

## Adverse drug reaction of the month

# Haemolytic anaemia associated with indinavir

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Treatment for HIV infection is advancing rapidly. Many new drugs are becoming available and the life expectancy of diagnosed HIV patients has improved dramatically since the introduction of combination antiretroviral therapy. Protease inhibitors have been introduced recently; saquinavir, zidovudine, indinavir, and nelfinavir are currently available in the UK, and there are several new compounds entering the late phases of drug development. Their efficacy has been established,<sup>1,2</sup> although less is known about their toxicity, particularly when used long-term. We report a case of severe haemolysis occurring after the initiation of indinavir therapy.

### Case report

A 20-year-old man who was first diagnosed as being HIV positive in 1989 was referred to the Genitourinary Medicine Clinic in February 1994 with fatigue and oral candidiasis. He was treated with fluconazole. His CD4 count at the time was 310 cells/mm<sup>3</sup>. Over the next two years, the CD4 count showed a progressive decrease to below 200 cells/mm<sup>3</sup>. He refused antiretroviral therapy and prophylaxis for opportunistic infections.

In June 1996, the patient was admitted with *Pneumocystis carinii* pneumonia (PCP) and labial herpes simplex which were treated with prednisolone, famciclovir and high-dose intravenous co-trimoxazole. He responded to the treatment and was discharged in July on PCP prophylaxis (co-trimoxazole 960 mg three

times weekly). Antiretroviral therapy was again refused by the patient. The CD4+ count at the time of discharge was 77 cells/mm<sup>3</sup>, and the haemoglobin level ranged from 8.7 to 10.8 g/dl over the next 3 months.

In November 1996, the patient was again admitted to hospital unwell, lethargic and anorexic. He was on oral co-trimoxazole, fluconazole, valaciclovir, and stanozolol. The haemoglobin was 10.7 g/dl (see figure) and CD4+ count was <10 cells/mm<sup>3</sup>. At this time, the patient agreed to start antiretroviral therapy. Zidovudine (AZT; 250 mg bid), lamivudine (3TC; 150 mg bid) and indinavir (800 mg tid) were therefore commenced. This appeared initially to bring about a recovery with CD4+ count increasing up to 74 cells/mm<sup>3</sup>.

In early January 1997, the patient was admitted to another hospital with breathlessness, chest pain and lethargy. His haemoglobin was found to be 2.4 g/dl (see figure). The direct Coomb's test was found to be positive. At this time, the patient was on indinavir, zidovudine, lamivudine, co-trimoxazole, fluconazole, prednisolone, valaciclovir, and stanozolol. He was transfused eight units of blood and later discharged with a haemoglobin of 12.5 g/dl.

Less than 2 weeks after discharge, the patient was re-admitted with jaundice and diarrhoea. The patient had raised total, conjugated and unconjugated bilirubin levels, and a haemoglobin of 10.1 g/dl. The direct Coomb's test was negative. The haemoglobin continued to fall and was 8.9 g/dl 3 days later. The patient was diagnosed as having *Mycobacterium avium intracellulare* infection and was started on clarithromycin (500 mg bid). Because of the anaemia, the AZT was stopped while indinavir and 3TC were continued. He was discharged at the beginning of February, but was re-admitted two weeks later with end-stage AIDS. His haemoglobin had dropped further to 7.6 g/dl. He soon became too ill to tolerate his medications and shortly afterwards he was transferred to a hospice on clarithromycin and co-trimoxazole only. He died a month later.

### Discussion

The treatment of patients with AIDS is becoming increasingly complex and necessitates the use of many different medications to combat the virus, to prevent the myriad of opportunistic infections, and to treat tumours that can occur in these patients. Therefore, when an adverse drug reaction occurs in such a patient, it may be difficult to establish a causal link between the drug and an adverse reaction.

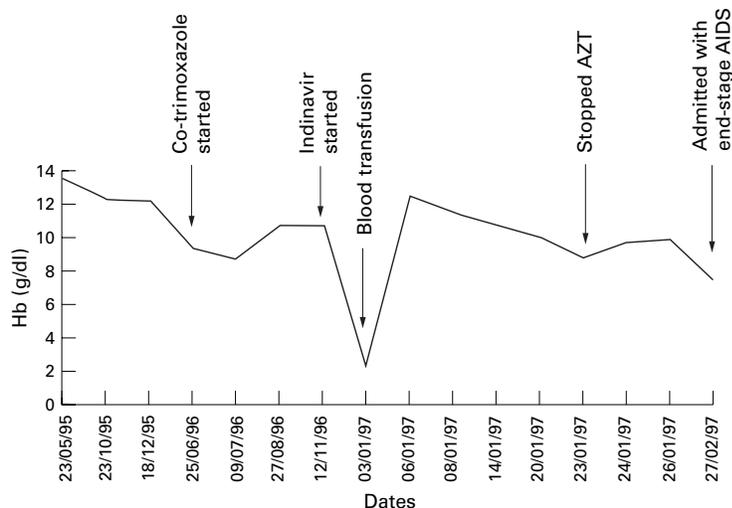


Figure Changes in haemoglobin level in relation to drug therapy

In trying to decide whether a particular drug has caused an adverse reaction, various factors should be evaluated, including the temporal relationship between the start of the drug and onset of the reaction, the type of reaction, effect of drug withdrawal and whether there have been any previous reports of the reaction.

Of the drugs the patient was taking, co-trimoxazole can cause haemolysis, although this usually occurs in patients with glucose-6-phosphate dehydrogenase deficiency. The patient in this case had been taking co-trimoxazole for many months and his haemoglobin had remained stable at around 10 g/dl suggesting that this was not the cause. AZT has been reported to cause chronic anaemia, but not haemolysis.<sup>3</sup> None of the other drugs has been reported to cause haemolysis apart from one report of Coomb's positive haemolytic anaemia with stanazolol on the Medicines Control Agency (MCA)/Committee on Safety of Medicines (CSM) database.

There have been a number of cases of haemolytic anaemia with indinavir reported world-wide but at the time of this patient's death the suspected link was not recognised. In May 1997, a letter was sent by the MCA to doctors working with HIV-infected individuals, warning of the possibility of haemolytic anaemia with indinavir.<sup>4</sup> Indinavir was started 6 weeks prior to the patient's admission to hospital with Coomb's positive haemolytic anaemia (haemoglobin level 2.5 g/dl). The patient was transfused and indinavir was continued because its role was not recognised. The haemoglobin level continued to fall while the patient was on indinavir, the last recorded level being 7.6 g/dl, compared to a level of 12.5 g/dl following transfusion 6 weeks previously. We now consider that indinavir was responsible for the acute episode of haemolysis initially observed in the patient, although we cannot completely exclude other disease-related factors, including lymphoid malignancies and bacterial infections (although none were diagnosed at the time), or indeed HIV infection itself, as causative factors. In the later stages of the disease, the patient was extremely ill, which may have contributed to the slow decrease in the haemoglobin level.

The mechanism of haemolysis associated with indinavir is unknown. It is important to note that mild hyperbilirubinaemia, predominantly an elevation of unconjugated bilirubin, has been reported in 10% of patients (Summary of Product Characteristics), which may partly be indicative of sub-clinical haemolysis. A positive direct Coomb's test in this patient at the time of the haemolysis suggests an immune mechanism. In general, drug-induced immune haemolysis may be due to one of three mechanisms,<sup>5,6</sup> which are not mutually exclusive:

- autoimmune, where the immune response is directed towards a red cell auto-antigen, such as is seen with methyl dopa
- drug adsorption where the drug by acting as a hapten binds to the red cell surface and

### Summary points

- HIV-positive patients are usually on multiple drug therapy which increases the chances of adverse drug reactions and interactions
- antiretroviral compounds are often novel chemical entities whose full toxicology profile is unknown at the time of their marketing. Thus, it is important to report any suspected adverse drug reactions to these compounds; this will help in improving the benefit to risk ratio of these drugs
- HIV-positive patients often have a higher incidence of adverse reactions to drugs such as co-trimoxazole; the reasons for this are unclear
- indinavir, a protease inhibitor, can cause unconjugated hyperbilirubinaemia in 10% of patients, and has also been associated with red blood cell haemolysis

this is recognised as being antigenic; this has been described with penicillin

- immune complex mechanism where the drug binds to an antibody forming an immune complex which subsequently attaches to the red cell surface, resulting in activation of complement and intravascular haemolysis.

In this patient, the direct Coomb's test was positive with both anti-IgG and anti-C3 reagents which suggests that drug adsorption may have been responsible for the haemolysis.<sup>6</sup> Clearly, this would need to be defined by specific laboratory tests, especially since it is known that several mechanisms may be operating in the same patient at the same time.<sup>5,6</sup>

Spontaneous reporting of suspected adverse drug reactions is lower from doctors working in medical specialties than from general practitioners.<sup>7</sup> This is also true of HIV medicine: between July 1996 and July 1997, there were only 91 reports in the UK for all anti-HIV drugs. At the time of reporting, the MCA/CSM had received three reports of indinavir-associated haemolysis from the UK. Many new chemical entities are being developed for treatment of HIV, and at the time of marketing, data on their safety are limited. Taken together with the inherent susceptibility of this patient group, it is important to report any suspected adverse reactions to anti-HIV drugs, despite the difficulties that may be experienced in assigning causality, as exemplified by the patient described in this report. In order to maximise our understanding of drug safety in these patients and to improve reporting, an extension of the Yellow Card Scheme (using blue reporting cards) has recently been launched in the UK by the MCA/CSM in collaboration with the MRC HIV Clinical Trials Centre.<sup>7</sup> Spontaneous reporting schemes form the cornerstone of post-marketing surveillance for all drugs. In the HIV field, the recent description of unexpected adverse effects such as haemolysis with indinavir and diabetes with protease inhibitors highlights the importance that such schemes may have in reducing the morbidity associated with drug treatment.

**Keywords:** haemolytic anaemia; adverse drug reaction; indinavir

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## Images in medicine

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### Multiple left ventricular thrombi in dilated cardiomyopathy

A 57-year-old woman was evaluated for chronic progressive effort intolerance and dyspnoea on exertion. On clinical examination she was found to be in congestive heart failure. Transthoracic echocardiography revealed four-chamber dilation, severe global hypokinesis and severe systolic dysfunction. Three non-pedunculated thrombi of 3.1, 2.5, and 1.8 cm<sup>2</sup> were seen in the apical area of the dilated left ventricle (figure). All the thrombi were of glistening appearance, which suggested that they had been organised.

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**Figure** Transthoracic echocardiogram in apical four-chamber view demonstrating multiple glistening thrombi (T) in the apical area of the dilated left ventricle (LV)

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