



He's got renal failure – better order Dilaudid instead of morphine!
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Case: JC was a 57 year old man with a history of gastroesophageal junction carcinoma that had spread throughout his abdomen and peritoneum. In February, JC was admitted to the hospital for uncontrolled pain, and he was started on a hydromorphone PCA. He was discharged with a hydromorphone PCA for home use, and was using, at discharge, the equivalent of about 3 milligram per hour of intravenous hydromorphone through the PCA, with good pain control. However, he was re-admitted three weeks later for pain control, and was found to have severe myoclonus, delirium, and complaints of increasing pain despite a hydromorphone patient dose increased to 2 milligrams per hour, a continuous infusion of 3 milligrams per hour, and a 3 milligram RN bolus; he was receiving on average, 8 milligrams of hydromorphone per hour. His pain was localized to the abdominal area, and there was no evidence of hyperalgesia or allodynia. His kidney function had worsened since his previous admission. His creatinine had increased from 1.5 to 6.0, showing that he had progressed from moderate to severe renal impairment.

Discussion: In our hospital system the electronic medication ordering system prompts clinicians to consider substituting hydromorphone for morphine in patients with chronic or acute renal failure, so this is what is often selected if intravenous opioids are required in this population. Morphine is the most well-studied opioid and most clinicians are aware that morphine is unsafe in renal failure. Morphine is metabolized in the liver to morphine-3-glucuronide (M3G), morphine-6-glucuronide (M6G), and normorphine. All of the metabolites are excreted by the kidneys, and accumulate in renal failure. M6G is an analgesic and its accumulation can contribute to respiratory depression, while M3G has no analgesic activity and is thought to cause hyperalgesia (heightened sensitivity to painful stimuli)

and allodynia (when a non-painful stimulus induces pain), as well as neuroexcitatory effects such as myoclonus, agitation, delirium, and, in the setting of prolonged exposure, seizures.

Hydromorphone has been less-studied than morphine, and is recommended with caution and at reduced doses in renal failure (1). However, the metabolism of hydromorphone is similar to that of morphine. Hydromorphone is also metabolized to an activated metabolite in the liver, hydromorphone-3-glucuronide (H3G). Like M6G, H3G has no analgesic activity, but has been shown to be neuroexcitatory in rats. Studies on neuroexcitatory effects in humans have been mixed; most reports of neuroexcitation with hydromorphone have occurred with intravenous infusion and often in patients with renal insufficiency. The ratio of H3G to hydromorphone in patients with normal renal function is 27:1, but in patients with impaired renal function the ratio can be as high as 100:1 (2). One retrospective analysis of patients in an inpatient hospice unit with a GFR (Glomerular filtration rate is the best overall index of kidney function) less than 60 who were prescribed intravenous hydromorphone found that 20% experienced myoclonus, 48% experienced agitation, and 39% had cognitive dysfunction, and this effect was related to the hydromorphone dose and duration of the infusion, though not to the degree of renal insufficiency (3). Another small, non-controlled study found that neuroexcitation increased markedly with doses greater than 20 milligrams of hydromorphone per hour, or durations of infusions greater than 15 days (4). Neuroexcitation does not resolve with administration of naloxone (5).

When treating patients with renal failure, it may be safer to use opioids which are hepatically cleared and do not have active metabolites. These include fentanyl, oxymorphone, and methadone.

For palliative care consultations please contact the Palliative Care Program at PUH/MUH, 647-7243, beeper 8511, Shadyside Dept. of Medical Ethics and Palliative Care, beeper 412-647-7243 pager # 8513 or call 412-623-3008, Perioperative/ Trauma Pain 647-7243, beeper 7246, UPCI Cancer Pain Service, beeper 644-1724, Interventional Pain 784-4000, Magee Women's Hospital, beeper 412-647-7243 pager #: 8510, VA Palliative Care Program, 688-6178, beeper 296. Hillman Outpatient: 412-692-4724. For ethics consultations at UPMC Presbyterian-Montefiore, and Children's page 958-3844. With comments about "Case of the Month" call David Barnard at 647-5701.

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Fentanyl, often considered one of the safest opioids in renal failure, is metabolized in the liver primarily to norfentanyl (99%), which is not metabolically active, and is eliminated hepatically. However, uremia may impair hepatic metabolism of fentanyl. The general approach with using any opioid in a patient with renal failure is to start at a lower dose and proceed cautiously, watching for side effects such as sedation as well as neuroexcitatory effects.

Resolution of Case: In JC, opioid-induced toxicity due to hydromorphone use in the setting of renal failure was suspected. He was rotated to a fentanyl PCA at a continuous rate of 75 microgram per hour with a 75 microgram patient bolus; both the myoclonus and his pain control improved in 24 hours. Presumably, H3G had accumulated, causing toxicity but providing no analgesic benefit, leading to the patient's delirium, myoclonus, and uncontrolled pain.

Opioid-induced neuroexcitation has the potential to increase suffering at the end of life. Clinicians must be able to distinguish neuroexcitation from increased pain due to disease progression. The presence of myoclonus and cognitive symptoms are clues to the diagnosis, as is a history of increasing pain despite increasing opioid doses, and the use of opioids with active, neuroexcitatory metabolites such as morphine and hydromorphone.

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