6 mo of the study. Furthermore, six study patients treated with ursodeoxycholic acid failed therapy, indicating that not all PBC patients treated with ursodeoxycholic acid therapy respond. Of equal importance, no patient in either group was noted to have a complete clinical, biochemical and histological remission, which remains the gold standard by which we judge treatment efficacy.

Thus, in summary, the results of this study evaluating ursodeoxycholic acid therapy in PBC suggest we may have yet another drug that is associated with hepatic biochemical improvements and that may have some modest effect on reducing pruritus. However, with regard to hepatic fibrosis, little or no effect was apparently seen. Furthermore, the study falls short in telling us whether a difference exists in response in subgroups of patients based on disease severity. Patients in the clinically most advanced stages of disease were excluded from this study, and the investigators failed to address whether patients with histologically early stage disease responded better than patients who had histologically advanced (fibrotic/cirrhotic) stage disease. It is important to point out that preliminary studies from other centers (10) have suggested that those patients with histological stage 3-4 disease (fibrotic/cirrhotic) have little or no response to ursodeoxycholic acid therapy. Furthermore, studies (11) have suggested that the beneficial biochemical effect of ursodeoxycholic acid therapy may be only temporary and that after a certain period of time hepatic biochemistries again worsen and the disease appears to progress. Finally, other studies (12) have suggested no beneficial effect of ursodeoxycholic acid is seen in PBC patients after 1 yr of therapy.

Clearly, a major advantage of ursodeoxycholic acid therapy is its low toxicity rate. However, its substantial cost will make it important to clearly establish the efficacy of this drug before widespread use in the treatment of PBC. Thus the major questions not answered by this study are the following: (a) Are the beneficial effects of ursodeoxycholic acid in PBC sustainable? (b) Will treatment with ursodeoxycholic acid prolong time to development of cirrhosis, prevent or prolong time to development of complications of portal hypertension and prolong survival time free of liver failure? It appears essential to continue to evaluate ursodeoxycholic acid therapy in long-term, controlled clinical trials to further address these very important questions concerning efficacy.

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HEPATITIS A: NEW INFORMATION ON AN OLD VIRUS

Rosenblum LS, Villarino ME, Nainan OV, Melish ME, Hadler SC, Pinsky PP, Jarvis WR, et al. Hepatitis A outbreak in a neonatal intensive care unit: risk factors for transmission and evidence of prolonged viral excretion among preterm infants. J Infect Dis 1991;164: 476-482.

ABSTRACT

An outbreak of hepatitis A virus (HAV) infection in a neonatal intensive care unit (NICU) provided the opportunity to examine the duration of HAV excretion in infants and the mechanisms by which HAV epidemics are propagated in NICUs. The outbreak affected 13 NICU infants (20%), 22 NICU nurses (24%), 8 other staff caring for NICU infants, and 4 household contacts; 2 seropositive infants (primary cases) received blood transfusions from a donor with HAV infection. Risk factors for infection among nurses were care for a primary infant-case (relative risk [RR], 3.2), drinking beverages in the unit (odds ratio [OR], ∞), and not wearing gloves when taping an intravenous line (OR, 13.7). Among infants, risk factors were care by a nurse who cared for a primary infant-case during the same shift (RR, 6.1). Serial stool samples from infant-cases were tested for HAV antigen (HAV-Ag) by enzyme immunoassay and HAV RNA by nucleic acid amplification using the polymerase chain reaction. Infant-cases excreted HAV-Ag (n = 2) and HAV RNA (n = 3) 4-5 months after they were identified as being infected. Breaks in infection control procedures and possibly

prolonged HAV shedding in infants propagated the epidemic in a critical care setting.

COMMENTS

Hepatitis A virus (HAV) has been a known important cause of viral hepatitis since the discovery of the viral antigen in feces in 1973 (1). Despite the strict attention paid to infection control in most neonatal intensive care units (NICUs) several large outbreaks of HAV infection have occurred in these settings over the past decade (2-5). Although HAV infection is usually spread by way of a fecal-oral route, the index case in this report and others (3, 4) was not an infected health care worker or parent but an infant who received a blood transfusion contaminated with HAV. Transmission of HAV by blood transfusion is uncommon, but donors in the prodromal phase of hepatitis A have been shown to transmit the infection by way of blood transfusion. HAV viremia is estimated to last 2 to 3 wk at most and occurs during the late incubation period of the virus. During this incubation period the donor's AST and ALT are often normal, and thus contaminated blood is not identified by AST or ALT screening (5). As expected from previous studies, no evidence was seen in this report for direct maternal-fetal transmission of HAV infection (6).

Breaks in infection control procedures used in NICUs had obviously occurred because 27% of the susceptible full-time nursing personnel, 16% of the respiratory technicians and 32% of the infants became infected. Furthermore, two household contacts of infected nurses and two family members of infected infants also had HAV infection develop. The novel and important finding of this study was that the authors were able to identify risk factors for the subsequent infection of health care personnel and infants. Not surprisingly, those nurses who cared for one of the two primary infant cases were 3.2 times more likely to be infected than nurses who had not cared for these infants during the period of active infection. Other risk factors for HAV infection included working the night shift, easily contaminating the hands (e.g., not wearing gloves when taping intravenous lines or endotracheal tubes and having long fingernails) and engaging in behaviors that resulted in direct hand-to-mouth contact (e.g., smoking and drinking beverages in the unit). Surprisingly, the practice of not wearing gloves during diaper changes was not associated with a significant increased risk of infection; which had been the case with other enteric infections in day-care centers. The study does not exclude the possibility that blood-borne exposure may have played a role in the spread of the infection within the neonatal intensive care unit because the procedures that placed nurses in contact with blood and other bodily secretions also placed them at a high risk for infection, whereas diaper changing did not. The authors were able to confirm that hospital personnel did facilitate infection of other infants because care by a nurse who cared for a primary infant case was associated with a sixfold increased risk of infection among secondary infant cases. This report again emphasizes the need for strict adherence to infection control procedures for all health care personnel.

Impaired clearance of the organism from infected neonates was investigated by the authors as a possible reason for the large size of the outbreak. Adults infected with HAV are not infectious and cease to excrete fecal HAV antigen within 3 wk after the onset of symptoms (7). Although HAV infection in children is much more likely to be asymptomatic than in adults, fecal excretion studies of HAV antigen have not been performed in children. One study showed that during the second week of illness children were more likely to have detectable fecal viral antigen (46%) than adults (14%), suggesting that children do indeed harbor the virus for a longer period of time; however, this study was not extended for a greater length of time (8). In the present study, three infected infants were observed for longer than 2 mo, and continued fecal excretion of HAV antigen was seen for 1 to 4 mo longer than expected. The authors correctly concluded that this prolonged excretion of the virus probably worsened the HAV outbreak. One might question whether the neonatal immune response was brisk enough to clear the virus promptly. Although the immune response in neonates and preterm infants is poor, all 11 infected neonates had anti-HAV IgM develop within 8 wk of exposure, which is similar to studies in adults. Although the development of anti-HAV antibodies is associated with HAV immunity in adults, the role of the cell-mediated immune response in clearing the initial infection remains to be explained (9). Future studies will no doubt be conducted on the role of the cell-mediated immune response to HAV infection not only in the clearance of the virus but also its possible effect on determining the severity of infection.

As has been the case with other viral infections such as hepatitis B, more sensitive methods of viral detection have better defined the period of infectivity. The polymerase chain reaction (PCR) is currently the most sensitive assay for the detection of viral RNA or DNA. In this study the authors extracted fecal RNA and reverse transcribed the HAV RNA to form a complementary DNA strand that was subsequently amplified. PCR has been used in the past to amplify HAV RNA and sequence the produced complementary DNA to identify different HAV genotypes in different parts of the world (10). Consistent with the sensitivity of the technique, the authors were able to detect HAV RNA by PCR for 1 to 2 mo longer than they were able to detect HAV antigen. Although it remains unclear whether the detection of HAV RNA in the absence of HAV antigen represents true infectious virus, one infant in the present study continued to excrete HAV RNA for 6 mo after the onset of infection without detectable HAV antigen in the stool. This infant was the probable source of HAV infection for a nurse at least 5 mo after the infant had been identified as being infected. At that time the infant's stools were positive for HAV RNA, suggesting that HAV RNA detection by PCR represents true infectivity. Unfortunately, the authors were unable to amplify and sequence the HAV RNA in the nurse's stools and compare it with

that of the infected infant to determine whether the infant was the true source of infection. This report does, however, raise several important clinical questions that can be answered with further studies using PCR technology. The questions include the following: (a) Because PCR is much more sensitive than any previous method for the detection of HAV, what is the actual length of time for HAV fecal shedding? (b) Does the detection of HAV RNA without antigen represent true infectivity? (c) Does prolonged shedding of infectious virus occur in neonates and older children? (d) Because the study suggests prolonged shedding in neonates, does this extend to other immunocompromised hosts as well? (e) Although only one HAV serotype exists, can PCR be used to identify HAV genotypes responsible for more severe or prolonged infections? PCR has proven to be an important tool for the detection of HBV DNA, for the identification of HCV RNA and now will undoubtedly be used to further our understanding of hepatitis A as well.

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