Exit strategy for opioids; impact of CYP3A4 pathway

What exit strategy do you recommend for discontinuing opioid therapy?

— Ed Thomas, RN, OCN

Sudden discontinuation of opioids can produce symptoms of withdrawal which, while not often life-threatening, are very uncomfortable and concerning to patients. Symptoms may include

- anxiety, insomnia, restlessness, or yawning
- excessive lacrimation (tearing) or rhinorrhea, and sweating
- stomach cramps, nausea or vomiting, or diarrhea
- fever, chills, and piloerection (goosebumps)
- muscle spasms, tremor
- tachycardia and hypertension

My advice does not apply to settings in which addiction or drug abuse is an issue and is suggested for patients whose cause of pain is resolved. This should be done under the supervision of a physician who has experience with pain management and/or opioids. In general, the best practice is to discontinue opioids gradually. Specific plans should be individualized for the patient's situation. Patients who have taken high doses of opioids or who have been taking opioids for a longer period of time will need a slower titration schedule than patients who have taken fewer opioids. Decrease doses gradually while monitoring the patient for signs and symptoms of opioid withdrawal or increased pain. A breakthrough pain medication should be available for patients who experience pain with lower doses of opioids.

How does the CYP3A4 pathway impact metabolism of the new oral targeted agents in oncology?

—Lani Moss, RN

Many oral targeted anticancer drugs are metabolized through cytochrome P450 (CYP) enzymes in the liver. CYP3A4 is one enzyme in this system. Many other medications and some foods (eg, grapefruit and related citrus fruits) can inhibit or induce this enzyme, affecting the metabolism of drugs that are metabolized by the enzyme (called *substrates*). Avoidance of strong CYP3A4 inhibitors and inducers is recommended, if clinically appropriate, when the anticancer medication is a CYP3A4 substrate.

CYP3A4 inducers increase synthesis of the CYP3A4 enzyme, and the full effects are not typically seen until approximately 10 to 14 days after initiating the CYP3A4 inducer. Higher enzyme levels may result in lower concentrations of the anticancer drug and may reduce the effectiveness of the treatment. If coadministration of a CYP3A4 inducer and a substrate cannot be avoided, the prescriber may consider increasing the dose of the substrate (in this case the anticancer agent) and should monitor the patient closely for efficacy.

CYP3A4 inhibitors tend to inhibit the enzyme immediately; how long this effect lasts depends on the amount of time the inhibitor is present in the body. This may increase the concentration of the anticancer agent, increasing the potential for toxicity to the patient. If coadministration cannot be avoided, the patient should be monitored closely for toxicity. The dose of the anticancer agent should be adjusted as indicated.

Some anticancer medications have specific dosing recommendations for when they are administered with a strong or potent CYP3A4 inhibitor or inducer. For example, the dose of the tyrosine kinase inhibitor dasatinib should be reduced from 100 mg to 20 mg or 140 mg to 40 mg once daily if it is administered with certain strong CYP3A4 inhibitors (see prescribing information for details).

Although not all oral anticancer drugs are metabolized through CYP3A4, metabolism of the anticancer drug may be affected by other enzymes in the body. Patients should be advised to keep a complete list of all their medications with them as they may have their oral anticancer prescriptions filled at a different pharmacy than the one that fills their other prescriptions. Patients also should be advised to report all their medications to their health care providers in order to detect and manage potential drug-drug interactions. ■

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