Diabetic ketoacidosis and hyperosmolar crisis in adults

Ketan Dhatariya

Abstract

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) remain two of the most commonly encountered metabolic emergencies. They are both potentially life-threatening when not managed correctly. DKA occurs most frequently (but not exclusively) in people with type 1 diabetes mellitus, who are absolutely insulin-deficient. HHS (formerly known as hyperosmolar non-ketotic state) occurs most frequently (but not exclusively) in older people with type 2 diabetes, who have insufficient insulin concentration to lower blood glucose, but enough to prevent ketone production. Diabetes can present for the first time as DKA or less commonly as HHS; however, these occur more frequently in people known to have diabetes, with the most common causes being infection and other intercurrent illness, or non-concordance with medication. The treatment of DKA and HHS differs because the conditions are biochemically dissimilar. In DKA the emphasis of treatment has changed: with increasing access to bedside plasma ketone monitors, β-hydroxybutyrate concentration rather than blood glucose is often used to guide therapy. In HHS, glucose-lowering should be undertaken predominantly using fluid rehydration, with insulin being gently introduced only when the rate of glucose-lowering has stabilized.

Keywords Diabetes; diabetic ketoacidosis; hyperosmolar hyperglycaemic state; metabolic emergency; MRCP; treatment

Key points

- Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) remain among the most commonly encountered metabolic emergencies
- The diagnosis of DKA requires all three components to be present — hyperglycaemia or a history of diabetes ('D'), raised plasma ketone concentration ('K') and low pH or low bicarbonate ('A'). In some cases, however, glucose levels remain in the normal range (euglycaemic ketoacidosis)
- There is no formal definition of HHS, but raised plasma osmolality, high glucose concentrations and absence of acidosis is usually sufficient. However, acidosis caused by associated morbidity (infection, myocardial infarction, etc) can be encountered
- Although fluid rehydration remains key to the initial management of both conditions, subsequent management differs
- DKA requires a fixed-rate, weight-based intravenous insulin infusion from the start; a similar regimen is required in HHS only when the glucose concentration stops falling with adequate fluid rehydration

Introduction

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) are acute severe metabolic complications of uncontrolled diabetes mellitus. They are potentially life-threatening and require swift recognition and treatment.[1] Although each can be seen in 'pure' form, features of the two disorders can coexist. Increasing rigour has been applied to diagnosis and treatment recommendations for both conditions over the last 5 years.

Diabetic ketoacidosis

Definition and pathophysiology[1,2]

DKA is defined by the presence of all three components: 'D' — a blood glucose >11.0 mmol/litre or known diabetes mellitus; 'K' — ketonaemia >3.0 mmol/litre or >2+ ketonuria on standard urine sticks; and 'A' — a serum bicarbonate <15.0 mmol/litre and/or venous pH <7.3 (usually with a raised anion gap). It is important to remember, however, that the glucose may not be raised in DKA. This is known as euglycaemic DKA, and concerns have been raised that this condition occurs more frequently with the use of the sodium glucose co-transporter 2 (SGLT-2) inhibitors.

DKA usually occurs as a consequence of absolute or relative insulin deficiency, accompanied by an increase in counter-regulatory hormone secretion. This leads to unrestrained hydrolysis of triglycerides (triacylglycerols) in adipose tissue, increasing delivery to the liver of free fatty acid, which serves as a ketogenic substrate. Ketones include β-hydroxybutyrate, acetoacetate and acetone. Concurrently inappropriate hepatic gluconeogenesis and glycogenolysis result in hyperglycaemia that can be severe. Figure 1 shows the pathways involved in the development of DKA, and how it differs from HHS.

Dehydration is a cardinal feature of DKA, resulting initially from osmotic diuresis caused by hyperglycaemia, and exacerbated later by vomiting, and eventually by inability to take in fluid as a result of impaired consciousness. A clinical threat is also posed by hyperkalaemia, which occurs at presentation — a consequence of acidosis and loss of insulin-driven uptake of potassium into cells — and hypokalaemia, which commonly occurs during rehydration and intravenous insulin treatment.

Morbidity and mortality

Mortality rates have fallen significantly in the last 25 years from approximately 8% to <1%.[3] It is likely that the standardized guidelines, including on insulin administration and close

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Competing interests: KD is the lead author on the Joint British Diabetes Societies (JBDS) Guidelines on the Management of Diabetic Ketoacidosis in Adults and one of the lead authors on the JBDS guideline on the management of the Hyperosmolar Hyperglycaemic State. He has received travel expenses and honoraria for speaking about these, and for other JBDS guidelines he has co-authored.

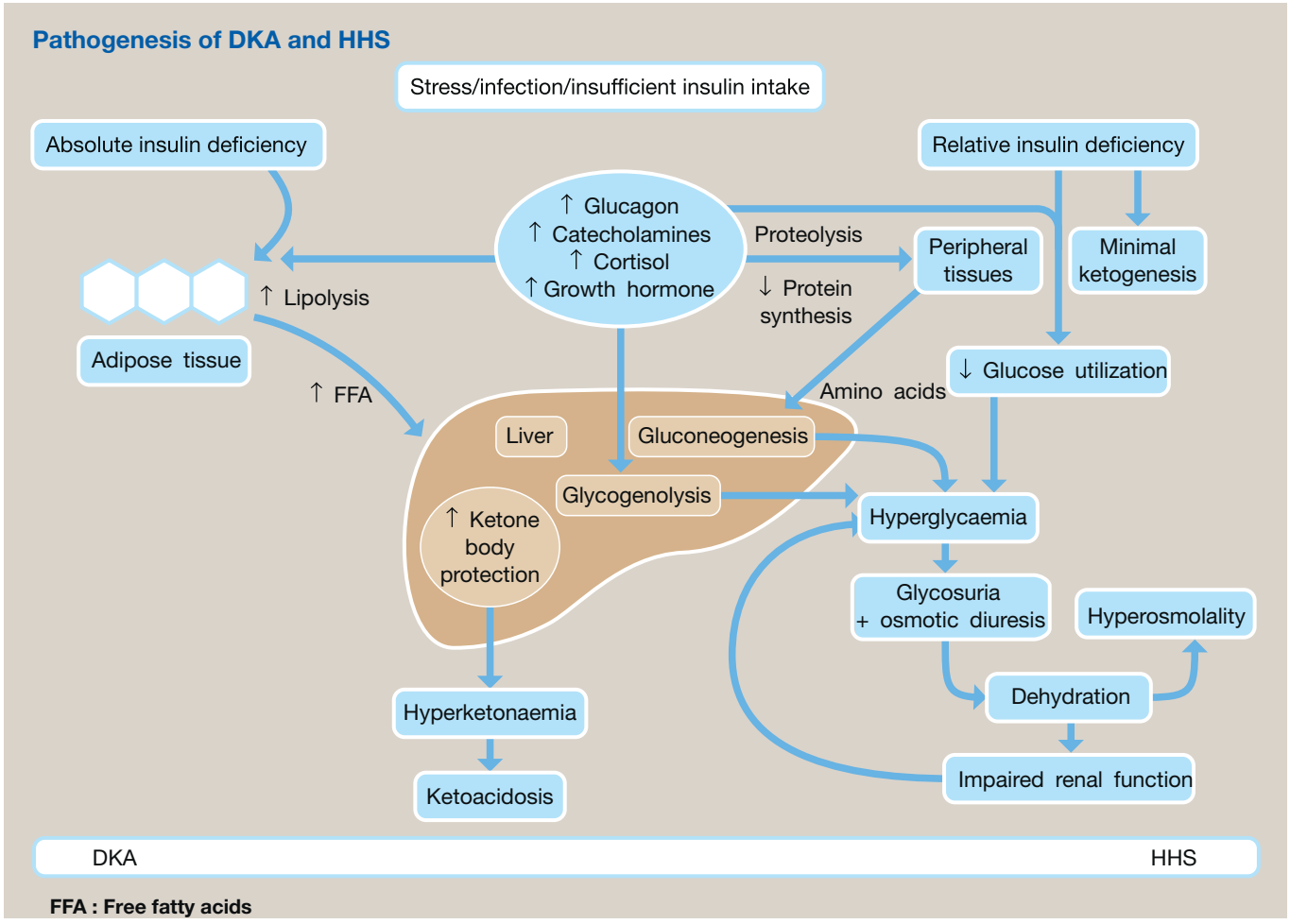

Figure 1 Reproduced from English P, Williams G. Hyperglycaemic crises and lactic acidosis in diabetes mellitus. *Postgrad Med J* 2004; **80:**253–261 with permission from BMJ Publishing Group Ltd.

monitoring of fluid and electrolyte status, have driven this fall. The main causes of mortality in the adult population include the underlying co-morbidity that may have precipitated the DKA, such as pneumonia, acute myocardial infarction or sepsis, and also the severity of any hypokalaemia arising during treatment of DKA. Other complications, such as adult respiratory distress syndrome, are now much rarer causes of death. DKA represents the most the most common cause of death in children and adolescents with type 1 diabetes, and the most common reason remains cerebral oedema, possibly secondary to overaggressive fluid replacement. Children and adolescents are not considered further in this chapter.

Management of DKA

The principles of managing DKA centre on:

- replenishing the fluid deficit, which serves to reduce counter-regulatory hormones as well as enhancing organ perfusion
- delivering adequate insulin to suppress lipolysis and ketone production
- identifying and treating precipitants
- restoring euvolaemia, euglycaemia and a normal pH without inducing iatrogenic hypokalaemia or hypoglycaemia.

With recent technological advances, the delivery and monitoring of treatment have evolved in several ways. Thus, measurement of blood ketones, venous (rather than arterial) pH and serum bicarbonate are recommended as key treatment markers, with ketones and glucose measured using bedside meters when available and operating within their quality assurance range.[4] Electrolytes are commonly analysed on near-patient blood gas analysers with only intermittent laboratory confirmation. Widely used variable-rate intravenous insulin infusions have been replaced by weight-based, fixed-rate intravenous insulin infusions (FRIIIs), starting at 0.1 U/kg/hour. Long-acting basal insulin (human or analogue) is either continued in patients already taking it, or started at a dose of 0.25 U/kg subcutaneously once daily in those for whom DKA is the first presentation of type 1 diabetes.

Resolution of DKA is defined as a venous pH >7.3, serum bicarbonate >15.0 mmol/litre, and blood ketones <0.6 mmol/litre.

Initial assessment focuses on resuscitation, determining the severity of fluid deficit and acidosis, and a search for likely precipitants such as sepsis or myocardial infarction. The presence of any of the following on admission to hospital indicate admission to a level 2/high-dependency unit HDU environment:

- severe ketoacidosis (blood ketones >6.0 mmol/litre; serum bicarbonate <5.0 mmol/litre; venous or arterial pH <7.1; anion gap >16 mmol/litre)
- hypokalaemia (<3.5 mmol/litre)
- impaired consciousness (e.g. abnormal Glasgow Coma Scale (GCS) score or AVPU (Alert, Voice, Pain, Unresponsive) score)
- oxygen saturation <92% when breathing air (if baseline respiratory function is normal)
- haemodynamic compromise (systolic blood pressure <90 mmHg and/or heart rate >100 or <60 beats/minute).

If systolic blood pressure is >90 mmHg, vigorous fluid replacement should be commenced, using a regimen such as that illustrated in Table 1. Insulin should be delivered intravenously using a weight-based FRIII. The FRIII should use an infusion pump with human soluble insulin 50 U made up to 50 ml with sodium chloride 0.9% solution. It should be infused at an initial rate of 0.1 U/kg/hour. If the patient's exact weight is not known, it can be estimated. If the patient is pregnant, her present weight should be used and senior advice sought urgently. A bolus dose of subcutaneous or intravenous insulin should be used only if there is a delay in setting up an FRIII. If the patient normally takes a long-acting basal insulin (human or analogue) subcutaneously, this should be continued at the usual dose and usual time to reduce the problem of rebound hyperglycaemia after withdrawal of the intravenous infusion.

Hyperkalaemia is common at presentation of DKA, and, if severe, should be treated as an emergency. However, high serum potassium masks a deficiency of intracellular potassium in DKA, and because potassium is driven into cells by treatment with insulin and fluids, serum potassium can fall sharply; it should be replaced proactively to avoid dangerous hypokalaemia. Serum potassium should be checked regularly, ideally using a near-patient venous blood gas machine. A typical replacement regimen is shown in Table 2.

After admission, regular — initially hourly — clinical and biochemical assessment is mandatory to ensure continued improvement after initial therapy. The use of urine ketone sticks is discouraged, because although β-hydroxybutyrate is found predominantly in the blood — and this is detected by the point-of-care bedside plasma ketone meters, urine ketone sticks detect only acetoacetate, which is the predominant ketone in urine. Thus, because β-hydroxybutyrate is converted to acetoacetate, if urine sticks are used, it can give the (false) impression that the DKA is not resolving. In addition, because the urine tests are an average of acetoacetate concentrations since the bladder was last emptied, their use can prolong treatment.

Recommended rates of change of blood ketones, bicarbonate and glucose are shown in Table 3. Detailed management of DKA beyond 60 minutes is described in the UK national guidelines (http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_DKA_Adults_Revised.pdf). These are used by >90% of all UK hospitals. It is crucial to longer term management, and to pre-empt future admissions, that the diabetes specialist team be involved as soon as possible after admission.

Typical fluid replacement regimen for DKA if systolic blood pressure is >90 mmHg

Fluid	Volume
Sodium chloride 0.9% 1 litre	1000 ml over first hour
Sodium chloride 0.9% 1 litre with potassium chloride	1000 ml over next 2 hours
Sodium chloride 0.9% 1 litre with potassium chloride	1000 ml over next 2 hours
Sodium chloride 0.9% 1 litre with potassium chloride	1000 ml over next 2 hours
Sodium chloride 0.9% 1 litre with potassium chloride	1000 ml over next 4 hours
Sodium chloride 0.9% 1 litre with potassium chloride	1000 ml over next 4 hours

Reassessment of cardiovascular status at 12 hours is mandatory, as further fluid may be required.
If the blood glucose concentration drops to <14mmol/litre, then 10% dextrose should be added to provide a substrate for the insulin. This should be in addition to the sodium chloride 0.9% which acts as the resuscitation fluid.
The fixed rate intravenous insulin infusion should be continued until the ketonaemia resolves — i.e. <0.6mmol/litre.

Table 1

Recommended potassium replacement regimen in DKA and HHS

Serum potassium in first 24 hours (mmol/litre)	Potassium concentration in infusion solution (mmol/litre)
>5.5	0
3.5–5.5	40
<3.5	>40 (requires senior clinical review)

Table 2

Hyperosmolar hyperglycaemic state

Definition and pathophysiology[5]

HHS is a condition characterized by severe dehydration, hyperglycaemia in the absence of ketoacidosis, and hyperosmolarity. Diagnostic criteria adopted in the UK require the presence of hypovolaemia and severe hyperglycaemia (>30.0 mmol/litre), with serum osmolality usually >320 mOsm/kg and an absence of significant ketonaemia. HHS is believed to result from the presence of sufficient insulin to suppress hepatic ketone production,

Recommended metabolic targets in the management of DKA

- Reduction of blood ketone concentration by 0.5 mmol/litre/hour
- Increase in venous bicarbonate concentration by 3.0 mmol/litre/hour
- Reduction of capillary blood glucose by 3.0 mmol/litre/hour
- Maintenance of serum potassium between 4.5 and 5.5 mmol/litre

Table 3

but not to suppress blood glucose. The ensuing hyperglycaemia leads to osmotic diuresis, which itself leads to dehydration and haemoconcentration, and a vicious cycle begins. The pathophysiology of HHS is illustrated in Figure 1.

HHS usually presents in elderly patients and can be the first presentation of type 2 diabetes mellitus. However, because this condition is being diagnosed in ever-younger adults and teenagers, it is increasingly likely that HHS will present in younger age groups as well. Unlike DKA, which usually evolves over a matter of hours, HHS evolves over many days, and consequently the dehydration and metabolic disturbances are more extreme. However, a mixed picture of HHS and DKA can occur and can be a trap for the unwary.

Hyperglycaemia induces osmotic diuresis and renal losses of water in excess of sodium and potassium. Fluid losses are estimated to be severe, at 100–220 ml/kg. Despite this, typical patients with HHS may not look as dehydrated as they are, because of redistribution of body water resulting from blood hypertonicity and preservation of intravascular volume.

Morbidity and mortality

Because patients with HHS tend to be older than those with DKA they often have other co-morbidities and are thus at greater risk of developing the complications of not only diabetes, but also its treatment. Atherosclerosis, thrombosis and foot ulceration pose particular risks. The reported mortality of HHS has fallen from around 40% to 5–16%, which is 10-fold higher than for DKA.

Management of HHS

Clinical assessment should determine the extent of dehydration, evaluate mental state and look for evidence of a precipitating cause, for example infection, sepsis, myocardial infarction or a recent change in medication. The recent addition of high-dose glucocorticoids is a prime example of the latter. Risk of foot ulceration should also be assessed at the time of admission and daily afterwards, with obtunded or uncooperative patients assumed to be at particularly high risk.

Investigations should determine the biochemical severity of hyperglycaemia and acidosis, and should include calculation of osmolarity (e.g. $2Na^+$ + glucose + urea). End-organ damage, in particular acute kidney injury, should be looked for.

Immediate aims of management are to:

- replace approximately 50% of the estimated fluid loss within the first 12 hours and the remainder in the following 12 hours – the rate is determined by initial severity, degree of renal impairment and associated co-morbidities, particularly heart failure
- achieve a target blood glucose of 10.0–15.0 mmol/litre
- treat the underlying cause
- prevent complications such as arterial or venous thrombosis, cerebral oedema, central pontine myelinolysis and foot ulceration.

Complete correction of electrolytes and osmolality can take up to 72 hours. The presence of any of the following on admission to hospital indicate admission to a level 2/HDU environment:

- serum osmolality >350 mOsm/kg and/or serum sodium >160 mmol/litre
- venous/arterial pH <7.1
- severely deranged serum potassium (<3.5 or >6.0 mmol/litre)
- impaired consciousness (e.g. GCS <12 or abnormal AVPU score)
- oxygen saturation <92% when breathing air (if baseline respiratory function is normal)
- haemodynamic compromise (systolic blood pressure <90 mmHg and/or heart rate >100 or <60 beats/minute)
- hypothermia
- acute or serious co-morbidity (e.g. myocardial infarction, congestive cardiac failure or cerebrovascular accident)
- urine output <0.5 ml/kg/hour or other evidence of acute kidney injury.

If there is a problem obtaining intravenous access, critical care support should be requested immediately. Fluid resuscitation should be guided by clinical state and co-morbidity, but often starts with giving sodium chloride 0.9% 1 litre over 1 hour. If the osmolality is no longer declining despite adequate fluid replacement with 0.9% sodium chloride solution AND an adequate rate of fall of plasma glucose is not being achieved, then 0.45% sodium chloride solution should be substituted. It is usually mandatory to insert a urinary catheter to monitor hourly urine output and calculate fluid balance. A monitoring regimen appropriate to the patient should be established – this is usually hourly determination of blood glucose, serum sodium, potassium and urea and calculated osmolarity for the first 6 hours, and then 2-hourly osmolarity if the response is satisfactory (ideally a fall in 3–8 mOsm/litre/hour).

Fluid replacement alone lowers blood glucose, which reduces osmolality, causing a shift of free water into the intracellular space. This inevitably results in a rise in serum sodium – another trap for the unwary, because even though the sodium concentration can rise, the corresponding fall in glucose and urea should result in a fall in the calculated serum osmolarity. Serum sodium concentrations should be monitored frequently, and the concentration of sodium in infusion fluids adjusted to promote a gradual decline in corrected serum sodium. Although there are no data to indicate an optimal rate of decline in serum sodium, a rate of 0.5 mmol/litre/hour has been recommended for hypernatraemic dehydration. Potassium should be replaced as in DKA (Table 2).

Significant ketonaemia (β-hydroxybutyrate >1.0 mmol/litre) indicates relative hypoinsulinaemia, so insulin should be started at once. If significant ketonaemia is not present (β-hydroxybutyrate <1.0 mmol/litre), insulin is not indicated. Fluid replacement alone, with sodium chloride 0.9%, reduces blood glucose; therefore, because most patients with HHS are insulin-sensitive, there is a risk of lowering osmolality dangerously and quickly, resulting in central pontine myelinolysis. Insulin treatment before adequate fluid replacement can result in cardiovascular collapse as water moves out of the intravascular space, with an attendant decline in intravascular volume. A fall of blood glucose of <5.0 mmol/litre/hour is ideal. Once blood glucose has ceased to fall after initial fluid resuscitation, fluid intake and renal function should be reassessed. Insulin can be started at this point using an FRIII given at 0.05 U/kg/hour).

Because of the increased risk of arterial and venous thromboembolism, all patients should be given prophylactic low-

weight heparin for the duration of admission unless contra-indicated. Full-treatment-dose anticoagulation should be considered only in patients with suspected thrombosis or acute coronary syndrome. Heel protectors should be applied in individuals with neuropathy, peripheral vascular disease or lower limb deformity, and the feet should be re-examined daily.

Longer term management of HHS is discussed in the recently developed UK national guidelines (http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_HHS_Adults.pdf). ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 37-year-old-woman presented to the antenatal clinic feeling generally unwell with frequent vomiting. She was 28 weeks' pregnant and this was her first presentation to the clinic. She had a 3-year history of type 2 diabetes. Her glycaemic control had been poor, with clinic HbA_{1c} concentrations of 86–110 mmol/mol for the last 2 years. She had declined pre-conception counselling. Her medication was metformin 500 mg 12-hourly, gliclazide 160 mg 12-hourly and dapagliflozin 10 mg once daily.
On clinical examination, she appeared unwell and was confused, Her heart rate was 130 beats/minute and blood pressure 96/55 mmHg. A capillary glucose concentration measured 9.7 mmol/litre. Urine ketones showed +++ on the urine stick.

What is the most important diagnosis to consider?

A. Euglycaemic ketoacidosis
B. Hyperemesis gravidarum
C. Hyperthyroidism
D. Placental abruption
E. Pre-eclampsia

Question 2

A 64-year-old woman presented with a 3-day history of lethargy. She had type 2 diabetes mellitus with previous good glycaemic control with diet alone. She had recently been treated with prednisolone for polymyalgia rheumatica.
On clinical examination, her temperature was 36.6°C, heart rate 114 beats/minute, and blood pressure 104/52 mmHg lying down. Urinalysis was normal.
She was given sodium chloride 0.9% 1 litre intravenously over 1 hour.

Investigations

- Serum sodium 165 mmol/litre (137–144)
- Serum potassium 3.6 mmol/litre (3.5–4.9)
- Serum bicarbonate 23 mmol/litre (20–28)
- Serum urea 16 mmol/litre (2.5–7.0)
- Serum creatinine 154 micromol/litre (60–110)
- Estimated glomerular filtration rate 38 ml/minute/1.73 m^2 (>60)
- Random plasma glucose 54 mmol/litre
- Capillary blood ketones 0.9 mmol/litre (<0.3)
- Chest X-ray was normal

What is the most appropriate next step in management?

A. Insulin infusion 0.05 U/kg/hour with intravenous sodium chloride 0.9%
B. Insulin infusion 0.1 U/kg/hour with intravenous sodium chloride 0.9%
C. Insulin infusion 0.1 U/kg/hour with intravenous glucose 10%
D. Intravenous sodium chloride 0.45% without insulin infusion
E. Intravenous sodium chloride 0.9% without insulin infusion

Question 3

A 27-year-old man presented with diabetic ketoacidosis. He had a 17-year history of type 1 diabetes. He had a history of alcohol misuse, drinking over 100 units per week. He also had chronic low back pain for which he took aspirin. He was treated appropriately using a fixed-rate intravenous insulin infusion and intravenous 0.9% sodium chloride solution. Twenty-four hours

after admission he was eating and drinking normally. He was back on his usual doses of subcutaneous insulin and his urinary ketones were undetectable.

His venous blood gases on room air 6 hours previously showed:

- PO_2 13.6 kPa (11.3–12.6)
- PCO_2 3.6 kPa (4.7–6.0)
- pH 7.29 (7.35–7.45)
- Bicarbonate 14 mmol/litre (21–29)
- Base excess −2 mmol/litre (±2)
- Lactate 1.2 mmol/litre (0.5–1.6)

What is the most likely cause of these readings?

A. Concurrent aspirin ingestion
B. Continued ketonaemia
C. Continuing alcohol toxicity
D. Hyperchloraemia
E. Renal tubular acidosis type IV