Personalized Medicine Corner

My patient complains that "opioids are not working." Should I consider a genetic reason?

The analgesic effects of some opioids result from metabolism through the cytochrome P450 (CYP450) enzyme system. For example, codeine by itself is basically inactive. Unless the CYP2D6 enzyme converts codeine to morphine, there is little to no pain relieving activity. The gene that encodes for CYP2D6 is highly variable and leads to a wide range of enzyme expression. This genetic variability can contribute to clinical differences in the effects of codeine and some other opioids.

In the case of codeine, approximately 5% to 10% of individuals have no CYP2D6 activity. These "poor metabolizers" will not metabolize codeine into morphine and therefore have insufficient pain relief from codeine-containing analgesics. At the other end of the spectrum, another 5% of patients have too much CYP2D6 activity. These "ultrarapid metabolizers" quickly convert codeine to morphine, which can lead to toxic morphine levels with usual codeine doses. There have been reports of children and adults who developed serious adverse events including death after taking usual codeine doses. These individuals were later found to be ultrarapid metabolizers. A 2006 case describes the death of a breastfed infant of a mother taking codeine who was an ultrarapid metabolizer.[1] In 2013, the FDA released a safety communication regarding the use of codeine in children to help avoid toxicity.[2]

Tramadol also depends on CYP2D6 for conversion to its primary active form with similar clinical effects in poor and ultrarapid metabolizers. Hydrocodone and oxycodone are also metabolized to more active forms by CYP2D6, but the impact of genetic variability on these agents is less clear.

Based on this information, could genetic variability in CYP2D6 be affecting pain control in your patient? It depends. Codeine and tramadol have the most evidence supporting clinically relevant effects caused by CYP2D6 genetic variability. With these agents, approximately 10% to 15% of patients are at risk for getting too much or too little of the drug based on their CYP2D6 activity. This is also a possibility with hydrocodone and oxycodone, but the evidence is not as strong for these agents.

The question at this time is when should one order a pharmacogenetic test? Clinicians can consider pharmacogenetic testing if a patient complains of inadequate pain relief, especially with codeine and tramadol.

Pharmacogenetic testing is offered by a number of commercial laboratories. There are clinical guidelines that can help with interpreting and applying test results.[3] Guidelines advise against using codeine or tramadol in poor or ultrarapid metabolizers. Oxycodone and hydrocodone may not be good alternatives in these patients. A nonopioid (i.e., acetaminophen or an NSAID) may be best for mild pain in CYP2D6 poor or ultrarapid metabolizers; morphine or other opioids not affected by CYP2D6 variability are preferred for moderate-to-severe pain.

Codeine use has decreased in recent years. However there were still nearly 2 million prescriptions written for codeine-containing drugs in 2011, and many expect these numbers to increase with the recent hydrocodone's switch to a Schedule II.

Want to know more about ordering and reimbursement for CYP2D6 testing? Email UF Health Personalized Medicine Program at PMP-HELP@ctsi.ufl.edu. You can also request our *CYP2D6-Opioids Clinical Summary* for a short review of the most relevant studies in this area.

1. Koren G, et al. Lancet 2006;368:704.
2. FDA Drug Safety Communication. February 2013. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm.
3. Crews KR, et al. Clin Pharmacol Ther 2014;95:376-82.

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