Iloprost-induced rash

We report a 59-year-old woman with a background history of CREST syndrome (calcinosis, Raynaud phenomenon, (g)esophageal dysmotility, sclerodactyly and telangiectasia) and secondary pulmonary hypertension who presented with a bilateral lower limb vasculitic rash.

A couple of weeks earlier she had been initiated on nebnilised iloprost (Ventavis; Bayer New Zealand, Auckland, New Zealand) for progression of her pulmonary hypertension while on treatment with Sildenafil. She started on 20 µg three times a day, increasing every 3 days to a total of 20 µg every 4 h. Within a few days of reaching the maximum dose she developed a painful vasculitic rash over both lower limbs, which did not respond to analgesia and emollients (see fig 1). The dose of iloprost was reduced slowly over a couple of weeks to 15 µg three times a day. During this time, the rash improved considerably.

Unfortunately, she continued to deteriorate and was admitted to hospital profoundly hypoxic. Oxygen therapy and diuretics were increased with minimal effect. The decision was made to re-challenge with an increased dose of iloprost, hoping that dual therapy with appropriate dosing may ameliorate her pulmonary hypertension.

After only two doses at 20 µg, the rash recurred dramatically and became intolerable. On reducing the iloprost dose to 15 µg, the rash again improved. She was discharged home with assistance from palliative care and died a week later.

Iloprost is a stable analogue of prostacyclin which is synthesised in the vascular endothelium, and it shows a pharmacological profile similar to that of endogenous prostanol. Its vasodilating effects are used clinically to treat moderate to severe pulmonary hypertension. Various side effects of iloprost have been reported, including flushing, dizziness, cough, headache, spasm of the jaw muscles, back pain, vomiting and diarrhoea.

Bleeding events were common in clinical trials, especially in patients also taking anticoagulants. Iloprost is known to interfere with platelet aggregation; however, this effect is more common and more pronounced with intravenous use. Of note, our patient did not develop thrombocytopenia.

Cutaneous drug reactions are common, with an incidence of 2–5% in hospital patients. Almost any drug can cause rash; most common are antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs). Drug-induced small vessel vasculitis (or hypersensitivity vasculitis) is rarer. This is generally limited to the skin, but can occur as an element of a systemic illness. The rash is purpuric, palpable and occurs in dependent areas. Biopsies show a cellular infiltrate of small vessels often with leukocytoclasia. The most common causes are drugs and infection.

Adverse drug reactions can be difficult to diagnose, and scoring systems may help. In our patient the vasculitic rash appeared after initiation of iloprost and improved when the dose was reduced. More importantly, it deteriorated with a repeat drug challenge. This gives a high probability of a drug reaction. In a different clinical scenario, cessation of the drug may well result in complete resolution of the rash.

To our knowledge, this is the first reported case of iloprost-induced vasculitic rash. The precise mechanism and frequency are unknown. Clinicians should be aware of this potential adverse effect, and the drug should be reduced or stopped if possible.

M Wildman, C Sanderson
Respiratory Medicine Department, Northern General Hospital, Sheffield, UK

Correspondence to: Dr M Wildman, Respiratory Medicine Department, Northern General Hospital, Herries Road, Sheffield S5 7AU, UK; martin.wildman@sth.nhs.uk

Competing interests: None.

Provenance and peer review: Not commissioned; not externally peer reviewed.

Accepted 25 June 2009


Figure 1 Iloprost-induced vasculitic rash.
Hepatotoxicity and antituberculosis therapy: time to revise UK guidance?

Hepatotoxicity associated with antituberculosis therapy is an important clinical problem. Guidelines recommend baseline liver function tests (LFTs) before commencing treatment. In patients with risk factors for hepatotoxicity (e.g., chronic viral hepatitis or liver disease, pregnancy or significant alcohol history) or abnormal baseline LFTs, further monitoring is indicated whilst on treatment. In all other cases repeat liver function testing is reserved for patients developing symptoms suggestive of liver dysfunction (fever, malaise, nausea, vomiting, abdominal pain, jaundice or unexplained fatigue). HIV coinfection is not specifically mentioned within UK guidance. Given increasing national rates of tuberculosis/HIV, we assessed how this might impact upon current guidelines.

A retrospective case-note review was undertaken of patients treated for active tuberculosis over a year (1 June 2006–31 May 2007) at our central London hospital. Hepatotoxicity was defined as elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than three times the upper limit of normal (>3ULN).

A total of 103 patients started antituberculosis treatment; 55 were male. The median age was 43 years, with two patients under the age of 16 (range 0–82 years). The population was ethnically diverse: 24 Asian, 46 Black African, 22 European, 11 other. Seventy-nine percent of patients were tested for hepatitis B (9% were positive), 77% for hepatitis C (9% were positive), 5% were pregnant, 5% had a significant alcohol history and 2% had other chronic liver diseases.

The minimum prevalence of HIV co-infection was 23%; 19 patients were known to be HIV positive at baseline. A further 60/84 (71%) had HIV tests; and five patients were new HIV diagnoses.

Seven patients (four of whom were HIV co-infected) with ALT/AST >3ULN at baseline and two patients with no LFTs performed were excluded from analysis. In the remaining 94 subjects, the incidence of hepatotoxicity was 15% (14/94). Of these 57% (8/14) had symptoms consistent with hepatotoxicity, indicating the need for LFT testing; however, 21% (3/14) were asymptomatic. For the remainder, data on symptoms was not clearly available. Ten percent (9/94) developed ALT/AST >3ULN (here, 67% of patients were symptomatic; 11% asymptomatic, 22% symptom data not available). The median time to first abnormal and highest ALT/AST was 6.5 days (range 2–18 days) and 29.5 days (range 7–176 days), respectively. There was a significant difference in hepatotoxicity between HIV-positive and HIV-negative populations: 7/20 (35%) vs 4/55 (7%), respectively (p = 0.006, Fisher’s exact test). Concurrent use of antiretroviral therapy did not increase the risk in the former (p = 0.11, Fisher’s exact test) (fig I).

In 51 patients with normal baseline LFTs and no risk factors for hepatotoxicity, the incidence of hepatotoxicity was 10% (5/51). When HIV-positive individuals were excluded, this fell to 2% (1/44). Furthermore, all three subjects who were asymptomatic at the time of their rise in ALT/AST were HIV co-infected.

In conclusion, most cases of hepatotoxicity continue to be identified by current guidelines, although HIV co-infection does appear to impact upon both the incidence of hepatotoxicity and the use of the recommended algorithm (where LFT monitoring on treatment is indicated according to symptoms). The 1998 British Thoracic Society guidance implies that testing for viral hepatitis should be undertaken at tuberculosis diagnosis. Our results suggest that routine HIV testing would identify patients not only requiring treatment for HIV but also at risk of hepatotoxicity. Although a small sample size, we believe our findings will be reproducible in other tuberculosis populations, and that this strengthens the argument for HIV testing to be offered universally in this setting; an approach which avoids “risk assessment” for HIV, which in itself can generate anxiety and stigma.

Figure 1 Tuberculosis/HIV co-infected patients (with normal baseline liver function tests). Comparison of antiretroviral (ARV) use in hepatotoxic and non-hepatotoxic populations.

REFERENCES


HIV, which in itself can generate anxiety and stigma.

N F Walker,1 M Kliner,1 D Turner,2 S Bhagani,2 I Cropley,2 S Hopkins,4 M Lipman2
1Department of HIV, Royal Free Hospital, London, UK; 2Department of Infectious Diseases, Royal Free Hospital, London, UK; 3Department of Respiratory Medicine, Royal Free Hospital, London, UK

Correspondence to: Dr N Walker, Department of Clinical Infectious Diseases, Imperial College, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK; nwalker@doctors.org.uk

Competing interests: None.

Provenance and peer review: Not commissioned; not externally peer reviewed.
Accepted 3 June 2009

Thorax 2009; 64:918. doi:10.1136/thx.2009.115469

REFERENCES