Adverse Outcomes in Stabilized Patients

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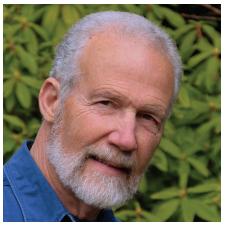

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ADVERSE OUTCOMES DUE TO DRUG–DRUG INTERACTIONS (DDIs) often occur after the addition of a new drug that increases or decreases the effect of a drug a patient is already taking. The time course varies depending on the pharmacokinetics of the drugs involved in the DDI, but most adverse outcomes manifest themselves within the first week or two of starting therapy with a new drug. However, adverse outcomes can also occur in patients who have been stabilized on interacting drugs for weeks or months, and we address this in greater detail below.

PHARMACODYNAMIC DDIS

In some cases, the risk of an adverse outcome continues as long as a patient is receiving the 2 drugs. For example, the increased risk of bleeding when selective serotonin reuptake inhibitors (SSRIs) are given with warfarin is thought to be due to SSRI-induced inhibition of platelet function; this increased risk of bleeding probably does not diminish much over time. Although there is some evidence to suggest that the risk of bleeding may be somewhat higher in the first month of combined therapy, patients probably continue to be at risk as long as the 2 drugs are given.

ADDITION OF A THIRD DRUG

Sometimes a patient is on long-term therapy with 2 interacting drugs with no adverse outcomes, but then a third drug is added and a reaction occurs. For example, in a recent case, a patient on long-term therapy with atorvastatin and colchicine developed rhabdomyolysis after the addition of sofosbuvir/ledipasvir.[1] Atorvastatin has been shown to moderately increase colchicine plasma concentrations[2]; however, in this patient, the interaction by itself was not sufficient to result in myopathy. The addition of ledipasvir, a P-glycoprotein inhibitor, probably had an additive effect with atorvastatin in increasing colchicine plasma concentrations.

STOPPING A DRUG

In some cases, an object drug is titrated to a therapeutic effect in the presence of an enzyme inhibitor or an enzyme inducer. If the inhibitor or inducer is then stopped, the plasma concentration of the object drug may become subtherapeutic or excessive. For example, a patient stabilized on chronic warfarin therapy and an inhibitor of CYP2C9 may develop a subtherapeutic international normalized ratio (INR) if an inhibitor is stopped and may develop an excessive INR if an enzyme inducer is stopped.

CHANGE IN RENAL FUNCTION

Some DDIs are more likely to result in adverse outcomes in patients with impaired renal function. For example, patients with poor renal function who are taking angiotensin-converting enzyme inhibitors and potassium-sparing diuretics appear to have a greater risk of hyperkalemia. The same is true when colchicine is given with clarithromycin, for which most life-threatening and fatal reactions have occurred in patients with substantial renal impairment. For both of these examples, a patient may tolerate the DDI at one point and then manifest a serious adverse outcome due to deterioration of renal function.

DELAYED REACTIONS

Some DDIs can take many weeks to a month or more to develop. For example, a patient on azathioprine who is then given allopurinol may develop pancytopenia if the dose of azathioprine is not substantially reduced on initiation of the allopurinol. Pancytopenia generally develops gradually as normal cells mature and die and because the production of new cells is inadequate due to the excessive azathioprine. It is not uncommon for patients to present with an infection 5 or 6 weeks after allopurinol is started. Unfortunately, by this time, it is sometimes too late to save the patient.

SUMMARY

Adverse outcomes from DDIs usually occur in the first few weeks after starting a second drug, but some adverse outcomes can occur in patients stabilized on 2 interacting dugs, in which case they take a long time to develop and become manifest. This can occur because of pharmacodynamic DDIs, such as those that increase the risk of bleeding; when a third drug is started or stopped; or when a precipitant drug is stopped. Changes in renal function also can unmask a DDI that was not causing adverse outcomes until renal function deteriorates. ◆