Case report

Haematuria in HIV – an interactive web

A 55 kg nursing sister presented to a private hospital complaining of lower abdominal pain and frank haematuria. She was assessed as having a urinary tract infection, and started on ciprofloxacin. When seen at our institution a day later she complained of colicky flank and lower abdominal pain, was pale and had a pulse of 112 beats per minute with a blood pressure of 110/70 mmHg. There was mild left iliac fossa discomfort and a distal sensory neuropathy. She had frank haematuria, a haemoglobin concentration 4.8 g/100 ml, a platelet count of 650 x 10^9/l and an International Normalised Ratio (INR) that failed to clot. She settled after transfusion of fresh frozen plasma and packed cells. Her INR the following day was 6.1, and 2 days later was 1.6.

She was HIV positive and 3 months earlier had been diagnosed as having disseminated tuberculosis based on general debility, an elevated C-reactive protein (CRP), and a chest X-ray showing a miliary infiltrate. She had been started on weight-appropriate standard antituberculous therapy with rifampicin, isoniazid, pyrazinamide and ethambutol. Two weeks later she had presented with a painful swollen left calf, and a popliteal deep vein thrombosis was confirmed on Doppler ultrasound. She was anticoagulated with heparin and then warfarin with a planned therapy duration of warfarin of 6 - 8 weeks, assuming satisfactory clinical response. One week later her INR was 2.02 on warfarin 10 mg daily.

She was found to have a CD4 count of 19 x 10^6/l, and was entered into the ARV programme. An INR done during the preparation phase was 1.54, while on warfarin 10 mg daily, but when she was started on antiretrovirals, the INR was 2.22 on the same dose. Her antiretroviral regimen consisted of stavudine 30 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg at night. At that stage her anti-tuberculous therapy consisted of rifampicin 600 mg daily and isoniazid 300 mg daily.

She remained on warfarin because of ongoing active tuberculosis and general debility but was not started on co-trimoxazole in order to limit pill burden and medication-associated nausea.

Three weeks after starting ARVs she presented with the life-threatening haematuria described previously. Her warfarin was discontinued, and her tuberculosis resolved gradually on treatment. Thirty months later she was well, with an undetectable viral load and a CD4 count of 395 x 10^6/l.

Discussion

Many HIV-positive patients placed on ARVs either are being treated for intercurrent opportunistic infections or develop them as part of an immune reconstitution syndrome. They may also be on other prophylactic medications. A combination of three antiretrovirals, four antituberculous agents, co-trimoxazole (two drugs) and fluconazole is a common finding in ill AIDS patients who may also be hypoalbuminaemic and bed-ridden. Chronic meningitides or inflammatory CNS granulomata may have led to patients being placed on anti-epileptic treatment as well.

The development of deep vein thrombosis is also common under such circumstances. Warfarin is a highly protein-bound drug with a narrow therapeutic index. It is hepatically metabolised by highly inducible and inhibitable enzymes, so complex drug-drug interactions can be anticipated in the context of polypharmacy.

Exploring medication interactions in this field is complicated by the rapid rate of development and marketing of ARVs which means that sometimes clinical drug interaction studies may lag behind registration and marketing milestones. A further problem in evaluating potential medication interactions is that studies in healthy volunteers[1] may miss effects in sick older patients on multiple medications, and it is not always easy to determine the clinical magnitude of detected effects.

In our index patient, the potentially important medication interactions were between warfarin, rifampicin, efavirenz and ciprofloxacin.

Ciprofloxacin

A retrospective study[2] looking at the effect of ciprofloxacin on anticoagulation stability found that patients were on average 70 years old and on a mean of 6.5 different medications. Another study found that 19% of patients taking a fluoroquinolone (levofloxacin) concomitantly with warfarin developed an INR greater than 4.0, and 44% reached this level if on co-trimoxazole.[3] The mechanism for the interaction with the quinolones is unclear, but reduced protein binding and reduced metabolism have been proposed. In this patient haematuria was already present when ciprofloxacin was introduced, so it is unlikely to have been the main culprit.

Rifampicin

Warfarin is a racemic mixture of two enantiomers that are metabolised by different inducible isoforms of the cytochrome P450 family. The more biologically active S-isomer is metabolised mainly by CYP2C9 and the R-isomer by CYP3A4. Rifampicin induces CYP3A4-mediated metabolism (reduced levels of simvastatin, verapamil and azoles such as ketoconazole and fluconazole) as well as CYP2C9-mediated metabolism (reduced levels of S-warfarin and glibenclamide).[4] Reversal of enzyme induction is seen within 2 - 3 weeks of stopping rifampicin, leading to potentially dangerous over-anticoagulation if the higher warfarin doses are not subsequently reduced. At higher doses, isoniazid may inhibit the metabolism of warfarin, phenytoin and carbamazepine.[5] The clinical significance of this is usually swamped by the rifampicin effect. In this patient the INR appeared to have been stabilised on antituberculous therapy, but a late effect is possible.

Antiretrovirals

Efavirenz and ritonavir are both inhibitors and inducers of CYP3A4, so their effect on warfarin and phenytoin levels is variable.[6] However, in this patient the timing of the over-anticoagulation event suggests that efavirenz was acting as an inhibitor of warfarin metabolism at that stage, and was the main contributing agent leading to her acute presentation. Stavudine and lamivudine are not major substrates of the cytochrome P450 system, so are unlikely to have contributed to this adverse event.[7] Nevirapine is listed as an inducer of CYP3A4, leading to potentially important reductions in INR requiring higher warfarin dosages. It may also lead to lower levels of phenytoin and oral contraceptives. Ritonavir may also induce glucuronidation, potentially reducing levels of zidovudine, valproate, and lamotrigine.[8]

Other medication

Drugs not present in this patient but commonly encountered in similar scenarios have variable and not always predictable effects on anticoagulation

status. In a small study on volunteers, fluconazole inhibited the metabolism of both the S and R enantiomers of warfarin via its effects on CYP2C9 and CYP3A4 respectively.[9]

The anti-epileptics phenytoin and carbamazepine are important enzyme inducers, with potential to reduce the efficacy of the NNRTIs. For this reason it is commonly suggested that valproate may be an appropriate alternative, although it has been reported to exacerbate zidovudine-induced anaemia[10] (perhaps due to impaired zidovudine glucuronidation.)

A further possibility in this patient was differential adherence, such as continuing the same dose of warfarin but stopping or reducing antituberculous medication. On close enquiry she remained adamant that this was not the case.

Conclusions

Polypharmacy is common in AIDS patients, with considerable potential for serious medication interactions. Basic principles of management include:

- Ensure adequate access to details about all the medication the patient may be taking. This may entail a request for all medication at home to be brought in by a relative.
- Try to eliminate all non-essential medication during the often relatively short period that the patient will be on warfarin.
- Remember to watch for the opposite effect when stopping interacting medication in situations where ongoing anticoagulation is desirable. For example, the warfarin dose will usually need to be reduced gradually over the subsequent month after stopping rifampicin, to avoid over-anticoagulation as the induction wears off.
- In patients prescribed warfarin, the frequency of INR monitoring can be estimated from the expected timing and severity of potential interactions, which may occur either days or weeks after starting a new therapy.[11] In the absence of clear information about these, it may be advisable to err on the side of caution and opt for a 'half a week, one week, one week' guide – check the INR 3 or 4 days after the medication change, and again 1 week and then 2 weeks later, assuming no remarkable change on the first measurement. In this patient, life-threatening bleeding might have been avoided by earlier and more frequent INR testing.

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References

1. Israel DS, Stotka J, Rock W, *et al.* Effect of ciprofloxacin on the pharmacokinetics and pharmacodynamics of warfarin. *Clin Infect Dis* 1996; 22: 251-256.
2. Ellis RJ, Mayo MS, Bodensteiner DM. Ciprofloxacin-warfarin coagulopathy: a case series. *Am J Hematol* 2000; 63: 28-31.
3. Glasheen JJ, Fugit RV, Prochazka AV. The risk of overanticoagulation with antibiotic use in outpatients on stable warfarin regimens. *J Gen Intern Med* 2005; 20: 653-656.
4. Niemi M, Backman JT, Fromm MF, *et al.* Pharmacokinetic interactions with rifampicin: clinical relevance. *Clin Pharmacokinet* 2003: 42: 819-850.
5. Self TH, Chrisman CR, Baciewicz AM, *et al.* Isoniazid drug and food interactions. *Am J Med Sci* 1999; 317: 304-311.
6. Von Moltke LL, Greenblatt DJ, Granda BW, *et al.* Inhibition of human cytochrome P450 isoforms by nonnucleoside reverse transcriptase inhibitors. *J Clin Pharmacol* 2001; 41: 85-91.
7. Piscitelli SC, Kelly G, Walker RE, *et al.* A multiple drug interaction study of stavudine with agents for opportunistic infections in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 1999; 43: 647-650.
8. Hirata-Koizumi M, Saito M, Miyake S, *et al.* Adverse events caused by drug interactions involving glucuronoconjugates of zidovudine, valproic acid and lamotrigine, and analysis of how such potential events are discussed in package inserts of Japan, UK and USA. *J Clin Pharm Therapeutics* 2007; 32: 177-185.
9. Black DJ, Kunze KL, Wienkers LC, *et al.* Warfarin-fluconazole II. A metabolically based drug interaction: *in vivo* studies. *Drug Metabol Dispos* 1996; 24: 422-428.
10. Anoniou T, Gough K, Yoong D, *et al.* Severe anaemia secondary to probable drug interaction between zidovudine and valproic acid. *Clin Infect Dis* 2004; 38: e38-40.
11. Harder S, Thurmann P. Clinically important drug interactions with anticoagulants. An update. *Clin Pharmacokinet* 1996; 30(6): 416-444.