Hepatotoxicity caused by the combined action of isoniazid and rifampicin

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Abstract

A 35 year old black Somalian woman with miliary tuberculosis developed hepatotoxicity after a few days of treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol. After withdrawal of all drugs the liver profile returned to normal and remained so after challenge with isoniazid. Hepatotoxicity recurred when rifampicin was added, but it was well tolerated when reintroduced without isoniazid.

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Keywords: tuberculosis, hepatotoxicity, isoniazid, rifampicin.

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Most antituberculous drugs, with the notable exception of streptomycin, are prone to cause liver injury. The hepatotoxic potential of isoniazid given alone is well established,[1] while data on the hepatotoxicity of rifampicin, pyrazinamide, and ethambutol are difficult to interpret since these drugs are almost always used in different combinations.[2] The evidence supporting possible hepatotoxic interaction between rifampicin and isoniazid is circumstantial.[3]

The requirement of a hepatotoxic drug interaction is the absence of hepatotoxicity when the drugs are administered separately and the presence of hepatotoxicity when given together. We report the first case where a hepatotoxic drug interaction between rifampicin and isoniazid is firmly documented. This interpretation proved to be essential for optimal treatment of our patient.

Case report

A 35 year old black woman from Somalia was admitted to our department with a seven month history of dry cough, night sweats, and weight loss of 15 kg. A chest radiograph revealed diffuse fine nodular shadowing, and a diagnosis of miliary tuberculosis was confirmed by the presence of acid fast bacilli in the bronchoalveolar lavage fluid.

Treatment was initiated with the Danish four drug routine regimen of isoniazid 300 mg, rifampicin 450 mg, ethambutol 1 g, and pyrazinamide 1·5 g (body weight 46 kg) daily. Five days before the start of treatment the serum level of aspartate aminotransferase (ASAT) was slightly raised at 59 units/l (upper limit of normal (ULN) 35 units/l), whereas the bilirubin level was normal at 11 μmol/l (ULN 17 μmol/l) (fig 1). After four days of antituberculous treatment the patient developed abdominal pain, nausea, and malaise and ASAT levels started to increase (fig 1). Bilirubin rose to 26 μmol/l and alkaline phosphatase to 1·5 times ULN. The patient was not on any other potentially hepatotoxic drug and did not consume alcohol. IgM anti-HAV, HBsAg, and IgM anti-CMV were negative. An ultrasound scan of the liver was normal.

Drug treatment was discontinued and bilirubin and ASAT levels fell (fig 1). Treatment was reinstituted seven days later with a daily dose of 100 mg isoniazid, increased to 300 mg after three days. The liver profile remained stable and a dose of 150 mg rifampicin was added. After four days (the day after the dose of rifampicin was doubled to 300 mg) a steep increase in ASAT levels was observed (fig 1). Bilirubin levels reached 31 μmol/l and alkaline phosphatase rose to almost twice the ULN. The patient developed abdominal pain, nausea, and vomiting. Rifampicin was withdrawn and isoniazid treatment was supplemented by a daily dose of streptomycin 1 g, followed one week later by ethambutol. ASAT, bilirubin, and alkaline phosphatase levels returned to normal (fig 1).

The general condition of the patient did, however, gradually worsen, and 26 days after rifampicin withdrawal (58 days after starting antituberculous therapy) the isolated *Mycobacterium tuberculosis* proved to be resistant to isoniazid. Accordingly, isoniazid was withdrawn and rifampicin reintroduced at an initial dose of 150 mg/day. Pyrazinamide was added. Although the daily dose of rifampicin was gradually increased to 600 mg over the following six days, the ASAT level remained within normal limits (fig 1). At this time a further susceptibility testing of the tubercle bacilli revealed resistance to streptomycin which was replaced by ofloxacin 200 mg twice daily.

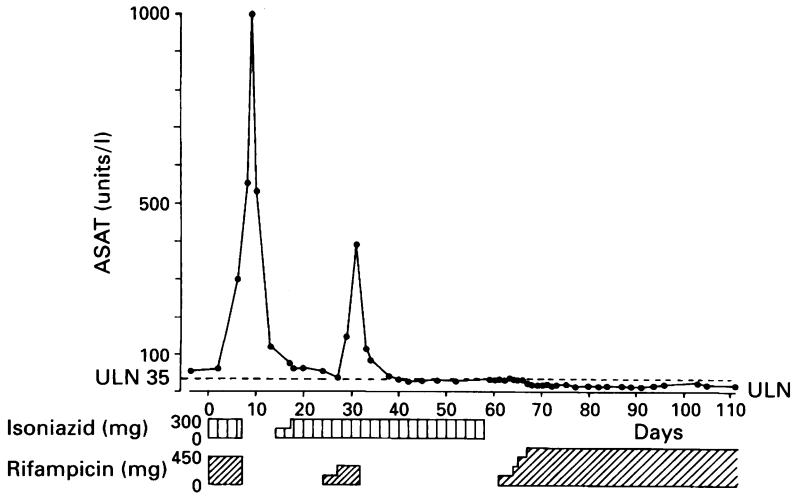

Figure 1 Time course of changes in serum levels of aspartate aminotransferase (ASAT) in units/l during administration of isoniazid and rifampicin separately and in combination. ULN = upper limit of normal.

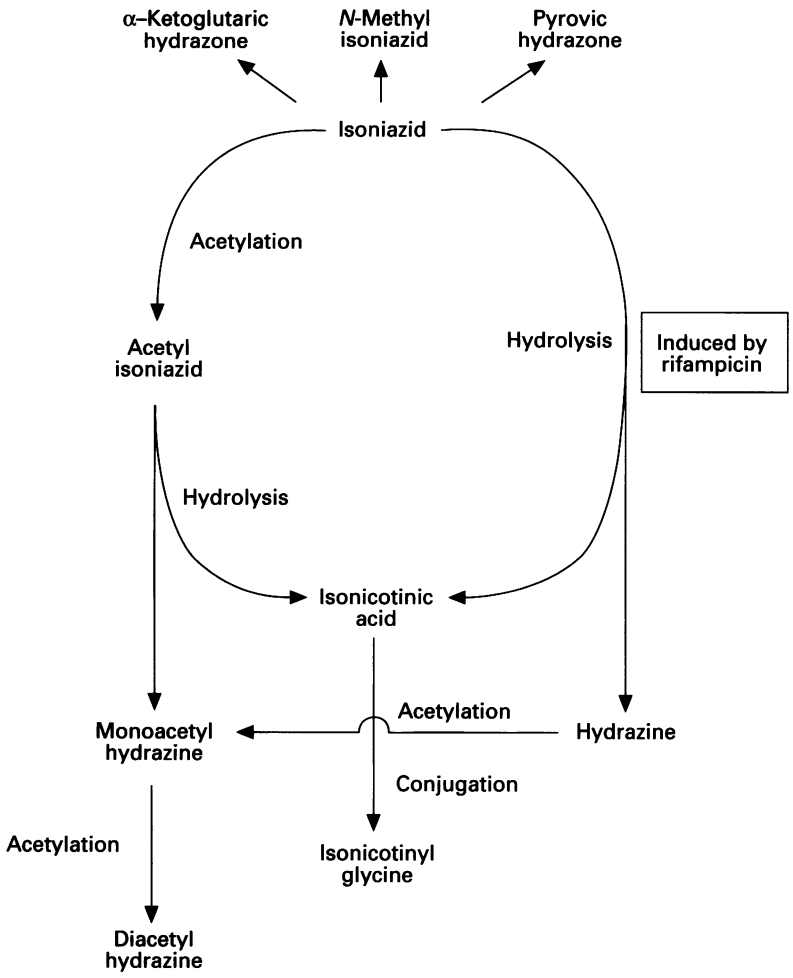

Figure 2 Rifampicin induction of the hydrolysis pathway of isoniazid metabolism into the hepatotoxic metabolite hydrazine.

Treatment finally consisted of rifampicin 600 mg, ethambutol 1 g, pyrazinamide 1·5 g, and ofloxacin 400 mg/day. The patient slowly recovered and gained weight, with persistently normal liver function (fig 1).

Discussion

We found a clear time course between drug administration and alterations in ASAT and bilirubin levels with a latency of a few days after both challenges. A shorter latency period and a more serious reaction after each exposure has been observed in most cases of halothane hepatotoxicity and has been claimed to favour an allergic mechanism for the liver injury.[4] In our case the latency period was similar after both drug exposures, and the second reaction was not worse than the first. This points to a dose-related hepatotoxic reaction in agreement with a stimulating effect of rifampicin on the non-acetylating hydrolysis metabolic pathway of isoniazid into a hepatotoxic hydrazine[5] (fig 2). The epidemiological evidence of a possible interaction between isoniazid and rifampicin is not convincing and is often hampered by concomitant exposure to alcohol or other drugs.[3] In virtually all previously published cases of "rifampicin hepatotoxicity" liver injury occurred during simultaneous administration of isoniazid and rifampicin.[6] In most of these studies the liver profile became normal after rifampicin was withdrawn and isoniazid treatment continued. Rifampicin was never re-administered without isoniazid. Accordingly, rifampicin may have been wrongly accused as the hepatotoxic agent when at least some cases might have been caused by the combined action of isoniazid and rifampicin.

To our knowledge this is the first reported human case of a proven hepatotoxic interaction between isoniazid and rifampicin. Due to isoniazid resistance of the mycobacterial strain our re-exposure drug trials were essential for the choice of optimal treatment. After isoniazid had been reintroduced in a full dose without liver problems, ASAT and bilirubin levels rose abruptly after rechallenge with rifampicin. If this had been interpreted as rifampicin being the offending agent, the patient would have been deprived of one of the most important first line antituberculous drugs.

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