Preliminary Communications

Glucagon and Haemodynamics of Acute Myocardial Infarction

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Summary: Glucagon was administered to six patients with acute myocardial infarction. Three of them had cardiogenic shock syndrome. Glucagon produced a positive inotropic response in all cases, which resulted in a significant rise in blood pressure, with only slight chronotropic effect. No arrhythmias were induced, and all patients with cardiogenic shock improved temporarily. Further evaluation of glucagon in shock syndrome to determine the dose and method of administration is required.

INTRODUCTION

The hormone glucagon is a polypeptide secreted by the alpha cells of the islets of Langerhans. Its effect on hepatic glycogenolysis and its use in the treatment of hypoglycaemia are well known (Sokal, 1966). Recently this hormone has been shown to have an inotropic and chronotropic effect in animals (Glick *et al.*, 1968 ; Lucchesi, 1968) and in humans with chronic heart disease (Parmley *et al.*, 1968 ; Brogan *et al.*, 1969 ; Williams *et al.*, 1969). Unlike catecholamines glucagon does not cause ventricular arrhythmias (Linhart *et al.*, 1968 ; Katz *et al.*, 1969). The purpose of this study was to assess the value of glucagon as an inotropic agent in acute ischaemic heart disease. When this action had been confirmed it was used therapeutically in patients with cardiogenic shock syndrome.

METHODS

Six men aged 46 to 73 were investigated. All had had an acute myocardial infarction within the preceding 24 hours. The diagnosis was confirmed in all cases by electrocardiography. Three (Cases 4, 5, and 6) had severe cardiogenic shock syndrome as judged clinically by cold extremities, low blood pressure, impaired sensorium, and severe oliguria. All patients were in sinus rhythm. As this was part of a larger study on cardiogenic shock (to be reported later), two patients (Cases 4 and 5) had received isoprenaline and adrenaline without a satisfactory response.

Glucagon (lyophilized glucagon hydrochloride dissolved in 1 ml. of the accompanying diluent, 1 mg./ml.) was injected into the pulmonary artery in doses of 1 to 3 mg. Basal haemodynamic measurements were recorded before therapy and at frequent intervals after the injection of glucagon for 40 minutes. Arterial pressures were recorded from a brachial artery catheter and pulmonary artery and pulmonary wedge pressures were recorded via a No. 6 Lehman catheter, which was passed via a median cubital vein with the aid of a bedside portable image intensifier. Pressures were recorded by a Mingograf 24 B and an Elema-Schonander E.M.T. 490 A transducer. Cardiac outputs were determined in three patients by a dye-dilution technique using indocyanine green and Waters's cuvette and densitometer, blood being withdrawn from the brachial artery by a Waters or Harvard pump. The peripheral vascular resistance was determined by dividing the mean arterial pressure by the cardiac output (litres per minute) and is expressed in units.

RESULTS

The haemodynamic results before and after glucagon for each patient are presented in the Table. The effect of glucagon on cardiac output and systolic blood pressure in a shocked patient (Case 6) is shown in Fig. 1. The maximal effect of glucagon on the cardiac output and systolic blood pressure in both the shocked and the non-shocked patients is shown in Fig. 2.

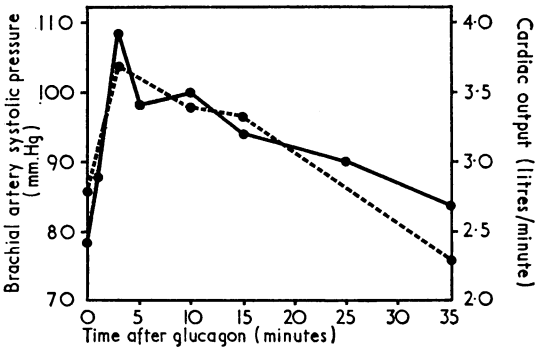

FIG. 1.—Case 6. Response of brachial artery systolic pressure (continuous line) and cardiac output (broken line).

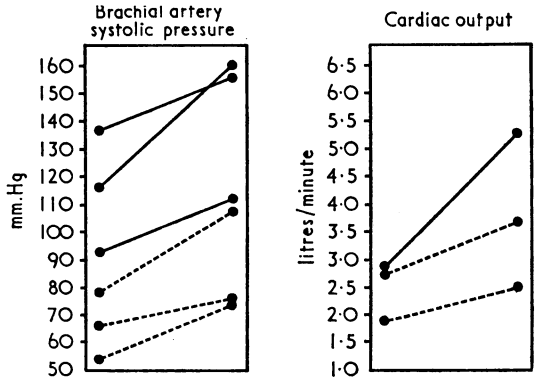

FIG. 2.—Maximal responses of brachial artery systolic pressure and cardiac output following glucagon. (●——●: non-shocked patients; ●---●: shocked patients.)

Heart rate: five patients had an increase which ranged from 5 to 16 (average mean 8·8) beats per minute. Systemic pressure: there was an increase in systemic and mean arterial pressures in all patients, ranging from 10 to 34 (average mean 22) mm. Hg and 6 to 32 (average mean 14) mm. Hg respectively. Pulmonary artery and wedge pressures: only small alterations were observed, but there was an increase in pulmonary wedge pressure in one patient with shock (Case 5) ; we were unfortunately unable to measure simultaneous pulmonary artery pressure in this case. Cardiac output and stroke volume: increases occurred in the three patients in whom these were measured ; two (Cases 5 and 6) were in shock ; the cardiac output increase was 0·6 and 0·9 l./min. in the two shocked patients and in Case 3 it was 2·4 l./min. ; the stroke volume increased by 4·4 and 4·1 ml. in Cases 5 and 6 and by 34·5 ml. in Case 3. Peripheral vascular resistance: there was a reduction in two of the three patients studied from 25 to 19·6 units and from 25 to 21 units (Cases 3 and 5). Electrocardiogram: P–R interval was unaltered ; no arrhythmias were induced. Side-effects: nausea occurred in three patients, and in one patient was accompanied by vomiting.

Haemodynamic Response to Glucagon

Case No.	Dose of Glucagon (mg.)	Time (mins.)	Heart Rate (beats/min.)	Pulmonary Wedge Pressure (mm.Hg)		Pulmonary Artery Pressure (mm.Hg)		Brachial Artery Pressure (mm.Hg)		Cardiac Output (l./min.)	Cardiac Index (l./min./sq.m.)	Stroke Volume (ml.)	Peripheral Vascular Resistance (units)
				Pressure	Mean	Pressure	Mean	Pressure	Mean				
1	2	0	125	17/13	15	25/12	18	136/85	100	—	—	—	—
		5	125	—	—	—	—	148/84	105	—	—	—	—
		10	125	—	—	—	—	156/84	110	—	—	—	—
		15–20	115	—	—	26/12	18	140/76	100	—	—	—	—
		30	115	—	—	27/11	16	128/72	88	—	—	—	—
2	1	0	70	17/5	8	27/8	13	93/50	64	—	—	—	—
		1	74	—	—	—	—	96/56	—	—	—	—	—
		5	80	—	—	35/8	16	100/54	70	—	—	—	—
		10	75	10/5	7	36/7	17	112/56	80	—	—	—	—
		30	74	10/3	5	38/7	17	102/54	61	—	—	—	—
		40	74	10/4	5	31/7	15	104/51	64	—	—	—	—
3	3	0	62	9/5	7	16/7	11	116/60	72	2·9	1·6	46·5	25
		2	68	—	—	—	—	140/68	88	—	—	—	—
		4	65	6/4	5	—	—	160/76	104	5·3	2·9	81	19·6
		10	62	12/8	9	—	—	142/66	88	4·2	2·3	67	20·9
		18	62	11/8	9	—	—	136/66	86	3·5	1·93	56	24·5
		25	62	11/8	9	—	—	132/64	83	—	—	—	—
		30	62	8/5	7	21/9	11	136/68	80	—	—	—	—
		40	62	—	—	—	—	120/64	76	2·7	1·49	43·5	28
Patients with Cardiogenic Shock													
4	3	0	83	17/9	12	51/27	33	66/40	50	—	—	—	—
		5	83	17/9	12	—	—	76/44	58	—	—	—	—
		10	88	—	—	—	—	68/42	54	—	—	—	—
		15	83	14/8	9	—	—	64/40	54	—	—	—	—
		20	83	14/8	10	—	—	—	—	—	—	—	—
		40	83	—	—	50/22	30	68/40	52	—	—	—	—
5	3	0	136	13/10	12	27/10	14	54/40	48	1·9	0·96	14	25
		3	143	26/20	22	—	—	72/46	52	—	—	—	—
		5	143	—	—	—	—	72/46	54	—	—	—	—
		10	136	31/25	27	—	—	74/48	54	2·5	1·26	18·4	21·5
		15–20	136	—	—	22/8	13	70/44	50	—	—	—	—
		30	143	—	—	—	—	64/41	46	—	—	—	—
6	3	0	120	16/4	7	28/8	12	78/44	48	2·8	1·71	23·3	17·2
		1	115	18/5	6	—	—	88/46	52	—	—	—	—
		3	136	—	—	33/12	16	108/58	64	3·7	2·25	27·4	17·3
		5	125	—	—	30/9	14	98/52	60	—	—	—	—
		10	125	—	—	33/11	14	100/56	62	3·4	2·06	27·1	18·2
		15	120	12/4	7	—	—	94/50	60	3·3	2·01	26·7	17
		25	120	—	—	—	—	90/50	60	—	—	—	—
		35	120	16/4	7	—	—	84/50	56	2·3	1·4	19·1	24·3
		50	115	15/5	7	—	—	80/48	54	—	—	—	—

Discussion

Following acute myocardial infarction complicated by cardiogenic shock the cardiac output, stroke volume, and brachial artery pressure are decreased (Shubin *et al.*, 1967), leading to decreased tissue perfusion and the clinical syndrome of shock. A drug which increases the cardiac output and systemic pressure without adversely affecting the cardiac rhythm or peripheral vascular resistance should be helpful in these circumstances. Isoprenaline, which has inotropic qualities, has a variable effect on blood pressure in shock syndrome, because it may significantly decrease the peripheral vascular resistance which results in hypotension (Shubin and Weil, 1967). It also increases the heart rate considerably and can cause serious tachyarrhythmias which nullify its inotropic effect. Similarly, the pressor agents, such as noradrenaline, exert mild inotropic effects and increase the peripheral vascular resistance (Kuhn, 1967), which has the disadvantage of increasing the work-load on the heart.

Our studies both in the control group and in three severely shocked patients show that glucagon has a positive inotropic effect which results in a significant rise in systemic blood pressure. The chronotropic effect was mild and did not interfere with ventricular filling or stroke volume. Unlike other inotropic agents, glucagon in our small series did not produce any arrhythmias. A fall in peripheral vascular resistance occurred in two of the three patients in whom this was calculated, but was not severe enough to decrease the blood pressure. The rise in pulmonary wedge pressure in one patient (Case 5) cannot be readily explained.

The three patients in cardiogenic shock all temporarily improved. The mean systolic blood pressure, cardiac output, and stroke volume, when measured in two patients, rose significantly. There was improvement in the sensorium, and one patient who was acutely ill survived for 22 hours. The other two patients died within 10 hours of starting treatment.

The lack of success in these patients might have been due to an inadequate dose of glucagon. After the administration of glucagon a rise in blood pressure was evident within five minutes in all patients, but the effect lasted less than an hour. Further evaluation of glucagon would appear to be indicated to determine the therapeutic dosage and method of administration. Linhart *et al.* (1968) gave repeated doses of glucagon intravenously in one patient with hypotension following major cardiac surgery with good effect. Brogan *et al.* (1969) administered an infusion of glucagon in the treatment of refractory cardiac failure. We used an intravenous infusion of glucagon in a relatively small dose (5 mg. of glucagon in 300 ml. of 5% dextrose) in only one patient (Case 6) after an initial intravenous dose of 3 mg. and a more sustained response was noted.

The mechanism of the haemodynamic action of glucagon is not fully understood, but it is thought to act as a beta-adrenergic receptor stimulator and is similar to catecholamines in this respect (Sutherland *et al.*, 1968). It differs from catecholamines in that its inotropic effect is not antagonized by beta-adrenergic blockade (Glick *et al.*, 1968).

We wish to thank the technicians of the cardiac department and the nursing staff of the coronary care unit, Dudley Road Hospital, for their assistance in carrying out this study. We are grateful to the physicians of Dudley Road Hospital for allowing us to treat patients under their care.

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Medical Memoranda

Acute Post-streptococcal Toxaemic Renal Failure

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Renal glomerular lesions are a recognized sequel to infection with Lancefield's group A beta-haemolytic streptococci (Longcope, 1936). Coincident tubular lesions have also been described (Watt *et al.*, 1959). We here describe a case of acute renal failure without significant glomerular damage occurring after what would appear to have been a streptococcal infection.

Case Report

A 33-year-old man initially complained of a sore throat. Two days later he was given oral penicillin by his family doctor. He did not improve, and over the next two days experienced malaise, anorexia, and persistent sore throat. Four days later he became delirious and had a high temperature. A small erythematous area appeared on the right wrist. Within a few hours the right arm became painful, red, and swollen. His legs were stiff and he had difficulty in walking. His speech became slurred and incoherent. At this stage he was admitted to Torbay Hospital under Dr. M. G. Thorne.

On admission he was found to have a pyrexia of 104° F. (40° C.), pulse 134/min., and blood pressure 130/80. He was distressed, and hyperventilating to the point of tetany. There was bilateral conjunctivitis and pronounced inflammation of the pharynx, with small pustules on the tonsils. Intramuscular ampicillin was substituted for the oral penicillin. Next day he remained febrile, appeared to be more disorientated, and had weakness of the right arm, right leg, tongue, and facial muscles. Patches of erythema had appeared on the left forearm and left leg. A diagnosis of streptococcal septicaemia was made. In view of the muscle weakness a polyneuritis was suspected and he was given hydrocortisone intramuscularly.

During the next 24 hours he became clinically jaundiced, incontinent of faeces, and semicomatose. Over this period he had passed only 224 ml. of urine, which contained numerous granular casts. In an attempt to prevent incipient renal failure 100 ml. of 10% mannitol was given intravenously with dextrose saline, but no diuresis resulted. The blood urea rose to 412 mg./100 ml., and he was transferred to the Royal Devon and Exeter Hospital for management of his renal failure—eight days after his initial sore throat.

Results of some of the investigations at this time were: blood pressure 170/100; haemoglobin 10·2 g./100 ml. (two days previously it had been 14·5 g./100 ml.); white blood cells 44,000/cu. mm., 80% neutrophil polymorphs; serum bilirubin 7·5 mg./100 ml.; serum electrolytes within normal limits; serum aspartate transaminase 195 S.F. units/100 ml.; serum albumin 3·2 g./100 ml. Two blood cultures were negative. Cold agglutinins were present in the serum. The urine contained sugar (1%), ketones, protein, and numerous granular casts.

It appeared that the patient was suffering from a septicaemia or bacteraemia, but the organism responsible was still unknown. He was therefore treated with ampicillin, cloxacillin, and cephaloridine. Hydrocortisone was continued. The renal failure required immediate dialysis. Haemodialysis was performed with a twin-coil Kolff apparatus and the use of indwelling femoral-vein catheters. Seven haemodialyses were undertaken during the next 16 days, each for an average of seven hours. In the first seven days of this period he needed four dialyses, as his blood urea tended to rise rapidly, owing, it seemed, to his hypercatabolic state. Post-dialysis blood ureas averaged about 217 mg./100 ml., larger falls being avoided in order to prevent the "disequilibrium state." For the first 10 days of admission he passed a total of 2,540 ml. of urine. Thereafter daily urine volumes increased until he reached the diuretic phase of renal recovery 19 days after admission.

Within a week of admission his jaundice had faded, but he was still drowsy and a little disorientated. Electroencephalography at this time showed widespread slow activity consistent with a generalized cerebral disturbance. The serum aspartate transaminase had fallen to 59 S.F. units/100 ml. The white cell count remained about 20,000/cu. mm for about four weeks. Renal biopsy was performed 18 days after the onset of his illness. The pathologist, Dr. Stewart Smith, reported: "The glomeruli are not exceptional. There is oedema of the intertubular tissue and alteration of tubular epithelium in many places, suggesting regeneration after damage. There are focal collections of inflammatory cells, chiefly plasma cells and lymphocytes, particularly marked in the juxta-medullary region" (see Figs. 1 and 2).

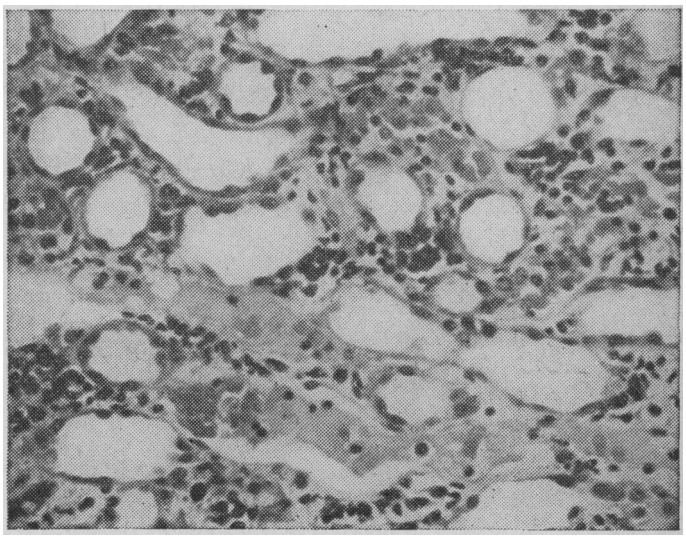

FIG. 1.—Juxta-medullary region showing interstitial cellular reaction and tubular casts. (H. and E. ×155.)

Progress

The patient made a gradual recovery and was discharged five weeks after the onset of his illness. At this time his urine was still about 1,006 S.G. and blood urea 47 mg./100 ml. After discharge he developed an asymptomatic urinary infection with *Escherichia coli*, which responded to the appropriate antibiotics. Seven months