Case Study

Opioid Induced Hyperalgesia Altered with Propofol Infusion

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Propofol is a common induction agent that is utilized worldwide in the field of anesthesiology. In recent years, its potential therapeutic role in a variety of patient states has been demonstrated. Controversy exists regarding Propofol mediated analgesic and antihyperalgesic properties. Recent studies have suggested a variety of different mechanisms of action, including modulation of N-Methyl-D- Aspartate receptors and the endocannabinoid system. The N-Methyl-D- Aspartate receptor is part of a larger family of glutamate receptors and is an important mediator of excitatory neurotransmission. In the case presented, the pain experienced by the patient was not well-controlled, in spite of increasing doses of opioids, potentially due to superimposed opioid induced hyperalgesia. In the present case, we demonstrate a cycle of opioid induced hyperalgesia which was successfully affected with a Propofol infusion. Controversial reports exist in animal studies on the analgesic properties of Propofol. Randomized controlled studies in animal models studying the effect of Propofol on pain sensation have shown that Propofol possesses an analgesic effect. This clinical case demonstrates that Propofol could possibly have antihyperalgesic effects on opioid induced hyperalgesia caused by high-doses of chronic opioids and worsened by fentanyl. We postulate that a probable mechanism of complete pain relief after the procedure could be the inhibition of activity of the N-Methyl-D-Aspartate receptor by Propofol because it was the only agent the patient received during the procedure, causing a break of the cycle of opioid induced hyperalgesia. Additional research is required to clarify Propofol mediated or modulated analgesic properties in humans.

Key words: Analgesia, hyperalgesia, opioids, propofol, antihyperalgesia, anesthesia

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Propofol is a highly protein-bound agent that is quickly distributed into peripheral tissues. It has been found to possess important properties in addition to being an induction agent and provides amnesia, sedation, and rapid onset (1,2). These properties include Propofol mediated or modulated antiemetic (3), antipruritic (4), anxiolytic (5), and analgesic effects. Propofol has been demonstrated to act primarily via potentiation of GABAA and slowing of sodium channels (6-10). Recent studies have suggested additional effects, including modulation of N-Methyl-D-Aspartate (NMDA) receptors and the endocannabinoid system (11-13). Previous research has shown a paucity of evidence relating to Propofol mediated responses to analgesic effects. Here we describe a clinical case where a Propofol infusion appeared to break a cycle of opioid induced hyperalgesia related to the opioid fentanyl, which has not been previously reported.

Case Report

A 63-year-old male with a history of Multiple endocrine neoplasia type 1 (MEN 1), metastatic neu-

roendocrine tumors, presented with chronic pain syndrome. Previously, the patient had undergone partial pancreatectomy, subtotal parathyroidectomy, and had a history of recurrent nephrolithiasis. The patient was admitted with exacerbation of back and flank pain. On initial review of the patient and physical examination, the pain was thought to be most likely related to bony metastasis. Pain medications at home included methadone 40 mg 4 times daily, Octreotide 100 mcg SQ twice a day for metastatic bone pain, and Dilaudid 24 mg every 3 hours, as needed, for breakthrough pain, and for episodic severe renal colic. The patient reported worsening of pain 2 days prior to admission and attempted to alleviate the discomfort with hydromorphone 48 mg every hour with minimum pain relief. The patient came to the emergency room and received 2 doses of hydromorphone 8 mg i.v., which was minimally effective.

In an attempt to resolve the ongoing discomfort, the Palliative Pain Service placed him on fentanyl PCA 200 mcg, continuous infusion, and 60 mcg every 6 minutes. Unfortunately, the patient reported diffuse back pain similar to his previous renal colic. Over the next 10 days, the fentanyl PCA was titrated to a maximum of 600 mcg an hour, with 100 mcg every 15 minutes boluses. The pain, however, continued to worsen in spite of increasing amounts of fentanyl and was described as unbearable by the patient. fentanyl PCA was discontinued and methadone 25 mg i.v. every 6 hours with oxymorphone 3 mg i.v., every 3 hours, as needed for breakthrough pain over 24 hours, provided inadequate pain control.

A change to Dilaudid 12 mg i.v. q one hour did not produce significant pain relief either. He was then switched back to fentanyl PCA, in a dose of 1100 mcg per hour, between basal rate and bolus, with moderate pain control. An evaluation by MRI was then arranged to rule out the worsening of spinal metastasis. A ketamine infusion was planned (but not needed) for better control of pain after the MRI. For the procedure, the fentanyl PCA was stopped. A Propofol infusion was started at a delivery rate of 150 mcg/kg/min, with a total of 430 mg administered during the procedure. The MRI showed stable bony metastasis without signs of progression. Surprisingly, after the MRI, the patient had no pain for about 3 hours without any opioids and dramatically reduced overall pain subsequently. He was then begun on a taper of his fentanyl PCA, which continued over the ensuing few days. Over this time, he reported being virtually pain free, and was discharged home with good pain control on oral medications. Discharge pain medications included methadone 50 mg q 6 hours, hydromorphone 24 mg q 3 hours as needed. Two weeks later the medication was further reduced to methadone 40 mg q 6 hours and Hydromorphone 8 mg q 3 hours, as needed.

Discussion

The NMDA receptor is part of a larger family of glutamate receptors and is an important mediator of excitatory neurotransmission. It is well known that hyperalgesic states can be induced by chronic and/or acute opioids administration and NMDA receptor activation plays an important role in metastatic carcinoma. In the case presented, the pain experienced by the patient was not well controlled, in spite of increasing doses of opioids, potentially due to superimposed opioid induced hyperalgesia (OIH). Worsening pain with increasing doses of opioids in the absence of other comorbidities is a hallmark of OIH, which was clearly seen in our patient. NMDA activation results in an increase in calcium influx, which leads to excitotoxic cell death (14).

Propofol is being used widely in the United States and in the world to provide induction for anesthesia and sedation for a variety of procedures. Structurally, the NMDA receptor contains 4 transmembrane channels activated by both glycine and glutamate. Propofol has been shown to interact with and block NMDA receptors by inhibiting the phosphorylation of NMDA receptor NR 1 subunits in neurons (12,13). In a recent study by Grasshoff et al, it was shown that high Propofol concentrations result in inhibition of NMDA receptor mediated calcium increases (15). Propofol has also been shown to have other beneficial neuroprotective effects such as modulation of the endocannabinoid system, activation of the GABAA receptors (16), and scavenging of free radical species by hydrogen abstraction. Other important clinical effects of Propofol include antiemetic, antiepileptic, and antipruritic properties (17).

In recent years, the NMDA antagonists, ketamine, has gained popularity for the effective treatment of OIH and neuropathic pain. It is unclear at this time whether Propofol can be a significant substitute for ketamine as a NMDA antagonist or whether Propofol interferes with the effects of low dose ketamine infusions in humans. There have also been reports that Propofol possesses analgesic and antihyperalgesic properties.

Controversial reports exist in animal studies on the analgesic properties of Propofol. Randomized con-

trolled studies in animal models studying the effect of Propofol on pain sensation have shown that Propofol possesses an analgesic effect (18-20). In this regard, a study by Anwar et al (20) in a mouse model showed that different doses of Propofol injected in subhypnotic doses, increased the latency of pain threshold and reduced pain in a dose-dependent manner.

A study by Bandschapp et al in 14 healthy volunteers revealed that Propofol had short-lasting analgesic properties during its administration on pain perception (21). However, there have been other studies, which have demonstrated the opposite effect showing that Propofol has pain-enhancing actions (22-23).

This clinical case demonstrates that Propofol could possibly have antihyperalgesic effects on OIH caused by high-doses of chronic opioids and worsened by fentanyl. We postulate that a probable mechanism of complete pain relief after the procedure could be the inhibition of activity of the NMDA receptor by Propofol because it was the only agent the patient received during the procedure, causing a break of the cycle of OIH (13,15-17,21). It is possible that by discontinuing the methadone and switching to fentanyl, the lack of the NMDA antagonism mediated by methadone promoted the OIH mediated by fentanyl. It is interesting to note that the duration of complete pain relief outlasted the duration of hypnotic effect of Propofol for about 3 hours in our patient. Conflicting reports exist regarding the property of Propofol as an analgesic and antihyperalgesic agent. More research is warranted to establish Propofol unequivocally as an analgesic and antihyperalgesic agent in humans.

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