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Sulphasalazine Treatment in Hepatitis B Virus (HBV) Associated Chronic Active Hepatitis (CAH) – A Pilot Study

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The optimum treatment of chronic active hepatitis (CAH) is unknown. Various immunosuppressive agents have been used in the past[1]. The use of prednisolone has been found to be beneficial in patients with severe chronic active hepatitis[2]. The criteria for treatment remain uncertain[3]. Long term follow-up of chronic active hepatitis of moderate severity treated with prednisolone showed that hepatitis B virus (HBV) associated chronic active hepatitis progressed more frequently to cirrhosis than non HBV associated chronic active hepatitis treated in the same way[4]. Another study showed that HBV associated CAH of severe degree responded less well 10 prednisolone than non HBV associated CAH but patients so treated had a better chance of survival than control patients. A more recent paper has implied that treatment of HBV[5] associated CAH with prednisolone was positively harmful[6].

Recent evidence suggests that sulphasalazine has an immunosuppressive effect in addition to its anti-inflammatory and anti-bacterial effects[7]. It has been reintroduced for the treatment of rheumatoid arthritis with apparent benefit[8]. For this reason we have used sulphasalazine for the treatment of HBV associated chronic active hepatitis, and in this paper report the results of a small pilot study.

Patients and methods

Five patients were studied. All were intravenous drug abusers who had been referred to us from the Drug Advisory and Treatment Centre at the Charitable Infirmary. Each patient was physically examined; stigmata of drug abuse, tattoos and stigmata of chronic liver disease were sought. Haematological and biochemical parameters were checked including alanine and aspartate aminotransferase levels and the presence of hepatitis B surface antigen (HB_sAg) was sought. Liver biopsy was carried out, following informed consent.

Histological diagnosis was made in accordance with the criteria suggested in a review by the International Group as published in the Lancet[9]. Each patient was treated with sulphasalazine one gram four times daily for one week followed by one gram three limes daily for six months. No other form of therapy was given. Each patient was seen at monthly intervals during therapy when clinical and biochemical parametres were checked. After six months therapy each patient was readmitted to hospital, clinical examination and laboratory tests were repeated and a second liver biopsy performed. Patients were asked if they had ceased drug abuse and if they had complied with prescribed medication.

Results

All patients were male, aged 20-26 (mean 24) years. Duration of drug abuse was nine to 48 (mean 30) months. All admitted to sharing syringes. All were HB_sAg positive. Four patients were jaundiced at the time of initial biopsy; the non-jaundiced patient had a history of jaundice. In those patients who were jaundiced this cleared during the course of therapy and did not recur. No patient developed any other symptom referable to their liver disease.

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Serum alanine and aspartate aminotransferase levels are tabulated in Tables 1 and 2. In all patients except one (LC) they had returned to normal or near normal levels by the end of six months. These histological findings are tabulated in Table 3. One patient (JM) had cirrhosis on his initial biopsy, this was confirmed on repeal biopsy. One patient (LC) had increased fibrosis on repeat biopsy; the degree of fibrosis was unchanged on a third biopsy although there was some reduction in the cellular infiltrate. Three patients showed histological improvement. All patients claimed to have ceased abusing drugs, four claimed compliance with prescribed medication, one (LC) admitted taking sulphasalazine intermittently only.

Discussion

Four of five patients with HB_sAg positive chronic active hepatitis treated with sulphasalazine showed marked

Table 1

Serum asparate aminotransferase u/1 (normal = 45<u/l)

Patient	Diagnosis	One Month	Six Months	Twelve Months
L.C.	200	78	360	112
J.H.	2090	156	50	–
J.M.	3540	51	23	–
J.R.	1168	230	34	–
S.B.	400	36	15	–

Table 2

Serum alanine aminotransferase u/1 (normal = 40<u/l)

Patient	Diagnosis	One Month	Six Months	Twelve Months
L.C.	54	45	126	70
J.H.	1100	49	42	–
J.M.	1669	33	30	–
J.R.	680	–	34	–
S.B.	174	36	20	–

Table 3

Summary of histological findings

Patient	Biopsy	Cellular Activity	Fibrosis	Cirrhosis
L.C.	1st	+ +	+ +	–
	2nd	+ +	+ + +	–
	3rd	+	+ + +	
J.H.	1st	+ + +	+ +	–
	2nd	+	+	–
J.M.	1st	+ + +	+ + +	Present
	2nd	+ +	+ + +	Present
J.R.	1st	+ +	+ +	–
	2nd	+	+	–
S.B.	1st	+ +	+ + +	–
	2nd	+	+ +	–

clinical and biochemical improvement. We were impressed by the alertness and general well-being of patients treated in this way compared with those treated with prednisolone and azathiaprine which was our previous practice. These four patients showed histological improvement (one had cirrhosis on his initial and repeat biopsy). The fifth patient (LC) felt better, but his biochemical parameters after initial improvement, disimproved. Repeat biopsy of this patient showed increased fibrosis but no alteration in cellular activity. This last patient was switched from sulphasalazine to prednisolone five milligrams twice daily and

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azathioprine 50 milligrams daily for a further six months at the end of which his enzymes were less elevated and liver biopsy showed less cellular activity. Only then did he admit he had taken sulphasalazine only occasionally after the first three weeks of therapy; initial biochemical response suggests that he may have improved had he persisted with therapy.

The treatment of chronic active hepatitis remains unclear. In the past various immunosuppressive agents have been used including 6-mercaptopurine, azathioprine, chlorambucil and cyclophosphamide. Several HB_sAg negative CAH has been shown to respond to therapy with prednisolone[2]. The combination of ten mgs. of prednisolone with 50 mgs. of azathioprine appears to be the safest, most effective, regimen[10]. There is no known therapy at present for HB,Ag positive CAH.

Sulphasalazine appears to have several different actions. It has an antibacterial effect on the gut[11]. It has an anti-inflammatory effect[12]. It inhibits numerous enzymes[13,14]. Sulphasalazine inhibits prostaglandin synthesase in vitro[15] and in human colon specimens[16]. However, another report suggests that the major effect is on prostaglandin dehydrogenase, inhibiting this enzyme and thus allowing a higher concentration of prostaglandin to form[17].

Recently sulphasalazine has been shown to have immunosuppressive effects. Laursen[18] presented data which showed that a prior inoculation of live ascitic tumour cells into the caecal lumen of mice protected against a subsequent graft with the tumour cells and that this protection was abolished by pre treatment with sulphasalazine. Implantation tumours were seen only in animals treated. Furthermore, the response to initial immunisation was also changed in mice treated with sulphasalazine, the protective immune response seen in non-treated animals was suppressed. Rubinstein and his colleagues[7] showed that in the active stage of ulcerative colitis and idiopathetic proctitis circulating complement receptor positive cells were increased whereas T cell percentage and lymphocyte functions were decreased. In severe forms of ulcerative EAC phagocytosing esterase positive cells, indicative of activated monocytes, were demonstrated. Treatment with sulphasalazine reversed these immunological changes.

Sulphasalazine has recently been re-introduced for treatment of rheumatoid arthritis[8] with apparent clinical benefit together with a fall in C-reactive protein and erythrocyte sedimentation rate. It was felt that this action was not due to the salicylate effect of sulphasalazine but could have been due to either its anti-bacterial or immunosuppressive effects.

The place of sulphasalazine in the management of chronic active hepatitis is not yet clear. Our results suggest that it may provide a safe and effective drug for the treatment of HB_sAg positive chronic active hepatitis. In non HBV associated disease it is possible that sulphasalazine also has a place in the management of less severe chronic active hepatitis, or in severe cases it may be possible to use it to maintain an improvement obtained with steroids in the same way as it is generally used in ulcerative colitis[19,20]. We believe the results from this pilot study warrant controlled trials to determine the exact role of sulphasalazine in the treatment of chronic active hepatitis.

Summary

In a pilot study we assessed the efficacy of sulphasalazine in the treatment of hepatitis B virus (HBV) associated chronic active hepatitis (CAH). All five patients showed a clinical and biochemical response at one month. Four patients showed clinical, biochemical and pathological improvement at six months. The fifth patient had deteriorated biochemically between the first and sixth month and histology showed increased fibrosis with no change in the degree of cellular activity. This patient subsequently admitted that he had only taken sulphasalazine for the first three weeks.

This study suggests that controlled trials are needed to test the efficacy of Sulphasalazine in the treatment of HBV associated chronic active hepatitis and probably also in mild cases of non-HBV associated chronic active hepatitis. Its role in maintaining remission induced by corticosteroids and azathioprine in severe chronic active hepatitis should also be determined.

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