LETTERS TO THE EDITOR

Hydrocodone Metabolism

I wanted to point out an important discrepancies in information regarding the metabolism of hydrocodone and its status as a prodrug.

The prescribing information for approved hydrocodone products (except the 12-hour sustained-release hydrocodone product Zohydro [Zogenix]), as well as review articles and *Practical Pain Management's* August 2014 supplement, *"Pharmacogenetics: Personalizing Pain Medicine,"* have reported that hydrocodone is metabolized via the cytochrome P450 (CYP) isoenzyme 2D6 to its primary active metabolite, hydromorphone. However, the prescribing information for Zohydro states that the metabolism is completely different, and is primarily mediated by CYP3A4. The product information also states that hydrocodone is not a prodrug but rather a primarily active opiate and that it mostly becomes the weakly active norhydrocodone. The information further notes that CYP2D6 is involved and produces hydromorphone but that it isn't clinically relevant to the drug's pain relieving affects.

This information comes from the measurement of blood levels of these hydrocodone metabolites in studies done by Zogenix. Previous studies showed that pain relief correlated with plasma concentrations of hydromorphone rather than hydrocodone.

Despite several discussions with the senior director of medical affairs for Zogenix, I have been unable to reconcile the previously widely accepted and the new conflicting hydrocodone data.

This discrepancy obviously brings up a very important and concerning clinical question. What is the most important finding in a patient's pharmacogenetic profile when hydrocodone is prescribed? With the recent rescheduling of hydrocodone and the approval of another extended-release 24-hour (Hysingla, Purdue Pharma), hydrocodone will be used in more than just "as-needed" situations.

As we become more aware of the clinical significance of allele polymorphism and attempt to personalize pain medicine, we must understand the correct metabolic pathway for these medicines. To improve clinical safety, we must publish materials to highlight the current discrepancies and demand reconciliation of this conflicting data by the FDA.

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Dr. Konen:

Thank you for your thoughtful comments regarding hydrocodone metabolism, particularly as it relates to statements within the professional package insert for Zogenix, Inc.'s product Zohydro ER. I have carefully reviewed your concerns and have outlined each point below.

"I wanted to point out an important discrepancies in information regarding the metabolism of hydrocodone and its status as a prodrug."

By definition, a prodrug has no pharmacological activity until after it is converted to one or more active metabolites. Since hydrocodone has been studied and shown to produce immediate analgesia following subcutaneous, intrathecal, and intracerebroventricular administration, thereby avoiding hepatic Phase I metabolism, by definition, it is not a prodrug.[1]

Several sources "have reported that hydrocodone is metabolized via the cytochrome P450 (CYP) isoenzyme 2D6 to its primary active metabolite, hydromorphone."

This is correct. Hydromorphone is in fact the metabolite of hydrocodone with the most analgesic activity. The Zohydro ER package insert is consistent with this, stating, "Hydromorphone is formed from the O-demethylation of hydrocodone and may contribute to the total analgesic effect of hydrocodone." The wording "may contribute" is entirely accurate because the effect depends on whether a patient is a poor 2D6 metabolizer, an extensive 2D6 metabolizer (considered normal with 2 wild type alleles), or an ultra-rapid 2D6 metabolizer. All of these various genotypes could have a profound effect on hydrocodone's analgesic and toxicity profile, but any one of these genotypes likely would still confer some level of analgesic benefit devoid any drug interactions.

While hydromorphone is the most active analgesic compared to the parent compound and the other metabolites, it does not translate to "no activity" for hydrocodone. For example, an extensive 2D6 metabolizer may have less analgesia compared to an ultra-rapid 2D6 metabolizer, but that same patient could have more analgesia if they were also receiving a potent 3A4 inhibitor that caused accumulation of the parent hydrocodone compound, because hydrocodone itself provides analgesia, as indicated above.

"The prescribing information for the recently approved 12-hour sustained release product states that the metabolism is completely different *and is primarily mediated by CYP*

3A4."

I am unable to confirm this within the current prescribing information. Specifically, their prescribing information states the following: "Hydrocodone exhibits a complex pattern of metabolism, including N-demethylation, O-demethylation, and 6-keto reduction to the corresponding 6-α-and 6-β-hydroxy metabolites. CYP3A4-mediated N-demethylation to norhydrocodone is the primary metabolic pathway of hydrocodone, with a lower contribution from CYP2D6-mediated O-demethylation to hydromorphone."

The prescribing information is accurate in stating that "...CYP3A4 mediated N-demethylation to norhydrocodone is the primary metabolic pathway." Nearly 60% of hydrocodone's metabolism is mediated through the combined CYP2D6 and CYP3A4 pathways, resulting in the formation of hydromorphone and norhydrocodone.[2]

Metabolism and excretion patterns of hydrocodone in urine found that norhydrocodone was the most abundant metabolite and was frequently detected in combination with hydrocodone within 2 hours of drug administration.[3,4]

"Previous studies showed that pain relief correlated with plasma concentrations of hydromorphone rather than hydrocodone."

I'm unfamiliar with any studies that dispute pharmacological activity of hydrocodone in favor of only hydromorphone. In fact, when administered by the intracerebroventricular route, norhydrocodone displayed similar potency to hydrocodone in producing analgesia.[1]

"What is the most important finding in a patient's pharmacogenetic profile when hydrocodone is prescribed?"

This is a very valid question to ponder, not just for hydrocodone but also for many other opioid analgesics and non-opioids alike. As discussed above, CYP2D6 is an important isoenzyme in the metabolism of hydrocodone, and, in fact, an ultra-rapid 2D6 metabolizer may respond with a higher level of analgesia and toxicity compared to a poor metabolizer of the same enzyme or to patients receiving a potent CYP2D6-inhibiting drug, such as paroxetine.

This is not unique to hydrocodone. In fact, oxycodone is metabolized by CYP2D6 to oxymorphone, which is twice as potent as the parent compound. Codeine is a prodrug that depends on CYP2D6 for conversion to morphine, an important consideration that has been attributed to deaths in ultra-rapid 2D6 metabolizers. And, tramadol has 5 metabolites (M1-5), including O-desmthyltramadol (MI), the most active metabolite, which requires conversion from the parent compound by CYP2D6. But, although the M1 metabolite contributes to more analgesia than the parent compound, the combination of which is likely enhanced by the scant norepinephrine reuptake inhibition, first-pass metabolism is required prior to any significant opioid analgesia by MI. Further metabolism of the M1 metabolite occurs via N-demethylation to N-desmethyl-tramadol (M2), which is ultimately catalyzed by CYP2B6 and CYP3A4.

So, you are correct that pharmacogenetics is an important consideration that, presumably, will be more consistently incorporated into unique drug selection in the future.

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Epidural Steroid Injections

Dear Dr. Tennant:

I think that your editorial on epidural steroid injection's is on the mark.[5] I would, however, like to add several comments coming from an interventional pain practitioner's point of view.

First, I am very familiar with the Radcliffe study, which was conducted in 2009 and published in 2012.[6] The essence of that investigation was clearly negligence in that the clinic had no supervising physician. The physician identified as the perpetrator of these 8 meningitis cases actually was observed by public health officials reusing epidural injection syringes to access shared medication vials, which clearly put patients at risk.

Not wearing a mask, though not considered good technique, was the least of the problems in that clinic. This was a poorly designed study because there was no mention of any confirmed cases of blood borne pathogens such as HIV, hepatitis B, and hepatitis C, which one would expect with reuse of needles and syringes. I am not sure of the physician's training, but obviously he and the clinic put many patients at risk with procedures. But, we should never hold a single clinic responsible for all of our issues.

Second, interventional pain practitioners should not, and in my experience do not, solely rely on epidural steroid injections as a panacea of treatment. Interventionalists have a wealth of procedures that can and should be used to help patients and at the same time reduce the need for additional opioids.

Third, my suggestion to primary care physicians and the patients they

Continued on Page 15 ››