Effects of lysine vasopressin and glypressin on the fibrinolytic system in cirrhosis

J. G. DOUGLAS¹, J. A. H. FORREST, C. V. PROWSE, J. D. CASH, AND N. D. C. FINLAYSON

From the Gastrointestinal and Liver Service, and the Regional Blood Transfusion Centre, Royal Infirmary, Edinburgh

SUMMARY In eight patients with cirrhosis of the liver and portal hypertension an intravenous infusion of lysine vasopressin induced a rapid increase in the plasma level of the fibrinolytic proenzyme plasminogen activator. In contrast, triglycyl lysine vasopressin (glypressin; GVP), in a dose known to lower portal venous pressure, produced no fibrinolytic response. This lack of fibrinolytic response represents an advantage of GVP over lysine vasopressin in addition to its longer *in vivo* half-life and lower cardiotoxicity. Clinical trials of GVP in the treatment of bleeding oesophageal varices are needed.

Lysine vasopressin is the standard drug used to treat bleeding oesophageal varices. Its disadvantages include a short half-life, tachyphylaxis, cardiotoxicity and, in normal subjects, it stimulates the systemic release of the fibrinolytic proenzyme plasminogen activator (Gader *et al.*, 1973b). Although the recently developed triglycyl form of lysine vasopressin (glypressin; GVP) does not increase the systemic release of plasminogen activator in normal subjects (Cash *et al.*, 1978), there is no information of its effect in cirrhosis, in which there may be raised levels of this substance and where excessive responses to physiological and pharmacological stimuli may occur (Das and Cash, 1969; Gader *et al.*, 1973a; Robertson, 1971).

We describe the fibrinolytic response to intravenous lysine vasopressin and GVP in cirrhotic patients with portal hypertension. GVP has a lower cardiotoxicity and a long *in vivo* half-life (Aronsen *et al.*, 1975; Vosmík *et al.*, 1977) than lysine vasopressin and, if it produced no rise in plasminogen activator in cirrhosis, it would have potential advantages in the control of bleeding oesophageal varices.

Methods

PATIENTS

The clinical and laboratory details of the patients

¹Address for correspondence: J. G. Douglas, Gastrointestinal and Liver Service, Royal Infirmary, Edinburgh.

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studied are shown in Table 1. Patients 1-3 were deemed to have mild liver disease (albumin and vitamin K corrected prothrombin time ratio normal) and patients 4-8 severe liver disease (albumin and prothrombin time ratio abnormal). All but patient 2 had had ascites, and patient 5 had also had encephalopathy. In six patients the diagnosis was confirmed by liver biopsy. Two patients did not undergo liver biopsy; one because of severe lung disease and the other because of the abnormal PTR and thrombocytopenia. Both these patients had clinical and biochemical evidence of chronic liver disease and liver scans compatible with cirrhosis. All eight patients had portal hypertension, as evidenced by oesophageal varices on barium swallow. None was bleeding at the time of the studies.

Eight patients were infused with 10 µg lysine vasopressin, five with 750 µg GVP (a dose used previously in normal subjects (Cash *et al.*, 1978)), and eight with 2000 µg GVP. All patients gave their informed consent. The infusions were carried out between 9 a.m. and 11 a.m. at intervals of at least a week. All studies were performed in a similar manner. After a 15 minute rest period 50 ml saline were infused into a cubital fossa vein over 15 minutes via a 19 gauge butterfly needle with a Harvard constant infusion pump. The vasopressin, dissolved in 50 ml saline, was then infused over a 15 minute period. Pulse rate and blood pressure were measured at 15 minute intervals before and for 75 minutes after the vasopressin infusion. An electrocardiogram was taken before, every two minutes during each infusion,

Table 1 Clinical and laboratory details of eight cirrhotic patients

Patient no.	Age (yr)	Sex	Bilirubin ($\mu\text{mol/l}$) (3-17)	Alanine aminotransferase (units/l) (10-40)	Alkaline phosphatase (units/l) (15-100)	Albumin (g/l) (36-45)	Prothrombin time ratio (<1.3)
1	55	M	9	18	75	43	1.0
2	49	M	27	47	137	41	1.1
3	68	M	22	52	68	46	1.2
4	58	M	47	47	120	25	1.6
5	49	M	51	27	177	27	1.8
6	54	F	83	28	230	33	1.9
7	48	M	29	22	116	33	1.4
8	63	M	47	21	198	31	1.6

*Normal ranges in parentheses.

and at 15 and 45 minutes after the infusion. Serial blood samples were obtained either through an indwelling needle, or by separate venepuncture.

TECHNIQUES

The plasma plasminogen activator content was assessed by the euglobulin lysis time and unheated human fibrin plate techniques (Cash, 1966). Latex agglutination methods were used to measure serum fibrin degradation products (Thrombo-Wellcotest; Wellcome Reagents Limited, England) and plasmin-antiplasmin complexes (Collen *et al.*, 1977).

Statistical analysis was by Student's paired *t* test.

Results

PLASMINOGEN ACTIVATOR

All five patients with severe liver disease had resting levels of plasminogen activator significantly above those previously found in normal subjects, those with mild liver disease having levels within the normal range (Table 2). The pre-infusion plasminogen activator levels correlated significantly with the plasma albumin concentration ($r = 0.91$; $p = <0.01$) and the prothrombin time ratio ($r = 0.81$;

$p = <0.05$), but not with the plasma bilirubin concentration, alanine aminotransferase, or alkaline phosphatase activities. After infusion with lysine vasopressin, two of those with mild liver disease and all five patients with severe liver disease had rapid rises in plasminogen activator above the normal range. Although the levels after lysine vasopressin in those with severe liver disease were much higher than those with mild liver disease, the former did not have a greater percentage rise over pre-infusion levels than the latter or normal subjects. As in normal subjects, the plasminogen activator levels in the cirrhotic patients returned to pre-infusion levels 60 minutes after the end of the infusion. In contrast, both 750 μg and 2000 μg of GVP produced no change in the plasminogen activator. The results using the unheated fibrin plate technique confirmed the results of the euglobulin lysis time method. Pre-infusion levels of fibrin degradation products and plasmin-antiplasmin complexes were normal and there was no change after lysine vasopressin or GVP.

CLINICAL EFFECTS

During lysine vasopressin and GVP infusions there was a significant, but clinically unimportant, fall in

Table 2 Plasminogen activator levels (as euglobulin lysis time units) in eight cirrhotic patients before and after infusion of 10 μg lysine vasopressin

Patient no.	Minutes					Baseline values before 2000 μg GVP
	0	15	30	60	90	
1	9.4	4.9	54.2	22.4	13.8	5.0
2	13.0	11.1	27.7	14.6	16.3	3.6
3	8.7	5.6	36.1	18.6	6.8	6.1
4	93.0	62.0	118.0	100.0	72.0	59.1
5	52.0	52.0	108.3	52.0	23.6	59.1
6	76.5	46.4	108.0	65.0	46.4	37.1
7	43.3	39.4	76.5	43.3	29.6	26.0
8	21.7	20.6	52.0	32.5	25.0	43.3
Range for normal subjects (n = 5)	4.4-13.8	5.5-12.6	20.0-34.9	10.0-24.5	8.0-18.7	—

The drug was infused from the fifteenth to the thirtieth minute.

GVP infusions induced no change in euglobulin lysis time, though similar pre-infusion values were seen.

the pulse rate and rise in blood pressure which returned to pre-infusion levels within 15 minutes after the infusion. No ECG changes were noted. Facial pallor was seen during all infusions, persisting longer with glypressin. Lysine vasopressin produced abdominal colic in six of eight patients, 750 μg glypressin in one of five patients and 2000 μg glypressin in four of eight patients.

Discussion

In patients bleeding from oesophageal varices, lysine vasopressin is used to reduce portal venous pressure in the hope that this will help stop bleeding. Tachyphylaxis and cardiotoxicity are well recognised problems associated with the use of lysine vasopressin and its ability to increase plasma plasminogen activator may constitute a further less well-recognised difficulty. Although lysine vasopressin did not produce frank fibrinolysis, as evidenced by a lack of increase in fibrin degradation products in the cirrhotic patients, the increased plasma plasminogen activator levels could lead to the lysis of fibrin deposited at the site of variceal bleeding. This might be of great importance in patients with more severe liver disease whose already raised plasma plasminogen activator levels are further increased.

In contrast, GVP, in doses which will lower portal venous pressure (Vosmík *et al.*, 1977), did not increase the plasma levels of plasminogen activator. In addition, GVP has the advantages of a longer *in vivo* half-life and less cardiotoxicity than lysine vasopressin. Although the mode of action of GVP is uncertain, it probably acts as a depot from which lysine vasopressin is slowly released into the circulation. As GVP may have significant advantages over

lysine vasopressin in the treatment of bleeding oesophageal varices, clinical trials would seem indicated to establish its therapeutic efficacy.

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