Patients, methods, and results

Twenty-four patients (15 men, 9 women) whose mean age ($\pm$ SE) was 37.6 ± 20.1 years (range 14-76) were treated for spontaneous bacterial meningitis with continuous intravenous infusion of ampicillin 150 mg/kg body weight/day. Ampicillin 50 mg/kg was diluted in 20 ml distilled water and infused at a constant rate with an intravenous perfusor pump. Under these conditions ampicillin remains stable for eight hours. No other drug was infused.¹ The serum antibiotic concentration was measured on treatment day 5. Three blood samples were drawn at one-hour intervals. Simultaneously with the second blood sampling the cerebrospinal fluid (CSF) antibiotic concentration was measured.² Assays were performed by microbiological methods using *Bacillus subtilis* as a test micro-organism. The sensitivity of the test was as high as 0.1 mg/l.

No significant difference was found in the concentrations in the different blood samples drawn at one-hour intervals in each patient. Thus it may be considered that in each individual the concentration of antibiotic remained constant during this period. But the differences in the concentrations among the 24 patients were large (from 9.4 mg/l to 92 mg/l). These differences could not be explained by the difference in the antibiotic doses received during 24 hours and recalculated for body weight. No correlation was found between blood concentration and sex or age. Since the rate of metabolism of ampicillin is relatively high (35 to 40%)³ hepatic metabolism is likely. Anticonvulsant drugs such as phenobarbitone and diazepam are hepatic enzymatic inductors⁴ and may modify serum ampicillin concentrations. In fact, nine of our patients were taking an anticonvulsant but there was no significant difference between their serum ampicillin concentrations and those of the remaining 15 patients. On the other hand, there was a significant correlation between the creatinine clearance and serum antibiotic concentration (figure). But the creatinine clearance variations may only partly explain the range of serum concentrations.

Relations between serum ampicillin concentrations and creatinine clearance in 24 patients under constant-rate infusion.

Comment

No definite conclusions can be reached from this study. Too many complex factors are concerned, and there is probably more than one reason for the differences in serum ampicillin concentrations, including variation in antibiotic distribution, protein binding of the drug, extrarenal metabolism, and differences in tubular function.⁵

Three considerations must be borne in mind. Firstly, though the serum concentration of a drug infused continuously may be estimated accurately in a normal healthy subject, this may not be the case in a critically ill patient. Secondly, when the dose-dependent toxicity of an antibiotic is small large doses must be given even against very sensitive micro-organisms (as for ampicillin in treating pneumococcal or meningococcal meningitis). Thirdly, when the minimum inhibitory concentration of an antibiotic is close to the available concentration the concentrations in serum and in situ must if possible be checked.

¹ Brodlie P, Henney C, Wood AJJ. Problems of administering drugs by continuous infusion. *Br Med J* 1974;i:383-5.

² Bouvet E, Gibert C, Witchitz J, et al. Diffusion méningée de deux bêta-lactamines du groupe A au cours des méningites purulentes. *Ann Med Interne (Paris)* 1978;129:657-60.

³ Von Simon C, Malerczyk V, Zierott G, Lehmann K, Thiesen U. Blut-, Harn- und Galle Spiegel von Ampicillin bei intravenöser Dauerinfusion. *Arzneim Forsch* 1975;25:654-6.

⁴ Heubel F. Interferenz von Diazepam und Phenobarbital and der rattee und am Menschen. *Arch Exp Pharmacol* 1969;264:246-9.

⁵ Whelton A. Intrarenal antimicrobial distribution modulating factors, therapeutic and toxicologic implications. In: JP Fillatre, ed. *Nephro-toxicity*. New York: Masson, 1978:95-126.

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Hydrallazine-induced hepatitis?

Hydrallazine has been widely used for treating hypertension, and its toxic effects are well known. Hepatotoxicity in the form of acute hepatic necrosis has only recently been reported¹ to be associated with its use. We report on a patient in whom we believe the drug was implicated in otherwise unexplained asymptomatic disturbance of liver function.

Case report

A 37-year-old woman presented with epistaxis. Her blood pressure was 215/150 mm Hg, and initial treatment with oxprenolol and a diuretic failed to achieve adequate control. She was found to be a rapid acetylator, and treatment with hydrallazine 25 mg twice daily was started. At this stage routine liver function tests were normal. Blood pressure was controlled at 175/110, but two weeks later she returned to the clinic complaining of malaise and palpitations. Hydrallazine was stopped and attempts were made over the next three months to control her hypertension with methyldopa and prazosin. Because of inadequate control and complaints of side effects she was readmitted for restabilisation of hypertension. Oxprenolol and bendrofluazide were continued and hydrallazine 25 mg twice daily reintroduced. Routine liver function tests done immediately before this were normal (see table). Three days after starting treatment with hydrallazine tests showed a

Results of liver function tests after treatment for hypertension

Date	Medication (total daily dose)	Liver function tests*		
		γ -glutamyl transpeptidase (IU/l) (normal range 0-35)	Alanine transferase (IU/l) (normal range 0-35)	Alkaline phosphatase (IU/l) (normal range 60-260)
20 Mar 1979	Bendrofluazide 5 mg	18	17	184
16 Aug 1979	Bendrofluazide 5 mg	11	11	161
17 Aug 1979	Oxprenolol 480 mg			
	Prazosin 20 mg			
	Prazosin replaced by hydrallazine 50 mg	12	11	153
20 Aug 1979		121	504	733
23 Aug 1979	Hydrallazine 100 mg	165	234	995
24 Aug 1979	Hydrallazine 150 mg	162	177	1077
31 Aug 1979	Hydrallazine stopped, prazosin started	—	—	—
4 Sept 1979		63	23	422
17 Sept 1979		32	12	222

*Serum total bilirubin remained within normal limits ($<17 \mu\text{mol/l}$; 0.99 mg/100 ml) throughout.

mixed hepatocellular-cholestatic picture of liver function abnormality with normal total bilirubin. The dose of hydrallazine was increased over the next four days to 150 mg daily. The liver function tests were still grossly abnormal but the patient remained asymptomatic and blood pressure was well controlled at 150/90. All other investigations including HBsAg were normal. After 10 days hydrallazine treatment was replaced again by prazosin. Liver function tests performed at follow-up 9 days and 5 weeks later had returned to normal.

This patient showed biochemical evidence of liver function abnormality within three days of starting on a low dose of hydrallazine. Liver enzymes were persistently raised throughout the two weeks of treatment but fell over the next two weeks after hydrallazine was discontinued. No other pathological causes of liver dysfunction could be found from viral and autoantibody studies. The patient had no evidence of pre-existing liver disease.

Comment

Recently Bartoli *et al*¹ described a patient with acute hepatic necrosis that occurred two days after treatment with hydralazine 50 mg daily. The diagnosis was supported by biopsy and rechallenge with the drug. The patient was definitely jaundiced and complained of right upper-quadrant pain with nausea and vomiting. We think that our case is important because it provides corroborative evidence of an acute hepatitis-like reaction caused by hydralazine, in this instance without symptoms. Liver function tests may not routinely be performed during follow-up of patients taking hydralazine, and the long-term effect of this otherwise unsuspected biochemical disturbance is unknown.

The recent findings of unrecognised hydrazine metabolites in the urine of patients receiving hydralazine² indicates a possible aetiology in this case. Hydrazine and acetylhydrazine are known to be involved in hepatotoxic reactions—the latter is thought to be responsible for mediating isoniazid-induced liver damage via microsomal oxidation to a reactive hepatotoxic intermediate.³ Our patient was a rapid acetylator, which may have increased the risk of acetylhydrazine-induced hepatic necrosis, although this is presently disputed in the case of isoniazid.^{4,5} Exposure to microsomal enzyme inducers may also increase the risk, although our patient was not exposed to any such drugs. Further evaluation of abnormal liver function tests in asymptomatic patients receiving hydralazine is indicated.

¹ Bartoli E, Massarelli G, Solinas A, Faedda R, Chiandussi L. Acute hepatitis with bridging necrosis due to hydralazine intake. *Arch Intern Med* 1979;139:698-9.

² Timbrell JA, Harland SJ. Identification and quantitation of hydrazine in the urine of patients treated with hydralazine. *Clin Pharmacol Ther* 1979; 26:81-8.

³ Mitchell JR, Zimmerman HJ, Ishak KG. Isoniazid liver injury: clinical spectrum, pathology and probable pathogenesis. *Ann Intern Med* 1976;84:181-92.

⁴ Mitchell JR, Thorgeirsson UP, Black M, *et al*. Increased incidence of isoniazid hepatitis in rapid acetylators: possible relation to hydrazine metabolites. *Clin Pharmacol Ther* 1975;18:70-9.

⁵ Ellard GA, Mitchison DA, Girling DJ, Nunn AJ, Fox W. The hepatic toxicity of isoniazid among rapid and slow acetylators of the drug. *Am Rev Respir Dis* 1978;118:628-9.

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Circulating immune complexes appearing in Goodpasture's syndrome

The role of antibodies directed against glomerular basement membrane is now well established in both the renal and the pulmonary manifestations of Goodpasture's syndrome.¹ Recent data suggest, however, that immune complexes may also have a role in this disease. We report here a case of Goodpasture's syndrome in which circulating immune complexes were found during a recurrence of pulmonary haemorrhage.

Case report

A 57-year-old Caucasian woman was admitted on 3 August 1978 with a five-week history of macroscopic haematuria, fever, and haemoptysis. Before admission she received an injection of corticosteroids. On admission her chest radiograph was normal; serum creatinine was 980 $\mu\text{mol/l}$ (11.1 mg/100 ml) and urinary protein excretion was 1.4 g/day with microscopic haematuria. A renal biopsy was performed on 8 August and haemodialysis started. On 29 August, acute pulmonary distress occurred with severe hypoxaemia (PaO_2 : 6 kPa (45 mm Hg)) and pulmonary haemorrhages without infection. Bilateral alveolar opacities increased despite ultrafiltration, which induced a hypovolaemic shock. The patient underwent her first plasma exchange and received a pulse of intravenous methylprednisolone (1500 mg) on 1 September. The pulmonary haemorrhages and radiological abnormalities

rapidly disappeared. Three other plasma exchanges each removing 3700 ml were performed on 6, 8, and 11 September and combined with prednisone 60 mg/day and cyclophosphamide 125 mg/day. There was, however, no parallel improvement in renal function and regular haemodialysis was required. Three weeks later she developed an extensive pulmonary infection and died.

Pathology—On light microscopy all the glomeruli were necrotic and surrounded by huge epithelial crescents. No acute angitis was observed. Immunofluorescence showed a diffuse linear fixation of IgG and C3 along the glomerular basement membrane. Intense staining with fibrinogen antiserum was noted in Bowman's space.

Immunological studies—On admission immunological results were: cryoglobulinaemia and Farr assay negative, C3 and C4 normal; no immune complexes were detected using radiolabelled Clq. Radioimmunoassay detected anti-glomerular basement membrane (GBM) antibodies at a slightly positive level (6%). When pulmonary haemorrhages recurred, anti-GBM antibodies were at the same level (6.9%). By contrast, circulating immune complexes were raised on 1 September (73%) and dramatically decreased after the first plasma exchange and bolus of steroids (22% on 4 September). On following days they became barely detectable (figure). The Clq assays were performed in triplicate, and the high value on 1 September was confirmed by retesting with new radiolabelled Clq, which gave a result of 66%.

Serial measurements of C3, IgG, and immune complexes (measured by Clq binding test) during treatment. Normal range on Clq binding test: <10.

Comment

Goodpasture's syndrome was suggested by the combination of pulmonary haemorrhages and a crescentic glomerulonephritis with linear and diffuse fixation of IgG along the glomerular basement membrane. In this case relatively low titres of circulating anti-GBM antibodies could have resulted from the assay performed rather late and from the prior administration of steroids.

In the absence of triggering factors, such as infection or hyperhydration, pulmonary haemorrhages were observed to recur simultaneously with a very high level of circulating immune complexes, whereas the level of anti-GBM antibodies did not vary significantly. The treatment strategy combining plasmapheresis, high-dose steroid therapy, and immunosuppressors led to a rapid and definitive disappearance of both pulmonary haemorrhage and circulating immune complexes.

Tung *et al*² and more recently Pussell *et al*³ reported the existence of circulating immune complexes in anti-GBM antibody glomerulonephritis. Other authors have shown that in Goodpasture's syndrome granular deposits could occur after or at the same time as linear IgG deposits, suggesting the presence of superimposed immune complexes.⁴ In addition, the experiments of Brentjens *et al*⁵ showed that circulating immune complexes could induce pulmonary lesions. Even though lung biopsy was not performed in our patient, the parallelism between pulmonary involvement and the levels of circulating immune com-