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Case Report Open Access

The Use of Methadone in Refractory Headache Pain in an Opiate Naive Patient with Non Metastatic Burkitt's Lymphoma and HIV - A Case Report

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Abstract

In extreme cases Methadone has been used for severe pain in oncologic patients; frequently cancer patients have severe headaches in addition to their pain. This patient is a 50 year old Hispanic female with metastatic Burkitt's Lymphoma and controlled HIV on triple therapy. Throughout her inpatient hospitalizations of chemotherapy with R-EPOCH and then salvage chemotherapy in addition to pancytopenia she experienced consistent pain of 9-10 out of 10 on the pain scale and headaches of 9-10 in severity out of 10. The patient underwent various methods of pain and headache control including PCA of hydromorphone, intravenous and oral hydromorphone, intravenous morphine, intravenous Tylenol, Fioricet and oral analgesics. The patient received moderate relief with oral Methadone of both her pain and headaches, bringing the pain and headache scale down to a 4-5 out of 10. This is the first case of intractable pain and headaches in an opiate naive patient with non-metastatic Burkitt's Lymphoma and HIV that received with 50 percent reduction in symptoms from the addition of oral Methadone that has no prior use of opiate abuse or dependence.

Introduction

Methadone typically is used in patients with addiction, tolerance, dependence and withdrawal symptoms of illicit opiate use, particularly heroin [1]. Methadone is also used in less common cases for pain control as a potent opiate with a longer half-life than the comparable standard of morphine [2].

Typically, patients with metastatic cancer require large doses of opiates to control systemic and local pain. In the inpatient setting, patients undergoing chemotherapy often experience acute on chronic pain episodes and frequently experience new and more severe pain from their disease. This could result from nosocomial drug side effects or change in the burden of their disease in the acute inpatient setting.

One of the most common side effects patients experience in the inpatient setting is headache both in non-cancer and cancer wards [3]. Frequently the pain of headache is transient with a tension like bilateral cranial distribution [4], however more commonly headache pain has a wide range of distribution, severity and frequency in the inpatient setting, especially in patients with metastatic cancer. The majority of headaches in the inpatient setting are transient and relieved by rest, oral analgesics or acetaminophen [5]. Less frequently more severe headaches exist that require larger and or more frequent doses of oral analgesics or acetaminophen and can be complicated and masked by the patient's systemic symptoms from their disease or pharmaceutical side effects. In extreme cases of pain, particularly in patients with cancer, intravenous opiates are required in combination with oral opiates [6].

Burkitt's Lymphoma is an aggressive type of non-Hodgkin B cell lymphoma that often involves multiple parts of the body, lymph nodes and frequently causes a wide spectrum of pain in patients [7]. Furthermore, Burkitt's lymphoma often requires systemic inpatient chemotherapy, which can also cause pain and headaches from treating the burden of disease in addition to the side effects of the chemotherapy [7]. Pain during treatment is not unique to Burkitt's Lymphoma, yet it is found in the majority of these patients in the inpatient setting.

Case Report

This patient is a 50 year old Hispanic female with metastatic Burkitt's Lymphoma and controlled HIV, compliant on triple therapy. She presented to the hospital for a scheduled salvage chemotherapy with R-ICE (Rituximab, Ifosfamide, Carboplatin, Etoposide) after failing to go into remission from treatment with R-EPOCH regimen. (Rituximab, Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin). On her admission she had mild baseline pain of 5 out of 10 in her knees and lower lumbar back, both sites were known to be negative for involvement of disease.

During her treatment with R-ICE, she experienced mild headaches transiently and daily that was 3-5 out of 10 in severity; she did not require more than oral acetaminophen for these headaches in addition to her daily 5 mg oxycodone doses for pain as needed. After her chemotherapy treatment, she remained in the hospital for 7 additional weeks due to pancytopenia with intermittent fevers requiring systemic antibiotics for neutropenic fever. Further, during this time frame her severe pain and headaches required constant adjustment in her pain regimen.

Initial exam occurred during the patient's second week in the hospital when severe headaches initiated. On physical exam the patient had stable vital signs. She had severe headaches 9-10/10 in severity and pain on palpation to the entire cranium with mild focus in the occipital region. The remainder of the physical exam was remarkable for mild diffuse abdominal tenderness; tenderness around the knees, shoulders, shins, calves, wrists and forearms; and mild distress from the uncontrolled pain. The patient's headache did not include any visual aura or area of focal tenderness. The patient did report sensitivity to

light and loud stimuli at times exacerbated the headache, but this was not consistent throughout serial physical exams.

Throughout the hospital course the patient's labs were remarkable for pancytopenia with normal serial renal function, hepatic enzymes, coagulation studies, electrolytes and ECG and ESR. The patient's chest X-ray showed no acute pulmonary disease. The patient was on intravenous meropenem and intravenous vancomycin for her neutropenic fever episodes with blood, sputum and urine cultures all negative for bacteria and fungi. The patient underwent CT of the chest, abdomen and pelvis that showed no increase burden in her disease and no signs of local infection.

The patient underwent various methods of pain and headache control. All pain titrations were made with goals of pain reduction to at most 5/10 in severity; the details of the pain adjustment regiments, pain relief and total morphine equivalents can be viewed in the below Tables 1 and 2. All dosing of pharmaceuticals were in line with manufacturer recommendations in addition to consultation recommendations of Pain Management/Palliative Care consultants.

Initially, oral morphine and intravenous morphine were titrated to the patient's pain. The patient required increasing amounts of PRN [Pro Re Nata (as needed)] morphine pushes for pain control and was escalated to oral and intravenous hydromorphone combinations with combination of oral and intravenous morphine. The patient continued to develop intractable headaches in similar distribution. At this point Neurology and Pain Management/Palliative Care specialists were consulted for aid in pain control. Furthermore, at this stage CT and MRI of the brain were performed and resulted negative to rule out metastatic disease as the etiology of the headaches. At week 3, the palliative care/pain management consult initiated a PCA (Patient Controlled Anesthesia) pump of hydromorphone with maximum dose and Naloxone rescue parameters. This had mild relief of symptoms for less than a week. The patient then was placed on fioricet by Neurology consultation for similarities in migraine headaches, which did yield some synergistic relief of pain. The patient's headaches continued to rebound to the 9/10 out of 10 in severity despite the PCA. The patient's pain regimen was escalated to long acting oxycontin twice daily in combination with increasing doses of oral hydromorphone. Furthermore, at this stage intravenous acetaminophen pushes were given with maximum dose of 4000 grams per day; this did yield some relief in symptoms. The final stage of pain adjustment was the addition of oral Methadone per recommendations of the Palliative Care/Pain Management consultation assessments and the uptitration of Methadone to reach a tolerable headache pain. This in combination with long acting morphine and PRN Oxycodone, the patient was able to reach a stable 3-5/10 pain scale at the time of hospital discharge. Upon discharge the patient was scheduled for follow up with Pain Management/Palliative care for monitoring and titration of her pain regimen in addition to a Neurologists and her regular Hematologist/Oncologist. This is the first case of intractable pain and headaches in an opiate naive patient with non-metastatic Burkitt's Lymphoma and HIV that received with 50 percent reduction in symptoms from the addition of oral Methadone that has no prior use of opiate abuse or dependence.

Adjustment	Morphine	Oxycodone	Oxycontin	Hydromorphone	Fioricet	Acetaminophene	Methadone	Pain Scale
1	80 mg							9-10
2	60 mg			10 mg				8-10
3	30 mg			20 mg		3000 mg		8-10
4	25 mg	20 mg		20 mg		3000 mg		7-9
5				(PCA) 0.2 mg per dose with lockout of 10 min and maximum hourly dose of 1.4 mg/hour		3000 mg		5-8
6	10 mg	30 mg	40 mg	20 mg	3 capsules	2000 mg		5-7
7		20 mg	30 mg	40 mg	4-6 capsules			4-7
8		15 mg	20 mg	20 mg	6 capsules		20 mg	4-7
9		15 mg	20 mg	10 mg	5 capsules		40 mg	4-6
10			20 mg		5 capsules		60 mg	4-6
11		10 mg			4-5 capsules		80 mg	3-6
12			20 mg		2-4 capsules		100 mg	3-5

Table 1: Analgesic dose and type adjustment detail with pain scale measurement.
All doses in above table are for oral doses of medications. Dosing of Morphine and Hydromorphone in above is the total dose of the drug combining oral and intravenous dosing. Conversion factor was used of 1 mg of intravenous morphine is equivalent to 3 mg oral morphine.
Conversion factor of Hydromorphone was used that 1 mg of intravenous Hydromorphone is equivalent to 3 mg oral Hydromorphone. One Fioricet capsule contains 50 mg Butalbital; 325 mg Acetaminophen; 40 mg Caffeine.

Pain Scale measurements are subjectively patient reported and measured at a maximum of 10 being unbearable excruciating pain and minimum of 0 of being absolutely pain free.

Adjustment	Total opiate dose morphine equivalent
1	80 mg
2	110 mg
3	130 mg
4	145 mg
5	168 mg
6	180 mg
7	250 mg
8	255 mg
9	285 mg
10	320 mg
11	410 mg
12	520 mg

Table 2: Total opiate dose.
Conversion factor used 1 mg oral Morphine is equivalent to 5 mg oral hydromorphone and 5 mg of methadone.

Discussion

The cause of headache pain the inpatient setting is multifactorial with a wide spectrum of etiologies, exacerbating factors and treatment combinations. Patient's undergoing inpatient chemotherapy frequently experience headaches throughout their hospital course, most of which remain uncomplicated and treated with oral acetaminophen [8]. Frequently, headache pain is masked by more severe and chronic systemic pain from other medical conditions not limited to cancer patients.

The use of opiates in the inpatient setting is very common and it is used to treat a wide spectrum of acute and chronic pain [3]. Typically intravenous opiates are used in the acute setting until a stable oral regimen can be used and titrated. The ultimate goal is to wean patients off opiates to tolerate only oral acetaminophen, NSAIDS (non-steroidal anti-inflammatory drugs) or no pharmacological treatment all for their acute and/or chronic medical conditions. Opiates and other pain medications are a symptomatic approach to aiding pain and do not provide a definitive cure. Additionally, the use of potent opiates such asmethadone or hydromorphone carry a high risk of developing addiction, tolerance and abuse among patients [9,10]. Furthermore, the side effects of opiates may cause many side effects including headaches themselves and may contribute further to pain by hypersensitivity or drug to drug interactions. It is imperative to monitor the patient frequently in the inpatient setting when introducing potent and long acting medications to ensure no acute reactions or worsening of symptoms occur. Further, drug to drug interactions must be kept in mind in addition to the synergistic effect of opiates when combined in the same patient. Attention must ensure that no harm befalls the patient and allows the patient to maintain their necessary home medications, active inpatient mediations required to treat their current active medical conditions and the prevention overdosing of patients on opiates.

This patient is a rare case where an opiate naïve patient with no history of opiate or drug abuse required such great amounts of opiates as seen in Table 2 above, whereby upon discharge the patient required 520 mg of equivalent oral morphine to maintain mild control of her headache pain. These amounts of opiates must be handled strictly by an experienced and specialized physician to avoid fatal consequences of overdose and mismanagement of medications. It is important to recognize the favoring of long lasting opiates over shorter acting in a patient with chronic pain [11]. Additionally, it is important to start treating pain in an opiate naïve patient with low doses of medications with short half lives in the acute setting to avoid and monitor for acute reactions [12]. Increasing the dose of a medication is much easier than reacting to an overdose and is much safer for patients; treating an overdose of a medication with a short half-life is much easier and safer than treating an overdose of a medication with a long half-life. The approach to treating pain should not involve the initiation of opiates until oral milder analgesics are attempted first such as acetaminophen and/or NSAIDS [13] barring no serious medical contraindications. In this case fioricet was added and likely yielded synergistic relief of pain to the patient's headache. This is likely because the nature of her headache was classified more of a severe tension headache type with the bilateral cranial nonspecific distribution of pain rather than the inconsistent exacerbation of pain with light or loud noise, which is more typical of a common migraine [14]. Furthermore, the inpatient setting allows for frequent and consistent monitoring by physician and nurse staff and more frequent and more potent medications can be administered rapidly if needed in an acute pain crisis.

In a patient with an aggressive cancer like Burkitt's Lymphoma, it is imperative to rule out increasing burden of disease and metastasis as the cause of worsening pain, thus imaging and frequent lab monitoring is mandatory [15]. Treating a specific target such as a local metastasis provides more definitive treatment and relief of symptoms and does not dispose the patient to unnecessary risks and side effects of potentially abusive and dangerous medications [16]. In this case the MRI and CT of the brain were imperative to rule out acute and treatable causes of a new headache including metastatic disease in the brain, midline shift from mass effect, or an acute hemorrhage.

This is the first reported case of intractable pain and headaches in an opiate naive patient with non-metastatic Burkitt's lymphoma and HIV and no prior use or abuse of opiates that received a 50 percent reduction in symptoms from the use of oral Methadone. The patient's headache greatly reduced from initially of 9-10/10 in severity to a final 3-5/10 in severity on oral methadone, oxycontin and fioricet. The patient was discharged home with close follow up with pain management/palliative care, Oncology and Neurology. This patient will need close attention under these physician specialists to ensure adequate titration of such high doses of medications in addition to her monitoring her aggressive disease that can cause rapid extreme changes in symptoms. Additionally, it is important to recognize that this patient at high risk for opiate abuse, tolerance and overdose and it is important to attempt to down titrate her opiate regimen as much and fast as possible while maintaining relief of her pain. If further pain

or headaches ensue, they should be approached individually and initiated with safer oral acetaminophen and/or NSAIDS without the immediate jump to potent long acting opiates. Opiates can be added and uptitrated as necessary; this approach ensures the maximum safety of the patient with the lowest risk of abuse and overdose of opiates.

Conclusion

New onset severe headaches must be approached conservatively and with caution generally and specifically in an opiate naïve patient. Further, acute medical diseases such as acute hemorrhage, mass effect and metastatic disease must be ruled out as the cause for these headaches, especially in a patient with a known aggressive systemic cancer. Methadone can be effective in treating severe headaches not due to a definitive medical condition, however it must be used with great caution, close follow up and used only by a trained and experienced specialist.

Disclosures

None.

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