CASE REPORTS

Increased amino acid clearance and urea synthesis in a patient with glucagonoma

T P Almdal, H Heindorff, L Bardram, H Vilstrup

Abstract

Fasting concentrations, clearance of exogenous infused amino acids, and lean body mass were studied in a patient with glucagonoma syndrome (fasting glucagon = 380 pmol/l, normal range 15-45 pmol). The fasting concentrations of all amino acids were reduced. The clearances of alanine, arginine, glycine, isoleucine, leucine, lysine, methionine, proline, serine, threonine, and tyrosine were increased. The urea synthesis rate during amino acid infusion was 27 μ mol/kg per minute (normal range 20-24 μ mol/kg per minute). The lean body mass of the patients was reduced to 59% of the expected value. It is suggested that the weight loss of patients with glucagonoma syndrome is partly due to increased hepatic conversion of amino acid nitrogen to urea nitrogen, resulting in decreased blood amino acid concentration, and secondary to this, organ protein catabolism, as shown by the decreased lean body mass.

The glucagonoma syndrome is associated with loss of body weight and decreased concentrations of blood amino acids.¹ In normal man, hyperglucagonaemia reduces the amino acid concentration,^{2,3} but despite this urea synthesis is increased.^{2,3} In rats, glucagon increases the hepatic uptake of amino acids⁴ and the rate of urea synthesis resulting in loss of organ nitrogen.⁵ This suggests that the decreased blood amino acid concentrations may be caused by increased hepatic clearance and conversion of amino acids to urea. Moreover, it suggests that the loss of body weight seen in the glucagonoma syndrome represents loss of body protein, and that this is secondary to the increased hepatic conversion of amino acids to urea. In man, the total protein content can be assessed by determination of the lean body mass.⁶

We have studied clearance of amino acids, rate of urea synthesis, and lean body mass in a patient with a glucagonoma.

Case report

The patient is a 52 year old woman (weight 52 kg, height 172 cm) suffering from non-specific skin lesions (pruritus and vesicles on the hands).

One year before the present investigation, increased urinary excretion of 5 hydroxyindole-

acetic acid was found. Ultrasound showed multiple focal liver lesions in both lobes, but no primary tumor, and especially no lesions of the pancreas, were found. Liver biopsy specimen histology suggested a neuroendocrine tumor, and immunohistochemistry showed glucagonoma.

The plasma concentrations of glucagon were considerably raised (1500-1600 pmol/l; normal range 15-45 pmol/l) and high concentrations of pancreatic polypeptide were also found. The concentrations of gastrin vasoactive intestinal polypeptide, somatostatin, secretin, and calcitonin were within the normal range.

Since diagnosis the patient has been treated with repeated courses of streptozotocin. Since then there has been a decrease in the plasma glucagon concentrations (to 380 pmol/l at the time of investigation).

Methods

The investigative procedure has already been described in detail.⁷ After an overnight fast blood samples were drawn for determination of fasting concentrations of plasma amino acids, total blood α amino-nitrogen, blood urea, blood glucose, plasma pancreatic glucagon, and insulin. An amino acid mixture (Intrafusin 10%, Pfrimmer and Co, W Germany) was given as a two step intravenous infusion, firstly at a constant rate of 41.2 μ mol of α amino-nitrogen/kg body weight per minute for 60 minutes, followed by a constant infusion for 180 minutes at a rate of 22.3 μ mol of α amino nitrogen/kg per minute. This resulted in constant amino acid concentrations for the last 120 minutes. During these 120 minutes the blood clearance of amino acids was calculated as the ratio between the infusion rate and the steady state concentration of the individual amino acids. Urine was collected quantitatively. The urea nitrogen synthesis rate (UNSR) during amino acid infusion was calculated as:

$$\text{UNSR} = (E \times A) / (1 - L)$$

where E is the urinary excretion of urea-N, A is the accumulation of urea-N in total body water, and L is the fractional gut hydrolysis taken to be 17%.^{8,9}

The lean body mass (LBM) was calculated from three 24 hour urinary creatinine excretions⁶:

$$\text{LBM} = 24 \text{ hour creatinine} \times 3.29 + 7.28$$

Division of Hepatology
and Department of
Gastrointestinal Surgery
C, Rigshospitalet,
Copenhagen, Denmark
T P Almdal
H Heindorff
L Bardram
H Vilstrup

Correspondence to:
Dr T Almdal, Department of
Medicine A-2151,
Rigshospitalet, 9 Blegdamsvej,
DK-2100 Copenhagen,
Denmark.

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TABLE I Fasting amino acid concentrations ($\mu\text{mol/l}$) in a patient with glucagonoma

Amino acid (95% CI of normal mean value)	Patient values (% of normal mean value)
Alanine (231–255)	34 (9)
Arginine (62–134)	10 (10)
Glutamine (481–553)	63 (12)
Glutamate (43–58)	22 (44)
Glycine (263–317)	47 (16)
Histidine (71–87)	42 (53)
Isoleucine (35–59)	18 (38)
Leucine (74–162)	34 (29)
Lysine (146–166)	71 (46)
Methionine (13–23)	2 (11)
Phenylalanine (50–84)	31 (46)
Proline (198–262)	35 (15)
Serine (107–167)	27 (20)
Threonine (112–160)	18 (8)
Tyrosine (53–67)	17 (28)
Valine (170–276)	57 (26)

CI=confidence interval.

The results were expressed as a percentage of the expected value:

Expected LBM = $0.74 \times$ expected body weight

The equation was derived from studies of body composition,¹⁰ and the expected body weight was calculated from the equation:¹¹

Expected body weight = $0.62 \times$ height (cm) – 41

The individual amino acid concentrations were determined by ion chromatography followed by postcolumn derivatisation with orthophthaldehyde and fluorescent detection, total blood α aminonitrogen values were determined by the dinitrofluorobenzene method,¹² urea in blood and urine by the urease-Berthelot method,¹³ blood glucose by enzymatic analysis,¹⁴ and plasma insulin and pancreatic glucagon by radioimmunoassay techniques.^{15 16}

The individual results for the patient are given together with the normal range, stated as the 95% confidence limits of normal individuals derived from,⁷ in parenthesis.

Results

Fasting blood glucose was 8.3 mmol/l (normal range 4.0–5.0 mmol/l), fasting glucagon was 380 pmol/l (normal range 15–45 pmol/l), and fasting insulin was 11 mU/l (normal range 5–7 mU/l). Fasting blood concentrations of all amino acids were reduced (Table I). Amino acid infusion raised the concentration of total α aminonitrogen to an average of 2.2 mmol/l (normal range 4.7–5.5 mmol/l). The urea nitrogen

synthesis rate during amino acid infusion was increased to 27 $\mu\text{mol/kg}$ per minute (normal range 20–24 $\mu\text{mol/kg}$ per minute).

The clearances of all amino acids were increased apart from those of glutamine + glutamate, histidine, phenylalanine, and valine (Table II).

The body weight (52 kg) of the patient was 79% of the expected value, whereas the lean body mass was 59% of the expected value.

Discussion

This study confirms previous observations of decreased amino acid concentrations in patients with the glucagonoma syndrome.^{1 17} It shows that this is probably caused by an increased clearance of amino acids. The most noticeable changes were seen in the gluconeogenic and ureagenic amino acids: alanine, glycine, methionine, proline, and serine. Since glucagon does not increase muscular uptake of amino acids² but increases urea synthesis,^{2 3} the increased clearance is probably the result of increased hepatic uptake and conversion, and this is also indicated by the increased rate of urea synthesis.

Infusion of amino acids raised the total amino acid concentration to 2.2 mmol/l, which is less than 50% of the value reached in normal people.⁷ Despite this, the rate of urea synthesis was increased in the patient. This is in accordance with studies in rats, where chronic hyperglucagonaemia reduced the amino acid concentration but increased the rate of urea synthesis, resulting in loss of nitrogen from organ proteins.⁵

Both the total body weight and the lean body mass were reduced in the patient, but the latter was reduced to a much greater extent suggesting that most of the weight loss in patients with glucagonoma syndrome is accounted for by loss of organ proteins.

It is therefore possible that the weight loss of patients with glucagonoma syndrome is due to an increased hepatic clearance and conversion of amino-N to urea-N leading to reduced amino acid concentrations, and organ protein catabolism.

This observation supports the hypothesis that changes in hepatic conversion of amino acids may regulate actively the rate of catabolism in organs.¹⁸

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TABLE II Clearance (ml/sec) of amino acids in a patient with glucagonoma

Amino acid (95% CI of normal mean)	Patient values (% of normal mean)
Alanine (8.1–9.9)	25.1 (260)
Arginine (5.8–12.2)	17.0 (190)
Glutamine + Glutamate (5.8–21.0)	19.1 (142)
Glycine (6.6–10.0)	15.2 (180)
Histidine (3.7–4.6)	4.6 (107)
Isoleucine (6.9–8.1)	9.9 (132)
Leucine (6.9–8.2)	9.9 (150)
Lysine (5.2–7.2)	10.3 (160)
Methionine (9.9–13.9)	24.4 (205)
Phenylalanine (6.0–9.6)	7.1 (91)
Proline (3.7–8.8)	14.5 (230)
Serine (6.7–10.7)	20.2 (230)
Threonine (3.7–5.9)	13.8 (290)
Tyrosine (2.5–6.2)	12.4 (282)
Valine (2.7–3.7)	3.3 (103)

CI=confidence interval.

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