Late-onset drug fever associated with minocycline

D.A. Gorard

Queen Mary's Hospital, London SW15 5PN, UK.

Summary: A patient presenting with a pyrexial illness and transiently deranged liver function tests is described. He had been taking minocycline for 12 months. The causal association with this drug was demonstrated by withholding and then rechallenging with minocycline. This report documents drug fever as an adverse reaction to minocycline, and its late onset is of added interest.

Introduction

I report a case of pyrexia, malaise, myalgia and altered liver function tests occurring in a patient who had been taking long-term minocycline. The patient's symptoms resolved on cessation of the drug, and returned on rechallenging with minocycline.

Case report

A 37 year old banker presented with a 6-week history of an influenza-like illness associated with malaise, aching of his calves and excessive nocturnal perspiration requiring changes of bed-linen. Taking his temperature at home, he noted a rise to 38–39°C during most evenings. There was no past medical history of note except acne, for which he had been taking minocycline 50 mg once daily for 12 months. He was on no other medications.

Complete physical examination, repeated on several occasions, was unremarkable. The only abnormality was torrential perspiration at night with a simultaneous temperature rise up to 39°C confirmed during hospital admission.

Investigations revealed a haemoglobin of 14.5 g/dl, white cell count of 6.6×10^9 /litre (normal differential), platelet count of 301×10^9 /litre and ESR of 4 mm/hour. Chest radiograph was normal. Urine microscopy was normal; cultures of urine, stool and throat swab were sterile. Repeated blood cultures and blood films, often taken at the height of pyrexia were unremarkable. Glandular fever screen was negative. Paired viral antibody titres

excluded recent infection with influenza A, B, mycoplasma, psittacosis, *Coxiella burnetti*. Serum biochemistry revealed abnormal liver function tests – aspartate transaminase (AST) 165 U/litre (reference range <35), alkaline phosphatase 196 U/litre (reference range <150). Bilirubin and albumin were normal. Creatine kinase and lactate dehydrogenase levels were normal. Hepatitis B surface antigen was negative, Hepatitis A IgG antibody was positive but IgM antibody was negative. Autoantibody screen was negative apart from positive smooth muscle antibodies. Abdominal ultrasonography was completely normal. Liver biopsy was histologically normal and subsequent culture sterile.

Other investigations that failed to help in the diagnosis of this patient's spiking pyrexia of unknown origin included normal bone marrow biopsy and culture, normal intravenous urography, a negative Mantoux test and negative *Treponema pallidum* haemagglutination test.

Over the following weeks during which his symptoms and pyrexia persisted, the patient's liver function tests were monitored. A progressive fall in the activity of AST and alkaline phosphatase was observed so that liver function tests were completely normal at 3 months. Nevertheless his nocturnal pyrexias persisted and there was no improvement in his symptoms which now included arthralgia.

Four months after initial presentation he was asked to stop his minocycline therapy – prior to this he had only briefly discontinued the drug at times of blood culture. Eight days after discontinuing the minocycline he reported a resolution of his symptoms and no further nocturnal pyrexias. One month later he was rechallenged with minocycline and within 72 hours his symptoms and nocturnal pyrexias began to occur. He consequently stopped the drug again and has remained well.

Correspondence: D.A. Gorard M.B., M.R.C.P. (UK), Department of Gastroenterology, Central Middlesex Hospital, London NW10 7NS, UK.
Accepted: 23 November 1989

Discussion

Minocycline is used for a variety of skin disorders and is often prescribed for long term use in acne. Side effects are rare but include nausea, vertigo and a variety of dermatological reactions. In 1984, Burette *et al.* reported a case of hepatotoxicity associated with minocycline.¹ Two patients have recently been described with exfoliative dermatitis and deteriorating liver function tests whilst taking minocycline² – one patient developed hepatic failure and died. Hepatic injury associated with minocycline is otherwise not as well recognized as that associated with its parent drug tetracycline.^{3,4} In this patient on minocycline, derangement of liver function tests was observed in the absence of histological abnormality on liver biopsy or serological markers of recent viral infection.

The predominant features in this patient's illness were nocturnal pyrexia and perspiration – a careful search for infection was unrewarding. There has previously been one other report⁵ in which an influenza-like syndrome occurred shortly after beginning minocycline treatment, but possible coincident simultaneous infection was not inves-

tigated.

Recognized side effects of tetracycline compounds are numerous,⁶ and include gastrointestinal disturbances, photosensitivity reactions, pigmentation of teeth and other tissues, hepatotoxicity (as above) and nephrotoxicity. However, drug fever due to tetracycline compounds has not been previously described. This present report is the first well documented case of drug fever induced by minocycline.

In this case I have reported, a drug reaction as a cause of pyrexia of unknown origin was initially overlooked since the patient had been taking minocycline for 12 months prior to the onset of his illness. Although pyrexia due to drug sensitivity has been described with a variety of drugs,⁷ the onset of fever is usually early, within days/weeks of starting the offending drug.

As well as illustrating a rare adverse reaction to minocycline, this case emphasizes the need for clinicians to consider drugs as a cause of obscure pyrexia. Drugs that a patient may have taken for a considerable time, without apparent side effect, should not be overlooked.

References

1. Burette, A., Finet, C., Prigogine, T., De Roy, G. & Deltenre, M. Acute hepatic injury associated with minocycline. *Arch Intern Med* 1984, **144**: 1491–1492.
2. Davies, M.G. & Kersey, P.J.W. Acute hepatitis and exfoliative dermatitis associated with minocycline. *Br Med J* 1989, **298**: 1523–1524.
3. Schultz, J.C., Adamson, J.S., Workman, W.W. & Norman, T.D. Fatal liver disease after intravenous administration of tetracycline in high dosage. *N Engl J Med* 1963, **269**: 999–1004.
4. Peters, R.L., Edmondson, H.A., Mikkelsen, W.P. & Tatter, D. Tetracycline-induced fatty liver in nonpregnant patients – a report of six cases. *Am J Surg* 1969, **113**: 622–632.
5. Rosin, M.A. Viral-like syndrome associated with minocycline. *Arch Dermatol* 1984, **120**: 575.
6. Kucers, A. & Bennett, N.McK. *The Use of Antibiotics: a Comprehensive Review with Clinical Emphasis*, 4th edn. William Heinemann Medical Books, London, 1987, pp. 1002–1013.
7. Townsend, Y. & Cranston, W.I. Disorders of temperature regulation. In: Davies, D.M. (ed) *Textbook of Adverse Drug Reactions*, 2nd edn. Oxford University Press, Oxford, 1981, pp. 597–601.