Insulin resistance and development of diabetes mellitus associated with megestrol acetate therapy

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Summary
We describe a case of diabetes mellitus induced by megestrol acetate in a patient with the acquired immunodeficiency syndrome. Metabolic studies including an arginine infusion test excluded an insulinopenic state and suggested insulin resistance as the underlying mechanism for hyperglycaemia. Withdrawal of megestrol acetate resulted in rapid correction of all metabolic abnormalities and eliminated the need for exogenous insulin therapy.

Keywords: diabetes mellitus, megestrol acetate, AIDS, insulin resistance

Megestrol acetate, a synthetic orally active progestational agent has recently been used for the treatment of weight loss and cachexia associated with cancer and the acquired immunodeficiency syndrome (AIDS). It is thought that megestrol acetate promotes weight gain by stimulating appetite; however, the exact mechanism remains unknown. In general, the drug is well-tolerated with few potential adverse effects including peripheral oedema, impotence, menstrual irregularities, deep vein thrombosis and hyperpnea. Recently, we encountered a case of diabetes mellitus induced by megestrol acetate in a patient with AIDS.

Case report

A 36-year-old homosexual man with AIDS was admitted to hospital with a diagnosis of hyperosmolar nonketotic syndrome. One year prior to admission, the patient had suffered from *Pneumocystis carinii* pneumonia, successfully treated with intravenous pentamidine. Since then he had been maintained on dapsone for secondary prophylaxis without recurrence of the *P carinii* pneumonia. Antiretroviral therapy consisted of dideoxyinosine which was discontinued six months prior to admission because of persistent but asymptomatic elevation of pancreatic enzymes.

Physical examination revealed dehydration, mild confusion and slurring of speech. No organomegaly or signs of localised infection were noted. His height, weight and body mass index were 172 cm, 66 kg and 22.3 kg/m², respectively.

Laboratory data included the following: blood glucose 51 mmol/l, sodium 129 mmol/l, potassium 5.4 mmol/l, bicarbonate 17 mmol/l,

triglyceride 11.5 mmol/l, cholesterol 5.7 mmol/l, amylase 111 U/l (normal 7–59 U/l), and lipase 140 U/l (normal 0–88 U/l). Arterial blood gas: pH 7.45, pCO₂ 20 mmHg, pO₂ 127 mmHg on room air. Serum osmolality was 322 mOsm/kg. Serum and urinary ketone were negative. Chest X-ray, electrocardiogram and computed tomography (CT) scan of the abdomen were normal.

Intravenous fluids and insulin were administered with resultant rapid improvement in condition. Over the next several days, the patient required up to 75 units of insulin in 24 hours for glycaemic control.

Careful review of his records revealed that the patient was started on megestrol acetate, 240 mg/day, three months prior to admission for progressive anorexia and weight loss. One week after starting megestrol acetate, hyperglycaemia was noted for the first time on random blood glucose testing. An oral glucose tolerance test six weeks later was abnormal (table 1). Megestrol acetate induced diabetes mellitus was therefore strongly suspected and further metabolic studies were pursued. A fasting C-peptide level was 1.09 mmol/l (normal 0.1–1.22 mmol/l). Anti-insulin antibodies were negative. Pancreatic islet cell function was studied after intravenous infusion of arginine (0.5 g/kg over 30 min). C-Peptide, insulin and glucagon responses were normal (table 2). These results demonstrated that islet cell function was intact. Megestrol acetate was subsequently discontinued, and insulin requirements rapidly declined, stopping altogether after one week. The patient remained euglycaemic and a repeat oral glucose tolerance test after two weeks was within normal limits (table 1). A repeat serum triglyceride at this time was 2.86 mmol/l, also consistent with the correction of insulin resistance.

Table 1 Oral glucose tolerance test after 75 g of glucose performed six weeks after starting megestrol acetate and two weeks after withdrawing the drug

Time (min)	Blood glucose (mmol/l)	
	Six weeks after starting	Two weeks after stopping
0	5.0	4.3
30	11.5	6.9
60	11.5	8.2
120	12.0	7.6

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Table 2 C-Peptide, insulin, glucagon response after intravenous infusion of arginine (0.5 g/kg over 30 min)

Time (min)	C peptide*	Insulin**	Glucagon†
0	1.0	136	210
30	2.0	230	530
60	2.4	244	530
90	2.7	179	210
120	3.5	244	260

*Normal 0.1–1.22 mmol/l; **normal 35–145 pmol/l; †normal 50–100 ng/l

Discussion

Many observations suggest that megestrol acetate precipitated diabetes mellitus in this patient. A strong temporal relation was noted between initiation of megestrol acetate therapy and the onset of hyperglycaemia and an abnormal oral glucose tolerance test. While receiving megestrol acetate, the patient required large doses of insulin to maintain adequate glycaemic control after correction of his hyperglycaemic nonketotic state. Rapid decrease in insulin needs, subsequent maintenance of euglycaemia without insulin, and normalisation of oral glucose tolerance test upon discontinuation of the drug clearly indicate a primary role of megestrol acetate.

Various endocrine abnormalities have been observed in patients with AIDS (box 1).^{1–4} We strongly suspect megestrol-induced insulin resistance to be the cause of diabetes mellitus in our patient. A high-normal fasting C-peptide level during the hyperglycaemic state and an adequate insulin and glucagon secretory response to arginine infusion ruled out the possibility of drug-induced islet cell damage resulting from prior pentamidine therapy. Insulin resistance is also suggested by the presence of gross hypertriglyceridaemia when the patient was admitted to hospital, with rapid normalisation of triglyceride levels after megestrol acetate therapy was withdrawn.

The exact metabolic alterations leading to weight gain with megestrol acetate therapy are unknown. Loprinzi *et al*⁵ performed body composition studies before and two months after starting megestrol acetate in 12 patients with advanced cancer and showed that increases in fat account for most of the weight gained during therapy. In an *in vitro* model, megestrol acetate promoted differentiation of 3T3-L1 Swiss mouse embryo fibroblasts to adipocytes.⁶ The effects of megestrol acetate, a progestational agent, on glucose metabolism are also poorly understood. Henry *et al*³ postulated glucocorticoid-like activity of megestrol as the possible cause of insulin resistance in their patient. Inhibitory effects of progesterone on phosphorylation of glucose into glucose-6-phosphate⁷ and inhibition of insulin-stimulated transmembrane glucose

Endocrine abnormalities and AIDS

- acute pancreatitis: complication of dideoxyinosine, pentamidine, and trimethoprin - sulfamethoxazole therapy
- hypoglycaemia: complication of intravenous pentamidine therapy (beta cell toxicity)
- diabetes mellitus: complication of intravenous pentamine and megestrol

Box 1

Summary/learning points

- in appropriate clinical settings, megestrol acetate-induced insulin resistance should be included in the differential diagnosis of hyperglycaemia in patients with AIDS
- withdrawal of megestrol acetate may result in rapid correction of all metabolic abnormalities

Box 2

transport,⁸ noted in animal studies, may partly explain a progesterone-induced insulin resistant state. In humans, mild and subclinical alterations in glucose tolerance and presumably insulin resistance has been noted with the use of continuous subdermal levonorgestrel.⁹ Interestingly, no adverse effect on blood glucose¹⁰ or lipid profile⁵ have been noted in cancer patients treated with high-dose megestrol acetate. It is commonly accepted that patients with AIDS show a higher incidence of adverse drug reactions. For this reason, patients with AIDS may be particularly at risk of developing severe glucose disturbances while taking megestrol acetate.

We realise that some patients presenting with hyperosmolar nonketotic coma show rapid improvement in metabolic profile after receiving intensive supportive care with intravenous fluid and insulin. This is especially true when an underlying precipitating cause is promptly identified and corrected. Some of these individuals may not require long-term insulin therapy to control blood glucose. However, a majority of these patients continue to show some evidence of metabolic derangement on formal glucose tolerance testing. Although we cannot exclude this possibility with absolute certainty, complete normalization of all metabolic abnormalities after the withdrawal of megestrol acetate argue against this scenario in our case. Therefore, we suggest that blood glucose should be monitored during megestrol acetate therapy in AIDS patients. This is especially important since life-threatening metabolic derangements may occur, as in our patient, which rapidly normalise once the medication is discontinued, obviating the need for insulin therapy. Further studies are needed to define the incidence and mechanism of insulin resistance induced by megestrol acetate in patients with AIDS.

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Digoxin toxicity presenting as encephalopathy

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Summary
We describe two cases of digoxin toxicity presenting with clinical and electroencephalographic evidence of encephalopathy without other features of digoxin toxicity.

Keywords: digoxin toxicity, encephalography

Digoxin toxicity often presents with gastrointestinal side-effects such as anorexia, nausea or vomiting.¹ Other side-effects include cardiac dysrhythmias, visual disturbance and drowsiness.²

Case 1
A 68-year-old woman was admitted to hospital with a one-week history of profound somnolence. She had been non-specifically unwell in the preceding month and had fallen twice without any history of head injury. There was no history of anorexia, nausea, vomiting or visual disturbance. Her past medical history consisted of ischaemic heart disease, congestive cardiac failure, atrial fibrillation, cerebrovascular disease and chronic airflow limitation. Medication comprised frusemide 120 mg, spironolactone 100 mg, prednisolone 5 mg, ranitidine 150 mg, digoxin 250 µg, all daily, with isosorbide mononitrate 20 mg and nifedipine SR 10 mg both twice daily.

Clinical examination revealed no focal neurological signs but confirmed extreme drowsiness. Investigations revealed no abnormality of full blood count, urea and electrolytes, liver function tests, blood glucose, thyroid function tests or B12 and folate. Blood cultures and VDRL were negative. Chest X-ray was normal and electrocardiogram showed sinus rhythm with lateral ST depression. Computed tomography (CT) scan of brain revealed no abnormality and lumbar puncture resulted in clear, colourless cerebrospinal fluid with no

growth, normal glucose and mildly raised protein at 0.63 g/l (normal <0.4 g/l). Electroencephalogram (EEG) showed focal right anterior quadrant delta slowing consistent with Herpes encephalitis. However, following a telephone conversation with her general practitioner it transpired that her digoxin dose had been doubled to 250 µg daily approximately one month prior to admission. Her digoxin level when checked was >5 µg/l. Digoxin was withheld and the patient gradually woke up. One week later she was back to normal (digoxin level 0.3 µg/l).

Case 2
A 66-year-old woman with a previous history of rheumatic valvular heart disease (mitral and aortic valve replacements), atrial fibrillation, chronic congestive cardiac failure and angio-

Digoxin: CNS side-effects
<ul style="list-style-type: none">● lethargy and fatigue● weakness● headache● visual disturbances (colour perception problems (including xanthopsia), reduced visual acuity, visual field defects, pain on eye movement)● depression● psychosis● drowsiness● confusion● delerium● encephalopathy● hallucinations● epileptic seizures● choreiform movements● dysphonia● dysphagia● trigeminal neuralgia

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