function is normal, and that 30 min after the end of a 30 min infusion of 4 mg/kg the concentration of either would be about 16 mg/L, then the concentration 23 h later would theoretically be less than 0.5 mg/L. This was confirmed by a study of netilmicin given at then the concentration 23 h later would theoretically be less than of 4 mg/kg the concentration of either would be about 16 mg/L, the majority of patients had trough concentrations of netilmicin less than 1 mg/L. It is likely, therefore, that a trough concentration of 2 mg/L would be associated with significantly impaired renal function and theoretically with a plasma half life of some 8 h following a post-distribution serum concentration of 16 mg/L. Although currently no direct evidence to link a trough concentration of 2 mg/L with toxicity during once-daily dosing, the available evidence with dosing three times a day suggests an association between raised trough concentration and ototoxicity. Inexperienced prescribers may be lulled into the false security of thinking that a trough concentration of 2 mg/L is indicative of normal renal function and unmodified gentamicin pharmacokinetics. We realise that Parker and Davey emphasise the importance of measuring renal function in the first 24 h of therapy as a guide to further dosing. However, even when renal function deteriorates rapidly in a seriously ill patient, it takes at least 24 h for the rise in plasma creatinine to become significant, and measurement of creatinine clearance is necessarily retrospective. This contrasts with the immediate change that can be observed in the clearance of an exogenous substance, such as an aminoglycoside, and we feel, therefore, that there is no substitute for trying to avoid toxicity by measuring trough concentrations. We urge caution, therefore, in taking 2 mg/L as a satisfactory trough concentration and suggest the maximum acceptable concentration should be 1 mg/L with once-daily therapy. This value is more in keeping with the known pharmacokinetics of gentamicin. However, there is a practical difficulty in recommending 1 mg/L in that many laboratories will have no direct evidence to link a trough concentration of such a low concentration. Indeed, we know from UK National External Quality Assurance results that accuracy of clinical assays for concentrations below 1 mg/L is poor. A possible solution to this problem may be to take earlier samples, for example 8 or 12 h after the dose, when the higher concentrations present would yield more accurate measurements, but such an approach would need validation and may be defeated by inaccurate timing of specimens. Rather than asking clinicians to take samples at set times, it might be more productive for them to provide blood 8–12 h after dosing while taking note of the exact time of sampling.

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ROXITHROMYCIN-INDUCED OR HERPES HEPATITIS?

SIR,—Dr Pedersen and colleagues (Jan 23, p 251) report a case of fulminant hepatitis in a young woman with a possible genital chlamydia infection treated with roxithromycin. The term fulminant seems inappropriate since signs or symptoms of hepatic encephalopathy did not occur.1 “Severe” would be a more suitable term, even though information is missing that would indicate whether the prolongation of prothrombin time was due to cholestasis or liver failure. Pedersen and co-workers favour in this patient the hypothesis of a drug origin, on the basis of liver test anomalies discovered 8 days after roxithromycin was started and reverting to normal after cessation of the drug. However, a more probable alternative cause could have been considered in this clinical context.

First, headache and influenza-like symptoms suggest a viral infection. Second, the considerable increase in transaminases (over 130 times the upper limit of normal), the focal liver necrosis, and the mild inflammatory infiltration are common in typical cases of herpes hepatitis.2 The recent varicella-zoster ophthalmitic infection and the high serum titre (1/1600) of the specific antibody are quite compatible with a varicella hepatitis, although this infection is rare in immunocompetent adults. A second hypothesis, even more probable than the first, is that the varicella herpes infection in this young woman suspected of having a genital chlamydia infection. Has a herpes simplex virus (HSV) been sought? This hypothesis is supported by the fact that all signs and symptoms are compatible with HSV hepatitis, which is not so rare even in apparently immunocompetent adults.3 Furthermore, genital herpes is often underdiagnosed in patients suspected of having a sexually transmitted infection.4 As Pedersen et al state, hepatic injuries attributed to roxithromycin are usually of the cholestatic or mixed type.

Thus, this case of severe hepatitis cannot be assessed as reasonably related to the use of roxithromycin. Herpes hepatitis seems a more likely alternative cause which could have been supported by specific evidence such as positive virusemia of herpes, the presence of nuclear inclusions in hepatocytes, and positive direct immunofluorescent staining on the liver sample.

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Authors’ reply

SIR,—Dr Danan and Dr Bénichou do not agree with our hypothesis of a drug-induced hepatitis (roxithromycin) in our patient, but suspect herpes simplex virus or varicella zoster as the cause of the hepatitis. Herpes simplex type 1 and 2 are rare causes of hepatitis in adults. About 30% of patients have an ophthalmic or genital focus; 90% die. The diagnosis is made on liver biopsy findings. We are aware of 10 cases of fulminant herpes simplex hepatitis in immunocompetent adults.1–3 Varicella zoster virus occasionally causes hepatitis in both normal and immunosuppressed patients. A vesicular rash from which the virus can be isolated is a prominent feature,4 although there have been patients in whom rash is absent. Our patient was treated with roxithromycin because of a diagnosed genital chlamydia infection in her partner. She had no signs or symptoms of genital chlamydia or herpetic infection, nor had she any signs of a varicella zoster infection. Serological tests for varicella zoster virus were consistent with a known earlier infection. Liver biopsy showed no intranuclear inclusions, nor staining for haemorrhage. Furthermore, immunoperoxidase studies were negative for herpes simplex type 1 and 2, cytomegalovirus, and chlamydia.

Whether the hepatitis was fulminant or severe is debatable. There is no international definition consensus on these terms. Encephalopathy is not necessarily present in fulminant hepatitis.5 We feel that our patient had fulminant hepatitis, but we accept others’ opinion that the term “severe” is more appropriate.

We do not state, as Danan and Bénichou claim, that the hepatic injuries attributed to roxithromycin, are usually of the cholestatic or mixed type. It is not, on the basis of two earlier reports, possible to draw conclusions about the types of hepatic injuries induced by roxithromycin. We still believe that roxithromycin was the cause of hepatic injury in our patient, but, as always, other possibilities remain. However, it is good clinical practice to consider the most likely reasons before the rare ones. It is notable that our patient remained negative for hepatitis C (a more likely differential diagnosis) when tested on Feb 10, 1993.

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CLAUS FENGER

Continuous aerosolised tribuvirin for respiratory syncytial virus infection in lung transplant recipients

Sir,—Respiratory syncytial virus (RSV) is common in childhood. Several cases of RSV pneumonitis have also been reported in elderly and immunocompromised adults. Benefit with tribuvirin, well-established in infants with severe bronchiolitis or pneumonia, remains debatable in other patients. We report two cases of RSV pulmonary infection in single-lung transplant patients (one for idiopathic pulmonary fibrosis 18 months ago, the second one for emphysema 19 months ago) admitted in February, 1993, for severe respiratory symptoms. They presented with cough, fever, and intense dyspnoea. Examination revealed crackles, ronchi, and wheezing in both lungs. Blood gas samples showed severe hypoxaemia (PO₂ 7-2 and 6-4 kPa) with moderate hypocapnia. Chest radiography and computed tomography revealed an alveolar pattern of the lower lobe in one patient and were normal in the other. RSV was identified rapidly in bronchoalveolar lavage (BAL) by immunofluorescence. No other pathogens were isolated and transbronchial biopsy specimens showed no evidence of rejection. Both patients were treated by aerosolised tribuvirin over 5 days (6 g per day over 20 h). Respiratory status improved dramatically within 2 days. After 5 days, physical examination was almost normal and blood gas samples had returned to previous baselines. The chest radiograph of the patient who had previously shown abnormalities had also improved. RSV was not detected in a new BAL in one patient on day 5.

RSV respiratory infection is acquired by inhalation of aerosolised infectious particles. The disease is prevalent in the community in late winter and spring but may be acquired nosocomially. The infection is often severe in bone marrow recipients, despite specific treatment. In solid organ recipients (other than lung), the intensity of symptoms due to RSV infection is variable. Our observations underline the potential severity of this viral disease in lung transplant patients. Fast detection of viral antigens with monoclonal antibodies is highly sensitive in BAL and sputum, allowing rapid diagnosis. Improvement of symptoms and blood gas samples demonstrated the efficiency of aerosolised tribuvirin in these cases. Rapid treatment might also decrease the risk of bacterial superinfection, a classic complication of RSV infection, and could be important in preventing nosocomial transmission in other immunocompromised patients.

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