Old Drug Interactions Harming New Patients

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A report has appeared describing a 52-year-old heart transplant patient on cyclosporine, azathioprine, and prednisone who was admitted to the hospital for life-threatening pancytopenia.[1] It turned out that—without the knowledge of the transplant physicians—the patient's primary physician had ordered allopurinol 300 mg daily for hyperuricemia. The ensuing drug interaction resulted in a dramatic increase in azathioprine effect, leading to a 31-day hospital stay to treat the life-threatening drug interaction at a cost of $181,000.

The irony of this current catastrophe is that 35 years ago the same 2 drugs—azathioprine and allopurinol—resulted in the death of a patient, and the event received considerable attention in the medical and pharmaceutical literature.[2] For many pharmacists and physicians practicing at the time, this 1970 case was a needed wake-up call signaling that drug–drug interactions can cause serious outcomes and should not be ignored.

But in the 34 years between the first case in 1970 and the recent report in 2004, numerous patients on azathioprine have developed life-threatening bone marrow suppression after allopurinol was added.[3-5] The result has been considerable distress or death for the affected patients and substantial cost to the health care system.

What Is the Nature of the Interaction?

Allopurinol inhibits the metabolism of azathioprine by xanthine oxidase and can substantially increase azathioprine plasma concentrations. The elevated azathioprine concentrations can lead to azathioprine toxicity, primarily manifested as bone marrow suppression. The resultant reduction in white blood cells and platelets can lead to adverse outcomes such as infections and bleeding.

What Is the Time Course of This Interaction?

In most reported cases, complications from the drug interaction appeared between 1 and 2 months after the allopurinol was added to the azathioprine therapy. One should consider the possibility, however, that, in any given patient, adverse effects could be observed sooner than 1 month or after 2 months.

How Can the Interaction Be Managed?

Those working with transplant patients generally agree that this interaction is best avoided. Some have tried to reduce the likelihood of an adverse outcome by reducing the dose of azathioprine when the allopurinol was added.[5] Nonetheless, even with substantial reductions in azathioprine dose, some patients still develop myelotoxicity.

Summary

The concurrent use of azathioprine and allopurinol has caused life-threatening and fatal adverse outcomes for several decades, and yet cases continue to be reported. The adverse effects on the patient are our primary concern, but these serious reactions can also be very costly: $181,000 in the recent case. The following recommendations may help reduce the number of people harmed by this drug interaction:

- Patients on azathioprine and other immunosuppressants should be strongly advised not to take any medications (prescription, OTC, or alternative) without checking with their transplant team first. This advice should be repeated at regular intervals. Some of the reported adverse outcomes from concurrent use of azathioprine and allopurinol could have been prevented if the patients had followed the advice that they no doubt received about taking other medications.
- Pharmacists should be particularly careful about drug interactions when dealing with transplant patients. If there is any doubt about a possible drug interaction, the patient's transplant team should be contacted. Alert community pharmacists could have prevented some of the reported adverse outcomes from the azathioprine–allopurinol interaction if they had inquired about medications that the patient may have received from the transplant clinic.
- Computerized drug interaction detection systems need to be implemented that will search all of the medications that each patient is receiving. The risk of adverse drug interactions is increased when no single computer system has all of the medications. This risk would apply to people who go to different pharmacies, such as those who get some of their medications from a pharmacy at a specialty clinic and other medications from a pharmacy in their community. PT

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