PALLIATIVE CARE
CASE OF THE MONTH

"Mythical Methadone"

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Volume 14, No. 42 **November 2014**

Case: AW was a 35-year-old man with a recent diagnosis of metastatic gastric cancer. He was diagnosed three months prior with metastatic gastric cancer after months of abdominal pain. He and his family pursued many different treatment options, deciding to trust a prominent cancer treatment center with his care. They were unfortunately told from diagnosis that all treatment would be palliative and not curative. Despite this plan, AW's largest complaint and most intolerable symptom was intractable abdominal and back pain. He was unable to lie flat for a thorough abdominal examination and rated his pain a 10/10 without any relief with previous treatments that included oral opiates, low-dosed intravenous opiates and adjuvant therapies including heat and repositioning. After this pain was unable to be controlled at an outside hospital, he was transferred to UPMC for the placement of an intrathecal (IT) opiate pump. Upon admission, the palliative care team was consulted for pain management until the patient's pump could be placed. Regardless of rapid titrations and dramatic increases in his hydromorphone PCA (eventually requiring roughly 5,000mg of oral morphine equivalents a day) AW continued to writhe in pain and was unable to lie in his bed. As his goal was to return home to be with his young children and wife, a decision was made to switch him to oral methadone in addition to the placement of his IT pump.

Discussion: Methadone is a diphenylheptane, synthetic opioid. It was first synthesized in 1939 (during World War II) at the pharmaceutical laboratories of IG Farben in Frankfurt, Germany. It was named Dolophine® (its current propitiatory name) for "the end of pain". After the war, American investigators Isbell and Vogel found that methadone's pharmacological profile was similar to that of morphine, and demonstrated that methadone could be substituted for morphine in morphine-dependent subjects to help relieve the withdrawal symptoms associated with abstinence [1]. Since then, in addition to being effective for the treatment of opioid dependence, methadone has also been shown to be effective in the management of several other pain syndromes. Methadone is a μ-opioid agonist (similar to other opioids), as well as an N-methyl-D-aspartate (NMDA) antagonist and serotonin reuptake inhibitor. Its NMDA properties have been thought to contribute to its effectiveness in treating neuropathic pain.

Methadone is a basic, lipophilic drug. Oral bioavailability is approximately 60-80%, and methadone is rapidly absorbed after administration. Onset of analgesia occurs within 15-45 minutes, and peaks within 2.5-4 hours. Less than 10% of an oral dose is extracted by the liver during first pass metabolism. Methadone is highly bound to plasma proteins, particularly α1-acid glycoprotein, while also having a large volume of distribution due to its highly lipophilic properties. These properties influence methadone's retention and release back into the plasma during its redistribution and elimination phase, also contributing to its long half-life. Despite methadone's extensive metabolism (including CYP 3A4, 2B6, 2C8, 2C9, 2C19 and 2D6), methadone does not have any clinically active metabolites. This metabolism is important to note, however, due to methadone's long list of drug interactions. The half-life of methadone is on average 20-35 hours (however, it can be as long as 130 hours), and thus it takes 4-10 days to reach steady-state when initiating therapy and with any dosage changes.

As methadone carries a unique mechanism of action for analgesia, it also carries the risk of one specific and serious adverse drug reaction. This risk is for QTc interval prolongation, which can increase the risk of ventricular arrhythmias, especially Torsades de Pointes, which can be fatal.

Transitioning to Methadone from Other Opioids: Safely transitioning a patient from an opioid to methadone is a clinical challenge as there is no fixed equianalgesic ratio between methadone and other opioids. To help guide clinicians, there are many published and supported methods in the literature[2], of which I will focus on three methods of converting opiates to methadone. This will highlight the importance of having a specially trained clinician involved in management.

Ayonrinde and Bridge [3] developed the conversion method as delineated in the table below. The caveat of this method is that a patient is given a loading dose of 25-50% of their total daily dose of methadone in addition to the calculated daily dose the first two days of treatment. This ensures saturation of the receptors. The loading dose is omitted in elderly and frail patients. Using this method, the patient's equianalgesic dosing (5g oral morphine equivalents (OME)) would be 250mg of methadone without reduction for cross tolerance. Decreasing it 30% for cross tolerance one would come to 166 mg of methadone.

(Discussion Continued)

Morphine Dose	<100	101-300	301-600	601-800	801-1000	>1001
Morphine:Methadone Ratio	3:1	5:1	10:1	12:1	15:1	20:1

Given this equation, our patient would be started on Methadone 75mg q8H for the first two days of treatment and then reduced to Methadone 50mg q8H.

The Morley Makin Method [4] is another method for oral morphine to methadone conversion. This method requires close supervision as on Day 1 the patient's previous opiates are stopped and methadone started. The patient is started on 10% of the total daily dose of morphine (with an upper limit of 30 mg) every three hours as needed for pain. This is continued for five days. On the sixth day the average use on days four and five is divided into two doses that are to be given every 12 hours as the long acting medication. The patient is also given a breakthrough dose at that point in time that is equivalent to ten percent of the total daily dose of methadone every three hours as needed for breakthrough pain.

It is important to note the upper limit of Methadone given in this equation. Our patient mentioned above was on 5000mg and this would have made him have a dose of 50mg every three hours as needed strictly using 10% of his total daily dose of morphine. This would not be correct since the upper dose limit is 30mg every three hours for a total daily dose of 240mg. Using the Morley Makin Method, the patient in the case would be started on Methadone 30mg every three hours as needed for pain.

A final method for converting from another opiate to methadone is the method described by Mercadante [5] (see the table below). Using this method the patient's equianalgesic dosing would be 416mg of Methadone without reduction for cross tolerance. Reducing for cross tolerance, one would use 277mg of Methadone.

Morphine Dose	30-90	90-300	>300
Morphine:Methadone Ratio	4:1	8:1	12:1

Given this equation, our patient would be started on Methadone 90mg q8H.
Comparing the three above mentioned methods, our patient could have received 150-270 mg daily of methadone according to the calculations. This illustrates the wide range of methadone starting doses with different calculations.

Overall methadone has important therapeutic applications for those patients with pain complaints. Since methadone has such a wide range of side effects and dosing ranges, it requires a practitioner with special training. Practitioners who have received special training regarding methadone treatment include pain and palliative care physicians. They should be involved in the initiation and management of a patient who is starting and continues to receive methadone.

Resolution: The patient was started on 30mg of methadone every three hours as needed for pain with an additional dose of 5 mg of hydromorphone intravenously every hour as needed for additional breakthrough pain. He was taking 240mg of methadone daily for three days with a reducing amount of hydromorphone. He passed away suddenly on the fourth day of treatment. On reviewing the chart after death, the patient went into cardiac arrest without signs of Torades de Pointes.

Monitoring: The patient's sudden death highlights the importance of close monitoring. Methadone was attributed to 1 in 3 deaths from prescription opiates in 2009. It is important to monitor a patient's QTc interval on EKG as it can prolong this and lead to Torsades de Pointes, a fatal cardiac rhythm. As with any patient receiving opiates, it is important to monitor usage to identify individuals who may be diverting, misusing, or abusing their methadone. Education on safe use, storage, and disposal is key in any patient who is prescribed opiates.

References:

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