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Cytochrome P450 Gene Implicated in Need for High-Dose Pain Medication

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Authors and Disclosures

December 17, 2009 (Los Angeles, California) — Genetic abnormalities in cytochrome P450 may cause some patients to metabolize opioids at an accelerated or retarded rate, prompting the need for higher doses of medication to control pain, according to a new research presented here at the American Academy of Addiction Psychiatry 20th Annual Meeting & Symposium.

Chronic pain patients who require high doses of opioids may lead clinicians to suspect them as possible addicts or abusers, but Forest Tennant, MD, lead author of the study and a physician with the Veract Intractable Pain Clinic in West Covina, California, said other factors are at play.

"I have long felt, as have others, that there could be genetic metabolic abnormalities in some people who require very high or unusual regimens to control pain," Dr. Tennant said.

"The general idea has been that these people must be drug addicts and abusers, but some felt there was perhaps something behind all of this. A lot of these patients have no history of abuse; they don't even smoke cigarettes and just don't fit the profile of drug addict."

To evaluate the issue, Dr. Tennant recruited 15 chronic pain patients who required 1000 mg or more of a morphine equivalent per day and who tested for deficiencies in one or both of the cytochrome P450 2C9 or 2D6 genotypes. The subjects' opioid serum concentrations were determined about 1 hour after administration of their usual opioid dose.

Lazy Gene?

The results showed that all 3 patients with cytochrome P450 genotype abnormalities achieved only 1 to 2 hours of pain relief after receiving the medication. Two of 8 patients who tested for the 2C9 genotype were poor metabolizers, with both showing very high serum concentrations of fentanyl (8.1 and 16.4 ng/mL) 1 hour after dosing. One of the patients with the 2D6 genotype was also a poor metabolizer and had no detectable serum concentrations of oxycodone and its metabolite, oxymorphone, 1 hour after dosing.

The findings offer some evidence, albeit highly preliminary, of genetic cytochrome P450 abnormalities in at least some high-dose pain medicine patients, Dr. Tennant said.

"There are about 50 known genetic abnormalities of the cytochromes, and we can only test 3 or 4 of these at this time," he said. "But even with the tests we did here, the results suggest that there may be metabolic factors with these patients that need to be taken into consideration and may explain why these patients need odd [medication] regimens [requiring dosages that are higher than normal]," he said.

Dr. Tennant added that he suspects that the abnormalities involve a "lazy gene" that only responds to higher doses of a medication.

"We believe those very high blood levels of the drug may be necessary to make the lazy gene work — you need to sort of force feed it," he said. "This has been seen in other areas of pharmacology, such as blood thinners. You have to get a very high dose to make the defective gene work."

Although the research is still in its early stages, genetic testing for such abnormalities may have the potential to help clinicians identify and more effectively treat this patient population.

Possible Screening Tool

It may also help clinicians better detect which patients may be at a greater risk of becoming opioid dependent.

"That's the corollary to this — high doses could cause dependence," Dr. Tennant noted. "I don't know if it could be enough to cause people to go to the street and become addicts, but in order to get even a modicum of pain control, they may be extremely dependent on taking high doses on a regular, round-the-clock basis."

The findings also raise the question of whether these genetic factors could prompt abuse of other substances, including alcohol. At least one of the study subjects fueled that suspicion, he said.

"One of the 5 with the 2C9 genotype did report being an alcoholic at one point, and she said 'It's funny, I would go out and drink with friends and everyone would be getting drunk and nothing would be happening to me'."

Dr. Tennant noted he has subsequently tested 25 additional subjects and found that about 20% of high-dose patients had these genetic abnormalities. He suggested that now that these genetic tests are available commercially, physicians may want to consider testing for these genotypes.

"Eighteen months ago, I wouldn't have been able to do this research because the test wasn't available, but I feel every patient who is taking opioids for some pain should now be tested," he said. "Not just to add to a database but to give essential information to insurance companies and any other parties who are paying for the drugs."

"They need to know what's going on, why these people are taking higher doses of drugs, and they likely wonder whether these patients are addicts."

Controversial Area

With pain medication addiction widespread, the temptation to suspect addiction in many cases only makes sense however, and Jon Streltzer, MD, a professor of psychiatry at the University of Hawaii, Manoa, said he questions the very assumption that some patients "require" high-dose opioids to treat chronic pain.

That is a controversial concept that has much evidence against it at the cellular, physiological, and clinical levels. It may be instead that patients have different susceptibilities to high-dose opioid dependence," said Dr. Streltzer, who is president of the International College of Psychosomatic Medicine.

That doesn't mean genetic factors aren't at play, but they may be part of a bigger puzzle involving multiple mechanisms, he suggested.

"It has long been believed that genetic factors are involved in opioid dependence, although which genes are involved and what the mechanisms are is not understood," Dr. Streltzer told *Medscape Psychiatry*.

"In addition, chronic opioid intake induces changes in the brain itself, changing the way the cells respond. This is thought to involve the development of craving, which in chronic pain patients can be experienced as pain and the need for more pain medicine."

Patients can then in fact become more sensitive to pain — as a result of pain medications themselves. "Numerous reports demonstrate enhanced pain sensitivity results from chronic opioid intake by multiple overlapping mechanisms," Dr. Streltzer said. "Patients in programs to alleviate opioid dependence report that their pain improves."

However, Dr. Tennant said clinicians should not rule out the possibility that patients who say they need high doses may have such genetic abnormalities.

"The bottom line is that when we see a patient who claims to have severe pain and needs a very high dose, we shouldn't jump to conclusion that this is abuse," Dr. Tennant said. "There may be metabolic factors here that have to be taken into consideration and may explain why these patients may need odd regimens."

Dr. Tennant and Dr. Streltzer have disclosed no relevant financial relationships.

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