day subcutaneously, equivalent to an oral daily dosage of 80 mg. Ketamine therapy was continued until death 8 days later.

5 Case 5

Mr HSP was a 50-year-old man with bronchogenic carcinoma and liver metastasis. He complained of severe left-sided chest pain with numbness and allodynia. His pain was not controlled with morphine 94 mg/day, amitriptyline 20 mg nocte, sodium valproate 200 mg tid and naproxen 250 mg bd. He was then prescribed oral ketamine 30 mg qid. Pain was eventually controlled four days later with oral ketamine 40 mg qid, amitriptyline 20 mg bd, ibuprofen 400 mg tid, sodium valproate 200 mg tid, and morphine at an equivalent oral dosage of 300 mg/ day. He did not suffer from psychotomimetic or

cardiovascular adverse effects of ketamine. Ketamine therapy was continued until he died 3 days later.

6 Case 6

Mr NCW was a 54-year-old man suffering from carcinoma of oesophagus with metastasis to pelvis. He complained of moderate to severe pain and numbness in the right side of his pelvis radiating to right thigh. The patient described that the pain was like lightning. He was given morphine by subcutaneous infusion, because of vomiting, at an equivalent oral dosage of 50 mg/day, but the pain remained uncontrolled. The next day after admission, he was started on oral ketamine 25 mg tid. After three days, there was significant improvement of pain with oral ketamine 40 mg tid, celecoxib 200 mg bd, amitriptyline 10 mg nocte and morphine at an equivalent oral dosage of 90 mg/day. On the following day, however, his general condition deteriorated. All oral drugs were stopped, and pain was managed with subcutaneous infusion of morphine until death five days after commencing ketamine.

7 Case 7

Ms HSL was a 38-year-old lady who suffered from nasopharyngeal carcinoma with metastases to the base of skull and right femur. She complained of moderate to severe pain in the right thigh. On admission, she also complained of difficulty in swallowing and was started on continuous subcutaneous infusion of morphine 20 mg/day, in combination with ketamine 50 mg/day which was gradually increased to 100 mg/day. Two days later, as she was found to be able to tolerate oral food, ketamine was given by the oral route instead of subcutaneously, at a dosage of 30 mg qid. On the following day, pain was controlled with the same dosage of oral ketamine, with the addition of gabapentin 400 mg tid, amitriptyline 10 mg nocte and morphine 50 mg/day. She complained of nightmares which were controlled with droperidol. Nine days after starting oral ketamine, she developed dysphagia again and ketamine had to be given by subcutaneous infusion. She died 17 days after admission.

DISCUSSION

Our experience confirmed the role of oral ketamine in pain management in patients with advanced cancer. Six of the patients had pain related to cancer; the other had low back pain due to degenerative disease of the spine. Elements of neuropathic pain were present in six, while the remaining patient suffered from bone pain in the right thigh due to metastases to right femur. All but one patient had their pain controlled to the patients' satisfaction, despite the variable nature of the pain in these patients. In five, pain was controlled with oral ketamine, dosages ranging from 30 mg tid to 40 mg qid. The other had his pain controlled after switching to subcutaneous infusion because of intestinal obstruction. Pain control was achieved with or without the addition of other analgesic drugs such as opioids, non-steroidal anti-inflammatory drugs or cyclo-oxygenase II inhibitor, anti-convulsants and anti-depressants. The remaining patient was referred for hospice care at a very late stage. His pain was significantly improved within three days of treatment with oral ketamine. He, however, died six days after admission, before his pain could be well controlled. In these seven patients, oral ketamine was maintained for three to 43 days.

In our patients, the starting dosage of oral ketamine was 45-160 mg/day in divided doses. We used a relatively high starting dosage in order to achieve rapid pain control. Indeed, in five of our seven patients, pain control was achieved within five days. In one of the patients, ketamine 100 mg/day by subcutaneous infusion was substituted with oral ketamine 30 mg qid. The conversion ratio of subcutaneous to oral ketamine was approximately 1:1, as recommended in the literature. Opioid sparing effect was demonstrated in only one patient, with the daily equivalent oral dosage of morphine reduced from 144 mg to 80 mg.

Nightmares occurred in only one patient, managed successfully with droperidol. One patient had palpitations, which subsided spontaneously. Ketamine was withdrawn in two patients because they could not take oral drugs in the terminal stage. Their pain could be managed with subcutaneous infusion of morphine without ketamine.

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