MEDICINAL MISHAP

Death from diltiazem–ibrutinib interaction

Case study

A 68-year-old male presented to the emergency department because he woke with shortness of breath, central chest pain and dizziness. He had a past history of hypertension and gastro-oesophageal reflux disease and had been taking ibrutinib (560 mg daily) for the previous three months for mantle cell lymphoma.

The patient was diagnosed with a pulmonary embolism and anticoagulated with rivaroxaban. He was found to have atrial fibrillation with a rapid heart rate. This was attributed to ibrutinib therapy. Metoprolol, digoxin and diltiazem were started to control the heart rate. A haematologist advised withholding ibrutinib while the patient was in hospital.

The patient was discharged after one week, on all three drugs for rate control. Ibrutinib was recommenced on hospital discharge after consultation with the haematology team.

Two weeks after discharge he was reviewed in the haematology clinic and was managing well. The patient was to be closely monitored with two-monthly haematology reviews.

Three months after discharge the patient was hospitalised following a cardiac arrest. Despite intensive care, he suffered extensive neurological injuries and died three days later. While no autopsy was conducted, a CT pulmonary angiogram following the cardiac arrest did not show another pulmonary embolism. The patient's arrhythmias and subsequent cardiac arrest were deemed to be secondary to ibrutinib toxicity as a result of concomitant treatment with oral diltiazem.

Comment

Ibrutinib is an immune modulator indicated for the treatment of certain lymphoma subtypes.[1] It is metabolised primarily by cytochrome P450 (CYP) 3A4, to produce a prominent dihydrodiol metabolite that inhibits the enzyme Bruton's tyrosine kinase, thereby inhibiting B-cell receptor signalling. This kinase has a key role in survival for patients with B-cell malignancies.[2]

A notable adverse effect of ibrutinib is atrial fibrillation. It is a common reason for ceasing ibrutinib. Regular cardiac monitoring during treatment is recommended for patients with cardiac risk factors.[1] Atrial fibrillation is thought to occur due to the inhibition of Bruton's tyrosine kinase and tec protein tyrosine kinase, expressed in the heart, reducing phosphoinositide 3-kinase-protein kinase B signalling, which has a cardio-protective role during cardiac stress.[3]

While there is increasing awareness of the cardiovascular adverse effects of ibrutinib therapy, what is less well recognised is the potential for severe drug–drug interactions with drugs, such as diltiazem, used to treat arrhythmias. As diltiazem is a moderate inhibitor of CYP3A4 and ibrutinib is a substrate of this enzyme, prolonged co-administration of the two drugs is likely to result in reduced ibrutinib clearance and subsequent cardiotoxicity.[4] Given the grave consequences of this interaction, treatment guidelines for ibrutinib-induced atrial fibrillation should be updated to clearly state the risks of drug interactions and which drugs to avoid.

This case highlights the essential role of a clinical review of the drugs taken, particularly by patients at high risk, at every transition in care. For patients who present with atrial fibrillation requiring rate control while taking ibrutinib, the recommended treatment sequence is:

- beta blockers (with optimisation of dosage as tolerated)
- digoxin if required (doses should be spaced six hours apart from ibrutinib to minimise the potential for P-glycoprotein interactions in the gastrointestinal tract).

If further rate control therapy is needed and diltiazem is prescribed, the dose of ibrutinib should be reduced by 50% to 75%, depending on the patient's clinical requirements.[2,4]

For patients on high-risk drugs, with the potential for interactions, clinicians should consider searching beyond traditional interaction checking software, which may underestimate the risk of drug–drug interactions. Instead, consult a specialist pharmacist for advice and always consider the pharmacokinetic and pharmacodynamic effects of the combination therapy.

Conclusion

With increased prescribing of tyrosine kinase inhibitors, it is likely that clinicians less familiar with these drugs will be involved in managing patients

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taking ibrutinib. This highlights the need for education related to drug interactions with targeted therapies, as well as practice guidelines. These guidelines should include recommendations on baseline cardiac assessments for high-risk patients as well as management of new onset cardiac toxicities, developed in collaboration with haematologists, cardiologists and pharmacists to optimise the management of cardiovascular drugs in patients receiving ibrutinib.

Conflicts of interest: none declared

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