who is actively bleeding. If no lesion is found at endoscopy (20%),¹¹ or if it is not clear that an ulcer seen on endoscopy is the site of bleeding (a further 20%)¹¹ then arteriography may be carried out if and when there is evidence of further active bleeding.

It has been shown⁸ that arterial drug infusion is effective in the short term in stopping haemorrhage in most cases, as judged by repeat arteriography immediately after stopping the infusion. Our results suggest that it may be of value in aiding resuscitation before surgery, since there was no active bleeding in six out of seven patients treated in this way. Several of these patients were bleeding severely, and the improvement in their clinical condition after drug infusion accompanied by continuing blood transfusion was striking.

The role of arterial drug infusion as a definitive treatment for acute gastrointestinal bleeding is dubious. There was no clinical evidence of a recurrence of bleeding in six out of 10 patients so treated. Probably, however, this proportion of patients would have shown no evidence of further bleeding in the absence of vasoconstrictor infusion. Seven of the 10 patients who received a trial of drug infusion as definitive treatment had a chronic ulcer, and these included the four patients in whom bleeding recurred. The results of Rosch *et al*¹⁰ agree with ours in sug-

gesting that this treatment is of dubious value in such patients. Disappointing results have also been reported in patients bleeding from oesophageal varices.¹² On the other hand, encouraging results^{10 13} have been reported in patients with acute lesions, and further studies, preferably in the form of a controlled clinical trial, seem warranted in this group of patients.

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Plasma cyclic adenosine-3', 5'-monophosphate response to glucagon in patients with liver disease

TERRY F DAVIES, KEN PRUDHOE, ADRIAN P DOUGLAS

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Summary

The change in plasma cyclic adenosine-3', 5'-monophosphate (AMP) was measured after intravenous injection of 1 mg of glucagon in 10 normal subjects and 30 patients with various forms of liver disease. Patients with cirrhosis and those with intrahepatic cholestasis responded normally but in patients with extrahepatic obstruction the plasma cyclic AMP response was considerably increased. Six of the eight patients with cirrhosis and a surgically created portacaval shunt had very reduced responses. This test may prove to be diagnostically important, particularly in differentiating surgical from non-surgical jaundice.

Introduction

Glucagon increases the plasma concentration level of cyclic adenosine-3', 5'-monophosphate (AMP),^{1 2} and the source of this nucleotide is primarily the liver.^{2 3} It therefore seemed likely that this response would be impaired in liver disease and that such studies might yield a diagnostically useful test. We studied the plasma cyclic AMP response to intravenously administered glucagon in normal subjects and those with liver

disease to see how the response differed in various types of hepatic disorder.

Subjects and methods

All subjects were selected randomly as they presented in the clinic. Informed consent was always obtained and the study was approved by the hospital ethical committee. Ten volunteers from the medical staff were studied for control data. All had normal results on standard liver function tests and no history of liver disease. The following patients were studied: 10 patients with established cirrhosis of differing aetiology and severity, none of whom had encephalopathy (they included two with portal hypertension); a further eight patients with cirrhosis who had had shunt surgery from six months to eight years earlier; and 12 patients with cholestatic jaundice, of whom six had severe extrahepatic large duct obstruction and the remaining six had intrahepatic cholestasis (one hepatitis A, three drug jaundice, two sclerosing cholangitis). Table I summarises the liver function test results in these subjects.

After fasting from midnight a cannula was inserted into a peripheral arm vein between 8 am and 10 am. Basal venous samples were

TABLE I—Results of liver function tests in groups studied

	No of subjects	Mean age (years)	Mean aspartate aminotransferase (normal 4-20 IU/l)	Mean alkaline phosphatase (normal 20-90 IU/l)	Mean bilirubin (normal 1.7-17 μmol/l)
Controls	10	27.4	12.9	46.7	7.7
Patients with:					
Cirrhosis	10	58.2	64.2	185.6	118
Portacaval shunts	8	45.0	27.0	146.0	32.5
Extrahepatic obstructive jaundice ..	6	45.2	25.2	257.0	260
Intrahepatic cholestasis ..	6	42.6	52.6	312.7	119

Conversion: SI to traditional units—Bilirubin: 1 μmol/l ≈ 0.058 mg/100 ml.

Department of Medicine, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP

TERRY F DAVIES, MB, MRCP, senior research associate

KEN PRUDHOE, BSC, PHD, biochemist

ADRIAN P DOUGLAS, MD, MRCP, consultant gastroenterologist

obtained for estimating plasma cyclic AMP and glucose concentrations. Glucagon (Eli Lilly) 1 mg in 1 ml of diluent was added to 10 ml of sterile water and injected intravenously via the cannula over 60 seconds at least 10 minutes after the cannula had been inserted. Four of the normal subjects experienced nausea but only one considered it severe. Many of the patients experienced nausea of varying degrees and three with obstructive jaundice actually vomited. Venous samples were obtained at 15, 30, 45, and 60 minutes for plasma cyclic AMP and glucose estimations.

Samples for the cyclic AMP assay were collected on ice into 32-mM theophylline solution with heparin. All samples were centrifuged together, after the final sample was drawn, at 2500 rpm for 10 minutes at 5°C and subsequently stored at -70°C until assayed. A simplified competitive protein-binding assay for cyclic AMP that required no plasma extraction was used.⁴ Tritium-labelled cyclic AMP was obtained from the Radiochemical Centre, Amersham, and pure crystalline adenosine-3', 5'-cyclic monophosphoric acid from the Sigma Chemical Company, St Louis. Glucose was estimated using a Technicon AutoAnalyzer. Statistical analyses were made using Student's *t* test and Simpson's rule for areas under curves.

Results

Blood glucose—The changes from fasting levels after glucagon are shown in table II. Most patients showed a peak glucose response at 30 minutes although those with extrahepatic obstruction often peaked at 45 minutes. The expected reactive hypoglycaemia seen in the controls was absent in all the patients, but no clear-cut differentiation was observed between the different groups of patients.

TABLE II—Blood glucose response to glucagon. Results expressed as mean increase ($\pm$ SE of mean) in mmol/l

Time (min)	Controls (n = 10)	Patients with:			
		Cirrhosis (n = 10)	Cirrhosis and shunt (n = 8)	Intrahepatic cholestasis (n = 6)	Extrahepatic obstructive jaundice (n = 6)
15	1.74 $\pm$ 0.16	1.34 $\pm$ 0.27	0.65 $\pm$ 0.16	1.38 $\pm$ 0.27	0.76 $\pm$ 0.20
30	1.97 $\pm$ 0.41	1.96 $\pm$ 0.31	1.13 $\pm$ 0.33	2.10 $\pm$ 0.33	1.13 $\pm$ 0.34
45	0.64 $\pm$ 0.32	1.72 $\pm$ 0.32	0.67 $\pm$ 0.29	1.18 $\pm$ 0.21	1.97 $\pm$ 0.50
60	-0.47 $\pm$ 0.28	0.97 $\pm$ 0.33	0.54 $\pm$ 0.27	1.48 $\pm$ 0.49	0.84 $\pm$ 0.26

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 10 mg/100 ml.

Plasma cyclic AMP—The mean fasting plasma cyclic AMP ($\pm$ SE of mean) in our normal subjects was 14.3 $\pm$ 2.6 nmol/l (0.47 $\pm$ 0.09 μ g/100 ml). The basal values for the patient groups were significantly higher ($P=0.01$)—at 52.5 $\pm$ 22.00 nmol/l for those with cirrhosis, 41.1 $\pm$ 10.9 nmol/l for those with cirrhosis plus shunt, and 67.6 $\pm$ 27.0 nmol/l for those with extrahepatic obstruction—except for those with intrahepatic cholestasis, whose mean plasma AMP was 20.8 $\pm$ 7.1 nmol/l. The plasma cyclic AMP responses to glucagon in the groups studied are shown in fig 1. The response of the cirrhotic patients was not significantly different from normal. In contrast, however, the patients with cirrhosis plus a surgical shunt showed a significantly lower response than normal ($P=0.001$). Fig 2 shows that only two of these patients achieved a peak response that was within two standard deviations of the normal mean peak cyclic AMP level. One of these patients was thought clinically to have a blocked shunt. The six subjects with severe extrahepatic obstruction showed significantly increased plasma cyclic AMP responses compared with those of the normal controls ($P>0.01$).

Discussion

The changes from normal in the plasma cyclic AMP response to glucagon that we found may prove to be diagnostically useful, particularly in differentiating surgical from non-surgical causes of severe jaundice.

The raised basal plasma cyclic AMP values in many of our patients could not be explained by reduced excretion⁵ since they all had normal creatinine clearance values. Plasma glucagon levels are raised in cirrhosis⁶ and other liver diseases and may contribute to the raised basal plasma cyclic AMP levels.

FIG 1—Plasma cyclic AMP response to glucagon in normal subjects and patients expressed as increase from basal levels (vertical lines show SE of mean).

Conversion: SI to traditional units—Cyclic AMP: 1 nmol/l $\approx$ 0.033 μ g/100 ml.

FIG 2—Increase in plasma cyclic AMP in response to glucagon in eight patients with cirrhosis and a surgically created portacaval shunt (shaded area shows 95% confidence limits of normal response).

Increased extrahepatic production of plasma cyclic AMP and the decreased hepatic clearance may also contribute to the raised basal levels of cyclic AMP.³ Finding membrane fragments in the peripheral circulation of jaundiced patients⁸ raises the possibility that cyclic AMP is released directly into the blood. There were considerable individual differences between the basal cyclic AMP levels within the patient groups, which negated the diagnostic usefulness of this isolated measurement.

The plasma cyclic AMP response to glucagon in our controls was similar to that obtained by others.⁹ The increased response in those with extrahepatic obstruction probably reflected interference with a normally important pathway of cyclic AMP excretion. Studies of patients with a biliary fistula have shown that bile cyclic AMP concentration increases 10 000-fold after intravenous glucagon (unpublished observations). Although, like liver adenylate cyclase, alkaline phosphatase is localised predominantly to the liver cell membrane there was no correlation between serum alkaline phosphatase levels and basal or stimulated cyclic AMP values.

The cyclic AMP response in patients with shunts indicates the possibility of predicting the patency of the shunt by a non-invasive procedure, but this obviously requires further study. The reduced response in six of the eight patients with portacaval shunts may have been due to the dynamic changes in the hepatic circulation reducing the "bolus" effect of the 60-second injection of glucagon. Actual hepatic arterial blood flow is increased in cirrhosis owing to intrahepatic shunting¹⁰ and all our patients with cirrhosis of varying severity and aetiology showed normal cyclic AMP responses. Total hepatic blood flow falls after portacaval shunts, the actual fall varying considerably (mean 50%);¹¹ the effect on hepatic arterial flow is less certain. Glucagon causes gastrointestinal vasodilation¹² but the effect of this on hepatic blood flow is again unknown. Constant hepatic stimulation by glucagon results in a reduced or absent cyclic AMP response^{13 14} and thus patients with raised basal glucagon levels may not be able to achieve a normal cyclic AMP response. Patients with portacaval shunts are known to have particularly raised plasma glucagon levels compared with cirrhotic patients.⁶ A third possibility for the reduced response is damage to the glucagon receptors or the adenylate cyclase system on the cell membrane. There is a large difference between the concentration of glucagon which gives a maximal effect on glucagon output and that which gives maximal binding and activation of adenylate cyclase. Glucagon interacting with only 1% of available receptors can stimulate sufficient cyclic AMP to achieve maximal glucose production.¹⁵ This may have happened in two of our

patients who showed a reduced plasma cyclic AMP response but maintained a reasonable rise in blood glucose.

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Trial of combination of guanethidine and oxprenolol in hypertension

R M PEARSON, M R BENDING, C J BULPITT, C F GEORGE, D R HOLE, F M WILLIAMS, A M BRECKENRIDGE

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Summary

Thirteen hypertensive patients entered a double-blind crossover trial of guanethidine and oxprenolol in combination. In nine patients who completed the trial there was an additive effect on blood pressure, but the combination had a smaller effect on heart rate than was expected from the individual effects, and side effects were not increased. During treatment with oxprenolol the plasma potassium concentration rose from 3.6 mmol (mEq)/l to 3.9 mmol (mEq)/l. No correlation was found between the plasma oxprenolol concentration and changes in blood pressure or response to injected isoprenaline, but measurements of plasma oxprenolol concen-

trations were of value in determining compliance with the protocol.

Introduction

Drug combinations are often used in hypertension both to improve control of blood pressure and to diminish dose-related side effects. Guanethidine, an adrenergic neurone blocking drug, is a powerful hypotensive agent but postural hypotension, diarrhoea, failure of ejaculation, and impotence may limit its use.¹ Oxprenolol, a beta-adrenergic receptor blocking agent, also lowers blood pressure.^{2 3} When two drugs are given together their effects may be equal to, greater than, or less than the sum of the effects of each drug given separately. This study aimed to show whether guanethidine and oxprenolol, which act by different mechanisms, when given in combination would produce an additive effect or potentiate or antagonise one another's action in lowering blood pressure.

Patients and methods

Thirteen outpatients (five men and eight women) with essential hypertension were selected for study. Their ages ranged from 40 to 65 (mean 45.6) years. Their average lying blood pressure at presentation was 203/120 mm Hg. Apart from two patients whose blood pressure was inadequately controlled with guanethidine alone none were on treatment before the trial. No patient had a history of angina, myocardial infarction, heart failure, stroke, or asthma. All had grade 1 or 2 hypertensive retinal changes and a plasma urea of less than 10

Department of Clinical Pharmacology, Royal Postgraduate Medical School, Hammersmith Hospital, London W12

R M PEARSON, MB, MRCP, research fellow (now honorary lecturer, Medical Unit, Royal Free Hospital, London NW3)

M R BENDING, MB, MRCP, research fellow

C J BULPITT, MSc, MRCP, honorary consultant physician

C F GEORGE, MD, MRCP, senior registrar (now professor of clinical pharmacology, Faculty of Medicine, University of Southampton)

D R HOLE, BSc, technician

F M WILLIAMS, PhD, assistant lecturer

A M BRECKENRIDGE, MD, FRCP, senior lecturer in medicine (now professor of clinical pharmacology, New Medical School, Liverpool)