Investigation vignette

A 17 Year old Woman with a Six Week History of Anorexia, Nausea and Intermittent Vomiting

CASE REPORT

A 17 year old previously healthy woman was admitted to the critical care unit with a six week history of malaise, nausea and intermittent vomiting. The nausea and vomiting had worsened following an upper respiratory tract infection that developed three days prior to her admission.

On admission she was drowsy but oriented. Her vital signs revealed a pulse rate varying between 85 - 92 beats per minute, blood pressure of 85/45 mmHg, respiratory rate of 18 breaths per minute and temperature of 35.4°C. On examination her tongue and mouth were dry and she had mild abdominal tenderness. Her breath smelt strongly of acetone. A provisional diagnosis of diabetic ketoacidosis was made and 1 litre of 0.9% saline was infused rapidly before blood for biochemical and blood gas measurements was taken. During the next 6 hr, she was treated with 1.5 litres of 5% dextrose and 80 mmol of potassium chloride with a sliding scale insulin infusion to control the blood sugar level. The blood gas and serum biochemical estimations during the first 6 hr are shown in (Figure 1).

Name	Age	Sex	Time of Collection	Date
Ms. J. H.	17	F		10.03.02

	04:30	**05:55**	**07:27**	**0934**	**10:30**	**hours**	
Sodium	141	141	140	138	137	mmol/L	(135 - 145)
Potassium	3.7	2.9	3.1	2.7	2.6	mmol/L	(3.2 - 4.3)
Chloride	121	123	120	120	118	mmol/L	(99 - 109)
Bicarbonate	4	4	4	7	8	mmol/L	(10 - 50)
Glucose	15.1	13.8	12.0	10.1	11.3	mmol/L	(3.0 - 6.0)
Anion Gap	19.7	16.9	19.1	13.7	13.6		
Urea	2.4			1.7		mmol/L	(3.0 - 8.0)
Creatinine	0.087			0.05		mmol/L	(0.05 - 0.10)
pH	7.14	7.2	7.16	7.23	7.22		(31 - 44)
PCO_2	11	12	13	17	20	mmHg	(21 - 49)
PO_2	170	131	132	128	112	mmHg	(21 - 49)
Base excess	- 24	- 24	- 23	- 20	- 19		
Acetoacetate	2.3				1.2	mmol/L	(< 0.1)
β Hydroxy-butyrate	7.4				1.8	mmol/L	(< 0.3)
Lactate	0.8	0.7	1.0	1.1	0.9	mmol/L	(< 2.0)

Figure 1. Arterial blood gas and biochemical profiles taken from the patient during the first 6 hr of treatment.

Diagnosis: Diabetic ketoacidosis with mild hyperglycaemia, a mild high anion gap acidosis and large normal anion gap acidosis

Type I diabetes mellitus is characterised by an absolute lack of insulin.[1] Glucagon secretion is increased which stimulates gluconeogenesis and inhibits the formation of malonyl coenzyme A (CoA). As malonyl CoA inhibits carnitine acyltransferase I (thereby inhibiting the initial step in the long chain free fatty acid oxidative sequence), low levels of malonyl CoA releases the inhibition of carnitine acyltransferase I, to augment hepatic oxidation of long chain free fatty acids (FFAs) and stimulate ketogenesis.[2,3] With low levels of insulin, mild sympathetic activation stimulates hormone-sensitive lipoprotein lipase (HS-LPL) and increases the release of FFAs from adipose tissue.[4,5] The excess FFAs are converted by the liver to ketones (i.e. acetoacetate, beta-hydroxybutyrate) which act as a substitute for glucose in brain and all other organs, except the liver.

Ketoacidosis may be found in starvation, insulin-dependent diabetes and alcoholism. The elevated plasma levels of acetoacetate and beta-hydroxybutyrate are due to the finite capacity of peripheral tissues to metabolise these substrates.[6] Acetone (which is not an acid) is produced by the spontaneous decarboxylation of acetoacetate. It is not metabolised by peripheral tissues and is excreted largely by the lungs. Acetoacetate and beta-hydroxybutyrate are in an equilibrium, controlled by the mitochondrial ratio of NADH:NAD^+ (i.e. the redox state). The beta-hydroxybutyrate: acetoacetate ratio is normally 3:1, and may vary from 1:1 to 10:1, increasing when the hepatic mitochondrial redox state decreases (e.g. hypoxia). The fasting level of beta-hydroxybutyrate is normally < 1.2 mmol/L, although with prolonged fasting the levels may rise to 2 - 5 mmol/L. The FFA concentration in plasma normally ranges from 0.4 to 0.8 mmol/L (most of which is bound to albumin) and seldom rises to more than 1 mmol/L. In diabetic ketoacidosis, the FFA levels may increase to 2 - 4 mmol/L,[6] with the keto acid levels (i.e. combined plasma concentrations of beta-hydroxybutyrate and acetoacetate) increasing up to 10 - 15 mmol/L and almost totally account for the anion gap.

Normal glucose production by the liver in the fasting adult is approximately 50 mmol/hr which rapidly increases to 100 mmol/hr when insulin is withdrawn (although hepatic glucose production returns to normal when ketoacidosis develops).[7] Hyperglycaemia, usually between 30 - 40 mmol/L, is characteristic of diabetic ketoacidosis, although rarely the blood glucose level may vary from less than 11.1 mmol/L to greater than 55.6 mmol/L.[8] In the patient described, the presenting blood glucose level was 15.1 mmol/L, indicating that the prolonged ketosis had reduced gluconeogenesis.

In diabetic ketoacidosis the rate of excretion of unionised betahydroxybutyrate (pKa 4.8) with maximum urinary acidity (e.g. pH 4.5) is 66%; so forming a large component (e.g. up to 250 mmol H^+/day) of urinary titratable acidity. Acetoacetic acid has a pKa value of 3.8 and therefore only 17% is excreted at maximum urinary acidity, although as the beta-hydroxybutyrate:acetoacetate ratio is usually 3:1 (which may increase up to 10:1 with reduced redox states) the predominant urinary ketone excretion is beta-hydroxybutyric acid. If diabetic ketoacidosis has been prolonged, then the continued renal loss of keto-acids produces an effective loss of HCO_3^-. Therefore, while insulin will inhibit ketone production and allow the ketones already present to be metabolised (regenerating the HCO_3^- that has acted as a buffer); when the ketoacidosis is finally corrected, a normal anion gap acidosis may remain.[9,10] This was demonstrated in the case described, as the combined plasma concentrations of beta-hydroxybutyrate and acetoacetate at 10:30 was 3 mmol/L, the anion gap was 13.6 mEq/L and the base excess was - 19 mmol/L (Figure 1), indicating that the predominant acid-base disturbance at this stage was a non anion gap acidosis (requiring bicarbonate replenishment).

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