older children with recovery, and late occurrence as adult cirrhosis may be the manifestations of an age-related variability in the expression of an abnormal gene.

Results of the ferric chloride test were positive in two of the eight patients with adult cirrhosis, and, though only xanthurenic acid excretion was significantly increased in the three patients tested, one belonging to a susceptible ethnic subgroup excreted other metabolites on the pattern of ICC. An increased prevalence of adult cirrhosis was also noted in the pedigrees of patients with ICC. A common metabolic defect may underlie both types of cirrhosis, particularly in susceptible ethnic groups.

The most probable mode of inheritance appears to be through an autosomal dominant gene of intermediate dominance with diminished expressivity and at times reduced penetrance in girls. Given a positive family history, children who excrete abnormally large amounts of two or more of the six metabolites, one of which must be 3-HAA, should be considered at risk. Adults excreting 3-HAA with or without kynurenine may be carriers. But about a quarter of adult carriers and some 10% of children liable to suffer from ICC cannot be detected. With early diagnosis it may be possible to arrest the disease with a low tryptophan diet and massive doses of vitamin B_6. Larger trials earlier in the disease are needed.

The association of ICC with an increased prevalence of peptic ulcer, asthma, diabetes, and migraine in the pedigrees may point to a genetic interrelation among these disorders, and this needs further study.

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HBsAg-positive chronic liver disease: inhibition of DNA polymerase activity by vidarabine

R G CHADWICK, M F BASSENDINE, E M CRAWFORD, H C THOMAS, S SHERLOCK

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Summary and conclusions

Four patients who had chronic liver disease and were positive for hepatitis B surface antigen (HBsAg) were treated with vidarabine, a synthetic purine nucleoside that inhibits DNA polymerase activity in vitro and in vivo. Before treatment all had raised serum DNA polymerase concentrations. Three also had hepatitis B e (HBe) and were shown by electron microscopy to have hepatitis B virus (Dane) particles in their serum. In all patients 10 days' treatment with vidarabine resulted in an immediate loss of DNA polymerase activity. In three patients the activity returned when treatment was stopped. In those three patients Dane particles and HBe antigen persisted during and after treatment; in the fourth patient, who remained negative for DNA polymerase, HBsAg titres fell.

Although vidarabine inhibited virus replication, virus particles did not disappear from the blood in these patients, presumably because the particles were cleared only slowly. Similar results with interferon suggest that the virus disappears, and HBsAg titres fall, some weeks after the fall in DNA polymerase activity. Continued treatment may therefore have a sustained effect on viral replication. Whether vidarabine can permanently clear HBsAg and so arrest chronic liver disease remains to be seen, but at the very least it could reduce the spread of infection.

Department of Medicine, Royal Free Hospital, London NW3 2QG
R G CHADWICK, MA, MRCP, research fellow
M F BASSENDINE, BSC, MRCP, H A M Thompson research fellow
E M CRAWFORD, research assistant
H C THOMAS, PHD, MRCP, lecturer in medicine
S SHERLOCK, MD, FRCP, professor of medicine

Introduction

Vidarabine (adenine arabinoside) is a synthetic purine nucleoside with antiviral activity against a broad group of DNA-containing viruses and some RNA tumour viruses.[1] It is relatively non-toxic,[2] probably does not affect cellular or humoral immune

function,[3 4] and appears to be non-teratogenic.[5] Although its exact mode of action has not been fully elucidated, it seems to block viral DNA polymerase activity and thus inhibits viral replication.[1]

Studies of carriers of chronic hepatitis B have shown the association of raised serum DNA polymerase activity, detectable hepatitis B e (HBe) antigen, and the presence of hepatitis B virus (Dane) particles in the serum.[6] These markers are associated with both high infectivity[7] and a poorer prognosis.[8] They probably reflect continuing replication of the hepatitis B virus.

A trial of vidarabine treatment in patients positive for hepatitis B surface antigen (HBsAg) with chronic hepatitis and detectable serum DNA polymerase activity was performed to see the effects on the markers of infectivity and on the presence of HBsAg in the blood and the liver.

Patients and methods

Four men, aged 23, 28, 31, and 45 years, were treated. Each had had chronic liver disease,[9] proved by liver biopsy, for six months to two years (three with chronic active hepatitis and one with chronic persistent hepatitis). Each had infected at least one other person.

Patients were observed for two to three weeks and then received vidarabine 10 mg/kg body weight/day intravenously in 2 litres of 5% dextrose for five consecutive days during each of two consecutive weeks. Blood samples were taken weekly during the observation period, three times a week during treatment, and then weekly for a further six weeks. Each patient then had another liver biopsy.

Investigations included full blood count, measurement of the prothrombin ratio, and routine liver function tests (serum bilirubin, alkaline phosphatase, aspartate transaminase, albumin, and globulin). Aliquots of serum were stored at −70°C. Serum HBsAg was measured by radioimmunoassay (Ausria II-125, Abbott Laboratories). HBe antigen was demonstrated by immunodiffusion.[10] DNA polymerase activity was measured by the method of Robinson, slightly modified to use 250 µl of serum per test.[11] Uncentrifuged serum samples were examined for 42-nm hepatitis B virus particles by immune electron microscopy using rabbit antibody to HBsAg (Hoechst Pharmaceuticals). Samples were stained with 3% phosphotungstate, pH 7·2 on formvar-coated grids, and examined on a Philips 301 electron microscope.

Results

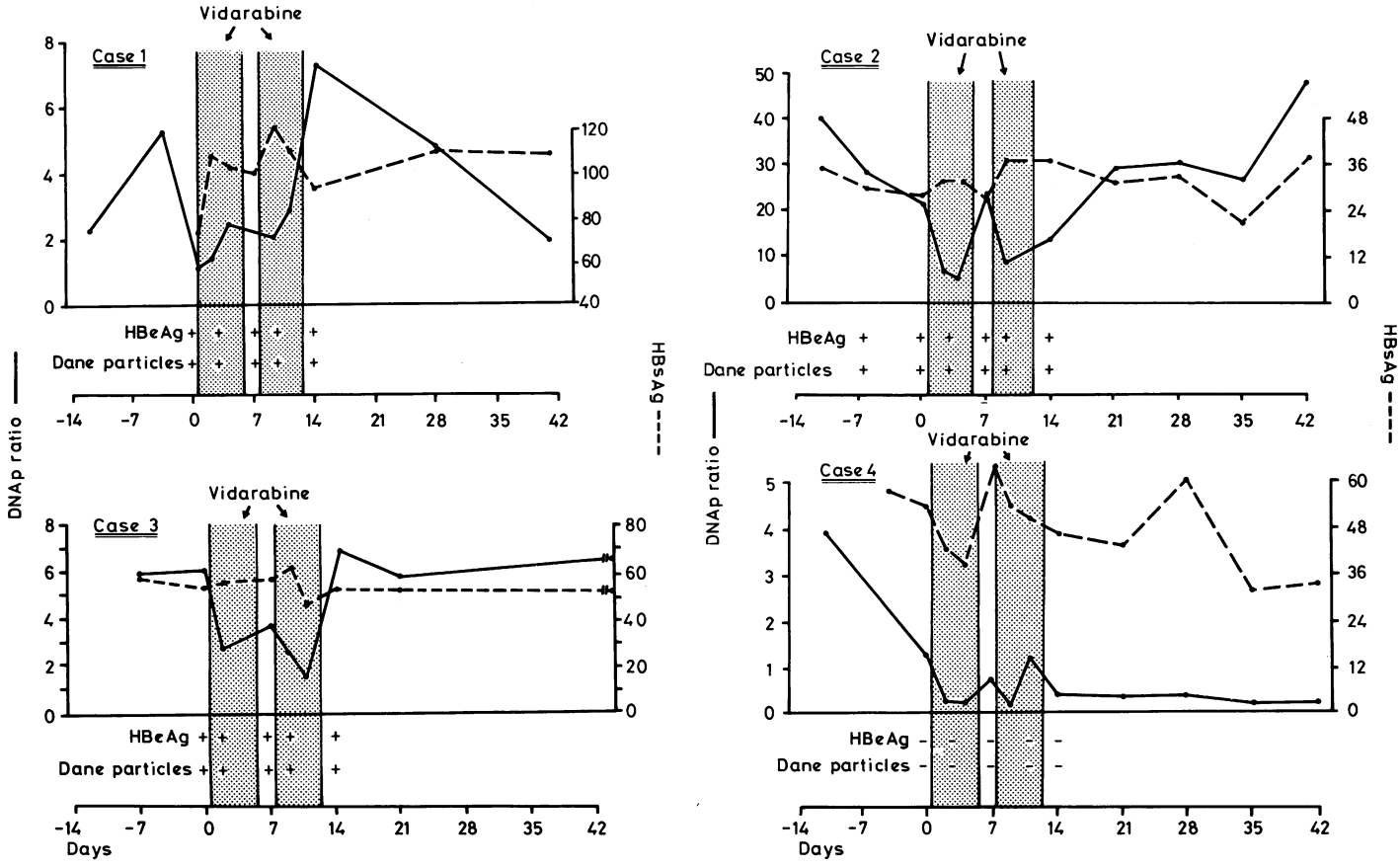
The patients remained well and asymptomatic throughout the trial. Full blood counts and prothrombin ratios remained normal, and liver function values did not change.

In all four patients serum DNA polymerase activity fell immediately towards negative control levels on starting treatment, but in cases 1, 2, and 3 it rebounded as soon as treatment was stopped, both between the two five-day courses and at the end of the course (see figure). In case 4 the DNA polymerase activity subsequently disappeared again and did not reappear.

Three patients (cases 1, 2, and 3) were positive for HBe antigen, and Dane particles were seen in serum samples taken before, during, and after treatment—that is, on days 0, 3, 7, 9, and 14. The fourth patient had no HBe antigen or Dane particles throughout the trial. HBsAg concentrations were essentially unchanged in cases 1, 2, and 3; but they fell to 42% of the pretreatment level in case 4. The liver showed no histological changes, and no change in the distribution of HBsAg in the liver was detected.

Discussion

Hepatitis B virus DNA polymerase activity was reduced to undetectable levels by intravenous infusion of vidarabine.



Hepatitis B viral markers in serum of four patients treated with vidarabine. HBsAg x - - - - - - x is expressed as dilution factor $\times \frac{\text{cpm patient}}{\text{cpm negative control}} \times \frac{1}{1000}$; DNA polymerase activity ●——● is expressed as dpm patient : dpm mean negative control. HBeAg and Dane particles are shown as present (+) or not detected (−).

This inhibition would be expected to inhibit viral DNA synthesis and thus to end viral replication. But we found that 42-nm ("infective virus") particles did not disappear from the blood during treatment, presumably because, although virus replication was inhibited, the clearance rate of the circulating particles was relatively slow in relation to the duration of treatment. Similarly, HBe antigen, a marker for the presence of infective virus, did not disappear from the blood during treatment. The slow clearance of viral particles was similar to that observed after inhibition of virus-specific DNA polymerase by human leucocyte interferon treatment in chronic hepatitis.[12] In these studies the serum titre of HBe fell several weeks after the fall in DNA polymerase activity, and not until then did HBsAg titres fall. The results of vidarabine treatment were also similar to those of interferon in that DNA polymerase activity increased after treatment was stopped. Nevertheless, in the case of interferon continued treatment produced a sustained effect, and vidarabine will probably do the same.

The advantage of vidarabine is ease of synthesis, so that sufficient quantities could be made at low cost for treating the many HBsAg carriers throughout the world. This is in contrast to interferon, which is difficult to prepare, costly, and so in short supply. Whether inhibition of viral replication by vidarabine will permanently clear HBsAg and so arrest chronic liver disease remains to be determined. At the least this form of treatment may, by reducing the concentration of circulating virus particles, reduce the infectivity of the patient, thereby restricting the spread of the infection. Furthermore, its effectiveness may be enhanced, and hence duration of treatment reduced, by the concurrent use of immunostimulants which accelerate the clearance of existing infected cells,[13] while vidarabine prevents further viral replication.

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Haemostatic defect in non-immune patients with falciparum malaria: no evidence of diffuse intravascular coagulation

J VREEKEN, TH M CREMER-GOOTE

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Summary and conclusions

Nine non-immune patients with imported falciparum malaria were examined for signs of diffuse intravascular coagulation (DIC). Although all had thrombocytopenia initially and some later had a decline in plasma fibrinogen concentrations, DIC was never detected, even in severely affected patients with coma and kidney damage. None of the patients were given heparin and all recovered without residual symptoms.

Heparin administration should probably be considered only when clear-cut DIC, which possibly never occurs in falciparum malaria, has been demonstrated.

Department of Internal Medicine, University Hospital "Wilhelmina Gasthuis," Amsterdam, the Netherlands
J VREEKEN, MD, professor of medicine
TH M CREMER-GOOTE, medical technician

Introduction

After diffuse intravascular coagulation (DIC) had been accepted as a clinical entity disorders of haemostasis in severe malaria (especially falciparum malaria) were often recorded as being due to DIC,[1-9] although some investigators disputed this.[10-12] Furthermore, whereas some workers advocate the use of heparin in such cases,[2 4 5 13 14] others do not.[10 15-18]

The past few years have seen an increasing number of non-immune patients who do not or only irregularly take prophylactic antimalarial drugs. Thus the disease may be imported in nearly all parts of the world. This gave us the opportunity to study non-immune patients with falciparum malaria outside the tropics to see whether they had evidence of DIC.

One difficulty in evaluating reports on the possibility of DIC in malaria is the lack of generally accepted criteria for diagnosing DIC. Some workers base the diagnosis on the presence of two or more of the following: decreased platelet count, raised concentrations of fibrinogen or fibrin degradation products (FDP), and decreased concentrations of fibrinogen or other clotting factors. We considered the possibility of DIC when evidence of all the following were present: activation of the clotting mechanism (presence of circulating fibrin monomers), activation of the fibrinolytic system (raised FDP concentrations), consump-