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The implementation of continuous ketamine infusions in Neuropathic Pain Syndrome

Abstract

Neuropathic pain is a chronic condition with potential deleterious effects on the patients' quality of life. Pharmacological treatment does not always bring the expected effects and it often brings about adverse effects of the administered drugs. One of the causes for the intensification of pain is central sensitization. Numerous trials, both experimental and clinical prove the effectiveness of NMDA receptor blockers in preventing and diminishing central hypersensitivity and, as a result, diminishing the degree of pain sensations. Here we present a patient with neuropathic pain syndrome related to chemotherapy for Hodgkin's disease, in which by cyclical intravenous ketamine infusions, significant and long-lasting pain alleviation has been achieved.

Key words: neuropathic pain, ketamine, NMDA receptor blocker

Introduction

Neuropathic pain is usually caused by a primary lesion of the nervous system. The frequency of neuropathic pain occurrence is 1,5% of all patients with chronic pains [1].

Neuropathic pain may appear due to a lesion of peripheral nerves (for example by compression, crushing or as a result of polyneuropathy), spinal ganglions (compression, tumour). The same pathological process in one patient may cause severe pain and in another patient it may cause no reaction at all. Factor that may influence this are the following: the place of lesion, time, activating factor, coexistence of other pathological processes, age, individual inclinations and psychological factors [2].

Three mechanisms play an important role in the formation of neuropathic pain — changes of electric irritability of the cell membranes of peripheral neurons, changes of signal processing within the dorsal horn and modification of central nervous system response to pain stimuli.

Central sensitization — hypersensitivity of spinal neurons and higher structures of the nervous system — is one of the causes of pain intensification and it is responsible for the chronic character of pain.

Central sensitization can at least for the great deal be explained by activation of the glutaminergic system. This causes the influx of calcium ions to the cell through ionic channels of NMDA (N-methyl-D-aspartic acid) receptors, which in turn activate protein and tyrosine kinases. As a result, proteins generating glutaminergic receptors are getting phosphorylated and boost activity of these receptors. Calcium ions also activate phospholipase, which launches the arachidonic acid cascade. Consequently, the synthesis of prostaglandins that lower the point of receptors' sensitivity is escalated [3].

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Neuropathic pain is a condition that is very difficult to treat. No method that would be effective for all types of neuropathic pain has been described so far. Analgesics, such as paracetamol, non-steroidal anti-inflammatory drugs and even opioids frequently do not help to alleviate the pain. The International Association for the Study of Pain suggests interdisciplinary treatment of patients with chronic pain, which also includes neuropathic pain. Numerous trials, both experimental and clinical prove the effectiveness of NMDA receptor blockers in preventing and diminishing central hypersensitivity and, as a result, diminishing the degree of pain sensations [4–6]. The drugs that are administrated are non-specific blockers of the NMDA receptor, such as: ketamine, dextromethorphan, memantine and amantadine. What is more, NMDA inhibitors diminish opioid-induced hyperalgesia [7] and ketamine is the most popular drug that is used in the prevention of increasing opioid tolerance [8].

This study discusses the case of a patient with an iatrogenic neuropathic pain, probably induced during chemotherapy against Hodgkin's disease, in which by means of cyclical intravenous infusions of ketamine, significant and long-lasting pain alleviation has been achieved.

Case description

In 1993 a man at the age of 55 was diagnosed with Hodgkin's disease type III MC (Mixed cellularity). The patient underwent chemotherapy according to MOPP scheme (chlormethine, vincristine, procarbazine, prednizone), which resulted in total remission. In June 1994 the patient started to complain about pain in right shoulder, which intensified a year later. The pain was of a paroxysmal character, prickly, burning, radiating along the shadow towards the hand. For this reason the patient was temporarily taking non-steroidal anti-inflammatory drugs (diclofenac), which alleviated the pain. In 1997 the doctors diagnosed a relapse of Hodgkin's disease. The patient was administered a second line chemotherapy according to the scheme MOPP/ABV — adriamycin, bleomycin, vinblastine, dacarbazine since August 1998. Since then until now the patient has been under the supervision of oncology clinic — no relapse of the disease has been diagnosed. In 1998 after chemotherapy the shoulder pain of the same character as before, but much stronger was accompanied by paresis of the pars flaccida of right upper limb. Due to pain symptoms the patient was administered first non-steroidal anti-inflammatory drugs, and in 1999 because of pain intensity escalation, the doctors included also tramadol (3 × 50 mg) joined with miorelaxants (baclofen) to the treatment. In 2000 the doctors added amitryptyline 50 mg/night and tetrazepam 15 mg/night to tramadol and this significantly alleviated the pain. Such a combination of drugs in some patients may cause serotoninergic syndrome. In this case however, no alarming symptoms were observed. After several months, the patient discontinued amitryptyline on his own and a psychiatrist that he consulted with later added mianserine 15 mg/night. In 2001 the patient was sent to Neurological Clinic due to further escalation of pain. Apart from a significant escalation of tearing paroxysmal pain, also periodical lividity of upper limb appeared. Nuclear magnetic resonance did not show any pathologic changes in the brachial plexus, spinal cord and spinal channel in the cervical part. The diagnose suggested neuropathic pain syndrome probably connected to iatrogenic lesion of brachial plexus after chemotherapy. The doctors tried to administer gabapentin (Neurontin), however the patient did not tolerate it. The patient was on sodium valproate, initialy in the dose of 2 × 300 mg and then 2 × 500 mg, paracetamol and tramadol when pain appeared. In 2003 the patient was diagnosed with diabetes treated with oral drugs (glipizide). Since 2002 the man was also a patient of Pain Treatment Clinic, where (13 times during 5 years) epidural blocks were conducted on the level C5–C6, C6–C7 by administration of 80 mg of polcortolon, brachial plexus blocks with 0.25 % of bupivacaine and right C6 root block. This treatment, according to the patient caused alleviation of pain for maximum of 2–3 weeks after each session.

Due to the escalation of pain, that did not decrease even after sodium valproate dose increase up to 2 × 600 mg and administration of paracetamol 3 × 1 g and 50 mg tramadol when pain appeared (the patient did not tolerate greater doses of this drug), the patient was kept on the Ward of Palliative Care, where he was given continuous intravenus ketamine infusions in growing doses from 100 to 500 mg a day, for 5 days. In order to prevent psychomimetic symptoms ketamine was administered with midazolam influsions 5 mg a day.

In the beginning of his stay in the hospital, the patient assessed his pain for 8 in a scale of 11. The pain was lowered already after one day of ketamine administration. When the patient was leaving the hospital, he assessed his pain as 2/10. During the hospitalization inflammatory reaction appeared in the place of ketamine infusion. The patient came to the hospital again after 35 days. He claimed that the pain remained at the level 3–4/10 for about 3 weeks

and then begun to increase up to 7/10. Ketamine was administered again in increasing doses with midazolam and 25 mg of hydrocortisone. The inflammatory reaction appeared again, but it was not that strong. Again the pain decreased significantly. The patient was hospitalized 7 times at an average interval between hospitalizations of 55 days. During the following ketamine infusions hydrocortisone was administered in the 50 mg dose and then 100 mg dose, which prevented inflammatory reactions. The inflammatory reaction was the only adverse effect of ketamine observed in this patient. The doctors introduced a modification of coanalgesics, adding fluoxetine, initially in a dose of 10 mg/d and later on 20 mg/d and discontinuing sodium valproate, which was replaced with gabapentin 3 × 300 mg, which this time caused no side effects. This modification did not cause any significant alleviation of pain. Only the repetitive ketamine infusions reduced the pain for a period of 3 to 4 weeks. Due to intolerance of tramadol, it was replaced by buprenorphine administered sublingually 3 × 0.2 mg. Neither this drug reduced the pain significantly according to the patient. During the last hospitalization the pain was reduced from 8/10 in the beginning of treatment to 3/10 when the patient was leaving the hospital.

Discussion

Ketamine is a derivative of phencyclidine. The available preparations are: a racemic mixture and much more expensive, but much more related to NMDA receptor, four times stronger analgesic and with much less adverse effects enantiomer S [9–11]. No oral preparation is available but diluted injectable fluid of ketamine are also administered orally.

In Poland ketamine is registered only as a drug used in anesthesiology, as a component of compound anesthesia and very rarely as an independent anesthetic drug.

Ketamine is a strong blocker of NMDA receptors [12]. It integrates by a calcium channel with the point of phencyclidine bond, when the channels are open and active [13]. The bonding of ketamine and NMDA receptor prevents the bonding of glutamate secreted by pain synapses in this location. The drug also integrates with another point of bonding, located within the membrane, where the channel does not need to be open, and this way the frequency of channels' openings is reduced [14]. Ketamine also inhibits noradrenaline reuptake. This has antidepressant effect even after a single intravenous dose. This effects appears 2 hours after administration and lasts up to one week. The immediate anti-depressive effect may be connected to the direct interaction with the glutaminergic system but not with dopamine and serotonin metabolism which is observed with traditional anti-depressants [15].

Ketamine brings the first effect after one minute if administrated intravenously. In case of intramuscular infusion — after 5 minutes. Due to the short time of action — from 30 min to 2 hours if administered intramuscularly — it is usually administered with a continuous subcutaneous or intravenous infusion. In anesthesiology it is used in doses 0.5–2 mg/kg body weight *i.v.*, in repetitive doses from 1/4 to full initial dose every 5–15 min *i.m.* 5–10 mg/kg body weight or continuous *i.v.* 2–6 mg/kg body weight/h. These doses are much higher than those used in the case described above.

Ketamine is water and lipid-soluble. Bioavailability 23% and 32% after oral and sublingual administration, respectively [16]. The effect seems to be correlated with the concentration of a metabolite — norketamine, which has analgesic properties of 1/5–1/3 of the strength of ketamine. After oral administration norketamine concentrations exceeds 4 times the concentration of ketamine, therefore, this metabolite may significantly contribute to the total analgesic effect. Norketamine undergoes hydroxilation and is excreted with urine. However, there are no records of intensified adverse effects in patients with renal failure, in which metabolite accumulation could occur [11].

Adverse effects appear in about 40% of patients and they are more often observed after subcutaneous than oral administration. Most often appearing were psychomotor symptoms (psychomotor slowdown, dysphoria, euphoria, hallucinations), hypertension, tachycardia, blurred vision, nystagmus, raving, dizziness. A very frequent side-effect of the drug in case of intravenous infusion is cutaneous reaction (focal lymphangitis) [17]. However, when ketamine was administered in sub-anesthetic doses usually no or minor effects of psychomotor incitement are observed [18]. Nevertheless, even the patients who exhibit symptoms such as hallucinations often decide to continue the drug because of significant effect on pain [19]. At the same time, administration of ketamine along with benzodiazepines effectively prevents psychomotor symptoms [20].

The available data suggests that ketamine is effective as an auxiliary drug for morphine that significantly improves the analgesic effect in patients with neoplasms [21]. In sub-anaesthetic doses ketamine can be used for diminishing the dosage of opioids and reduction of their side-effects [22]. It has been proven that ketamine is useful as coanalgesic in cas-

es of neuropathic pain on animals, volunteers and in small clinic trials [6, 23–25]. The effects of ketamine seem to be more significant in patients with neuropathic pain which has lasted for less than 5 years [26]. However, its effectiveness has not been proven in methaanalysis due to insufficient number of randomized trials all with small number of evaluable patients [17]. In most trials with ketamine, this drug was most often used together with morphine. Only in few cases the trials included hydromorphone, diacetylmorphine or combinations of these drugs. Good effects of ketamine were also reported in patients with phantom pains [27]. It has been confirmed that transitory administration of ketamine can bring long-lasting effects — alleviation of pain lasting even for several weeks [28–31]. In patients treated with opioids due to limb pain related to ischemia, a single four-hours' intravenous ketamine infusion in a dose of 0.6 mg/kg lowered the demand for opioids during a week's observation [29]. In patients with cancer, subcutaneous infusion of ketamine in a dose 100–500 mg/day for 3–5 days resulted in reduction of pain by 67%, and continuous intravenous infusions repeated every month in a dose of 100 mg/d for 2 days helped to reduce the dose of opioids in 70% of patients [30]. Similarly, in patients taking opioids, examined after 4 months, a beneficial effect was reported after 2 days' ketamine infusions in a dose of 0.5 mg/kg/day [31]. In another trial, in patients with neoplasm and neuropathic pain assessed around 6/11, taking maximum tolerated doses of morphine, amitriptyline, sodium valproate or a combination of these drugs after an oral administration of ketamine in a dose of 0.5 mg/kg 3 times a day, in 7 patients the pain reduced by 3 points in the scale of 11 points. These patients, however, were taking ketamine for a long time, therefore significant side effects were observed — 4 patients had nausea, 2 loss of appetite, 2 drowsiness [32]. The effectiveness of ketamine administered intravenously or orally has been proven in controlled trials [33] and case descriptions [34]. Currently, the Center in Edinburgh is conducting a double blind randomized trial of s-ketamine versus placebo in patients with neoplasm and neuropathic pain. The trial is supposed to be finished by the end of the year 2008 [35].

The case described in this case report supports the idea that ketamine is a precious drug for patients with neuropathic pain that is resistant to other pharmacological methods of pain treatment. Ketamine was administered when treatment with analgesics and coanalgesics despite numerous trials of drugs' rotation along with invasive treatment had not come up to the expectations.

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