ascites or abdominal organ enlargement. The laboratory results included: erythrocyte sedimentation rate 95 mm in first hour, conjugated bilirubin concentration 51.3 $\mu\text{mol/l}$ (3 mg/100 ml), serum alkaline phosphatase activity 420 IU/dl, serum aspartate aminotransferase activity 56 U/l, and serum alanine aminotransferase activity 68 U/l. Titres to hepatitis B surface antigen were negative. Antibody titres to hepatitis B surface and core antigens and hepatitis A associated antigen were positive on admission. Immunoglobulin G (IgG) concentration was initially raised (22.2 g/l), while concentrations of complement components were normal. Antibodies to smooth muscle and mitochondria were not detected.

Withdrawal of the drug resulted in a gradual decline of the temperature and return to normal of all laboratory values. An oral cholecystogram was normal. A liver biopsy was not performed.

The assessment of the feasibility of readministration of nifedipine seemed important because of the patient's continuing severe angina. Therefore, four months later and with the patient's informed consent we rechallenged him with a single dose of 10 mg nifedipine. Twelve hours later his temperature had risen to 37.5°C with a concomitant rise in serum alkaline phosphatase activity and IgG concentration but no changes in the activities of aminotransferases. Results of liver function tests at follow-up at 10 months were normal.

A macrophage migration inhibition factor assay² for nifedipine was performed two months after the acute icteric episode and gave positive results (figure). After rechallenge with nifedipine the migration indices abruptly returned to normal. In five control patients the migration inhibition factor test gave negative results (figure).

There was no lymphocyte stimulation³ with nifedipine, while lymphocyte response to regular mitogens was normal. An indirect mast-cell degranulation test⁴ gave negative results in the presence of nifedipine.

Migration index (migration of macrophages with donor lymphocytes in presence of antigen: migration of macrophages in control chamber) in patient and five control subjects. Arrow indicates time of challenge with nifedipine. Broken lines show limits of normal values.

Comment

The clinical features of this patient indicated that the liver damage may be attributed to hypersensitivity, since discontinuing the drug resulted in rapid and spontaneous improvement in his clinical condition and the biochemical findings. The positive challenge test with a small dose of nifedipine confirmed its causative role. The clinical course, normal cholecystogram, and results of viral hepatitis-associated tests could reasonably exclude other causes.

The raised alkaline phosphatase activity and IgG concentrations during the acute hepatic injury, their parallel decrease after withdrawal of nifedipine, and their concomitant rise on rechallenge are also important.

Migration inhibition factor production against nifedipine indicated that the patient's lymphocytes had become sensitised to that drug. The abrupt change of the positive result of the migration inhibition factor test to a negative one during challenge with nifedipine may reflect a shift of the sensitised lymphocytes from the peripheral blood pool to the site of injury.

Thus the immunological processes in the hepatic damage may include humoral and cellular mechanisms. The serial migration inhibition factor assays confirmed the clinical evidence when differentiating between allergic drug-induced and viral hepatitis. Nifedipine may be added to the list of drugs causing allergic hepatitis in susceptible people.

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Failure of rubella immunisation after blood transfusion: birth of congenitally infected infant

The dangers of maternal rubella in early pregnancy and the promotion of rubella immunisation programmes have been much publicised recently. This case of congenital rubella syndrome in the offspring of a mother who had received postpartum immunisation on two previous occasions illustrates the potential hazard of failure of immunisation when rubella vaccine is given shortly after blood transfusion.

Case report

The mother's obstetric and immunisation history is summarised in the table. Immunisation was with Almevax (Wellcome). In her fourth pregnancy (last menstrual period 4 November 1978) she was in contact with rubella between 6 and 8 weeks. All three of her children had a febrile illness with a rash diagnosed clinically as rubella by her family doctor. She remained asymptomatic. On 20 December her blood was reported to have "rubella antibodies present"—that is, an HAI rubella screening test titre of 1:80 or greater. The report on a specimen sent from the hospital antenatal clinic on 26 February 1979 was similar. Her baby was born on 22 August 1979 by normal delivery at term + 11 days weighing 3280 g. The infant was pale and had a generalised petechial rash. The platelet count was $34 \times 10^9/\text{l}$ ($34\,000/\text{mm}^3$). The right cornea was opaque and the left hazy. Tonometry showed bilateral glaucoma. The liver was palpable 3 cm below the costal margin and the spleen 1.5 cm. There was a systolic murmur at the 2nd-4th left intercostal spaces. Subsequent cardiological investigation (Dr G Watson) revealed a large patent ductus arteriosus, moderate ventricular septal defect, an atrial shunt through an incompetent foramen ovale, and slight pulmonary stenosis. Audiometry has since shown severe bilateral nerve deafness. The rubella HAI titre was greater than 1:960 and rubella-specific IgM was present. Retrospective testing of the mother's antenatal serum of 20 December 1978 showed a rubella titre of 1:1280 with rubella IgM present.

Obstetric and rubella immunisation history of mother who gave birth to an infected infant in her fourth pregnancy

Pregnancy	Antenatal screening (HAI titre)	Delivery date	Blood transfusion (date and amount)	Indication for transfusion	Immunisation date
First	Not done	6 April 1973	6 April 1973 2 units	PPH	Not given
Second	<1:20	21 June 1974	20 June 1974 2 units	Anaemia	21 June 1974
Third	1:20	31 May 1977	31 May 1977 4 units	PPH	3 June 1977

PPH = postpartum haemorrhage.

Comment

The mother's low HAI antibody titres recorded in 1974 and 1977 may be interpreted either as spurious or as representing antibody concentrations inadequate to protect the fetus. An immune disorder in the mother seems unlikely since normal HAI antibody and specific IgM responses occurred after exposure early in her fourth pregnancy. Failure of rubella vaccination to confer effective immunity may be due to improper storage of the vaccine or to an inherent defect in any particular batch of vaccine. The chance of such a failure occurring twice seems remote.

A small but definite number of persons receiving rubella vaccine fail to show serological conversion to the immune state. Various trials report failure rates of 2% to 5%, depending chiefly on the type of vaccine used. As many as one-third of those vaccinated may respond with a low HAI titre.¹ Reinfection in both immunised and naturally immune subjects is well documented.^{2,3} Such reinfection is more likely when HAI titres are low.^{1,3} Immunisation with RA27/3 strains of vaccine, such as Almevax, is, however, associated with low failure rates, low reinfection rates, and a pattern of immune response closely resembling that following natural infection.³ The evidence for reinfection causing fetal disease is scanty. In only three out of six reported cases of rubella reinfection during pregnancy is there documented evidence of fetal infection.⁴ Grillner and Forssmann⁵ have reported interference with rubella antibody formation when immunisation was given after blood transfusion. The amount of neutralising antibody likely to be present in a unit of donor blood may be sufficient to inactivate the vaccine. The immunisation failure in our patient may be explained in this way, since both her immunisations were immediately after a blood transfusion (table). We therefore suggest that when a blood transfusion has been given recently rubella immunisation should either be delayed or its effectiveness tested serologically.

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Frusemide-induced increases in serum isoamylases

Sporadic reports¹ have suggested that frusemide in some cases may be an aetiological agent in acute pancreatitis, but short-term studies have failed to show any effect of frusemide on the serum concentrations of amylases.¹ While treating patients with severe hypertension with frusemide we measured serum concentrations of pancreatic and salivary isoamylases and compared them with concentrations just before and two weeks after the end of the frusemide treatment.

Patients, methods, and results

We studied eight men and four women aged from 38 to 68 years (mean 56). All had essential hypertension. Frusemide 20 mg twice daily by mouth was added to the previous treatments, which included thiazides in all the patients, and the results were evaluated when the last patient admitted to the study had been treated for four weeks. This gave a mean treatment period of 12 weeks (range 4-27 weeks) and a mean frusemide dose of 75 mg/day (range 40-120 mg/day). Serum samples were taken just before frusemide was started, on the last day it was taken, and two weeks after the end of frusemide treatment. All samples were stored at -20°C until the study was completed,

when all individual samples were assayed, blindly, in the same batch. Amylase isoenzymes were measured by cellulose-acetate electrophoresis.² Mean ($\pm$ SD) concentrations measured in 26 healthy blood donors aged 37 to 60 years (mean 52) were: pancreatic isoamylase 98 ± 35 U/l, salivary isoamylase 91 ± 38 U/l, and total amylase 189 ± 50 U/l. Since amylases are excreted by the kidneys and diuretics cause haemoconcentration, creatinine and albumin concentrations were measured in the same serum samples.

During treatment with frusemide pancreatic isoamylase and total amylase concentrations were significantly higher than those in blood donors ($p < 0.05$ for both). Pancreatic isoamylase increased by 17% ($p < 0.02$, table), salivary isoamylase by 7% (NS), and total amylase by 12% (NS). Individual increments in pancreatic isoamylase correlated positively with increments in salivary isoamylase ($r = 0.76$, $p < 0.001$). No dose correlations could be found. Serum creatinine concentrations were raised by 27% ($p < 0.005$) and the increases in amylase isoenzymes correlated positively with the increases in creatinine ($r = 0.75$ and 0.67 for pancreatic and salivary isoamylases respectively, $p < 0.001$ for both). Albumin concentrations did not change. Individual pancreatic isoamylase:albumin ratios rose slightly higher by a mean 21% ($p < 0.01$). Two weeks after withdrawal of frusemide none of the values differed significantly from prefrusemide levels.

Mean ($\pm$ SD) serum concentrations of amylase isoenzymes, creatinine, and albumin in 12 hypertensive patients before, during, and two weeks after treatment with frusemide in a mean dose of 75 mg/day (range 40-120) for a mean period of 12 weeks (range 4-27)

	Before	During	After
Pancreatic isoamylases (U/l)	110 $\pm$ 41*	129 $\pm$ 56*†	114 $\pm$ 45†
Salivary isoamylases (U/l)	107 $\pm$ 50	114 $\pm$ 45	100 $\pm$ 48
Total amylases (U/l)	207 $\pm$ 62	243 $\pm$ 70†	214 $\pm$ 71†
Creatinine (μ mol/l)	97 $\pm$ 27§	124 $\pm$ 35§*	106 $\pm$ 27*
Albumin (g/l)	45 $\pm$ 2	45 $\pm$ 2	44 $\pm$ 2

* $p < 0.02$. † $p < 0.05$. ‡ $p < 0.01$. § $p < 0.005$.

Conversion: SI to traditional units—Creatinine: 1 μ mol/l $\approx$ 0.0113 mg/100 ml.

Comment

These results show that frusemide treatment is followed by small but significant increases in serum amylase isoenzyme concentrations. Frusemide stimulates pancreatic secretion,³ but no postprandial increases in serum isoenzyme concentrations have been shown.⁴ Therefore this does not seem a likely explanation for the rises in our patients, and the unchanged albumin concentrations in our study seem to eliminate the possibility of haemoconcentration as the cause. The rise in serum creatinine concentrations suggests that the increases in amylase isoenzymes may be explained by decreased renal excretion—especially in view of the highly significant correlation between the increases in the isoenzymes and those in the creatinine concentrations.

None of the patients complained of abdominal pain, but this does not exclude frusemide as causing acute pancreatitis in some cases. On the contrary, since the finding of low concentrations of pancreatic isoamylases is a diagnostic aid in pancreatic insufficiency, our findings suggest that false-normal values may be found in patients treated with diuretics.⁵

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