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Liv.52 in Viral Hepatitis with Special Reference to its use in Precoma and Coma

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INTRODUCTION

Viral Hepatitis is a systemic viral disease with predominant involvement of the liver. It is a disease of varying severity ranging from mild anicteric hepatitis to acute fulminating hepatitis leading to precoma and coma. The disease is widely prevalent in India. In the Marathwada region of Maharashtra it is endemic with periodic outbreaks of epidemics, especially in the summer and early rainy season.

The mortality rate of hepatic coma (deep) due to viral hepatitis is as high as 90 percent (Sherlock, 1978). Even today there is no specific treatment of viral hepatitis and its complications. The role of steroids is questionable. Corticosteroids have been advocated in acute fulminating hepatitis by many authors (Ducci and Katz, 1951; 1955; Katz and Evans, 1953; and Evans *et al,* 1953). But the mortality rate in cases of hepatic coma due to viral hepatitis remains high. In quest of a drug to treat these cases we were prompted to undertake a controlled clinical trial of Liv.52, an indigenous herbal preparation (The Himalaya Drug Co.).

Liv.52 has been used in various hepatic disorders with encouraging results. (Sule *et al,* 1968; Mukerjee and Dasgupta, 1971; Arora, 1969; Jaffari and Shyam Raj, 1969; Dayal *et al,* 1970; Patel *et al,* 1972).

The exact mode of action of this drug is not very clear. It has been shown to stimulate hepatic functions possibly by reducing intra-hepatic congestion and relieving cholestasis. The drug has diuretic, anabolic, choleretic, stomachic and regenerative properties (Damle and Deshpande, 1966; Kale *et al,* 1966 and Patel *et al,* 1972). It contains extracts of various plants.

Capparis spinosa	23%
Cichorium intybus	23%
Solanum nigrum	12%
Cassia occidentalis	6%
Terminalia arjuna	12%
Achillea millefolium	6%
Tamarix gallica	6%
Mandur bhasma	12%

MATERIAL AND METHODS

A study of 100 cases of viral hepatitis was instituted between the period February 1973 to September 1973. The results obtained were compared with an earlier series of 50 cases treated with corticosteroids. The cases were randomised into two groups: control, on standard supportive therapy without Liv.52; and trial, on standard supportive therapy plus Liv.52. Cases selected for the study were:

1. Cases with serum bilirubin of more than 10 mg/100 ml.
2. Cases with pregnancy having elevated serum bilirubin level (antenatal).
3. Cases of viral hepatitis falling in the immediate post-natal period.

4. Cases of viral hepatitis with precoma and coma.

The patients were classified as:
1. Uncomplicated cases.
2. Cases complicated by precoma and coma.

In both the groups treatment was identical and symptomatic except that cases in the trial group were given Liv.52 in doses of 3 tablets three times a day, crushed and fed through a nasal tube in comatose patients. Paediatric age group patients received Syrup Liv.52 four teaspoonful three times a day. None of the patients in these two groups received corticosteroids. Blood transfusions in both groups were given on the following criteria:

1. Prothrombin time more than twice the control value.
2. Presence of occult gastrointestinal bleeding as detected by Benzidine test.
3. Presence of frank gastrointestinal bleeding.

Cases of precoma and coma received the following additional treatment.
1. Protein-free diet.
2. Bowel wash 8 hourly.
3. Oral Neomycin 6-8 g. a day.
4. Dose of Liv.52 was increased to 4 tablets every 6 hours.

The following investigations were carried out in the present study:
1. Routine haemogram
2. Urine examination for urobilinogen, bilirubin, sugar, albumin and microscopic examination.
3. Urine cultures were done routinely in all cases of viral hepatitis with pregnancy.
4. Bleeding time and clotting time (B.T., C.T.)
5. Biochemical tests:
   (a) Serum bilirubin
   (b) S.G.O.T.
   (c) One stage prothrombin time.

During their stay in the hospital bleeding and clotting time and biochemical tests were done biweekly. In cases of precoma and coma, bleeding time, clotting time and Prothrombin time were done daily. Cases were discharged on the following biochemical criteria:
1. Serum bilirubin less than 4 mg%.
2. S.G.O.T. below 50 units.
3. Prothrombin time showing normal values.

The results of this study were compared with the retrospective analysis of an earlier trial on 50 patients treated with corticosteroids and supportive therapy. Criteria for selection in these cases were similar as in the current study. All these patients had received corticosteroids (Prednisolone 30-40 mg. a day or beta-methasone 4-8 mg. six hourly initially and later tapered off).

Table 1: Table showing sex distribution in the control and trial groups

Sex	Control group on standard supportive therapy without Liv.52	Trial group on standard supportive therapy plus Liv.52	Group on corticosteroids
Male	30	33	38
Female	20	17	12
Total No. of cases	50	50	50

OBSERVATIONS

Table 2: Table showing incidence of various symptoms encountered in 100 cases of viral hepatitis		
Sl. No.	Symptoms	No. of cases
1.	Loss of appetite	80
2.	Yellowness of urine	100
3.	Yellowness of eye	100
4.	Fever	21
5.	Easy fatiguability	45
6.	Nausea	60
7.	Vomiting	43
8.	Abdominal discomfort	65
9.	Itching	23
10.	Oedema feet	13
11.	Disturbances of consciousness	29
12.	Bleeding diathesis	24

In the uncomplicated cases the rate of recovery in all the three groups was more or less the same till the patients left the hospital (Table 2A). However, results in the group with complications showed remarkably significant difference in the survival rate in the Liv.52 treated group (Tables 5 and 6).

Table 2A: Table showing the mean biochemical findings in uncomplicated cases of infective hepatitis							
Sl. No.	Biochemical investigation	Trial group on Liv.52 Uncomplicated cases		Control group without Liv.52 Uncomplicated cases		Corticosteroids group Uncomplicated cases	
		O/A Mean+SD	O/D Mean+SD	O/A Mean+SD	O/B Mean+SD	O/A Mean+SD	O/B Mean+SD
1.	Serum bilirubin (mg%)	11.58 ±3.103	4.617 ±1.651	12.45 ±3.159	4.478 ±1.551	12.57 ±3.19	4.405 ±1.49
2.	SGOT (Units/ml)	131.26 ±40.402	43.39 ±14.82	136.973 ±13.109	41.973 ±13.109	135.972 ±34.33	43.702 ±12.502
3.	Prothrombin time (Sec.)	23.142 ±0.946	18.83 ±3.87	24.76 ±10.236	18.923 ±2.74	+ -	+ -
Normal prothrombin time is 18-22 seconds. There is no statistical difference in the biochemical recovery as analysed by 't' test. + Values of P.T. in corticosteroid group were not available hence not analysed.							

Table 3: Table showing the mean biochemical findings in complicated cases of infective hepatitis in three groups							
		Trial group on Liv.52 Uncomplicated cases		Control group without Liv.52 Uncomplicated cases		Corticosteroids group Uncomplicated cases	
Sl. No.	Biochemical investigation	O/A Mean+SD	O/D Mean+SD	O/A Mean+SD	O/B Mean+SD	O/A Mean+SD	O/B Mean+SD
1.	Serum bilirubin (mg%)	12.08 ±3.62	3.25 ±1.73	12.216 ±1.935	-	12.264 ±2.811	4.26 ±2.09
2.	SGOT (Units/ml)	128.25 ±41.44	31.15 ±11.46	118.75 ±30.837	-	119.65 ±22.96	40.43 ±9.47
3.	Prothrombin time (Sec.)	142.533 ±133.257	21.6	100.750 ±120.624	-	-	-
Normal prothrombin time is 18-22 secs. Since all the patients with complications expired in the control group within a short period, subsequent biochemical values could not be assessed.							

Table 4: Table showing incidence of infective hepatitis in cases associated with pregnancy and relative incidence of precoma/coma in the same group

Sl. No.	Type of cases	No. of cases studied	Cases showing precoma and coma		Cases of improvement from percoma and coma		Remarks
			No.	%	No.	%	
1.	Pregnant antenatal-post-natal patients	29	15	51.7	7	46.6	All the 11 cases which showed improvement
2.	Cases not associated with pregnancy	71	12	16.9	4	33.3	Belonged to the trial group on Liv.52.
3.	Total no. of cases	100	27		11	40.7	
This table indicates that the incidence of precoma and coma in cases of viral hepatitis associated with pregnancy is quite high (51.7%).							

Table 5: Table showing relation of blood transfusion, prothrombin time indices, bleeding diathesis to rate of mortality in complicated cases of infective hepatitis

Case No.	PT	Trial group on Liv.52		Clinical result	Case No.	P.T.	Control group without Liv.52		Clinical result
		Evidence of bleeding	No. of transfusions received in units				Evidence of bleeding	No. of transfusions received in units	
1.	5’	++	3	Expired	1	60"	++	2	Expired
2.	5’	++	2	"	2	45"	+	2	"
3.	5’	++	1	"	3	40"	+	2	"
4.	5’	++	1	"	4	5'	++	1	"
5.	45’	+	1	Improved	5	60"	+	1	"
6.	5’	++	7	"	6	50"	+	1	"
7.	5’	++	8	"	7	30"	—	—	"
8.	22”	—	—	"	8	5'	++	1	"
9.	45”	+	2	"	9	5'	++	3	"
10.	65”	++	2	"	10	2'	+	2	"
11.	20”	—	—	"	11	45"	+	1	"
12.	2’	+	2	"	12	5'	++	2	"
13.	60”	+	2	"					
14.	40”	+	1	"					
15.	60”	+	2	"					

Table 6: Table showing percentage surviving in three groups of complicated cases

Types of cases	Control group without Liv.52				Trial group with Liv.52				Corticosteroids group			
	No. of cases studied	No. of cases improved	Survival	Percentage survived and improved	No. of cases studied	No. of cases impro-ved	Survi-val	Percen-tage survi-ved and impro-ved	No. of cases studied	No. of cases impro-ved	Survi-val	Percen-tage survi-ved and impro-ved
Viral hepatitis with precoma/coma												
With bleeding	11*	Nil	Nil	Nil	13■	9□	9	69.23	9+	Nil	Nil	Nil
Without bleeding	1	Nil	Nil●	Nil	2	2	2	100	4◆	4	4	100
	12	Nil	Nil	Nil	15	11	11	73.33	13	4	4	30.7%

*Out of 11 cases, 5 cases were ante-natal and one post-natal.
●Case was ante-natal.
■Out of 13 cases, 7 cases were ante-natal and one Post-natal.
□Out of 9 cases, 6 cases were ante-natal and one post-natal.
+Out of 9 cases, 2 cases were ante-natal.
◆Out of 4 cases, one case was post-natal and one ante-natal.
The improvement and survival rate with Liv.52 was 73.3% in the cases treated with Liv.52 as compared to zero in the control group and 30.7% in the group on corticosteroids. This is highly significant.
There was no death in uncomplicated cases.

Since all the patients with complications expired in the control group within a short period, subsequent biochemical values could not be assessed.

The amount of blood transfusion was decided by the severity of bleeding, raised prothrombin time and availability. Two patients in the group on Liv.52 were given 7 and 8 transfusions respectively, and in the control group without Liv.52, 1-3 transfusions were given because of short stay due to early death—the patients survived only long enough to receive from 1-3 transfusions.

DISCUSSION

To date despite all measures mortality of hepatic coma (deep) in viral hepatitis is as high as 90 percent (Sherlock, 1968). No specific treatment exists so far in preventing or treating the complications of the disease. A tendency to bleeding is a frequent complication of acute hepatic necrosis. The haemorrhagic diathesis of acute hepatic necrosis is due to intravascular coagulation in addition to impaired hepatic synthesis of the coagulation factors (Rake *et al,* 1970).

In the past and even today the major interest regarding the therapy of viral hepatitis has centred around the use of corticosteroids. The question has been the subject of interest and many discussions. Corticosteroids have been tried by many workers without encouraging results.

In our institute with corticosteroids the mortality rate with hepatic coma remained high. In a retrospective study 50 cases which were admitted in the recent past, were analysed (Table 6). The cases who had evidence of bleeding and were diagnosed as precoma and coma, succumbed to death. While 4 cases who had no evidence of bleeding but had manifestations of precoma/coma improved. In all, percentage improvement in complicated cases was 30.7%.

In the present study, we are particularly impressed by the clinical improvement shown after Liv.52 administration and the significant high percentage of improvement and survival in complicated cases (73.3 percent).

Prothrombin time is considered to be one of the best indices of hepatic dysfunctions (Cook *et al.,* 1965). Prothrombin time was elevated remarkably in the complicated group and hence cases were given transfusion to bring the prothrombin time within normal limits, in order to prevent bleeding. Fifteen patients of the trial group on Liv.52 plus standard supportive therapy received blood transfusion as per criteria mentioned before. They received from one to eight units of blood. In the trial group two patients received 7-8 units of blood, the rest received 0-2 units while in the control group 11 cases received blood transfusion ranging from one to three units. Since most of the patients died early in the control group further transfusions could not be given. It was observed that in the patients who received blood transfusions either the prothrombin time dropped to normal, or despite transfusions the patient continued to bleed with elevated prothrombin time and died. The cases who showed a drop in the prothrombin time after transfusion, improved.

Even with profound changes and virtually incoagulable blood, bleeding is not particularly common unless there is a local lesion of the blood vessels (Flute, 1972). Corticosteroids are known to deplete serum vit. C level (Courtenay, Bartholomew, 1972). In cases of acute fulminating hepatitis where border line vit. C deficiency exists, corticosteroids may aggravate the condition probably by affecting the cement substance of the blood vessels (Courtenay, Bartholomew, 1972), and enable incoagulable blood to leak.

It is interesting to note the incidence of precoma and coma in pregnancy. The effect of pregnancy on the course of hepatitis, or of hepatitis on the course of pregnancy has been a subject of controversy (Bokus, 1965). There are a number of reports that warn that hepatitis does not always run a benign course in pregnancy. the reported data on hepatitis in pregnancy indicate that although the disease

may occasionally be mild it has often proved fatal (Bokus, 1965). In our study (Table 4) out of 29 cases of viral hepatitis associated with pregnancy 15 were with precoma/coma (51.7 percent). While out of 71 cases of viral hepatitis other than the pregnancy group, 12 cases were in encephalopathy (16.9 percent). Urinary tract infection was detected in 20 out of 29 cases of viral hepatitis with pregnancy. We believe that urinary tract infection could be a contributing factor for higher incidence of precoma/coma in this group. In view of this higher incidence of urinary tract infection in this group, routine urine culture of these cases is of utmost importance and an appropriate non-hepatotoxic antibiotic should be administered.

In the present study, we have come across 27 patients of hepatic coma, 15 in the Liv.52 group and 12 in the control group. Eleven patients improved and survived in the Liv.52 group (73.3%), while none improved in the control group. This significantly higher survival rate in the Liv.52 treated group indicates the protective and regenerative effect of the drug Liv.52.

Particularly striking to us is the high rate of survival of patients with hepatic coma, who started bleeding, occult or manifest, through the gastrointestinal tract, and their recovery after administering Liv.52. It would be interesting to study the various causes of bleeding in this group and whether Liv.52 has any role to play in controlling the bleeding diathesis.

SUMMARY AND CONCLUSION

Hundred cases of viral hepatitis, 50 each in the trial and control group, were studied and compared with a retrospective series of 50 additional cases who were on corticosteroids regimen and thus making a total study of 150 cases.

The rate of recovery seemed more or less the same in patients without complication till they left the hospital.

Incidence of precoma/coma is higher in cases associated with pregnancy (51.7%) compared with 16.9% in the rest.

In the trial group, out of 15 cases with precoma/coma, 11 cases improved and survived with Liv.52 (73.3%). In the control group, out of 12 cases of precoma/coma none survived.

In cases who received corticosteroids (13 cases), 4 cases had shown improvement (30.7%). The improvement with Liv.52 in patients with precoma and coma is statistically highly significant.

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