hepatitis as defined by spontaneous PSE (8). Thus this study agrees in large measure with this conclusion, extending the benefit to nonencephalopathic patients with severe hepatic decompensation. However, a number of questions remain. What is the mode of therapeutic action of steroid therapy? Is prednisolone, the initial hepatic metabolite of prednisone, more effective? Interestingly, this drug at this dose and for this period of time exactly reproduces the first positive trial 20 years ago! The North Carolina group produced two positive trials with the randomization of only 37 and 14 patients respectively. What irony! What is the optimal dose regime for this therapy? Finally, having salvaged the patients from early death, should one then introduce long-term therapy with agents such as propylthiouracil (9) or colchicine (10) to prevent a death later? That is, should the patient be enrolled in a therapeutic program rather than be allowed to die from the same cause sometime in the future?

The answer to these and other questions will have to await further careful studies. In the meantime, we appear to have made significant progress in the acute treatment of severe alcoholic hepatitis.

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STATISTICS AND CLINICAL TRIALS: THE CASE OF PREDNISOLONE IN ALCOHOLIC HEPATITIS

The paper by Ramond et al. is the latest in a series of studies that address the effect of prednisolone or similar compounds on survival in patients with acute alcoholic hepatitis. All are well designed and carefully controlled. This paper is no exception. The recommendations made on the basis of all these publications, however, are inconsistent. Why, in such a deceptively simple disease? First, an element of unpredictability is seen in patients with alcoholic liver disease. It has been known for some time that treatment with steroids lowers life expectancy in patients with alcoholic cirrhosis (1), yet there is a rationale to evaluate their use in patients with alcoholic hepatitis even though many patients' studies have both cirrhosis and alcoholic hepatitis. Which lesion is dominant? Secondly, the patient sample evaluated may be heterogeneous. Patients could gain entry to this study by exceeding a value of 32 of Maddrey's discriminant function (D.F.), (2), having encephalopathy or both. Given that the D.F. is composed of only two elements (the serum bilirubin concentration and prothrombin time) and assuming that no patient with a prothrombin ratio greater than 1.5 will have a biopsy, it can be calculated that patients who meet the entry criteria will fall within a range of minimum serum bilirubin concentration of 4.9 mg/dl and a prothrombin time of about 18 sec, or a normal prothrombin time and a bilirubin concentration of at least 32 mg/dl. The fact that 15 of the patients meeting these criteria also had encephalopathy does not necessarily modify the homogeneity of this group. However, patients with less abnormal prothrombin times and bilirubin concentrations could qualify for entry primarily on the basis of encephalopathy, suggesting the possibility that the study population was indeed heterogeneous. In this instance the impact of this reservation is small because it accounts for only four patients. A third and serious problem illustrated by this article is the requirement that placebo and treatment groups be truly similar. Ramond et al. have been singularly unfortunate because, despite their painstaking efforts to randomize at the time treatment started, the prednisolone group was much less ill than the control group, thus favoring a treatment effect. True, no "statistically significant" differences were found, but this may not be the issue. The objective is not to prove "non-difference" but reasonable similarity. Both groups of patients started off with similar D.F.s, and the D.F. increased during the waiting period. In the prednisolone group this increase was significant ($p < 0.05$); in the placebo group this was much more striking ($p < 0.025$). Hence, at randomization the differences between groups could be calculated to have a p value of about 0.1, indicating a substantial probability that the two groups were indeed different. Doubts about the similarity of the two groups are increased when the creatinine values were examined. Expressed as multiples of upper limit of normal at randomization, the prednisolone group had a value of 0.79 ± 0.1 mg/dl, and the placebo group had a value of 0.98 ± 0.11 mg/dl. This suggests that almost one half of the placebo-treated patients had an abnormal serum creatinine value at randomization, compared with substantially fewer in the controls.

Clinicians have been trained to use statistics to identify differences and to reject apparent differences that may have occurred by chance. The objective of studies such as that by Ramond et al. is not to prove that the groups of patients are different at randomization but that they are similar. Similarity and therefore comparability are not necessarily the same as statistical nondifference. However, although it is reasonable to insist that differences at randomization should not favor the treatment effect, it is obviously unreasonable to insist that the groups should be similar to the point of near identify (i.e., a p value approaching 1). This issue may need to be addressed in a different context.

It has been suggested that steroids should be withheld in the management of patients with alcoholic hepatitis "even in desperation" (3). Ramond et al. have made another dent in that recommendation even if it is not as deep as initial inspection of the data suggests. However, they have served us well by raising another question that interaction with our statistical colleagues may be able to address.

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Editor's note: The earlier version of the next review appeared in the May issue (HEPATOLOGY 1992;15:973-974). The updated version is published below. The editor regrets the error.

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 improvements in sanitation and 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 during the last 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 infection have been shown to transmit the virus by way of blood transfusion. HAV viremia is estimated to last at most 2 to 3 wk 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, there was no evidence in this report for direct maternal-fetal transmission of HAV infection (6).

Obviously, breaks occurred in infection control procedures used in NICUs because 24% of the susceptible full-time nursing personnel, 16% of the respiratory technicians and 20% of the infants became infected before the identification of the epidemic. Furthermore, two household contacts of infected nurses and two family members of infected infants also had HAV infection develop. The novel and important findings in this study were 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, those that facilitate contamination of the hands (not wearing gloves when taping intravenous lines or endotracheal tubes and having long