function is normal, and that 30 min after the end of a 30 min infusion of 4 \text{ mg/kg} the concentration would be less than 0.5 \text{ mg/L}. This was confirmed by a study of netilmicin given at 4.5 \text{ mg/kg} once a day in which 97% of trough concentrations were less than 1 \text{ mg/L}, 76% were less than 0.5 \text{ mg/L}, and 56% were less than 0.1 \text{ mg/L}.

Similar results were reported by Parker and Davey and the majority of patients had trough concentrations of netilmicin less than 1 \text{ mg/L}. It is likely, therefore, that a trough concentration of 2 \text{ 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 \text{ mg/L}. Although there is currently no direct evidence to link a trough concentration of 2 \text{ 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 \text{ 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 antimicrobial agent.

Accuracy of clinical assays is critical, 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 \text{ mg/L} as a satisfactory trough concentration and suggest the maximum acceptable concentration should be 1 \text{ 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 \text{ mg/L} in that many laboratories will have no direct evidence to link a trough concentration such a low concentration. Indeed, we know from UK National External Quality Assurance results that accuracy of clinical assays for concentrations below 1 \text{ 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.

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 abnormalities 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.

A febrile, 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 ophthalmic 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, would be a genital 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.3,4 Furthermore, genital herpes is often underdiagnosed in patients suspected of having a sexually transmitted infection.5 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.

Regional Antimicrobial Reference Laboratory and National Centre for Antibiotic Therapy
Quality Assurance, Department of Medical Microbiology, Southmead Hospital, Bristol BS10 5NB, UK

DAVID S. REEVES
ALASDAIR P. MACGOWAN

Roxithromycin-induced or herpes hepatitis?

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.1-4 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,2 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 herpes simplex type 1 and 2 were negative on Sept 24, 1992, and on March 8, 1993. Test results for varicella zoster virus were consistent with a known earlier infection. Liver biopsy showed no intracellular inclusions, nor stasis or 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.


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.1-4 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,2 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 herpes simplex type 1 and 2 were negative on Sept 24, 1992, and on March 8, 1993. Test results for varicella zoster virus were consistent with a known earlier infection. Liver biopsy showed no intracellular inclusions, nor stasis or 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.

Department of Medical Gastroenterology, Odense University Hospital, 5000 Odense C, Denmark
Institute of Pathology, Odense University Hospital

LISE BATHUM
FINN MOLLER PEDERSEN
CLAUS FENGER

Acute compartment syndrome after aortocoronary bypass

Sir,-We describe two patients with acute compartment syndrome of the leg after coronary artery bypass.

A 61-year-old man underwent coronary artery bypass grafting with a segment of the great saphenous vein from the left leg. On the morning after surgery, the patient complained of increased pain in the left calf. He had good peripheral pulses and capillary return. After removing the elastic bandage, we saw painful tissue swelling in the lateral aspect of the leg with reduced touch sensation. The patient could not dorsiflex his left foot and toe, and the pain was worse on passive movement. Acute compartment syndrome was diagnosed and surgical decompression of all four compartments of the leg was done with double-incision. 7 days later an additional exploration with excision of necrotic muscle regions was done and the patient made a good postoperative recovery but some residual weakness on dorsiflexion of the left foot and distribution sensibility in the region of the deep peroneal nerve persisted 3 months after surgery.

The second patient, a 59-year-old man, underwent an uneventful aortocoronary bypass operation. The early postoperative course was stable, except the patient had an unexplained sinus tachycardia of 140-160 per min. Because of increased postoperative pain he received several doses of analgesics and sedation. 8 h after the operation, the patient complained of severe left-leg pain. The left foot was colder than the right, but arterial pulses of the posterior tibial and dorsal foot artery were palpable. The elastic bandage was removed to reveal painful tissue swelling in the anterolateral aspect of the calf, weak active movement, severe pain on passive dorsiflexion of the foot and toe, and decreased sensation in the dorsum of the foot. After immediate four-compartment fasciotomy, tachycardia returned to a normal heart frequency of 80 per min. Primary skin suture was done 7 days later, and the patient made a good recovery. A month after operation he still had paraesthesia in the distribution of the superficial peroneal nerve without muscular weakness.

Although acute compartment syndrome can be diagnosed only by history and clinical examination, the syndrome is easily overlooked during the early postoperative phase. Administration of potent systemic analgesics and inadequate evaluation of a leg dressed by elastic bandage may mask the real diagnosis. Moreover, palpable peripheral pulses do not rule out the diagnosis. If necessary, compartment pressures should be measured (indication for surgical decompression > 30 mm Hg). Careful evaluation after heart surgery and immediate recognition and early fasciotomy may Prevent this rare but dangerous complication.

MIRALEM PASIC
TIERRY CARREL
MARTIN TÖNZ
PAUL VOGT
LUDWIG VON SEGESSER
MARKO TURINA

Clinic for Cardiovascular Surgery, University Hospital Zurich, CH-8091 Zurich, Switzerland


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.1 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.2 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,3 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.

MARLANÈ MEURIS-ESPIN
ALAIN DIDIER
PHILIPPE CARRE
JOSÉPHINE IGART
SABINE HENRY
PAUL LELOPHE

Services des Pneumologie—Allergologie et Virologie, Centre Hospitalier Universitaire de Rangueil, 31054 Toulouse, France


