

Thorax

Editorials

Hepatotoxicity of antituberculosis drugs

Her Majesty's Coroner for Birmingham, where there is a major liver unit, has drawn attention to the number of deaths from liver failure associated with the antituberculosis drugs,¹ and has called for greater awareness by both patients and general practitioners of the occasional cases of hepatotoxicity. This was followed by a reminder from the Committee on Safety of Medicine (CSM) of fatal hepatic reactions.² The CSM advice was that liver function tests should be undertaken before treatment and, if abnormal, repeated during treatment, and that liver function should be checked in patients who develop symptoms or signs suggestive of hepatitis, or who become generally unwell during treatment. This advice differs from that given by the Joint Tuberculosis Committee's chemotherapy guidelines³ which state:

"Liver function should be checked pretreatment. Transient increases in hepatic transaminases are common after the start of treatment and require no action unless the patient has symptoms of hepatitis or jaundice. After the initial measurement liver function does not need to be monitored routinely except in alcoholics and those with other liver diseases. If jaundice or other symptoms of hepatitis develop all drugs must be stopped. It is usually possible to restart all drugs after liver function returns to pretreatment levels. If symptoms recur, however, the drugs should be introduced individually, once liver function has returned to normal, at a lower dose initially together with at least one drug which is unlikely to cause hepatic dysfunction (streptomycin or ethambutol)."

The data sheets for the individual and combined first line antituberculosis drugs give somewhat ambiguous advice on management where there is pre-existing liver disease or where abnormalities develop during treatment. Advice when given does not always conform to that of the CSM.² We shall review the evidence on hepatic reactions, their number and incidence, and make explicit recommendations.

In the United Kingdom since 1964 the CSM has received a total of 243 reports of hepatic drug reactions associated with isoniazid, rifampicin, pyrazinamide, and ethambutol, 45 of which were fatal (table). Whilst it is likely that all fatal reactions are reported, those which are non-fatal are almost certainly greatly underreported.⁴ When considering fatal drug reactions it should be borne in mind that pulmonary tuberculosis still has an overall mortality of some 5%,^{5,6} which is related mainly to age and extent of disease,⁷ and that about 272 000 notified cases of tuberculosis (all forms) have occurred in England and Wales since 1964.

The incidence of hepatic drug reactions to antituberculosis drugs depends on the drug itself, age, and possibly sex and ethnic group. Reports of adverse reactions

*Hepatotoxic drug reactions reported to the CSM**

Drug	Total reactions†	Fatal reactions	Date first drug reaction	Cumulative cases of tuberculosis since that date
Isoniazid				
Single constituent	46	9	1964	272 000
Multi constituent	77	16		
Rifampicin				
Single constituent	132	11	1969	197 000
Multi constituent	74	16		
Pyrazinamide				
Single constituent	30	11	1965	254 000
Multi constituent	19	3		
Ethambutol				
Single constituent	7	1	1969	197 000
Multi constituent	3	0		

* This table shows the number of hepatic adverse reactions received through the UK's spontaneous adverse drug reaction reporting scheme for isoniazid, rifampicin, pyrazinamide, and ethambutol. The number of reactions for each drug substance does not equate with the number of reports since, for each report, there may have been more than one reaction.

† The total number of hepatic adverse reactions and fatalities cannot be calculated from these data because reactions attributable to multi constituent products have been recorded against each of the individual active constituents.

are often in the form of general reviews⁸ which, in turn, are compiled from results reported in controlled trials which may not be representative of routine clinical practice. Hepatic reactions constitute a major proportion of drug reactions to antituberculosis drugs, being reported in 3% of cases treated with rifampicin/isoniazid in the USA,⁹ and 4% of cases treated with rifampicin/isoniazid with or without pyrazinamide in the UK.¹⁰ The overall rate of adverse reactions to isoniazid increases with age,^{11,12} and reactions have been reported to occur in both sexes in one series¹¹ with an incidence of 0.52%, but only in women in another series¹² with an incidence of 1.04%. The older age distribution of cases of tuberculosis in the white ethnic group in the UK may explain the higher drug reaction rates when compared with the Indian subcontinent.⁴ The incidence of hepatitis in clinical trials in which rifampicin and isoniazid have been used with or without pyrazinamide^{9,13,14} shows that there is no increase in hepatotoxicity with all three drugs compared with rifampicin and isoniazid alone. In a recently reported UK series of 1317 patients,⁴ retrospective from 1978-80 and prospective from 1981-92, hepatitis was reported in 1.4% of patients on rifampicin, 1.25% of patients on pyrazinamide, and 0.3% of patients on isoniazid. However, because pyrazinamide is only given for two months whereas rifampicin and isoniazid is used for six months or sometimes longer, the hepatitis rate per patient month was three times higher with pyrazinamide than with rifampicin, which in turn was five times higher than with isoniazid.

Hepatic reactions usually occur in the early weeks of treatment, but may happen at any time in the six month standard treatment period. Although hepatic reactions are usually due to a single drug, a recent case report¹⁵ shows that occasionally a combination of drugs which individually cause no problem may cause hepatitis, a phenomenon originally reported in 1975.¹⁶ Jaundice is usually preceded by a period of days or weeks of malaise or nausea.

There is clearly a requirement to balance the need for full compliance with treatment – which is the major factor in outcome¹⁷ and is essential to prevent the emergence of drug resistance – with the risk of the patient and/or doctor continuing the medication when the patient has become unwell or has symptoms consistent with hepatitis.

Mitchell *et al*¹⁸ have recently described four of the 243 cases of hepatotoxicity to antituberculosis drugs reported to the CSM. From the limited information given in the cases described, which did not include patient weights or drug dosages, none of the four cases was managed as advised in the Joint Tuberculosis Committee treatment guidelines,³ and it is not stated whether the drug therapy was being supervised by a thoracic physician or other appropriately experienced physician. Their paper attempted no risk/benefit analysis of antituberculosis drugs, and did not mention the significant death rate from tuberculosis as discussed earlier in this editorial. The risks of the disease itself, or of inadequate treatment, are clearly many times higher than the risks from currently recommended treatment regimens. One of their recommendations was that rifampicin and isoniazid should be stopped if the level of hepatic transaminases rose to three times the normal value or the bilirubin level was raised, but they did not suggest that treatment with pyrazinamide, which is also potentially hepatotoxic, should be discontinued, nor did they address the problem of cases of tuberculosis – who may or may not be infectious from examination of their sputum – who had abnormal liver function before treatment to the levels that they were suggesting. Since pretreatment liver function abnormalities are not uncommon in tuberculosis,¹⁹ patients may be denied necessary treatment, substantially increasing both the morbidity and mortality from their tuberculosis. Finally, they suggested alternative drug treatment with, for example, ciprofloxacin and streptomycin in patients after liver transplantation, which is not evidentially based and did not specify what they meant by “prolonged”.

After consideration of all the factors including recent publications, we offer the following recommendations on behalf of the Joint Tuberculosis Committee which update the relevant section in the 1990 treatment guidelines.³

(1) All tuberculosis patients should have pretreatment measurements of liver function.³

(2) Standard drug treatment should be given under the supervision of a respiratory or other suitably qualified physician.³

(3) All patients should be advised and informed of possible side effects, as should their general practitioner. This may be done by simple written information in English and the patient's own language, perhaps supplemented by access to a named health visitor. Instructions should be explicit as to the indications for stopping medication and seeking advice – that is, persistent nausea, vomiting, malaise, or jaundice.

(4) Regular monitoring of liver function is required in patients with known chronic liver disease – for example, alcohol, chronic active hepatitis, cirrhosis, and in those known to be hepatitis B or C antigen positive. Surveillance should be particularly frequent in the first two months of treatment with weekly liver function tests in the first two weeks, and then at two week intervals.

(5) If the patient has no evidence of pre-existing liver disease and normal pretreatment liver function, liver function need only be repeated (and treatment stopped) if fever, malaise, vomiting, jaundice, or unexplained deterioration during treatment occur. The possibility of coexisting acute viral hepatitis should be considered²⁰ and appropriate virology tests performed if indicated.

(6) Modest elevations of aspartate transaminase (AST) and alanine transaminase (ALT) are not uncommon in the pretreatment liver function tests of tuberculosis patients, or immediately after the introduction of treatment.¹⁹ If the AST/ALT levels are two or more times above normal, liver function should be monitored weekly for two weeks and then two weekly until normal. If the ALT/AST levels are just under twice the normal values, the liver function should be repeated after two weeks. If the transaminase levels have fallen, further repeat tests are then only required for symptoms. If the repeat tests show that ALT/AST levels have risen to more than twice the normal values, management should be as above. If the AST/ALT level rises to five times normal or the bilirubin level rises, rifampicin/isoniazid/pyrazinamide should be stopped.²¹

(7) What happens next depends on the circumstances: (a) If the patient is not unwell, and the form of tuberculosis is non-infectious,²² no treatment need be given until liver function returns to normal.

(b) If the patient is clinically unwell or the sputum is smear positive within two weeks of commencing treatment, then some form of drug therapy needs to be given, preferably as an inpatient, until liver function is normal. Streptomycin and ethambutol, with appropriate checks on renal function³ and visual acuity,^{3,23} should be used unless there is clinical suspicion or bacteriological evidence of resistance to these drugs. It may sometimes be better to interrupt treatment unless this is felt to be prejudicial to survival. If alternative medication is necessary, an individually tailored drug combination to which the organism is – or is thought likely to be – sensitive may be needed. This may have to include reserve drugs³ when the potential hepatotoxicity of ethionamide/prothionamide and macrolides needs to be considered.

(c) Once liver function is normal challenge dosages of the original drugs can be reintroduced sequentially in the order isoniazid, rifampicin, and pyrazinamide²⁴ with daily monitoring of the patient's clinical condition and liver function. Isoniazid should be introduced initially at 50 mg/day, increasing sequentially to 300 mg/day after 2–3 days if no reaction occurs, and then continued. After a further 2–3 days without reaction rifampicin at a dose of 75 mg/day can be added, increasing to 300 mg after 2–3 days, and then to 450 mg (<50 kg) or 600 mg (>50 kg) as appropriate for the patient's weight after a further 2–3 days without reaction, and then continued. Finally, pyrazinamide is added at 250 mg/day, increasing to 1000 mg after 2–3 days and then to 1500 mg (<50 kg) or 2000 mg (>50 kg).

(8) If there is no further reaction standard chemotherapy can be continued and any alternative drugs introduced temporarily can then be withdrawn.

(9) If there is a further reaction the offending drug should be excluded and a suitable alternative regimen used. Such an alternative regimen should be on the advice of, and under the supervision of, a respiratory physician.³ If pyrazinamide is found to be the offending drug, treatment will need to be continued for nine months with rifampicin and isoniazid, supplemented by ethambutol for the initial two months.³

(10) Occasionally the choice of alternative drugs is so limited – for example, by drug-resistant organisms – that desensitisation and reintroduction of the offending drug

may be necessary using conventional protocols.²⁵ To avoid the emergence of drug resistance during desensitisation the procedure must be carried out under the cover of two other antituberculosis drugs.

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