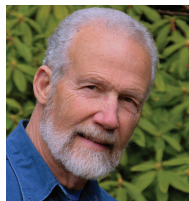


Another Thiopurine-Allopurinol Tragedy

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A recent news headline read, “Pharmacists’ failure to check drug risks leads to ‘horrible’ death.”¹ According to the CBC News report, a 76-year-old woman on mercaptopurine for colitis was started on allopurinol. Six weeks later, she developed a blister on her foot and went to the hospital; the hospital physicians recognized the problem as a drug interaction, but the patient died of severe infection and respiratory failure. Apparently, the interacting drugs were prescribed by the same physician, and they were filled at the same pharmacy.

What Is the Interaction?

The thiopurines (mercaptopurine and azathioprine) have complex metabolism, but one important pathway is via xanthine oxidase, leading to an inactive metabolite. Giving a xanthine oxidase inhibitor such as allopurinol or febuxostat with a thiopurine can substantially increase the effect of the thiopurine, leading to bone marrow suppression.

Is Allopurinol Contraindicated with Thiopurines?

Not at all. In fact, allopurinol is used with thiopurines in selected patients with inflammatory bowel disease and other diseases in order to improve efficacy and

reduce toxicity. Thiopurines can produce hepatotoxic metabolites, and there is evidence that allopurinol can shunt more of the metabolism to the metabolites that provide efficacy (6-thioguanine nucleotides) and away from those that produce hepatotoxicity.² If the combination is used, however, *it is absolutely necessary to substantially reduce the dose of thiopurine and monitor the patient carefully for evidence of bone marrow suppression.* There is substantial person-to-person variability in the magnitude of all drug interactions, and a rule-of-thumb dosage reduction may well be too much for one patient and not enough for another.

Is This an Old Interaction?

Very old. It was described in 1963 by Gertrude Elion, the scientist who won the Nobel Prize in 1988, partly for the development of all 3 of the drugs involved: mercaptopurine, azathioprine, and allopurinol. She reported in 1963 that allopurinol, as expected, reduced the metabolism of mercaptopurine by xanthine oxidase.³ By 1966, others warned that the mercaptopurine dose should be reduced to about 25% of the usual dose if allopurinol is given concurrently.⁴

Are There Other Case Reports?

In 1970, a clinicopathologic conference was published in which a 61-year-old man on azathioprine died of pancytopenia, bleeding, and sepsis after starting allopurinol therapy.⁵ Even though numer-

ous theories were proposed to explain the fatality, over a year later, the true cause was discovered and published: an interaction between azathioprine and allopurinol.⁶ Since this index case, the interaction between allopurinol and thiopurines has

been “rediscovered” repeatedly, often with fatal results. Some of the disasters occurred when the thiopurine was prescribed by one physician, and the allopurinol was prescribed by another. For this reason, it is necessary that the patient be advised about the dangers of adding allopurinol to thiopurine therapy unless it is done properly.

The published case reports are likely to represent only a small fraction of the actual cases. The drug interaction may not be recognized as the cause of the reaction, and even when it is recognized by prescribers, they may be reluctant to publish a fatal drug error that they committed.

In 2009, the New Zealand Health Department issued a safety notice after a patient on azathioprine and allopurinol died of pancytopenia.⁷ The patient was on azathioprine as an outpatient and upon admission to a hospital was given allopurinol by the physicians. The interaction was not detected by the pharmacy computer because the patient’s azathioprine prescription was not on the system.

Recommendations

- When thiopurines are intentionally used with xanthine oxidase inhibitors (allopurinol or febuxostat) to improve efficacy and reduce toxicity of thiopurines, there must be *both* a dosage reduction of the thiopurine and regular monitoring for bone marrow depression.
- Every patient taking thiopurines alone (without allopurinol or febuxostat) should be warned specifically about the dangers of taking allopurinol or febuxostat concurrently.
- Whenever allopurinol or febuxostat use is initiated in a patient, prescribers and pharmacists should investigate to ensure that the patient is not already taking azathioprine or mercaptopurine. ■

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