central suppression of the pituitary–adrenal axis.⁶ These findings are supported by another recent study on patients with cachexia and AIDS.² Neither the minimum dose, nor the duration of treatment with megestrol required to suppress the HPA axis is known, however doses of 160 mg/day and above frequently reduce cortisol levels⁶ and even doses as low as 20–40 mg/day may have some effect.⁷ One study suggests that 50% of patients treated with high-dose progestagens have biochemical evidence of HPA axis suppression.⁸ These patients are often not considered to be at risk of adrenal insufficiency. This increases the risk that adrenal insufficiency will go unrecognised in this group following withdrawal of progestagen, or during intercurrent illness.^{9–10} Since the majority of cases have disseminated malignancy and multiple symptoms, the diagnosis of adrenal suppression is easily overlooked. We feel it should be considered in all patients with a known malignancy with non-specific symptoms on megestrol or MPA.

The British National Formulary mentions the possibility of cushingoid side-effects which may occur with both megestrol and MPA. The

Learning points

- orthostatic hypotension can be caused by megestrol-induced adrenal suppression
- megestrol-induced adrenal suppression is independent of dose and duration of treatment
- polypharmacy can lead to difficulty in identifying medications responsible for side-effects

Box 2

natural corollary of this, in the form of suppression of the adrenal axis is not listed. Physicians involved in the care of patients on synthetic progestagens need to be aware of the profound effects which these agents have on the HPA axis.

Final diagnosis

HPA axis suppression secondary to megestrol administration.

Keywords: megestrol; orthostatic hypotension; adrenal suppression; polypharmacy; hypothalamic–pituitary–adrenal axis

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Fits and starts

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A 67-year-old woman was brought by ambulance to the casualty department, unresponsive with generalised fits. She was pyrexial at 39.3°C (axilla), her pulse was 140 beats/min and regular, blood pressure 60/35 mmHg, Glasgow Coma Score 6/15, stiff with down-going plantars. She was a known schizophrenic taking procyclidine, clomipramine and trifluoperazine. Her confusion and hallucinations had increased recently and her general practitioner had adjusted her medication. Laboratory investigations revealed the following: haemoglobin 9 g/dl, mean corpuscular volume 82 fl, white cell count $21.8 \times 10^9/l$, platelets $346 \times 10^9/l$, clotting screen normal, Na 151 mmol/l, K 4.7 mmol/l, urea 27.6 mmol/l, creatinine 287 $\mu\text{mol/l}$, creatine kinase 11 200 IU/l, lactate dehydrogenase 929 IU/l, aspartate transaminase 404 IU/l. Mg, Ca, total protein, alkaline phosphatase, gamma-glutamyl transferase, glucose, and amylase were normal. Septic screen was negative. Electrocardiogram revealed sinus tachycardia, arterial blood gas (on 60% O₂), pH 7.15, pCO₂ 2.57 KPa, pO₂ 14.9 KPa, HCO₃ 6.9 mmol/l, BE 19.1 mmol/l, O₂ sat 97%.

Questions

- 1 What is the diagnosis?
- 2 What precipitated the above crises?
- 3 What is the management of this condition?

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Answers

QUESTION 1

The diagnosis is neuroleptic malignant syndrome (NMS), which is characterised by hyperthermia, hypertonicity of skeletal muscles, and fluctuating consciousness, along with dysfunction of the autonomic nervous system.¹ Infrequent findings include oculogyric crisis, opisthotonos, seizures, chorea, Babinski's sign and trismus.² Leucocytosis with or without left shift is common. Liver function abnormalities may reflect acute fatty changes in the liver induced by hyperpyrexia. Electrolyte abnormalities may suggest dehydration. The creatine kinase level is often elevated and may result in acute myoglobinuric renal failure.

QUESTION 2

The recent increase in the dose of antipsychotic medication (trifluoperazine) precipitated this condition. Antipsychotic agents are well known for inducing NMS, and some have suggested that initiating treatment at high doses increases the risk.³ Predisposing factors include physical exhaustion, dehydration, concurrent organic brain disease and the use of long-acting depot neuroleptics.

QUESTION 3

Management consists of discontinuation of trifluoperazine and the use of general supportive measures. Dantrolene, bromocriptine and amantadine all show promise as treatments.³ These agents are believed to relax skeletal muscles, decrease fever and the level of creatine kinase. Isolated therapeutic success of plasmapheresis has been described where conventional therapy has failed.⁴ The role of electroconvulsive therapy in NMS with neuroleptic use is controversial. It should be reserved for cases that fail to respond to supportive and pharmacological therapy, and for psychiatric treatment of patients having recovered from NMS.⁵ In our case, fits were controlled by intravenous diazepam and intravenous fluid was started. She was intubated, ventilated and transferred to the intensive care unit.⁵ She was given intravenous dantrolene as well as mannitol and dopamine in renal perfusion doses for maintaining urine output.

Final diagnosis

Neuroleptic malignant syndrome precipitated by increase in the dose of trifluoperazine.

Keywords: neuroleptic malignant syndrome; trifluoperazine

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