THE USE OF GLUCAGON FOLLOWING OPEN HEART SURGERY IN CHILDREN

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SUMMARY
Glucagon 50 μg/kg was given intravenously to five children showing evidence of "low output failure" after open heart surgery. The glucagon was injected intravenously, via a tap in an intravenous infusion set, at half hourly intervals. The systolic and diastolic arterial pressures rose on average 32 and 41 per cent and there was a small fall in pulse rate. Therapy was given for periods of 14 to 40 hours. Blood sugar concentrations remained within the usual range found after this form of surgery. There was no clinical evidence of vasoconstriction during glucagon therapy. Glucagon may be useful in the treatment of low output states following cardiac surgery and cardiac arrest.

Glucagon is a polypeptide hormone produced by the alpha cells of the pancreas, and acts like catecholamines to stimulate phosphorylase activity in the liver, thus increasing glycogenolysis and so raising the blood sugar level. The glycogenolytic effect of glucagon and catecholamines increases the activity of adenylyl cyclase, an enzyme that catalyses the conversion of adenosine monophosphate (ATP) to cyclic adenosine 3' 5' monophosphate (AMP). Cyclic AMP stimulates phosphorylase activity with the production of glucose-1-phosphate from glycogen (Sutherland, Robison and Butcher, 1968).

Glucagon
\[ \text{Catecholamine} \]
\[ \text{ATP} \rightarrow \text{Adenyl Cyclase} \rightarrow \text{AMP} \]

Glycogen \[ \rightarrow \text{Phosphorylase} \rightarrow \text{Glucose-1-phosphate} \]

These authors have found that the actions of many hormones are related to their capacity to increase the activity of adenylyl cyclase in the target organ. This sets in motion a chain of actions which ultimately results in the physiological response of that organ. The beta inotropic effects of catecholamines are mediated via an increase in myocardial adenylyl cyclase activity and several workers have now shown that glucagon also increases the rate and force of contraction of the heart in animals (Farah, and Tuttle, 1960; Lucchesi, 1968; Glick et al., 1968), and in man (Linhart et al., 1968; Mahon, March and Klein, 1968; Parmley, Glick and Sonnenblick, 1968). Glucagon has been used in patients with refractory congestive cardiac failure (Williams et al., 1968; Brogan, Kozones and Overy, 1969; Lal and Fletcher, 1969; Nord, Fontanes and Williams, 1970), after prosthetic valve replacement (Sonnenblick, Parmley and Matloff, 1968), and following acute myocardial infarction (Diamond et al., 1970a, b).

Following open heart surgery, a clinical picture may develop that is often termed "low output failure". The features of this state are poor peripheral perfusion, low arterial pressure, low urine output, and raised central venous pressure. In this situation, catecholamines such as adrenaline or isoprenaline are often given intravenously for their inotropic effect, but they also increase peripheral vascular resistance, increase the irritability of the myocardium, and may cause serious cardiac arrhythmias. Digitalis is also indicated in these states of myocardial failure, but its use in combination with catecholamines administered intravenously can also induce serious cardiac arrhythmias. As a result of the above clinical reports of the use of glucagon in cardiac failure, 5 children who had developed the classical picture of "low output failure" following open heart surgery, were given glucagon intravenously for periods of 14 to 40 hr.

MATERIAL AND METHODS
The five children who were given glucagon (table I) had undergone repair of congenital heart defects using cardiopulmonary bypass at 36°C. The radial
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Table I. Relevant clinical details of 5 children who received glucagon intravenously in a dose of 50 μg/kg following open heart surgery.

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Wt. (kg)</th>
<th>Diagnosis</th>
<th>Duration of glucagon therapy (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>6</td>
<td>Fallot's Tetralogy</td>
<td>15</td>
</tr>
<tr>
<td>2.</td>
<td>5</td>
<td>Fallot's Tetralogy</td>
<td>32</td>
</tr>
<tr>
<td>3.</td>
<td>10</td>
<td>Fallot's Tetralogy</td>
<td>28</td>
</tr>
<tr>
<td>4.</td>
<td>6</td>
<td>Fallot's Tetralogy</td>
<td>14</td>
</tr>
<tr>
<td>5.</td>
<td>12</td>
<td>Coronary sinus fistula</td>
<td>40</td>
</tr>
</tbody>
</table>

artery was cannulated at the beginning of operation and connected to a Statham pressure transducer, the arterial trace being displayed on an oscilloscope during the operation and the postoperative period. Samples of arterial blood were taken during the operation, and twice daily during the postoperative period for measurement of pH, Pco₂, Po₂, and base excess. Base excess exceeding -5 m-equiv/l. was corrected with 8.4 per cent sodium bicarbonate i.v. The electrocardiogram was monitored during the operation and in the postoperative period by displaying the trace from lead II on an oscilloscope. Venous pressure measurements were made using a catheter passed through the saphenous vein into the inferior vena cava, the zero point being the mid-axillary line with the patient supine. Aortic crossclamping was used routinely during cardiac bypass to stop coronary blood flow and to keep the inside of the heart relatively free from blood. After operation, all patients were mechanically ventilated with 40 per cent oxygen in air, and Pco₂ levels were maintained within the range 30 to 40 mm Hg. Plasma electrolyte and blood sugar estimations were carried out twice daily and levels maintained within normal limits by appropriate supplementary therapy.

Patients who were in congestive cardiac failure preoperatively were digitalized. Glucagon, 50 μg/kg, was given at the end of bypass because previous experience had shown that a single intravenous injection at this stage invariably caused an increase in systolic and diastolic pressures which was sustained for 4 hour. Myocardial depression is arrested immediately after cardiopulmonary bypass, especially following aortic crossclamping (i.e., periods of myocardial ischaemia) and ventriculotomy. It is important to maintain a mean arterial pressure of at least 50 mm Hg after bypass so that both peripheral and coronary perfusion are adequate, and glucagon was found to be a satisfactory myocardial inotropic agent at this stage. Blood loss was estimated colorimetrically and replaced by transfusion, the central venous pressure being increased to 25 cm H₂O if this was necessary to produce a systolic pressure greater than 90 mm Hg. If in spite of these measures the arterial pressure, cardiac output as judged by peripheral perfusion, and urine output remained low continuous glucagon therapy was started. Previous experience had shown that a sustained increase in arterial pressure and cardiac output could be achieved by giving glucagon 50 μg/kg every 30 min by direct intravenous injection, usually through a three-way tap in the intravenous infusion. The hourly pulse and blood pressure record of 5 patients who were given glucagon in this way were studied for the first 12 hours of therapy, although cases 1–5 received glucagon for 15 hr, 32 hr, 28 hr, 14 hr, and 40 hr respectively. In each case continuous glucagon therapy was started when a clinical picture of "low cardiac output failure" developed despite adequate blood volume.

Case reports

Case No. 1.
Cardiopulmonary bypass lasted 84 min at 36°C, and the aorta was crossclamped for 40 min. Glucagon 1 mg was given at the end of bypass. Sinus rhythm returned spontaneously and a satisfactory cardiac output was established. During the postoperative period half strength Hartmann solution in dextrose 5% was given i.v. at a rate of 60 ml/hr. Glucagon therapy was started 4 hr after bypass and continued for 15 hr. This patient was not digitalized.

Case No. 2.
Cardiopulmonary bypass lasted 60 min at 36°C and the aorta was crossclamped for 30 min. Glucagon 0.75 mg was given at the end of bypass. Half strength Hartmann solution in dextrose 5% was given intravenously postoperatively at 50 ml/hr. Glucagon therapy was commenced 16 hr after cardiac bypass and continued for 32 hr. This patient was digitalised pre- and postoperatively. The clinical record of this case is shown in figure 1.

Case No. 3.
Cardiopulmonary bypass lasted 70 min at 36°C and the aorta was crossclamped for 63 min. Glucagon 1.3 mg was given at the end of bypass and sinus rhythm returned spontaneously. During the postoperative period half strength Hartmann solution in dextrose 5% was given intravenously at 60 ml/hr. Glucagon therapy was commenced 4 hr after cardiac bypass and continued for 28 hr. This patient was digitalised before and after operation.

Case No. 4.
Cardiopulmonary bypass lasted 70 min at 36°C and the aorta was crossclamped for 30 min. Glucagon 0.8 mg was given at the end of bypass. Simultaneously sinus rhythm returned. Ventricular tachycardia developed 30 hr after cardiac bypass and glucagon therapy commenced at this time and continued for 14 hr. During the postoperative period half strength Hartmann solution in dextrose 5% was given intravenously at 50 ml/hr. This patient was digitalised before and after operation.
Case No. 5.

Cardiac bypass lasted for 85 min at 36°C, and the aorta was crossclamped for 37 min. Glucagon 1.5 mg was given at the end of bypass and sinus rhythm returned spontaneously. One hour after bypass, atrial tachycardia developed and 5 hr later glucagon therapy was commenced and continued for 40 hr. During the postoperative period half strength Hartmann solution in dextrose 5% was given intravenously at 70 ml/hr. This patient was not digitalized. The clinical record of this patient is shown in figure 2.

FIG. 1. Clinical record of patient, age 5 years, weight 15 kg, who underwent repair of Fallot's Tetralogy and developed a "low output failure" situation following surgery. The effect on arterial pressure and pulse rate of intravenous glucagon, given half hourly in a dose of 50 μg/kg can be clearly seen.

FIG. 2. Clinical record of patient age 12 years, weight 30 kg, who underwent repair of a right coronary sinus fistula using cardiopulmonary bypass. Atrial tachycardia developed postoperatively and he went into "low output failure". Intravenous glucagon, given half hourly in a dose of 50 μg/kg resulted in a falling pulse rate with a rising arterial pressure and an improvement in the general condition of the patient.

RESULTS

The mean percentage changes in systolic and diastolic pressure, and pulse rate, during 12 hr of glucagon therapy are shown in figure 3. One hour after commencing glucagon therapy, there was a mean rise of 14% and 18% in the systolic and diastolic blood pressures, and a 4% fall in pulse rate. Subsequently the systolic and diastolic pressures continued to rise and after 8 hours the mean increases in systolic and diastolic pressure were 32% and 41% respectively. At 8 hours there was a small fall in pulse rate, mean 6%. The range of blood sugar levels before therapy were 100–345 mg%, during therapy 65–530 mg%, and during the 36 hr after discontinuing therapy 50–165 mg%. The blood sugar levels did not vary beyond those normally found in patients undergoing open heart surgery in this unit. No persistent cardiac arrhythmias were seen on the electrocardiogram which could be attributed to glucagon, and it was used effectively to increase cardiac output in cases 4 and 5 who developed ventricular and atrial tachycardia respectively.

DISCUSSION

In the 5 patients studied, it was found that intravenous administration of glucagon 50 μg/kg every half hour produced a consistent increase in systolic and diastolic pressures and a small fall in pulse rate. Previous experience in 45 patients who had low arterial pressure after cardiac bypass showed that a single intravenous injection of glucagon 50 μg/kg always caused a rise in systolic and diastolic pressures. It was noticed that the effect of isolated doses began to wear off after 30 min. This led to the use of this drug by intermittent intravenous injection every half hour. A sustained rise in arterial
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pressure is obtained by this means. Parmley, Glick and Sonnenblick (1968) and Diamond and associates (1970a), found that the inotropic effect of intravenous glucagon given at cardiac catheterization lasted for approximately 30 min, and that the inotropic effect was apparent whether the patients were digitalized or not. They found no increase in myocardial irritability. Although glucagon plays a part in the control of blood sugar levels, its use in the way described did not result in values being obtained which lay outside those normally encountered in postoperative open heart surgery patients in this unit, and did not result in any apparent complications in this respect. There was no "rebound" hypoglycaemia on discontinuing therapy.

Glucagon has been shown to have a positive inotropic effect on the myocardium in man (Linhart et al., 1968; Parmley, Glick and Sonnenblick, 1968; Murtagh et al., 1970), and may thus be useful in certain clinical situations of heart failure. The results suggest that it is an effective myocardial stimulant in children following repair of congenital heart defects under cardiopulmonary bypass. It appears safe to administer a dose of 50 /ig/kg every half hour by intermittent intravenous injection, for periods of 40 hr when it produces a sustained increase in arterial pressure with no apparent side effects.

Recently, Diamond and associates (1970a) compared the haemodynamic effects of glucagon and noradrenaline in patients with left ventricular failure following myocardial infarction. They concluded that glucagon produces the same increase in cardiac output with less myocardial oxygen cost. Goldschlager and associates (1969) investigated the effect of glucagon on the coronary circulation in adults with and without coronary artery disease. They noted significant increases in heart rate, mean arterial pressure, and tension time index dp/dt, and left ventricular work. Myocardial blood flow increased significantly whilst myocardial oxygen consumption remained constant, suggesting that the augmentation in blood flow was sufficient to meet the increased myocardial demands for oxygen. The effects of glucagon on the coronary circulation resemble those of isoprenaline rather than noradrenaline, without leading to the production of arrhythmias seen with catecholamines. Also, glucagon does not increase peripheral vascular resistance, but rather a reflex fall in peripheral resistance resulting from the increase in cardiac output (Parmley, Glick and Sonnenblick, 1968).

Experience with these cases has led to the use of glucagon as a myocardial stimulant following cardiac arrest, and in other situations of low cardiac output resulting from myocardial insufficiency, where previously isoprenaline or noradrenaline might have been used.

REFERENCES


On administra glucagon 50 mg/kg par voie intraveineuse à cinq enfants, manifestant des signes d'"insuffisance par débit peu élevé" après chirurgie à coeur ouvert. L'administration intraveineuse du glucagon se fit à intervalles d'une demi-heure via l'appareil d'infusion intraveineuse. Les pressions artérielles systolique et diastolique augmentèrent en moyenne de 32 et 41 pourcent et il y eut une légère réduction de la fréquence du pouls. Le traitement a été appliqué durant des périodes de 14 à 40 heures. Les glycémies restèrent dans les limites habituelles, trouvées après ce genre de chirurgie. Il n'y eut pas de signes cliniques de vasoconstriction durant le traitement au glucagon. Le glucagon peut être utile dans le traitement des états de débit peu élevé après chirurgie cardiaque et arrêt du coeur.

Fünf Kindern, die Zeichen eines "Versagens des niederen Herzschlagvolumens" aufwiesen nach offenem herzchirurgischem Eingriff, wurden 50 mikrogramm/kg Glukagon intravenös verabreicht. Das Glukagon wurde in halbstündigen Abständen intravenös injiziert mit Hilfe eines Hahmens im Infusionsystem. Systolischer und diastolischer arterieller Blutdruck stiegen im Durchschnitt


Fueren administrados 50 μg/kg de glucagón por vía intravenosa a cinco niños que mostraban signos de "insuficiencia por gasto bajo" después de cirugía de corazón abierto. El glucagón fue inyectado por vía intravenosa por intermedio de un orificio en un dispositivo para infusión intravenosa a intervalos de media hora. Las presiones arteriales sistólica y diastólica aumentaron un promedio de 32 y 41 por ciento y hubo un pequeño descenso en la frecuencia del pulso. Esta terapia fue administrada durante 14 hasta 40 horas. Las concentraciones de glucosa en sangre permanecieron dentro de los limites usuales después de este método operatorio. No hubo signos clínicos de vasoconstricción durante la terapia con glucagón. El glucagón pudiera ser útil para el tratamiento de estados de gasto bajo después de cirugía cardíaca y paro cardíaco.