Hyperglucagonaemia in the Surgical Patient

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Summary

Twenty-one patients had serial samples of blood taken before, during, and after operation for the measurement of plasma glucagon, plasma insulin, and blood glucose concentrations. A significant rise in plasma glucagon level was noted during the operation. In contrast the plasma insulin concentration fell during the operation and rose in the postoperative period despite hyperglycaemia during and after the operation. These findings show that hyperglucagonaemia is a physiological consequence of a surgical operation and that the relationship of plasma glucagon to plasma insulin is complex.

Introduction

Hyperglycaemia associated with haemorrhagic shock was first recorded by Bernard in 1877. Abnormalities in carbohydrate metabolism have been noted after surgery (Ross *et al.*, 1966). Investigations of these abnormalities have shown a failure of insulin response to a glucose load during the perioperative period (Allison *et al.*, 1967). Glucose utilization, as determined by blood-glucose and plasma-insulin measurements, has been found to be depressed during and after an operation to a degree which increased with the severity of the operation (Wright *et al.*, 1974).

Glucagon is considered to play a major role in the regulation of the fasting blood glucose concentration (Koerker *et al.*, 1974). A rise in the level of plasma glucagon has been shown to occur in patients with burns (Wilmore *et al.*, 1974) and after major trauma (Meguid *et al.*, 1973), where the change seems to be related to the severity of the injury (Meguid and Brennan, 1974). The changes that occur in the plasma glucagon level during and after common surgical procedures have not been studied. We report here a profile of plasma glucagon levels in relation to various phases of a surgical procedure and during the postoperative period.

Patients and Methods

Twenty patients, aged from 15 to 75 years (mean 52 years), admitted for elective surgical procedures and one patient with a perforated duodenal ulcer agreed to have repeated blood samples taken during and after the operation. The patients chosen were healthy apart from their surgical condition, had no history of diabetes, and had been on a normal diet up to the time of their admission. The following operations were performed: 12 gastric procedures (seven vagotomies, four partial gastrectomies, and one suture of perforation), three simple mastectomies, three colonic resections, one aortoiliac endart-

erectomy, one hysterectomy, and one cholecystectomy. At least two fasting preoperative samples were taken from each patient, and the mean value of the preoperative samples was used for comparison with those taken during and after the operation. Samples were taken at 10- to 15-minute intervals throughout the operation at the following stages: premedication, anaesthetic induction, towelling-up, incision, laparotomy (where an abdominal operation was performed), procedure when the actual operation was being done, and skin closure. If more than one blood sample was taken during a stage of the operation the peak glucagon level and the corresponding insulin and blood glucose level were used for analysis. After the operation samples were taken between 7 a.m. and 9 a.m. when the patient had fasted overnight. If the patient was on intravenous fluids normal saline was infused for at least one hour before sampling.

Degradation of glucagon in the blood samples was prevented by the addition of 1000 kallikrein inactivator units of aprotinin per ml of blood, immediate centrifugation, and storage of the plasma at -20°C until the time of assay. Plasma glucagon was measured by radioimmunoassay using a pancreatic glucagon specific antiserum (C-terminal reacting) at a final dilution of 1/400 000. This antiserum cross-reacts less than 5% with entero-glucagon preparations. Duplicate assay tubes contained 20% antiserum or, for the standard curve, glucagon-free plasma. A charcoal separation procedure was used after a four-day incubation at 4°C . Addition of plasma containing glucagon 50 pg/ml caused a 10% fall in the amount of ^{125}I -glucagon bound to antibody. Plasma insulin was measured by radioimmunoassay using a charcoal separation method (Albano *et al.*, 1972) with antibody supplied by Wellcome Reagents Ltd. and iodinated insulin supplied by the Radiochemical Centre, Amersham. Blood glucose was measured on the autoanalyser adapting the alkaline ferricyanide method (Hoffman, 1937).

Statistical analysis was by non-parametric methods throughout using Wilcoxon's signed rank sum test (Siegal, 1956).

Results

The mean basal plasma glucagon level ($\pm$ S.E. of mean) was 37.4 ± 3.2 pg/ml. There was no significant difference during the premedication, at induction of anaesthesia, nor while the incision was made. At laparotomy the plasma glucagon rose to 61.8 ± 6.9 pg/ml (fig. 1). This rise was significant ($P < 0.02$) and continued during the procedure to reach a peak of 79.8 ± 7.6 pg/ml, which declined during the closure of the wound

FIG. 1—Changes occurring during operation in plasma glucagon, plasma insulin, and blood glucose levels in 21 patients.

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to 54.6 ± 6.1 pg/ml. All these values were significantly raised ($P < 0.01$) above the basal level. The plasma insulin level was below basal throughout the operation, significantly so at the time of the incision ($P < 0.01$), during the laparotomy ($P < 0.02$), and during the procedure ($P < 0.01$). The blood glucose concentration rose steadily during the operation, being greatest at the end of the operation 98.5 ± 9.5 mg/100ml, and significantly above basal during the procedure and the closure ($P < 0.01$).

After operation the greatest rise in plasma glucagon was noted on the first day (fig. 2). The plasma glucagon level was

FIG. 2—Changes occurring in the first eight days after operation in plasma glucagon, plasma insulin, and blood glucose levels in whole group.

also raised significantly on the second ($P < 0.01$), third ($P < 0.05$), and fourth ($P < 0.05$) postoperative days. The level remained raised but not significantly (at the 5% level) until the seventh day but by the eighth day after operation it was less than basal. The plasma insulin concentration was likewise at maximum on the first day after operation (14.2 ± 2.5 μ U/ml) and significantly above the basal level ($P < 0.02$). Beyond this time a rise persisted throughout the postoperative period but was not significant at the 5% level. The blood glucose concentration followed a similar pattern; it was significantly raised on the first day after operation (108 ± 6.7 mg/100 ml; $P < 0.05$) but it was not significantly above the basal value throughout the postoperative period.

Three of the 21 patients in this series developed major complications— intraoperative haemorrhage during the aortoiliac endarterectomy, pelvic sepsis after a Hartmann's procedure, and an anastomotic leak after an anterior resection. The peak operative levels in these patients were 136 pg, 85 pg, and 140 pg/ml respectively, and on the first postoperative day the glucagon levels rose to 284 pg, 155 pg, and 700 pg/ml. The levels on the first postoperative day were all higher than in the series as a whole and suggest that in patients with complications or the events that may lead to them the changes in glucagon values are exaggerated.

The possibility that the larger rises in plasma glucagon concentration that occurred in some patients, such as those with complications, biased the results for the group as a whole was explored by examining the changes during and after surgery on the stomach in 12 patients (fig. 3). The results were similar to those of the group as a whole with significant rises during the operation and on the first four days after operation. On the fifth day there were three patients with glucagon values of 265 pg, 145 pg, and 122 pg/ml, who had all had a Polya partial gastrectomy and had postoperative pyrexia because of pulmonary complications. Finally, to confirm that the plasma glucagon increase occurs when complications are not present the six patients who underwent a selective vagotomy were examined. The basal plasma glucagon level for this group was 35.9 pg/ml, and the level rose during the vagotomy to 100 pg/ml and remained significantly raised with values on the first, second, third, and fourth postoperative days of 80.0 pg, 60.3 pg, 63.3 pg, and 53.6 pg/ml.

FIG. 3—Plasma glucagon levels during and after operation in 12 patients who underwent gastric surgery.

Discussion

These results show that there is consistently a rise in the plasma glucagon level not only after an operation but also during the procedure. We have confirmed that plasma insulin concentration decreased in the presence of a raised blood glucose during the operation and that both plasma insulin and blood glucose levels rose in the period after operation (Wright *et al.*, 1974). The greater rise in plasma glucagon noted in the three patients with major complications and the rise on the fifth day in the patients with chest complication confirms that the magnitude and duration of the insult is a factor which determines the degree of glucagon response. The fact that significant rises in plasma glucagon levels could be shown in the 12 patients who underwent gastric operations, however, and even in the six patients who had uncomplicated selective vagotomy—a relatively minor surgical trauma—shows that the changes seen during and after operation are a physiological response to injury. It is of interest that the level of plasma glucagon on the eighth postoperative day is less than the mean basal level. This suggests that apprehension before the operation also raises the plasma glucagon level.

The factors responsible for glucagon release have been studied in different ways in different species. Stress in the baboon (Bloom *et al.*, 1973 a), sympathetic nerve stimulation in the calf (Bloom *et al.*, 1973 b), and a vagal stimulation in man (Bloom *et al.*, 1975) have all been found of importance. It is possible that each of these factors contributes to the sustained rise in the period after operation, but the factors that control the autonomic system centrally or the alpha-cell peripherally remain to be elucidated.

The main physiological role of glucagon is to increase the hepatic glucose output, so raising the blood glucose (Cherrington *et al.*, 1972). It is possible that glucagon could play a part in the "insulin resistance" that occurs in the postoperative period. Nevertheless, both the plasma insulin and the blood glucose levels are still abnormal when the glucagon concentration is less than the basal. It is unlikely that there is a simple relationship between insulin and glucagon because in the operative phase there is a rise in glucagon with a fall in insulin whereas in the postoperative period both are raised.

Hence, glucagon in plasma rises after a stressful insult, whether this is operative, thermal, or traumatic, but the part played by the hormone in the metabolic response to trauma cannot be clarified until more is known of its mechanisms of secretion and actions.

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1 α -Hydroxycholecalciferol: A Treatment for Renal Bone Disease

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Summary

Three patients with chronic renal failure on maintenance haemodialysis have been treated with 1 α -hydroxycholecalciferol (1 α -OHCC), a synthetic vitamin D analogue. A daily dose of 2 μ g by mouth produced a significant increase in both calcium absorption from the gastrointestinal tract and calcium content of bone. Treatment with 1 α -OHCC appears to be effective in cases of metabolic bone disease associated with chronic renal failure.

Introduction

It has been known for more than a century that patients with renal failure may develop metabolic bone disease (Virchow, 1855; Lucas, 1883). The importance of this association has been appreciated only since advances in treatment have extended life expectancy and shown that bone disease is an important factor in limiting the full rehabilitation of many patients (Ogg, 1973). Though it was found that large doses of vitamin D could produce a marked improvement in the osteodystrophy of patients with chronic renal failure the dangers of vitamin D toxicity—prolonged hypercalcaemia, metastatic calcification, and nephrocalcinosis—were considerable (Stanbury, 1957; Dent *et al.*, 1961; Fletcher *et al.*, 1963).

In 1970 Fraser and Kodicek discovered that a potent metabolite of vitamin D was produced in the kidney. This substance, 1,25-dihydroxycholecalciferol, was shown subsequently to stimulate calcium absorption in nephrectomized animals (Boyle *et al.*, 1972). It is not detectable in the serum of anephric animals (DeLuca, 1973 a) or in the serum of patients with chronic renal insufficiency (Mawer *et al.*, 1973). 1,25-Dihydroxycholecalciferol is more polar, less lipid soluble, and more potent than vitamin D. Brickman and Norman (1973) suggested that when it is administered to patients with evidence of vitamin D

deficiency the lower dosages required and the reduced tissue stores may limit the toxic effects of inadvertent overdosage.

Though radiological improvement in renal osteodystrophy has been shown after treatment with 1,25-dihydroxycholecalciferol (Henderson *et al.*, 1974) this drug is unlikely to become generally available in the near future because of technical difficulties in its production (DeLuca, 1973 b). An analogue of vitamin D has been synthesized with a hydroxyl group at carbon-1. This substance, 1 α -hydroxycholecalciferol (1 α -OHCC), which may bypass the renal hydroxylating mechanism, is relatively simple to produce (Harrison *et al.*, 1973), has the same antirachitic activity as vitamin D, and promotes both calcium absorption from the gastrointestinal tract and calcium mobilization from bone (Holick *et al.*, 1973). It is effective at doses similar to those of 1,25-dihydroxycholecalciferol and functions equally well in anephric animals and animals with intact kidneys (DeLuca, 1973 a). The administration of 1 α -OHCC parenterally (Chalmers *et al.*, 1973) and by mouth (Peacock *et al.*, 1974) has been shown to increase calcium absorption in patients with renal insufficiency.

The present study was undertaken to evaluate the effect of 1 α -OHCC on the progressive osteodystrophy of three patients with chronic renal failure on maintenance haemodialysis.

Patients and Methods

All three patients gave informed consent to the investigation. None had symptomatic bone disease.

CASE HISTORIES

Case 1.—A 33-year-old man with hypoplastic kidneys started maintenance haemodialysis in March 1967. Small subperiosteal erosions were noted radiologically in 1972 and these remained unchanged; there was no further radiological evidence of metabolic bone disease. Bone biopsy showed increased osteoblastic and osteoclastic activity with wide osteoid seams and fibrosis of the marrow cavity. During the period of study his diet contained approximately 272 mg calcium and 616 mg phosphorus a day.

Case 2.—This patient, a 46-year-old man diagnosed as having chronic pyelonephritis, started maintenance haemodialysis in February 1969. Repeated radiological skeletal surveys showed only a slight diminution of bone density but a bone biopsy showed marrow fibrosis and wide osteoid seams. During the study his diet contained 269 mg calcium and 706 mg phosphorus a day.

Case 3.—A 43-year-old man with chronic glomerulonephritis started maintenance haemodialysis in June 1969. Though repeated skeletal surveys failed to detect any evidence of bone disease a bone biopsy showed wide osteoid borders, an increase in both osteoblastic and osteoclastic activity, and marrow fibrosis. His diet contained 374 mg calcium and 648 mg phosphorus a day.

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