

Hyperglycaemia and ketosis in a non-diabetic patient — an unusual cause of delayed recovery

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Abstract

We report a case of hyperglycaemia and ketosis developing in a non-diabetic patient who underwent a neurosurgical procedure under general anaesthesia. A 52-year-old non-diabetic female patient underwent excision of acoustic neuroma under general anaesthesia. Pancreatic function was not disturbed and she received a single dose of dexamethasone (8 mg) and paracetamol (1 g). Delayed recovery from anaesthesia occurred. On investigation, she was found to have hyperglycaemia and ketosis. She was further managed on the line of diabetic ketoacidosis. After 24 hours, when blood glucose had normalised and ketosis abated, she could be weaned from mechanical ventilation and extubated. The patient did not receive any drugs known to cause such a condition. To the best of our knowledge, hyperglycaemia and ketosis developing in a non-diabetic patient causing delayed recovery and extubation is here reported for the first time.

Key words: general anaesthesia, recovery, hyperglycaemia, ketosis, lactic acidosis, starvation

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Hyperglycaemia and ketoacidosis often complicate diabetes, mostly type I. Ketoacidosis with hyperglycaemia is rare in type II diabetes and has not been reported in non-diabetic individuals except those receiving some medications [1–3]. We report a case of a non-diabetic patient who underwent an uneventful neurosurgical procedure under general anaesthesia and who developed hyperglycaemia and ketoacidosis which delayed her recovery from anaesthesia and subsequent extubation.

CASE REPORT

We report the following case after obtaining approval from the institutional review board and consent from the patient. A 52-year-old female patient, body mass 61 kg, was listed for excision of cerebro-pontine (CP) angle tumour (acoustic neuroma). Six months prior to surgery, arterial hypertension was diagnosed and irregularly treated. A pre-anaesthetic check revealed blood pressure of 126/80 mm Hg

and heart rate of 92 bpm. Preoperative laboratory tests were unremarkable — Hb level 11.3 g dL⁻¹, total leukocyte count 8.8 G L⁻¹, platelet count 303 G L⁻¹, prothrombin time — 10.1 s (INR 0.88), APTT — 28.7 s, Na — 132 mEq L⁻¹, K — 4.6 mEq L⁻¹, and random blood glucose was 82 mg dL⁻¹. Chest radiograph (AP view) and 12-lead electrocardiogram were normal. After ten hours of fasting, she was taken to the operating theatre. The patient was premedicated with intravenous glycopyrrolate 0.2 mg, ondansetron 4 mg and fentanyl 200 µg. Anaesthesia was induced with intravenous propofol 150 mg and atracurium 50 mg to facilitate intubation. Mechanical ventilation of lungs was instituted with a tidal volume of 500 mL, respiratory rate 12 min⁻¹, I:E ratio — 1:2. After anaesthesia induction, the patient was administered 20% mannitol 300 mL, dexamethasone 8 mg, phenytoin 100 mg and ceftriaxone 2 g. In the course of the surgery, analgesia was supplemented by 50 µg of fentanyl, and paracetamol 1 g, and tramadol 100 mg. Anaesthesia was maintained with

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Table 1. ABG and ventilatory parameters after various time intervals in the postoperative period

	Day1, 1 hr*	Day1 2 hrs	Day1 4 hrs	Day1 6 hrs	Day1 10 hrs	Day1 18 hrs	Day1 24 hrs	Day2 2 hrs#
pH	7.102	7.233	7.107	7.216	7.353	7.399	7.382	7.390
pCO ₂ (mm Hg)	45.3	47.8	46.9	60.1	50.6	47.4	41.6	47.1
pO ₂ (mm Hg)	275	153	111	193	114	105	172	272
SpO ₂ (%)	98.7	98.7	96.2	98.9	98.3	98.3	99.3	99.7
Lactate (mmol L ⁻¹)	4.5	6.6	7.1	3.1	1.4	2.2	1.1	1.3
Base excess (mmol L ⁻¹)	-15.3	-7.4	-14.6	-4.2	1.6	2.8	-0.4	2.9
HCO ₃ ⁻ (mmol L ⁻¹)	13.5	19.4	14.1	23.5	25.8	27.9	24.1	27.9
Anion gap (mmol L ⁻¹)	11.2	5.9	12.7	6.4	6.0	4.1	7.2	1.0
Ventilatory parameters							SIMV, PC, PS, PEEP — 5, rate 12 min ⁻¹ , FiO ₂ — 0.5, PS — 28	O ₂ — 6 L min

*immediately postoperative; #post extubation

50% air oxygen mixture and isoflurane (1 — 1.5 vol%). End tidal concentration of carbon dioxide (E_TCO₂) was maintained between 28 and 30 mm Hg. CVP was maintained between 8 and 12 cm of H₂O. She was administered a total of 3 litres of 0.9% NaCl intraoperatively. Her urine output was 900 mL and blood loss was approximately 350 mL. At the end of the surgery, reversal of neuro-muscular block was attempted with neostigmine 2.5 mg and glycopyrrolate 0.4 mg. The patient, however, remained drowsy and failed to generate adequate tidal volume. Because after one hour of reversal of neuromuscular blockade she had failed to generate adequate tidal volume, she was moved to the neurosurgical ICU with an endotracheal tube in situ for mechanical ventilation (pressure support of 10 mm Hg, PEEP 5 mm Hg, FiO₂ 0.5). Capillary blood glucose done after the transfer to the ICU was found to be 451 mg dL⁻¹. Arterial blood gas analysis (ABG) revealed normal anion gap, and metabolic acidosis (lactic acidosis). Ketones were present in the urine.

Further management was instituted on the lines of diabetic ketoacidosis with normal saline, intravenous regular insulin — 5 U i.v. bolus followed by infusion at 5 U h⁻¹. Serum potassium concentration was monitored four hourly and potassium supplementation done adequately. After 3 L of normal saline infusion, 0.45% saline with dextrose infusion was started. Injection of multivitamins was also administered. The blood glucose, ABG (pH, bicarbonate, base excess, anion gap) and lactate levels were corrected within 24 hours and the trachea was able to be extubated after 24 hours of end of surgery. ABG and ventilatory parameters after various time intervals in the postoperative period are presented in Table 1. The rest of the postoperative course was uneventful. In the postoperative period, glycosylated haemoglobin (HbA_{1c}) and CT scan of abdomen (performed to rule out any pancreatic pathology) were normal.

DISCUSSION

Diabetic ketoacidosis is a syndrome characterised by hyperglycaemia, ketosis and acidosis. It occurs as a result of a relative or absolute insulin deficiency and an excess of insulin counter regulatory hormones (ICRH) [4]. The patient described here fulfils all the criteria of DKA. She, however, was a non-diabetic with a normal pancreas as evidenced by HbA_{1c} and CT scan of abdomen, done in the postoperative period. The patient had undergone a major neurosurgical procedure for which she fasted overnight (ten hours). The ketosis that developed eventually is, however, unlikely to be due to starvation. In fasting adult patients, ketone bodies (acetoacetic acid and β-hydroxybutyrate) levels are not elevated until 18 hours of fasting [5]. Also, in starvation ketosis, blood glucose ranges from mildly elevated (rarely more than 250 g dL⁻¹) to hypoglycaemic. Serum bicarbonate levels are not lower than 18 mEq L⁻¹ [4]. Our patient had a serum bicarbonate level of 13.5 mEq L⁻¹. Other differential diagnoses of elevated anion gap metabolic acidosis include chronic renal failure (CRF) and ingestion of drugs [4], both of which were absent, and lactic acidosis

Causes of Type A lactic acidosis such as shock, profound hypoxaemia, profound anaemia, and carbon monoxide poisoning were obviously not present. The patient also did not have sepsis, liver failure, malignancy or pheochromocytoma (type B1). Thiamine deficiency also had been implicated in causing lactic acidosis which could not be ruled out. Hence, the patient was administered vitamin B complex infusion. Other drugs implicated in causing lactic acidosis are adrenaline, salbutamol, ethanol, methanol, nitroprusside, salicylates, ethylene and propylene glycol, biguanides, fructose, sorbitol, xylitol, cyanide, isoniazide, propofol and paracetamol [6]. A single dose of propofol (2.45 mg kg⁻¹)

or paracetamol (2 mg kg⁻¹) has not been reported to cause lactic acidosis.

Hyperglycaemia and ketosis have been reported in non-diabetic patients treated with high dose salbutamol infusion (15 µg min⁻¹) [1]. Severe prolonged theophylline toxicity (15 g of slow release theophylline preparation) has also been reported to result in ketosis [2]. Theophylline has been shown to cause a dose-related increase in serum free fatty acid (FFA) levels. Metabolism of FFA in the presence of depleted hepatic glycogen stores, due to prolonged fasting and excessive β-adrenergic stimulation, results in ketosis [2]. The patient described here received neither of these drugs. A case of a non-diabetic renal transplant recipient, who was also receiving prednisolone (glucocorticoid) and cyclosporine (known to cause peripheral insulin resistance and a decrease in insulin secretion from the pancreas), developing gatifloxacin-induced severe hyperglycaemia and ketoacidosis has been reported [3]. The patient described in our report had been administered a single dose of 8 mg of dexamethasone intraoperatively. Dexamethasone, even after single dose administration, has been shown to increase blood glucose in non-diabetics undergoing abdominal surgery [7]. In non-diabetics given a single dose of 10 mg dexamethasone, maximum blood glucose observed was 7.9 ± 1 mmol L⁻¹ (range 5.8–10 mmol L⁻¹), and blood glucose concentration peaked at 120 min after dexamethasone administration. The peak increase in blood glucose was 30 ± 19% in non diabetics [7]. Dexamethasone-induced hyperglycaemia has not been reported to result in ketoacidosis.

Surgery and anaesthesia are stress factors, and they are known to cause hyperglycaemia and hyperketonaemia [8]. Blood glucose concentration is known to increase during surgery because of cortisol and catecholamine-induced increased hepatic glycogenolysis and gluconeogenesis and decreased peripheral utilisation of glucose [9]. Blood glucose concentration is related to the intensity of the surgical injury; the change closely follows the increases in catecholamines. In cardiac surgery, blood glucose concentration can increase up to 10–12 mmol L⁻¹ and remains elevated for 12 hours after surgery [9]. Surgery causes a reduction in insulin sensitivity, which is proportional to the length and technique of the procedure. It has been demonstrated that cholecystectomy performed as a laparoscopy caused significantly less reduction in insulin sensitivity compared to that of a conventional open surgical technique [10]. Data related to neurosurgical procedures is not available in the literature.

Volatile anaesthetics used for the induction and maintenance of general anaesthesia suppress insulin secretion and increase hepatic glucose production, thereby elevating blood glucose levels [11]. Inhalational anaesthesia of more than ten hours' duration increases epinephrine, noreph-

nephrine and anti-diuretic hormone (ADH) concentration, which was greater in isoflurane-nitrous oxide anaesthesia than in sevoflurane-nitrous oxide [12] anaesthesia. ACTH levels increase with surgical stimulation followed by an increase in cortisol levels. ACTH levels peak during surgery. Glucose concentration is increased and its clearance is decreased, but insulin levels did not change during surgery and increased after surgery [12]. Lukins et al. [13] compared the intra-operative blood glucose concentration of non-diabetic patients undergoing craniotomy for 12 hours, who received intra-operative dexamethasone 10 mg i.v. at induction and 4 mg i.v. repeated after six hours, to patients who did not receive any. The patients who received intraoperative dexamethasone had a large increase in blood glucose concentration. Mean peak blood glucose concentration observed was 11.0 mmol L⁻¹ (range 7.5–13.8 mmol L⁻¹), representing a mean 5.5 mmol L⁻¹ increase from baseline. The peak blood glucose concentration occurred 8–10 hours after the induction of anaesthesia. Blood glucose increases due to dexamethasone have been explained by an increase in gluconeogenesis with some reduction in end-organ sensitivity to insulin at larger doses [13]. The patient described here had received a single dose of 10 mg of dexamethasone and yet her blood glucose was 451 mg dL⁻¹ (25 mmol L⁻¹) one hour after the end of surgery.

It is not routine practice to measure blood glucose concentrations in non-diabetic patients administered dexamethasone during craniotomy [13]. The same practice if followed at our centre may have delayed the diagnosis and subsequent treatment of hyperglycaemia and ketosis.

To conclude, a non-diabetic patient underwent a neurosurgical procedure under general anaesthesia following a very common and widely followed protocol of overnight fasting, single dose of dexamethasone, propofol for induction, isoflurane for maintenance of anaesthesia, and paracetamol as an analgesic. She developed hyperglycaemia and ketosis, delaying her extubation and recovery. This remains unexplained and unreported in the literature. This raises questions regarding the pathophysiology and whether we need to monitor blood glucose in such patients too.

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