BEWARE THE INTERACTION BETWEEN THIOPURINES AND WARFARIN

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INTRODUCTION

• It is not uncommon for patients to require both immunosuppression and anticoagulation and therefore for thiopurines and warfarin to be prescribed concurrently.

• Limited evidence suggests that thiopurines can inhibit the actions of warfarin; conversely, reducing thiopurine dosage may increase INR.

• Combined reduced-dose thiopurine and allopurinol is increasingly used in IBD patients with high MeMP:TGN ratios (hypermethylators).

• However, because allopurinol may potentiate warfarin, combination therapy with allopurinol and a reduced dose of thiopurine could dangerously increase warfarin activity and INR.

AIMS

1. To record the effects of thiopurines with or without allopurinol on warfarin dosing and INR.

2. To raise awareness of a risk of harm from a clinically important interaction between thiopurines and warfarin +/- allopurinol.

METHODS

• We studied 8 patients identified from our anticoagulation database who were established on warfarin and then started on a thiopurine (Fig 1).

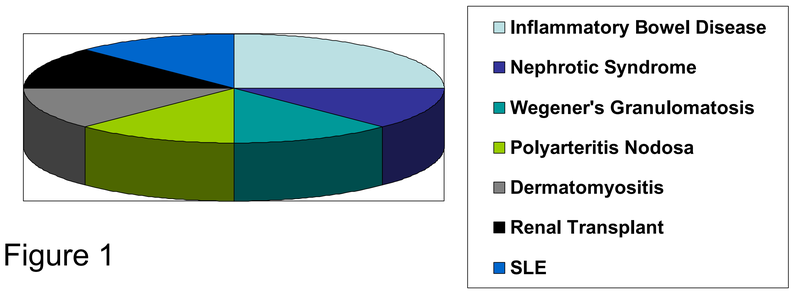


Figure 1

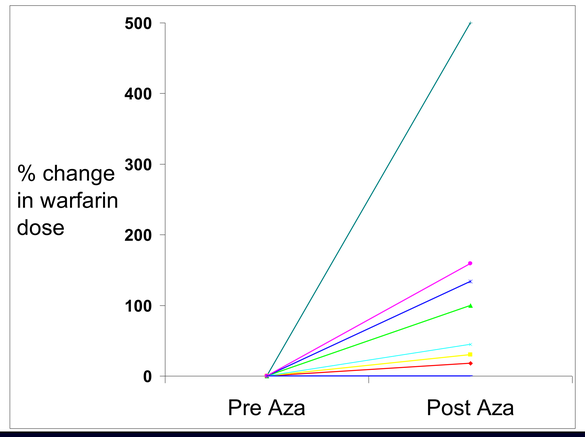
• The effects of the thiopurine on INR, and warfarin dose before and after starting the thiopurine was recorded.

RESULTS

Whole Group

• In 6/8 patients, after introduction of azathioprine or mercaptopurine, the warfarin dose had to be significantly increased in order to maintain therapeutic INR (Fig 2).

Figure 2



Hypermethylators

• In the 2 IBD patients, each with a high warfarin requirement, thiopurine metabolites were assayed, and both showed MeMP:TGN ratios >11.

• Thiopurine dose was reduced to 25% and allopurinol 100mg added.

• INR rose within a week in these patients to 6.9 and 11.2

• Warfarin doses had to be reduced by 33% and 50% to regain therapeutic INR and reduce risk of bleeding.

• Non-IBD patients did not have thiopurine metabolites measured

CONCLUSIONS

• Clinicians should be aware of the potential inhibitory action of thiopurines on warfarin's anticoagulant effect.

• In patients taking warfarin, close INR monitoring is essential when initiating or stopping thiopurines and when reducing their dose and/or adding allopurinol.

• Failure to monitor INR meticulously when reducing thiopurine dose or introducing allopurinol could result in bleeding.

• The high MeMP:TGN ratio in 2 of our patients raises the possibility that thiopurine metabolites may play a role in the interaction between thiopurines and warfarin.