EDITORIAL

Opioid safety

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In this issue, Gupta and Weber concisely review the literature on the renal effects of opioids, both acute and chronic. Several fascinating facts emerge, such as the following:

- Opioid receptors similar to those found in the central nervous system are expressed in the kidney.
- In the animal model, morphine stimulates angiogenesis-dependent tumor growth and ischemic wound healing.
- The central opioid pathway is activated by dietary restriction, resulting in maximum sodium retention.
- Morphine induces a transient dose-dependent reduction in blood pressure and a subsequent decrease in urine output.
- Extrapolation of the chronic use of opioids can be tied in with the occurrence of heroin-induced nephropathy.
- Opioids are likely to have physiologic renal effects and could potentially contribute to the progression or treatment of chronic kidney disease.

Now, speaking as a clinician, the authors appear to stretch some of the animal data considerably to hypothesize human outcomes; however, this may not be all that bad if it stimulates more thought and research in this area. As a medical oncologist, I find the suggestion that opioids stimulate angiogenesis-dependent tumor growth both tantalizing and worrisome. At some time during the course of their clinical diseases, the vast majority of cancer patients are treated with some sort of opioid drug. If these theories surrounding angiogenesis are on the mark, maybe we are doing our patients more harm than good. Viewing this point differently, will blocking the opioid receptors in cancer patients improve their survival as an antiangiogenesis tactic?

Although all this speculation is academically stimulating, there remains the clinical issue of opioid use and impaired renal function. Of all the natural and synthetic opioids, morphine is the drug of choice and the standard for comparison for severe pain. Orally administered morphine is subject to the first-pass effect of liver metabolism, which causes a large reduction in its potency. Hepatic biotransformation modifies the opioid through dealkylation, glucuronidation, hydrolysis, and oxidation. Once converted to water-soluble forms, 90 percent is excreted in the urine. Morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) are the two major metabolites of morphine. Both of these metabolites depend on renal excretion for clearance. M6G is a more potent analgesic than morphine, whereas M3G is associated with hyperalgesia and neurotoxicity. It has been suggested that morphine doses be reduced in patients with severely impaired renal function, and that they be substantially reduced if creatinine clearance is less than 30 ml/min/1.73m^2. Furthermore, there appear to be some pharmacokinetic differences with morphine in different age groups, with reduced renal clearance and smaller volume distribution in older patients.

Ultimately, all good research leads us to ask questions, sometimes more than it answers. I hope the articles in this current issue of *Journal of Opioid Management* encourage you in your investigations.

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