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S B Sinclair, … , R Cameron, G A Levy

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Research Article

The effect of PG on patients with fulminant and subfulminant viral hepatitis (FHF) was studied. 17 patients presented with FHF secondary to hepatitis A (n = 3), hepatitis B (n = 6), and non-A, non-B (NANB) hepatitis (n = 8). 14 of the 17 patients had stage III or IV hepatic encephalopathy (HE). At presentation the mean aspartate transaminase (AST) was 1,844 +/- 1,246 U/liter, bilirubin 232 +/- 135 mumol/liter, prothrombin time (PT) 34 +/- 18, partial thromboplastin time (PTT) 73 +/- 26 s, and coagulation Factors V and VII 8 +/- 4 and 9 +/- 5%, respectively. Intravenous PGE1 was initiated 24-48 h later after a rise in AST (2,195 +/- 1,810), bilirubin (341 +/- 148), PT (36 +/- 15), and PTT (75 +/- 18). 12 of 17 responded rapidly with a decrease in AST from 1,540 +/- 833 to 188 +/- 324 U/liter. Improvement in hepatic synthetic function was indicated by a decrease in PT from 27 +/- 7 to 12 +/- 1 s and PTT from 61 +/- 10 to 31 +/- 2 s, and an increase in Factor V from 9 +/- 4 to 69 +/- 18% and Factor VII from 11 +/- 5 to 71 +/- 20%. Five responders with NANB hepatitis relapsed upon discontinuation of therapy, with recurrence of HE and increases in AST […]

Biochemical and Clinical Response of Fulminant Viral Hepatitis to Administration of Prostaglandin E

A Preliminary Report

S. B. Sinclair, P. D. Greig, L. M. Blendis, M. Abecassis, E. A. Roberts, M. J. Phillips, R. Cameron, and G. A. Levy
Liver Disease Program, University of Toronto, Toronto, Ontario, Canada M5G 1X5

Abstract

The effect of PG on patients with fulminant and subfulminant viral hepatitis (FHF) was studied. 17 patients presented with FHF secondary to hepatitis A (n = 3), hepatitis B (n = 6), and non-A, non-B (NANB) hepatitis (n = 8). 14 of the 17 patients had stage III or IV hepatic encephalopathy (HE). At presentation the mean aspartate transaminase (AST) was 1,844±1,246 U/liter, bilirubin 232±135 μmol/liter, prothrombin time (PT) 34±18, partial thromboplastin time (PTT) 73±26 s, and coagulation Factors V and VII 8±4 and 9±5%, respectively. Intravenous PGE_1 was initiated 24–48 h later after a rise in AST (2,195±1,810), bilirubin (341±148), PT (36±15), and PTT (75±18). 12 of 17 responded rapidly with a decrease in AST from 1,540±833 to 188±324 U/liter. Improvement in hepatic synthetic function was indicated by a decrease in PT from 27±7 to 12±1 s and PTT from 61±10 to 31±2 s, and an increase in Factor V from 9±4 to 69±18% and Factor VII from 11±5 to 71±20%. Five responders with NANB hepatitis relapsed upon discontinuation of therapy, with recurrence of HE and increases in AST and PT, and improvement was observed upon retreatment. After 4 wk of intravenous therapy oral PGE_2 was substituted. Two patients with NANB hepatitis recovered completely and remained in remission 6 and 12 mo after cessation of therapy. Two additional patients continued in remission after 2 and 6 mo of PGE_2. No relapses were seen in the patients with hepatitis A virus and hepatitis B virus infection. Liver biopsies in all 12 surviving patients returned to normal. In the five nonresponders an improvement in hepatic function was indicated by a fall in AST (3,767±2,611 to 2,142±2,040 U/liter), PT (52±25 to 33±18 s), and PTT (103±29 to 77±44 s), but all deteriorated and died of cerebral edema (n = 3) or underwent liver transplantation (n = 2). These results suggest efficacy of PGE for FHF, and further investigation is warranted.

Introduction

Fulminant hepatic failure (FHF)[1] is defined as the development of severe impairment of hepatocellular function associated with hepatic encephalopathy (HE) in the absence of preexisting liver disease (1). FHF occurs with the onset of encephalopathy within 2 wk of initial jaundice, and subfulminant hepatic failure (SFHF) occurs with the onset of encephalopathy within 2 wk to 3 mo of initial jaundice (1). Causes of FHF include viral hepatitis, drugs, toxins, and vascular injury (2). The mortality of FHF ranges from 34% with stage II to > 90% with stage IV encephalopathy (3). Mortality in SFHF may be greater than that in FHF due to the increased proportion of cases of non-A, non-B (NANB) hepatitis infections in this group of patients (4–6). Death can be attributed to a number of complications (7). At autopsy the liver shows massive necrosis, collapse of reticulin fibers, and minimal evidence of hepatic regeneration (3).

Management of FHF consists of supportive measures including repletion of coagulation factors, glucose infusion, treatment of sepsis, and correction of fluid and electrolyte imbalances (8). No significant benefit was shown in a recent, randomized, controlled trial of charcoal hemoperfusion (9). Liver transplantation has been shown to be beneficial to patients with FHF; however, survival is reduced in patients with viral FHF with stage III and IV HE (10, 11). Thus, if transplantation is to be offered to these patients, it should be considered earlier in the course of FHF (12).

PG have received increasing attention as promising, efficacious agents in the treatment of FHF (13). Studies in mice infected with murine hepatitis virus 3 (MHV-3) demonstrated prevention of biochemical toxicity and confluent liver necrosis in animals treated with dimethyl PGE_2 ($dmPGE_2$; 14). The acute beneficial effects of PGE_1 infusion in 10 patients with FHF (6 due to NANB infection and 2 to hepatitis B virus [HBV] infection) have previously been reported (13). In this paper we report the course of 17 patients with fulminant (n = 9) or subfulminant (n = 8) hepatitis due to hepatitis A (HAV), HBV, and NANB viral hepatitis who were treated with PGE_1.

Methods

Patients. 17 consecutive patients presented with FHF or SFHF. Etiologies included NANB hepatitis (n = 8), HBV (n = 6), and HAV (n = 3; Table I). The diagnosis of HAV infection required the presence of IgM anti-HAV; HBV infection required the presence of hepatitis B surface antigen (HBsAg) with or without IgM anti-hepatitis B core antigen (HBcAg); and NANB hepatitis required the absence of IgM anti-HAV, HBsAg, and anti-HBcAg, as well as normal serum levels of copper, ceruloplasmin, and $alpha_1$ antitrypsin. None of the patients had positive antinuclear, antimitochondrial, or anti-smooth muscle antibodies or rheumatoid factor. Serum and urine drug screens were negative.

Please address reprint requests to Dr. Gary Levy, Mount Sinai Hospital, 429–600 University Avenue, Toronto, Ontario, Canada, M5G 1X5.

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1. *Abbreviations used in this paper:* AST, aspartate transaminase; $dmPGE_2$, dimethyl PGE_2; FHF, fulminant hepatic failure; HAV, hepatitis A virus; HBcAg, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HE, hepatic encephalopathy; ICP, intracranial pressure; MHV-3, murine hepatitis virus type 3; NANB, non-A, non-B; PT, prothrombin time; PTT, partial thromboplastin time; SFHF, subfulminant hepatic failure.

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Table I. Clinical Data on Patients with FHF and SFHF

Patient No.	Age	Sex	Etiology	Onset of FHF*	No. of d		Outcome
					PGE_1	PGE_2	
	yr			*d*			
1	56	M	HAV	8	16	—	Alive
2	47	M	HAV	12	10	—	Alive
3	28	M	HAV	4	21	—	Alive
4	38	M	HBV	8	24	—	Alive
5	22	F	HBV	12	28	—	Alive
6	31	M	HBV	9	21	—	Alive
7	33	M	HBV	15	22	—	Alive
8	38	F	HBV	5	4	—	Dead‡
9	28	F	HBV	6	1	—	Alive‡
10	11	F	NANB	34	28	122§	Alive
11	36	F	NANB	62	28	184	Alive
12	21	M	NANB	48	28	246	Alive
13	42	F	NANB	28	2	—	Dead
14	28	M	NANB	38	4	—	Dead
15	31	M	NANB	78	28	6	Alive
16	49	F	NANB	26	28	42§	Alive
17	26	F	NANB	4	1	—	Dead

* Onset of FHF from initial presentation.
‡ Liver transplant.
§ Continues on medication.

The average age was 33±11 yr. Nine patients were males and eight were females.

The diagnosis of acute hepatic failure required evidence of severe hepatocellular dysfunction with marked increases in aspartate transaminase (AST), bilirubin, and prothrombin time (PT), decrease in coagulation Factors V and VII, and the presence of HE as judged by standard criteria, including prolongation of the Trail test (15) and an abnormal electroencephalogram (Table II). All had biopsy evidence of necrosis without cirrhosis. Patients with HAV and HBV infection developed hepatic failure 8.7±3.6 d after initial symptoms, whereas patients with NANB hepatitis developed hepatic failure 40±22 d after initial symptoms.

Protocol of PG therapy. All patients underwent transjugular liver biopsy before study entry. Treatment consisted of an intravenous infusion of PGE_1 (Prostin VR; Upjohn, Kalamazoo, MI). Prostin VR (alprostadil; 500 μg) was diluted in 5% dextrose in water and infusion started at 0.2 μg/kg per h, increased by 0.1 μg/kg per h every 30 min to a maximum of 0.6 μg/kg per h. The dosage was adjusted to the patients' clinical response and the presence of adverse effects. Infusion was maintained for up to 28 d. If by this time there was no improvement in clinical and biochemical parameters, therapy was discontinued and liver transplantation considered. If the patient responded with improvements in both HE and biochemistry, the dose of PGE_1 was gradually reduced. If the patient relapsed upon tapering (rising AST, PT, partial thromboplastin time [PTT], and recurrence of HE), full dose PGE_1 was restarted and continued until remission was again induced. If further attempts to taper failed, intravenous PGE_1 was restarted with simultaneous oral PGE_2 therapy (dinoprostone; Upjohn). If the patient relapsed on combination therapy, he/she was considered for liver transplantation. As required, patients were treated with coagulation factors, glucose, and lactulose. Patients in stage III/IV HE were admitted to the intensive care unit, intubated, and ventilated as indicated.

Informed consent by the nearest relative was obtained until enough improvement occurred to enable the patient to give informed consent. Ethics approval was obtained from the Human Subjects Review Committees.

Outcome and analysis. Blood samples were drawn every 4 h during the acute elevation of enzymes and included hematology, biochemistry, and coagulation indices, including measurements of Factors V and VII. Data are expressed as the mean±1 SD.

Results

At presentation, all patients met the criteria for FHF or SFHF with an elevated AST (1,844±1,246 U/liter), bilirubin (231±135 μmol/liter), prolonged PT (34.2±18 s) and PTT (73.1±26 s), decreased synthesis of coagulation Factors V (7.8±3.9%) and VII (9.4±5.1%), HE (Tables II and III), and appropriate histologic criteria. At initiation of PGE_1 therapy 24–48 h after initial presentation there was a steady rise in AST (2,195±1,810 U/liter), bilirubin (341±148 μmol/liter), PT (36.2±14.6 s), and PTT (75.3±18.3 s), and 14 of 17 patients deteriorated to stage III or IV HE (Table II). Before initiation of PGE_1, patients received an average of 6.2±1.6 U of fresh frozen plasma and 16±8 U of cryoprecipitate per day. Patients were given 10% dextrose to maintain blood sugar at 4–7 μmol/liter. In three cases (patients 9, 13, and 14) intracranial pressure (ICP) transducers were inserted.

Histologic sections from patients 10–12, which are representative of the 17 cases, are shown (Fig. 1). Extensive lobular inflammatory changes were characteristic, with panlobular (n = 11; Fig. 1 *A*), bridging (n = 3; Fig. 1 *B*), or confluent (n = 3; Fig. 1 *C*) necrosis. Parenchymal viability was reduced by 30–95%. 12 of the 17 patients responded to PGE_1. At the time of discontinuance of PGE_1 (10–28 d) the mean AST in these responders was 188±324 U/liter and the PT and PTT improved from 27±7 to 12±1 s and 61±10 to 31±2 s, respectively. Coagulation Factors V and VII increased from 9±4 to 69±14% and 11±5 to 71±20%, respectively (Tables II and III). Requirements for fresh frozen plasma (0.16 U/d), cryoprecipitate (0 U/d), and dextrose were negligible. At cessation of PGE_1 the bilirubin decreased significantly but remained elevated (116±86 μmol/liter), probably reflecting the cholestatic phase of the injury. Liver biopsies performed at the time of cessation of intravenous therapy (4 wk), and subsequent biopsies from all patients showed progressive improvement towards normal. Previously necrotic areas were replaced with regenerating hepatocytes. At first these had a cobblestone pattern but were rapidly remodeled to linear single cell plates (Fig. 1, *D–F*).

A biochemical relapse occurred in all five responding patients with NANB hepatitis (patients 10–12, 15, and 16) when intravenous PGE_1 therapy was tapered, and HE recurred in two. Within 24 h of restarting intravenous PGE_1 improvement was observed in both clinical and biochemical parameters (Fig. 2). Further attempts to discontinue intravenous therapy again resulted in deterioration. To sustain remission, oral PGE_2 was begun at a dose of 2 mg/d simultaneously with intravenous PGE_1. Within 7 d, when clinical and biochemical parameters had returned towards normal, intravenous PGE_1 was tapered and oral PGE_2 was increased to the minimum effective dosage that maintained remission (4–8 mg/d). The liver biopsies in all five patients while on PGE_2 therapy showed significant improvement at 9 wk from start of therapy, but mild focal inflammatory changes remained.

In two of these patients oral PGE_2 was discontinued after 8 and 12 mo of treatment without subsequent relapse (patients

Table II. The Effect of PGE_1 Infusion on Hepatic Function in Patients with FHF

	Pre-PGE_1 infusion						Post-PGE_1 infusion		
	At presentation			At start of treatment					
Patient No.	AST	Bilirubin	HE	AST	Bilirubin	HE	AST	Bilirubin	HE
	U/liter	*μmol/liter*	*stage*	*U/liter*	*μmol/liter*	*stage*	*U/liter*	*μmol/liter*	*stage*
1	1,460	164	I	1,530	225	III	48	136	0
2	2,160	280	I	1,840	410	III	31	210	0
3	1,810	310	I	2,960	365	III	24	286	0
4	680	140	II	456	370	IV	84	160	0
5	1,550	180	II	1,420	214	III	65	110	0
6	1,420	210	II	2,295	345	IV	55	85	0
7	1,445	75	I	1,280	410	III	42	210	0
8	2,850	110	III	4,100	175	IV	978	320	IV
9	4,800	145	III	6,365	192	IV	3,950	184	IV
10	3,140	140	I	2,810	460	I	565	70	0
11	460	220	I	345	150	IV	45	20	0
12	1,740	458	II	1,585	680	IV	1,100	55	0
13	820	340	IV	810	355	IV	640	410	IV
14	663	536	III	1,367	522	IV	401	576	IV
15	1,200	184	I	846	410	II	41	38	0
16	916	384	I	1,116	410	I	156	11	0
17	4,240	60	III	6,195	110	IV	4,740	165	IV
Mean	1,844	232		2,195	341		763	179	
SD	1,246	135		1,810	148		1,398	150	

Normal range: AST, < 35 U/liter; bilirubin, < 18 μmol/liter.

Table III. Effect of PGE_1 Infusion on Coagulation

	Pre-PGE_1 infusion								Post-PGE_1 infusion			
	At presentation				At start of treatment							
Patient No.	PT*	PTT‡	Factor V§	Factor VII§	PT	PTT	Factor V	Factor VII	PT	PTT	Factor V	Factor VII
	s	*s*	%	%	*s*	*s*	%	%	*s*	*s*	%	%
1	22	58	8	12	26	61	7	9	12	31	45	36
2	36	64	4	18	38	72	4	12	11	29	85	75
3	21	57	6	8	29	58	7	9	12	31	57	82
4	28	67	7	22	31	90	5	11	13	32	74	65
5	38	68	5	11	40	54	7	9	13	29	100	90
6	36	72	12	6	32	81	4	8	12	30	65	74
7	28	68	11	3	29	71	7	6	11	29	45	69
8	26	90	7	6	28	110	5	8	24	85	43	71
9	62	90	2	3	58	84	3	4	27	60	38	81
10	16	40	9	14	22	51	7	11	11	31	82	65
11	24	60	5	7	28	72	6	9	14	32	55	42
12	26	54	11	6	32	61	7	6	14	34	58	65
13	84	150	2	6	78	110	3	5	65	>150	4	11
14	28	75	8	11	34	81	7	9	20	49	18	22
15	31	72	11	9	36	81	6	8	11	29	89	110
16	16	48	17	11	21	52	12	9	11	29	69	84
17	59	110	7	6	54	91	8	7	28	41	22	28
Mean	34	73	8	9	36	75	6	8	18	44	56	63
SD	18	26	4	5	15	18	2	2	13	31	26	26

* Normal range, < 11 s. ‡ Normal range, < 35 s. § Normal range, 70–110%.

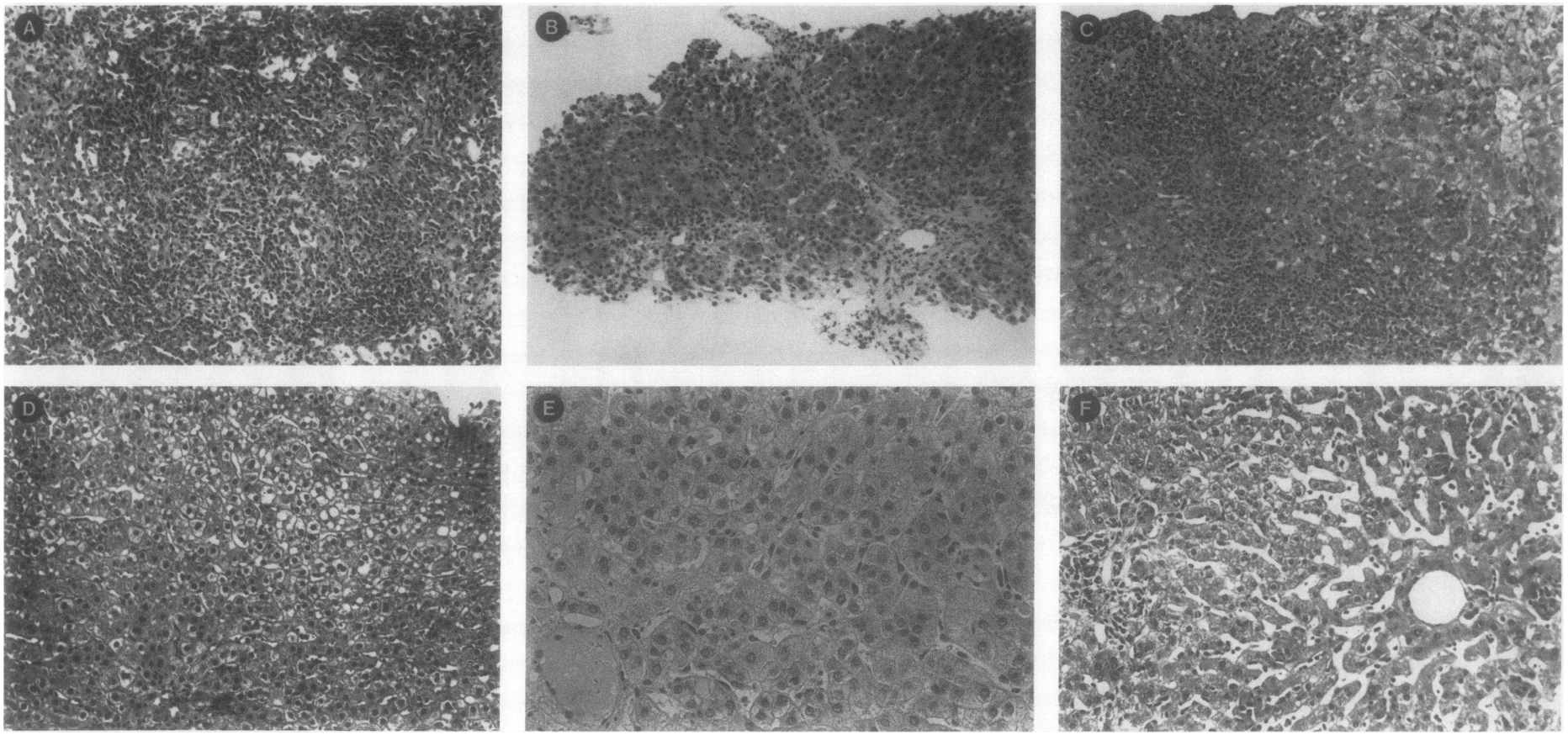

Figure 1. Liver histology in patients with FHF. Pretreatment biopsies: In patient 11 (*A*), acute hepatitis with massive hepatic necrosis (panlobular necrosis). The few hepatocytes that remain are the ballooned cells in the lower right corner of the photomicrograph. In patient 10 (*B*), acute hepatitis with bridging necrosis. A representative area of biopsy showing portal-central and central-central bridging necrosis of hepatocytes. Note the disarray of surviving hepatocytes in mononuclear inflammatory cell aggregates. In patient 12 (*C*), acute hepatitis, classical and severe. The two portal areas shown are both heavily infiltrated by mononuclear inflammatory cells that extend into the surrounding lobule. In the lower part of the micrograph the inflammation extends to the terminal hepatic vein, showing a moderate to severe phlebitis. Post treatment: Patient 11 (*D*) after 146 d of treatment with normal histology of the liver. A portal tract is present in the upper right and a terminal hepatic (central) vein in the lower left of the micrograph. Patient 10 (*E*), while still on maintenance therapy. The necrotic areas have been filled in by regenerating hepatocytes and a cobblestone pattern is noted. Rare mononuclear inflammatory cells are seen. Patient 12 (*F*) 39 d after treatment demonstrating near normal architecture. Liver cell cords are reconstituted and only occasional mononuclear cells are seen. Hematoxylin and eosin ×280.

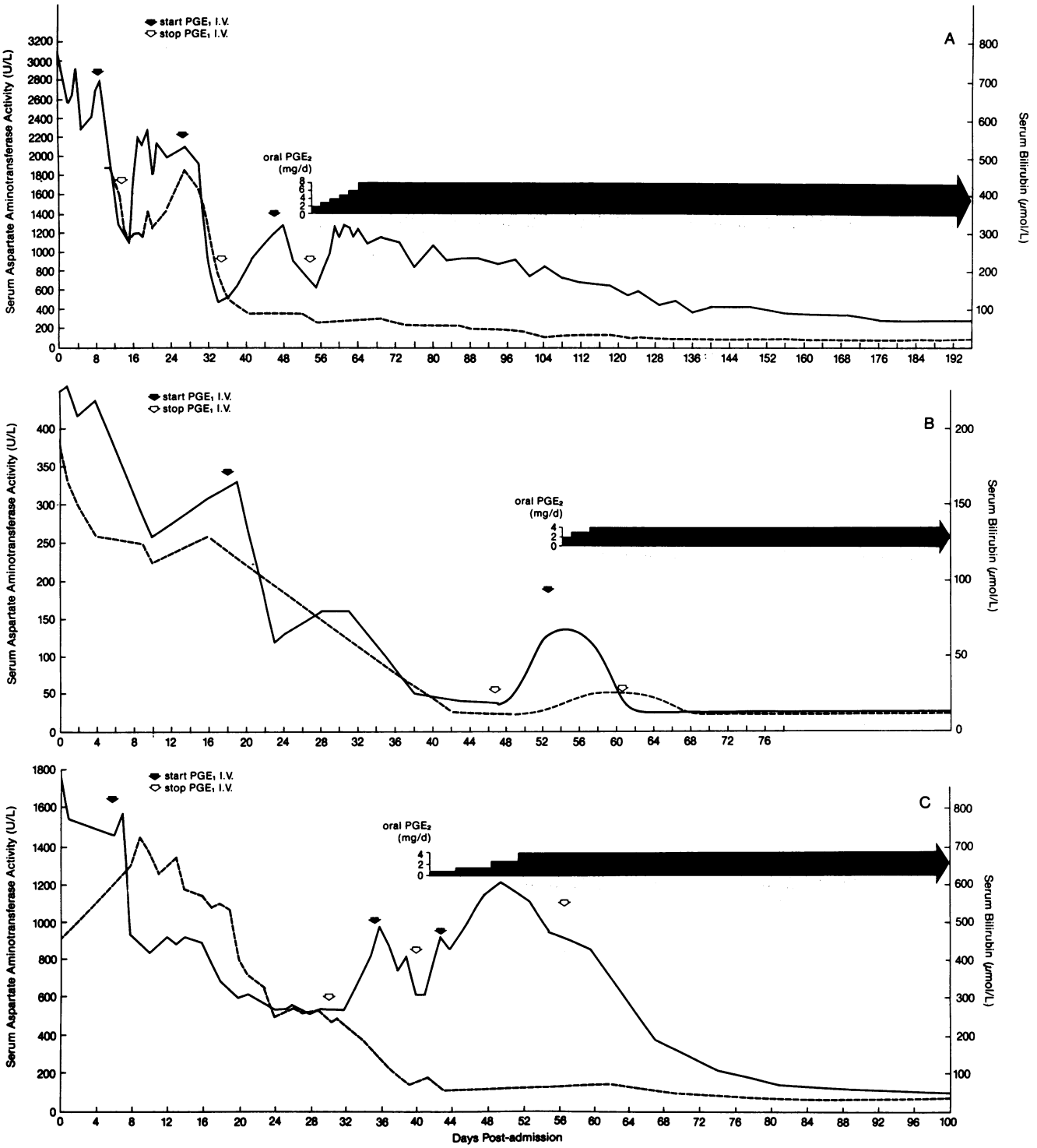

Figure 2. Effect of intravenous PGE_1 and oral PGE_2 on biochemical parameters in patients with fulminant NANB hepatitis. AST and bilirubin were measured in patients 10 (*A*), 11 (*B*), and 12 (*C*) before and after administration of PGE_1 and PGE_2.

11 and 12; Tables II and III). Liver biopsies at the time of discontinuance of PG and at 6 mo followup were both normal. Two other patients (16 and 10) continue on oral PGE_2 at 2 and 6 mo, respectively, with continued improvement in biochemical parameters (Table II) and histology. The fifth patient (15), who had recovered from FHF and was maintained in remission with oral PGE_2, died of biliary tract sepsis. In contrast, none of the patients with HAV and HBV infection who survived relapsed on discontinuation of PGE_1. All of the patients with HBV seroconverted.

Five patients (patients 8, 9, 13, 14, and 17) did not respond to therapy (Tables II and III). Three had NANB hepatitis and two had HBV infection. The onset of HE was rapid (16±16 d). Each had stage III/IV HE at presentation. Within 18 h of the development of FHF all were in stage IV coma. In response to PGE_1 there was a fall in AST (3,767±2,611 to 2,142±2,040 U/liter) and improvement in PT (52±25 to 33±18 s) and PTT (103±29 to 77±44 s) with a reduction in requirement for fresh frozen plasma (12.4 to 2.8 U/d). However, despite this improvement in hepatic function there was a rapid neurologic

deterioration. The ICP measurements in these patients (9, 13, and 14) did not correlate with the clinical findings (mean ICP, 4.7 mmHg; normal, < 10 mmHg). All were listed for liver transplantation, but three (13, 14, and 17) died a brain death. Liver transplantation was performed in the two other patients (8 and 9), but one died of infection shortly after surgery.

The principal side effects of PG therapy in our patients were headaches (n = 8), abdominal cramps (n = 10), fever (n = 6), diarrhea (n = 5), swelling, and paresthesseae in hands, face, or feet (n = 10). However, it was not necessary to discontinue the PG in any of the patients because of side effects.

Discussion

In this study 17 patients with severe FHF and SFHF were treated with PGE_1 and 5 patients with NANB hepatitis were treated with oral PGE_2. All patients had evidence of severe hepatocellular dysfunction with HE. In 12 of 17 patients initiation of intravenous PGE_1 was followed by a prompt and marked decrease in serum aminotransferase activity, improvement in coagulopathy, and resolution of HE. When survival was analyzed by grade of HE at the initiation of the drug, 100% survival was observed in patients with stages I and II HE (n = 3), 100% survival in patients with stage III HE (n = 5), and 45% survival in patients with stage IV HE (n = 9). Overall survival was 71%. These results are better than survival rates reported by several investigators (3, 7). Since all patients had viral FHF and eight had NANB FHF, known to have a worse prognosis (9), these data suggest this treatment is effective even in the most seriously ill patients.

The liver biopsies on admission in all patients showed acute lobular necroinflammatory changes compatible with fulminant viral hepatitis. Of 11 patients with > 80% necrosis, 6 survived. Thus, caution must be exercised in using the biopsy to predict prognosis. In all surviving patients the histology normalized.

In the patients with NANB hepatitis, the rapidity of the response to PGE_1, the relapse on initial cessation of therapy, and the reproducibility of the response during retreatment provide strong evidence that PG had an effect on disease activity, and that these changes were not merely coincidental. Indeed, the natural course of NANB hepatitis often includes spontaneous, wide fluctuations in serum aminotransferase activities (16). When PG administration was maintained at a constant rate, the expected fluctuations in aminotransferases were not observed, but there was a progressive decline in enzyme levels. However, initial attempts to taper or discontinue PG in patients with NANB resulted in a prompt rise in AST. Conversion of PG to oral tablets resulted in maintenance of the remission. After discontinuation of long-term treatment with oral PG, two patients remained in complete remission.

In patients with hepatitis A and hepatitis B no relapses were observed and liver function returned to normal upon tapering of intravenous therapy. There was no evidence of persistent HBsAg in the hepatitis B patients who survived.

Five patients did not respond to PGE therapy. These patients had a more aggressive disease with a short prodrome and development of stage IV hepatic coma within 12–18 h of onset of FHF. This suggests that PGE is ineffective late in the course of the disease. This is similar to our observations in a murine model of viral FHF (14). Whether earlier initiation of PGE would have been more beneficial in these patients is speculative.

PG are derived from 20-carbon essential fatty acids. Almost all cells of the body are able to produce PG, the most frequent type being PGE_2, a mediator of pain and edema in inflammation. PGE_1 is much less abundant than PGE_2, but elicits similar biologic effects. Both are equally potent in causing fever, promoting pain, and suppressing the synthesis of leukotriene B_4 by granulocytes (17, 18). PGE_1 induces the chemotactic response of neutrophils (19) and suppresses the effect of histamine and other mediators of increased vascular permeability (20). As with PGE_2, most of the PGE_1 effects may be explained by a stimulation of adenylate cyclase and the resulting elevated cAMP levels (21). PG have been demonstrated to inhibit IL-2 production (22).

PG have been shown to have a beneficial effect in a variety of animal models of hepatic failure due to toxins (CCl_4, acetaminophen, galactosamine, alcohol), hypoxia, ischemia, and immune mediated disease (23–29). Our group has shown hepatic cytoprotection by $dmPGE_2$ in fulminant MHV-3 infection (30). High titers of infectious virus were recovered from both $dmPGE_2$-treated and untreated animals, suggesting that hepatic cytoprotection occurs without influencing viral replication in this model.

The mechanism of the beneficial effects of PG in these patients has not yet been elucidated. The observation of a marked and sustained decrease in AST after initiation of therapy suggests that PG may be antiviral. In support of this, we have shown that PG treatment of liver transplant recipients with recurrent hepatitis B infection resulted in serologic and histologic clearance of the virus (Sinclair, S. B., H. Flowers, M. Sherman, L. M. Blendis, R. Cameron, M. J. Phillips, P. D. Greig, and G. A. Levy, manuscript in preparation). Alternatively, the ameliorative effect of PG may be through its immunosuppressive properties. PG decreases expression of HLA class I and II antigens (31–33) and PGE_1 inhibits T cell–mediated cytotoxicity against isolated mouse liver cells (28). Indeed, in MHV-3 infection we and others demonstrated increased expression of both class I and II antigens (34, 35), whereas treatment with PGE_1 resulted in decreased expression of these antigens (unpublished data).

Recently, Hoofnagle and others reported the benefit of alpha-IFN in patients with NANB hepatitis (36). The proposed mechanism was antiviral, as IFN resulted in a marked diminution in inflammation as characterized by a decrease in alanine transaminase. This is in contrast to the effect of IFN on patients with hepatitis B, where it is thought to increase immune-mediated destruction of HBV-infected hepatocytes (37). In contrast to the report of Hoofnagle et al., our patients had sporadic infections with no identifiable risk factors for viral hepatitis, suggesting a different etiologic agent.

In summary, 17 patients with fulminant and subfulminant viral hepatitis were treated with intravenous and oral PGE, with clinical, biochemical, and histological improvement. Overall survival was 71%. None of the patients with HBV or HAV infection flared upon tapering of therapy. Tapering of the drug was associated with relapse in the patients with NANB hepatitis, whereas continuous treatment was not associated with the fluctuations typically observed in these patients. Two patients with NANB have now discontinued oral PG and are free of disease 6 mo later. These results suggest that treatment with PG of the E series may be beneficial in patients with fulminant and subfulminant hepatitis. Experience with charcoal hemoperfusion has emphasized the need for controlled randomized trials in this disease (38), and a trial is now underway.

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