demonstrating its superiority. At a time when health authorities around the country are "having regard to" the views of winners and losers as they rationalise acute services and close hospitals, it is a judgment which bodes ill for those who choose to go to law over the adequacy of public consultation. It is, if nothing else, a judgment well fitted to radical change.

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Minocycline induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome

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Monocycline is the most widely prescribed systemic antibiotic for acne largely because it needs to be given only once or twice a day and seems not to induce resistance. Up to April 1994 11 cases of minocycline induced systemic lupus erythematosus and 16 cases of hepatitis had been reported to the Committee on Safety of Medicines. An analysis of these cases together with seven other cases shows the severity of some of these reactions. Two patients died while taking the drug for acne and a further patient needed a liver transplant. Acne itself can induce arthritis and is often seen in association with autoimmine liver disease, but the clinical and biochemical resolution seen after withdrawal of the drug, despite deterioration of the acne, suggests a drug reaction. In five cases re-exposure led to recurrence. Because reactions may be severe early recognition is important to aid recovery and also to avoid invasive investigations and treatments such as corticosteroids and immunosuppresants. Safer alternatives should be considered for treating acne.

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Minocycline is a semisynthetic tetracycline antibiotic with a broad spectrum of activity, which first became widely available in 1972.[1] Because it is more lipid soluble than the older tetracyclines an oral dose is almost completely absorbed and it has excellent sebum penetration. Its long half life, allowing once or twice daily dosing, makes it popular with both patients and doctors. Indeed, minocycline is now the most widely prescribed systemic antibiotic for acne,[2] and the only one to which drug resistance has not yet been described.[3] In 1993 there were 63 998 prescriptions for minocycline in the West Midlands region alone at a cost of £1·7m, reflecting the broad usage of this drug.

Until April 1994 there had been 11 reports to the Committee on Safety of Medicines suggesting drug induced systemic lupus erythematosus and 16 reports of hepatitis associated with the use of minocycline. In this paper we review these data and report on seven cases that show the clinical presentation and potential severity of these adverse reactions.

Subjects, methods, and results

The early inflammatory arthritis clinic at Selly Oak Hospital was set up in 1990 to identify, document, and follow up cases of inflammatory arthritis of recent onset. During the first three years two young women taking minocycline presented with a symmetrical polyarthritis affecting the small joints of the hands and wrists, and another presented with polyarthralgia of the same distribution (see table 1, cases 1-3). The clinical appearance suggested early rheumatoid arthritis or systemic lupus erythematosus. All three patients were strongly positive for antinuclear antibodies and had been taking minocycline for acne for two months to two years. One patient (case 3) had presented two years previously with a fever of unknown origin and similar polyarthralgia. She had started minocycline six weeks before this presentation and had subsequently discontinued it until two months before her second presentation. Withdrawal of the drug led to rapid resolution of symptoms on both occasions. This index case led to the suspicion that minocycline might be implicated, as all three patients had similar presentations and were positive for antinuclear antibody (but not for antibodies to DNA or to extractable nuclear antigens), and all symptoms resolved quickly on withdrawal of this drug.

At presentation another patient (case 1) was found to have hepatitis with a serum aspartate transaminase concentration of 385 IU/l. Viral hepatitis and liver autoantibody screens gave negative results. A liver biopsy confirmed chronic active hepatitis. The hepatitis resolved completely after minocycline was stopped. Furthermore, on review of the notes, the index patient was also noted to have had raised aspartate aminotransferase concentration of 98 IU/l at her first presentation. Again no cause was found, and these tests returned rapidly to normal after discontinuation of minocycline.

Having determined that minocycline could cause an autoimmune drug reaction leading to hepatitis, we looked for further cases prospectively in 1993 and found four more (table 1, cases 4-7). Three of these (cases 5, 6, and 7) were again young women taking minocycline who developed severe hepatitis and were positive for antinuclear antibody. The fourth (case 4) was a 37 year old man who had also been taking long term minocycline for acne. He initially became jaundiced in February 1993. He did not present to his doctor at this stage, but five months later, after the jaundice resolved, he became unwell again. He had severe hepatitis with an aspartate aminotransferase concentration of 2320 IU/l, with a strongly positive antinuclear antibody titre. Although he was still taking his minocycline at this stage, we do not know whether he took it continuously throughout. Cases 5 and 7 presented with jaundice and all three women experienced profound malaise and polyarthralgia in addition to their hepatitis. In all, liver biopsies showed moderately severe changes of acute or chronic active hepatitis. Apart from antinuclear antibody, hepatitis viral screens and other autoantibody tests gave negative results. All seven patients' symptoms and laboratory investigations returned to normal within three months of their discontinuing minocycline. Although their acne deteriorated, all seven have had no recurrence of symptoms or biochemical abnormalities to date, emphasising that these reactions were likely to be drug related.

Table 1—*Patients' presentation and outcome and laboratory details*

	Case 1	Case 2	Case 3		Case 4	Case 5	Case 6	Case 7
			1st presentation	2nd presentation				
Sex	F	F	F		M	F	F	F
Age	26	19	23	25	36	16	16	20
Dose and duration of minocycline	50 mg twice daily 2 years	50 mg twice daily 6 months	50 mg twice daily 6 weeks	50 mg twice daily 3 months	50 mg twice daily 2 years	50 mg twice daily 2 years	50 mg twice daily 2 years	100 mg twice daily 8 months
Presentation	Symmetrical polyarthritis, hepatitis	Symmetrical polyarthritis	Fever of unknown origin, polyarthralgia, hepatitis	Symmetrical polyarthralgia, malaise	Polyarthralgia, jaundice, rash	Symmetrical polyarthritis, hepatitis	Malaise, jaundice	Symmetrical polyarthritis, rash, fever jaundice
Outcome on withdrawal	Resolved <3/12	Resolved <3/12	Resolved <1/12	Resolved <1/12	Resolved <3/12 (with prednisolone course)	Resolved <3/12	Resolved <3/12	Resolved <3/12
Haemoglobin (g/l)	119	133	115	127	150	140	122	155
White cell count ($\times 10^9$/l)	7·6	7·6	6·4	Lymphopaenia	6·4	5·0	10·8	5·6
Aspartate transaminase (<40 U/l)	385	45	98	29	2294	684	915	>1200
Alkaline phosphatase (× upper limit of normal)	0·5	0·7	0·8	0·5	2	0·4	1	1
Bilirubin (<17 μmol/l)	10	6	6	6	334	9	170	186
Globulins (g/l)	47 (diff)	37	51 (diff)	35	40 (diff)	Globulins raised	43 (diff)	33
Erythrocyte sedimentation rate (mm in the first hour)	61	34	103	29	Not done	11	Not done	50
C reactive protein (<10 mg/l)	8	18	64	6	Not done	Not done	Not done	Not done
Nuclear antibodies	1/1600	1/100	Not done	1/1600	1/1600	1/80	1/640	1/400
Extractable nuclear antigens	Negative	Normal	Not done	Negative	Negative	Not done	Not done	Not done
DNA antibodies	Negative	Weak positive	Not done	Negative	Negative	Not done	Not done	Weak positive
Smooth muscle antibodies	Negative	Negative	Not done	Negative	Negative	Negative	Negative	
Mitochondrial antibodies	Negative	Negative	Not done	Negative	Negative	Negative	Negative	Negative
Lower kidney mitochondrial antibodies	Negative	Negative	Not done	Negative	Negative	Negative	Negative	Negative
Hepatitis A, B, C screen	Negative	Not done	Negative	Not done	Negative	Negative	Negative	Negative
Biopsy	Chronic active hepatitis	Not done	Not done	Not done	Acute hepatitis with confluent necrosis	Chronic active hepatitis with bridging and piecemeal necrosis	Chronic active hepatitis	Not done

We requested data from the Committee on Safety of Medicines regarding all minocycline reactions reported in the United Kingdom until April 1994. Table 2 summarises the available data on 11 cases of systemic lupus erythematosus and 16 cases of hepatitis. There is similarity between the cases we described and those reported to the Committee on Safety of Medicines, particularly the spontaneous recovery seen on drug withdrawal and the recurrence of symptoms on rechallenge. Nevertheless, two people died while taking this drug for acne—one after severe hepatitis and coma, and one from pancytopenia.

Discussion

The first report suggesting that systemic lupus erythematosus was exacerbated by tetracyclines was in 1959.[4] This report of three cases suggested that tetracyclines might exacerbate pre-existing systemic lupus erythematosus rather than induce it. However, there are now 11 suspected cases of minocycline induced systemic lupus erythematosus. One report described a 22 year old Japanese woman who had taken 100-150 mg minocycline daily for two years.[5] She presented with a symmetrical small joint polyarthritis, fever, malaise, cough, and pulmonary infiltrates. Antinuclear antibody was present in a diffuse pattern and DNA antibodies were not detected. She recovered one month after stopping the drug. Furthermore, this is not the only report of pulmonary infiltrates associated with minocycline.[6] There are also other cases suggesting a more allergic type reaction with fever, lymphadenopathy, and eosinophilia.[7-9] In one of these cases, rechallenging the patient led to a rapid recurrence of symptoms, with complete resolution on withdrawal of the drug.[8] A recent report of five cases of drug induced systemic lupus erythematosus with minocycline adds further weight to this evidence that minocycline can induce autoimmune disease.[10]

The ability of tetracyclines to cause liver disease became apparent soon after their introduction.[11] Early reports described fatal microvesicular fatty liver degeneration occurring in pregnant women given high doses of tetracycline intravenously.[12] However, similar reactions were soon reported in non-pregnant women[13] and men.[14] The first report of this type of liver injury with minocycline again followed high dosages given intravenously.[15] Liver transplantation after giving minocycline to a 17 year old girl has now been described.[16] This cumulative evidence suggests a direct, dose related, hepatotoxic effect common to all tetracyclines. Part of this direct hepatotoxic effect may be due to metabolites of minocycline, as has been shown in animals.[17] Although the principal metabolites of minocycline have been reported,[18] the complete details of its breakdown may still be unknown.[19]

A second form of fulminant hepatitis with minocycline can occur as part of an allergic, idiosyncratic reaction.[20] A 39 year old woman developed fever, malaise, lymphadenopathy, and eosinophilia four weeks after starting oral minocycline. She subsequently developed severe hepatitis with stage II hepatic encephalopathy before making a full recovery after minocycline was withdrawn.[20] No other cause was identified, although no immunological tests were reported. In another similar case a 17 year old woman developed a fatal hepatitis after a one month course of minocycline.[9] Again there were allergic features with rapid onset, fever, and eosinophilia. In this case exfoliative dermatitis and a streptococcal infection were additional complicating factors. However, liver failure was thought to be the cause of death, which occurred despite liver transplantation.

The cases we have identified with liver disease may represent a third type of hepatic injury. All these patients had chronic active hepatitis on biopsy, with no fatty change, eosinophilia, or allergic features. All occurred after prolonged oral treatment, had polyarthralgia or polyarthritis as a presenting feature, and were positive for antinuclear antibodies. This autoimmune type reaction has not previously been described. The four most recent cases all had severe hepatitis, requiring hospital admission, and may represent the more severe end of a spectrum. They were tertiary referrals from centres that had been unable to identify the underlying cause of these

patients' hepatitis. Minocycline may be responsible for a number of such cases, particularly among younger women, owing to their increased exposure to this drug. The incidence of abnormal liver function results on this drug has not been established prospectively. However, in a small study of the use of minocycline in rheumatoid arthritis two of the 30 cases developed an unexplained hepatitis which resolved on withdrawal of treatment (M Farr, personal communication).

Half the patients with autoimmune chronic active hepatitis present in their second decade and three quarters are women. Eighty per cent demonstrate antinuclear antibodies of homogeneous (diffuse) type and in 70% anti-actin smooth muscle antibodies are found. A high serum γ globulin concentration is characteristic. Given this profile of classical autoimmune chronic active hepatitis it would be easy to have categorised the hepatic illness in each of our patients as autoimmune chronic active hepatitis (six of our seven patients were women aged 16-26 years). Spontaneous and rapid resolution of liver function test abnormalities is, however, most uncommon in autoimmune chronic active hepatitis. Most patients require long term treatment with prednisolone or azathioprine and have a 50% chance of relapse on stopping treatment. One of our patients was treated with steroids and made a dramatic recovery, but in the other cases rapid resolution followed discontinuation of minocycline alone. Patients should, however, be followed for at least a year after normalisation of their tests to exclude autoimmune chronic active hepatitis.[21] Another form of autoimmune chronic active hepatitis is associated with liver kidney microsomal antibodies. These antibodies are targeted against P450 enzymes. In some of those patients a precipitating drug was recognised, and the hepatitis resolved on removal of the responsible agent (tienylic acid). However, in most forms of autoimmune chronic active hepatitis associated with

Table 2—*Reports of minocycline induced systemic lupus erythematosus-like syndromes and hepatitis (data from the Committee of Safety on Medicines)*

Case No	Sex	Age	Year	Dose	Reaction	Outcome
Systemic lupus erythematosus-like syndromes						
8	Data unknown	Data unknown	1986	100 mg daily	Rash, arthritis, hepatitis, antinuclear antibody	Recovered on drug withdrawal
9	M	26	1986	50 mg twice daily >7 months	Arthritis, antinuclear antibody	Recovered on drug withdrawal. Rechallenge led to recurrence with antinuclear antibody positive, deoxyribonucleic acid antibody negative
10	F	Data unknown	Data unknown	50 mg twice daily >2 years	Systemic lupus erythematosus	Unknown
11	F	22	1989	50 mg daily 5/12	Flare of known systemic lupus erythematosus	Unknown
12	F	20	1990	50 mg twice daily 3 years	Arthritis, systemic lupus erythematosus	Recovered on drug withdrawal
13	F	17	1990	50 mg daily 4 years	Disabling arthritis, myalgia, antinuclear antibody 1/3200, deoxyribonucleic acid antibody/extractable nuclear antibody/antinuclear antibody negative	Recovered on drug withdrawal (had been chair bound)
14	F	15	1991	50 mg twice daily 3/12	Systemic lupus erythematosus	Initially unable to hold a cup. Given corticosteroids. Outcome unknown
15	F	28	1991	50 mg twice daily 6 years	Disabling arthritis, myalgia, fever, antinuclear antibody 1/400, erythrocyte sedimentation rate 25 mm in 1 h, anticardiolipin antibody positive, smooth muscle antibody	Recovered on drug withdrawal. Antinuclear antibody remained 1/400
16	F	18	1992	50 mg twice daily 2 years	Arthralgia, erythrocyte sedimentation rate 29 mm in 1 h, antinuclear antibody 1/20	Recovered on drug withdrawal. Recurred on challenge and settled again. Deoxyribonucleic acid antibody negative
17	F	17	1992	50 mg twice daily 22 months	Arthralgia, antinuclear antibody 1/6400, erythrocyte sedimentation rate 23 mm in 1 h, anticardiolipin antibody, extractable nuclear antibody/ deoxyribonucleic acid antibody negative	Recovered with two weeks of drug withdrawal. Antinuclear antibody remains weakly positive, antinuclear antibody negative. Patient remains well
Autoimmune hepatitis						
18	M	39	1984	100 mg daily 10 days	Hepatitis	Recovered on drug withdrawal
19	F	Data unknown	1985	100 mg daily 3 years	Hepatitis	Also on oral contraceptive pill. Recovered on drug withdrawal
20	F	Data unknown	1985	100 mg daily 29 months	Hepatitis	Also on oral contraceptive pill. Recovered on withdrawal of drugs
21	F	39	1988	200 mg daily 1/12	Hepatitis, dizziness, taste change, headache	Unknown
22	F	Data unknown	1989	50 mg twice daily	Exfoliative dermatitis, fever, anaemia, hepatitis	Hepatic cause led to death. Had also recently taken proguanil, chloroquine, "tanning" tablets, and recent immunisations (cholera, typhoid, yellow fever)
23	M	17	1990	100 mg daily 3/12	Hepatitis	Recovered on drug withdrawal
24	M	18	1990	100 mg daily 1/12	Hepatitis, jaundice (infection screen negative)	Also on cephalexin. Rechallenge with minocycline led to recurrence of jaundice
25	M	22	1990	50 mg twice daily 28 months	Hepatitis	Recovered on drug withdrawal
26	F	22	1990	50 mg twice daily 5/12	Hepatitis, pancytopenia	Death as a consequence of pancytopenia
27	M	18	1991	100 mg daily 7/12	Hepatitis	Recovered on drug withdrawal
28	M	22	Data unknown	50 mg twice daily	Hepatitis (infection screen negative)	Recovered on drug withdrawal
29	M	20	1992	50 mg twice daily 1 year	Hepatitis, arthritis (infection screen negative)	Brufen, naproxen, sulphasalazine, temazepam used to treat arthritis, which then completely resolved on minocycline withdrawal
30	Data unknown	Data unknown	1992	6 g overdose	Erythroderma, hepatitis, renal impairment	Unknown
31	M	73	1992	50 mg daily 9 days	Hepatitis	Had also taken paracetamol and (much earlier) metoclopramide and astemizole
32	M	23	Data unknown	50 mg twice daily intermittent	Prolonged jaundice (maximum bilirubin 830), hepatitis nuclear antibody and infection screen negative, smooth muscle antibodies positive. Caeruloplasmin normal	Recovered on drug withdrawal
33	F	23	1993	100 mg daily 9/12	Acute hepatitis	Also on oral contraceptive pill. Recovered on drug withdrawal

liver kidney microsomal antibodies no causative xenobiotic has been recognised.

Acne itself could explain our findings, as it can induce arthritis,[22] and is often seen in association with autoimmune liver disease. However, the clinical and biochemical resolution after withdrawal of the drug, despite deterioration of the acne, weighs against this. Furthermore, in two of our cases, and in three of the Committee on Safety of Medicines reports, re-exposure to minocycline led to recurrence. If this does represent a drug induced systemic lupus erythematosus-like syndrome the finding of antinuclear antibodies with no antibodies to DNA is expected.[23] There have been reports of antibodies to histones being associated with drug induced systemic lupus erythematosus, but we were unable to show these in our first three cases (R Thomson, personal communication). The finding of two case reports from the Committee on Safety of Medicines of positive anticardiolipin antibodies is of interest. No clinically relevant sequelae to these antibodies were reported and both became negative at follow up.

Minocycline is understandably popular with general practitioners as compliance is likely to be better with a once or twice daily regimen. In 1993 there were 63 998 prescriptions for minocycline in the West Midlands region at a cost of £1·7m. The national figures for the same period were over 800 000 prescriptions at a cost of nearly £23·3m. This represents a considerable portion of the NHS drug budget, particularly because it is a relatively expensive drug compared with other treatments for acne. A cost-benefit analysis of its use would be appropriate.

By reporting these cases we hope to raise awareness of this type of drug reaction with minocycline, particularly among general practitioners, dermatologists, rheumatologists, and gastroenterologists. Reactions can be severe, so their recognition at an early stage may be important not only to aid recovery but also to avoid invasive investigations such as liver biopsy and treatments such as corticosteroids and immunosuppressants. In view of the severity of some reactions, including two deaths and one liver transplant, the use of minocycline for acne should be considered carefully. Monitoring of liver function tests may be necessary, although the true incidence of these autoimmune reactions to minocycline remains unknown and merits further study. Should routine monitoring of liver function tests be necessary, this would make the use of minocycline prohibitively expensive and inconvenient for patients. Safer and less expensive alternatives might therefore be more appropriate.

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A MEMORABLE PATIENT

My first successful resuscitation or a great Dane

In 1965 I was a senior registrar in anaesthesia and was seconded to the old Rigshospitalet in Copenhagen for three months. This hospital had seemingly endless corridors and one day I was the designated resuscitation anaesthetist and so I had the resuscitation scooter, complete with rack for resuscitation equipment and a large bicycle bell. I was suddenly summoned to one of the medical wards for a patient who had had a cardiac arrest. I scooted off down the corridors, frantically ringing my bell. On arrival I found an elderly man on the floor by his bed with some nurses giving external cardiac compression and artificial ventilation using an Ambu bag—and this was 1965.

The patient was clearly conscious and considerably distressed during these effective resuscitation measures. Having just read of some recent research on cerebral protection using sodium amytal in mice and seeing that sedation was clearly required, sodium amytal was duly administered. Unconsciousness supervened and the patient was intubated and transferred to the intensive care unit. There ventricular fibrillation was diagnosed and the patient was defibrillated. Sinus rhythm was restored but ventricular fibrillation returned. Defibrillation, followed by further fibrillation took place on seven successive occasions but eventually he remained in sinus rhythm. Over the next few days he steadily improved and soon returned to his ward.

I visited him frequently and, since he spoke no English, I had to find a nurse to interpret. This went on for over a month, at the end of which I had to return to Britain. I made a farewell visit. After I had said goodbye the patient thanked me for looking after him in immaculate English. I gently chided him for not having told me that he spoke English. He replied that he had spoken fluent English for all his adult life but that after he regained consciousness he could not remember a single word. His command of the language had, however, returned swiftly and completely over the past few days. Does the ability to speak a language other than your mother tongue reside in the highest level of the neocortex, which is presumably the last to recover from a hypoxic insult? I have never had the opportunity to test this hypothesis.—JOHN ZORAB *is a consultant anaesthetist in Bristol*