Controlled trials of immunosuppressive therapy in hepatitis

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Summary

Three types of hepatitis are seen in children—acute viral hepatitis, active chronic hepatitis and the neonatal hepatitis syndrome. Few adequate controlled clinical trials of immunosuppressive therapy have been performed in these conditions, and none specifically in children.

Many trials in the 1950s using corticosteroids were performed in acute viral hepatitis. Some showed that steroids were superior to controls and some showed no difference. Later trials confirmed that steroids were of no benefit in uncomplicated viral hepatitis, and further trials are now unjustifiable.

Active chronic hepatitis is seen in all age groups, and there is little clear-cut evidence that the disease differs significantly in children from adults. Three well controlled clinical trials using immunosuppressive agents have been performed in this condition, but all were predominantly in adults. The conclusions were that steroids are the treatment of choice, although azathioprine may have a steroid-sparing effect.

No prospective controlled trials of immunosuppressives have been carried out in the neonatal hepatitis syndrome, and in view of the variable prognosis there is an urgent need for one to be carried out. Large numbers, and a long follow-up period would be necessary and the trial need not be performed double-blind.

Introduction

Both acute and chronic hepatitis are seen in neonates and children, and both have at some time been considered responsive to immunosuppressive agents, particularly corticosteroids. Many conflicting reports have appeared regarding the usefulness of such therapy, but few adequately controlled trials have been performed. None of the reported trials has specifically involved children, although a few children and young adults have been included in some of these trials. This review covers the controlled trials that have taken place, assesses the results and the need for future trials in general and in children in particular. Three topics will be covered—acute viral hepatitis, active chronic hepatitis and neonatal hepatitis.

Acute viral hepatitis

Acute viral hepatitis is a common, but usually extremely mild gastrointestinal infection in childhood. In 1971 only eighteen deaths occurred in Great Britain from this disease in the under 14 age-group, compared to 2607 cases notified (Registrar-General, 1971). Many early trials using ACTH or corticosteroids gave conflicting results, and none was specifically performed in children. Evans, Spring and Nelson (1953) reported a study in which patients were treated with ACTH or placebo, and no difference in the rate of improvement between the two groups was seen. When cortisone was used, recovery was more rapid in the treated group but more patients relapsed. Sborov *et al.* (1954) found no difference in the rate of clinical or biochemical recovery between forty-nine patients treated with cortisone and thirty-six controls, and Ducci and Katz (1955) achieved similar results. Huber and Wylie (1955) found a more rapid improvement in patients treated with cortisone, but no statistics were presented. Naglo, Rydenstam and Silverstolpe (1959) found no difference in the rate of recovery between twenty-five patients treated with ACTH and twenty-five controls, and side-effects from ACTH were a serious problem. De Ritis *et al.* (1964) carried out a trial of prednisone 30 mg/day versus placebo, and no differences were found between the two groups with respect to rate of clinical or biochemical recovery, or duration of the disease. Vakil *et al.* (1965) found very similar results, again using prednisone.

In a series reported by Blum *et al.* (1969), patients with viral hepatitis in Zürich were admitted to one of two hospitals—in one they received steroids and in the other bed rest alone. Retrospective analysis of 457 uncomplicated cases, including children, showed the length of illness to be the same in the two groups, but the relapse rate to be three times as high in the steroid-treated group.

None of these trials was performed in a double-blind manner, and in the earlier ones reported, the statistical analyses were inadequate. However, reviewing the evidence suggests that no definite benefits are conferred by corticosteroids, and in view of their side-effects, further clinical trials in

uncomplicated acute viral hepatitis have not been performed. Indeed, Tygstrup (1969) has written that such trials would be unjustifiable.

Active chronic hepatitis

Active chronic hepatitis has characteristic pathological features (de Groote *et al.*, 1968) and a poor prognosis, even with treatment, with cirrhosis as the end result (Mistilis and Blackburn, 1970). As a disease believed to have an 'auto-immune' basis (Mackay, Taft and Cowling, 1956), immunosuppressive therapy may be beneficial, and early reports (Page, Condie and Good, 1964; Cook, Velasco and Sherlock, 1970) suggested this to be the case. The disease may be seen in all age groups, and though there are a few differences between the childhood and adult diseases, e.g. the presence of microsomal antibodies in younger patients (Walker *et al.*, 1973), the evidence is that they are basically similar. Of ninety-four patients seen in the Liver Unit over a 4-year-period (Reed *et al.*, 1973), six were aged 12 or under. The clinical course, immunological status and histological appearances of liver biopsy specimens obtained from these six children did not differ in general from active chronic hepatitis seen in adults. The results of controlled trials in this condition are probably applicable to children, but it has not been proven.

Three controlled trials of immunosuppressive therapy in active chronic hepatitis have been performed. None of these involved children alone, but a few children were included in all three. Cook, Mulligan and Sherlock (1971) reported a significant improvement in mortality, serum bilirubin, globulin and albumin in twenty-two patients treated with prednisolone 15 mg daily as compared to twenty-seven controls given placebo. Their youngest patient was aged 3½ years. In a trial reported from the Mayo Clinic (Solloway *et al.*, 1972), the liver function tests were significantly better in patients on prednisone 20 mg daily alone or prednisone 10 mg plus azathioprine 50 mg daily, than in patients on azathioprine alone or placebo, within the first 3 months, and at 3½ years patients in these two groups also had a lower relapse rate.

In the King's College Hospital trial (Murray-Lyon, Stern and Williams, 1973), comparing prednisone with azathioprine in a double-blind manner, two patients out of forty-seven were aged 2½ and 7 years respectively. Of the total, twenty-two patients were treated with prednisone 15 mg daily and twenty-five with azathioprine 75 mg daily. The survival, calculated by the life-table method, at 2 years was 95% for the prednisone-treated group and 72% for the azathioprine-treated group. The initial improvement in liver function tests was greater on prednisone and significantly fewer patients developed radiologically proven oesophageal

varices in this group. All the patients who bled from varices during the period of the trial were on azathioprine. However, over a quarter of the patients on steroids developed serious side-effects, such as vertebral fractures or hypertension, compared to none on azathioprine. The results in the children did not differ significantly from those in the adults.

Although relatively few patients included in these trials have been children, the disease and its outcome in this age-group have not differed greatly from that seen in adults. From these three trials there is no doubt that corticosteroids are now the treatment of choice in active chronic hepatitis. However, serious side-effects have been a problem in up to a third of patients, and it may be that a combination of a lower dose of steroids, combined with azathioprine would achieve just as good control without such serious side-effects. A trial of this nature is currently being carried out at King's College Hospital. If a trial were to be performed specifically in children, this combination would probably be preferable to using steroids alone.

Neonatal hepatitis

As discussed elsewhere in this symposium, neonatal hepatitis has a number of distinguishing features, of which one of the most characteristic is giant cell formation (Schaffner and Popper, 1963). The same clinical and pathological features may be seen in response to a number of different viruses, such as cytomegalovirus (Weller and Hanshaw, 1962), herpes simplex (Pugh, Newns and Dudgeon, 1954) and congenital rubella (Stern and Williams, 1966), may occur in congenital biliary atresia, and alpha-1-antitrypsin deficiency, but in most cases the cause is never found. The prognosis is extremely variable, and several reports (Stowens, 1966; Sherlock, 1971) have suggested that one-third die in the acute phase and one-third develop cirrhosis. Corticosteroids have been used (Nelson, 1969; Sherlock, 1971) but the results are conflicting. No controlled trials have been reported, and the need for one to be carried out is urgent. Such a trial should aim to answer the following questions.

- (1) Does treatment with an immunosuppressive agent, e.g. prednisolone, significantly alter the mortality?
- (2) Does treatment significantly reduce the incidence of cirrhosis?
- (3) Do the benefits outweigh the side-effects for the series as a whole?

Since large numbers of patients (seventy-five to one hundred) would be needed to show any clear differences, a trial would either have to be carried out in a special referral centre, or on a multicentre basis. The first question could be answered fairly quickly, but the second would need at least a 2-year

follow-up period on every patient. Patients would be assessed initially, and randomly allocated into a group treated with corticosteroids and a group given a placebo. The criteria for admission should be clinical (e.g. any child between 1- and 16-weeks-old with jaundice and abnormal liver function tests persisting for over 3 weeks) and pathological (e.g. liver biopsy appearances compatible with neonatal giant cell hepatitis) rather than aetiological.

The question of whether such a trial should be double-blind or not is difficult. As has been heard already, the dangers of giving steroids to children are considerable and most people would consider it preferable to know which children were receiving steroids and which were not. Furthermore, the important measurements to make will be the liver function tests, the presence or absence of cirrhosis on liver biopsy, and the mortality rate. Provided the pathologist looked at the liver biopsy specimens 'blind', these measurements are all objective, and the trial need not be conducted in a double-blind manner.

Straightforward statistical analyses may be performed, to compare the median survival time, the changes in liver function tests, and the proportion of patients developing cirrhosis, in each group. The probability of survival of a patient on steroids or on a placebo may be calculated by the life-table method (Bradford Hill, 1971).

Conclusions

It is now established that corticosteroids are of no benefit in uncomplicated viral hepatitis in childhood, although their role in fulminant hepatic failure is still controversial (Williams, 1972). However, either corticosteroids alone, or a lower dose combined with azathioprine, are the treatment of choice in active chronic hepatitis. This is probably true for all ages, although it has not been proven.

No prospective trials have yet been reported in neonatal hepatitis, and in view of the uncertain but generally poor prognosis, such a trial is urgently needed. This trial, for reasons discussed, need not be performed on a double-blind basis.

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Discussion

Professor Wright (Southampton) said he was a little concerned about Dr Stern's flat rejection of the use of corticosteroids in acute viral hepatitis. They may be of value in a small sub-group of patients who have 'bridging' necrosis on liver biopsy and who

have a poor prognosis. These may well have presented acutely but go on to chronic active hepatitis. He agreed, however, that the vast majority of patients with acute hepatitis do not need corticosteroids.