Stopping Medications Can Cause Adverse Effects

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"He doesn't play with toys. He doesn't feed himself. He's unable to talk. He's unable to do anything whatsoever for himself." This quote from the mother of a boy who developed severe theophylline; toxicity and brain damage after one of his other drugs (carbamazepine) was discontinued demonstrates an important general principle of drug interactions: discontinuation of a drug can sometimes cause severe adverse results.

The boy in this case had asthma and was receiving chronic theophylline therapy when 1 of his physicians (not the theophylline prescriber) discontinued the carbamazepine. The boy subsequently developed a dramatic increase in his theophylline serum concentrations with seizures and permanent brain damage. The boy's lawyers claimed that he had to take a large dose of theophylline to overcome the enzyme induction of carbamazepine, and after the carbamazepine was stopped, his theophylline dose was excessive.

Many patients chronically take drugs that can interact with each other, but when the medication regimen is stable, it is assumed these patients are not at risk of adverse drug interactions. Such patients can be at risk, however, because stopping the precipitant drug (the drug causing the interaction) may result in undesirable changes in the plasma concentrations of the object drug (the drug affected by the interaction).

What Patients Are at Risk?

Patients at risk of adverse drug interactions from stopping a drug are generally those with chronic diseases taking an object drug with a narrow therapeutic index and significant dose-dependent toxicity. Warfarin is a classic example of such a drug, and life-threatening bleeding episodes have been reported after patients taking warfarin stopped taking an enzyme inducer such as a barbiturate. In these cases, the warfarin dose had previously been increased to overcome the enzyme induction; when the enzyme inducer was taken away, the patient's warfarin dose became excessive.

Stopping 1 drug also can reduce the effects of another drug. Sometimes the plasma concentration of an object drug is being increased to a therapeutic level by a precipitant drug that is inhibiting the metabolism of the object drug. If the precipitant drug is discontinued, the plasma concentrations of the object drug drop into a subtherapeutic range.

Using warfarin again as an example, suppose a warfarin-treated patient is also on chronic therapy with another drug that inhibits the CYP2C9 metabolism of warfarin. The patient is likely to be on a small dose of warfarin to compensate for the drug interaction. If the CYP2C9 inhibitor is stopped, the patient becomes under-anticoagulated, and a serious clotting episode could be the result.

How Can We Prevent Adverse Outcomes?

Patient education. Patients who are on chronic therapy with interacting drugs need to be advised that stopping certain drugs can change their response to other drugs. This applies especially to warning patients against stopping a drug on their own, but it also applies to prescriber-directed discontinuation of medications.

Multiple prescribers. Pay particular attention when the patient is going to more than 1 physician. Often a drug prescribed by 1 physician interacts with 1 prescribed by another. Communication among prescribers often does not occur; the pharmacist may be in a unique position to prevent adverse interactions resulting from drug discontinuation.

Time course. In order to reduce the risk of adverse outcomes, it is important to know the likely time course of the interaction after the precipitant drug is stopped. If the precipitant drug is an enzyme inducer, it may take 1 to several weeks for the effect to completely dissipate in some cases. Enzyme induction from inducers with long half-lives such as phenobarbital tends to last considerably longer than inducers with short half-lives such as rifampin. If the precipitant drug is an enzyme inhibitor, the inhibition usually dissipates more quickly because inhibition is usually competitive and stops as soon as the precipitant drug is largely eliminated from the body.

Computers are designed to detect interactions when *starting* drugs. Computerized drug interaction detection systems cannot be relied upon to catch adverse drug interactions resulting from *stopping* a drug. Thus, the pharmacist has a pivotal role to play in educating patients about the risk of stopping certain medications. PT