Orthostatic hypotension in an elderly patient

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An 81-year-old woman was admitted following a collapse. She described feeling progressively dizzy and faint for several weeks prior to admission. Five years previously she had undergone oophorectomy and pelvic clearance for ovarian carcinoma. She had a history of hypertension and ischaemic heart disease. Medications on admission were: isosorbide mononitrate 10 mg bid, methotrimeprazine 25 mg bid, fluoxetine 20 mg od, amitriptyline 50 mg nocte, aspirin 150 mg od, adiometane 100 mg od, frusemide 80 mg od, and megestrol 160 mg od.

Examination was unremarkable other than an orthostatic drop in blood pressure from 113/69 mmHg lying to 83/50 mmHg on standing with postural-related dizziness. Her full blood count, electrolytes, urea, creatinine and glucose were all normal. A baseline cortisol (09.00 h) was < 50 nmol/l, with an adrenocorticotropic (ACTH) level of 16 ng/l (reference range < 47). A short synacthen test confirmed adrenal insufficiency with a baseline cortisol of < 50 nmol/l and a peak of 220 nmol/l at 30 minutes. Pituitary hormone profile showed gonadotropin levels to be suppressed with laterising hormone 0.1 IU/l, and follicle-stimulating hormone 0.7 IU/l, while her prolactin was 220 mU/l (60–600). Thyroid function tests showed a free thyroxine of 16.8 pmol/l (9.8–23.1) and a thyroid-stimulating hormone of 2.6 mU/l (0.35–5.5). An autoantibody screen was negative. CA-125 levels of 7 kU/l (0–35) and 17β-OH-oestradiol below the working range of the assay suggested that she did not have recurrence of an oestrogen-secreting, epithelial ovarian carcinoma. Computed tomography (CT) scan of the brain and pituitary was normal and a CT scan of the abdomen and pelvis demonstrated normal adrenal glands, with no evidence of recurrence of the ovarian tumour.

Questions
1 What are the potential causes of this patient’s orthostatic hypotension?
2 What is the most likely cause of her impaired hypothalamic–pituitary–adrenal (HPA) function?
3 What treatment would you advise for her orthostatic hypotension?

Answers

QUESTION 1
Orthostatic hypotension has many causes (box 1), however, in this woman, the major contributing factor is likely to be her medication. Isosorbide mononitrate, methotrexate, amitriptyline or frusemide may each cause orthostatic hypotension directly. Megestrol, a synthetic progesterone, can also cause suppression of the HPA axis and, in the face of a physical challenge, hypoadrenalism with orthostatic hypotension. As in this case, identifying the precipitating event in an elderly patient is not always possible.

Causes of orthostatic hypotension

Primary
- pure autonomic failure - idiopathic
- Shy-Drager syndrome: with parkinsonian features, with cerebellar and pyramidal features, or with multiple system atrophy (combination of above)

Secondary
- general medical disorders, eg, diabetes, amyloid, alcoholism
- autoimmune disease, eg, systemic lupus erythematosus, rheumatoid arthritis, Guillain-Barre
- carcinomatous autonomic neuropathy
- metabolic disease, eg, porphyria, B₁₂-deficiency
- hereditary sensory neuropathies
- central nervous system infectious disease, eg, herpes zoster, syphilis
- central brain lesions, eg, vascular, tumours, multiple sclerosis, Wernicke's encephalopathy
- spinal cord lesions
- renal failure
- aging

Drugs, including representatives from
- selective neurotoxic drugs, eg, alcohol
- tranquillizers, eg, phenothiazines, barbiturates
- antidepressants, eg, tricyclics, monoamine oxidase inhibitors
- vasodilator hypertensive drugs, eg, prazosin, hydralazine
- centrally acting hypertensive drugs, eg, methyldopa, clonidine
- adrenergic neurone blockers, eg, guanethidine
- adrenergic blockers, eg, phenoxybenzamine, labetalol
- angiotensin-converting enzyme inhibitors
- other cardioprotective/antihypertensive medications


Box 1

QUESTION 2
These results are consistent with HPA axis suppression secondary to megestrol, which is also responsible for the appropriately suppressed gonadotropins. Many studies indicate that basal, circadian, and stimulated cortisol secretion remains intact well into old age. Though metastases are found commonly in the adrenal glands they rarely compromise cortisol secretion. It is not necessary for the electrolytes to be disturbed or the random cortisol to be below normal for significant adrenal insufficiency to be present.

QUESTION 3
Initial therapy should revolve around omitting culprit medications and a trial of non-pharmacological methods, including instructing the patient to get up in stages from lying supine, exercises involving dorsiflexion of the feet prior to standing which may enhance venous return, increase the heart rate and increase blood pressure. In the absence of a history of cardiac failure, salt intake could be increased. Elastic/support stockings may help, and elevating the head of the bed 5 to 20 degrees may prevent nocturnal diuresis. On the assumption that the orthostatic hypotension in this patient was drug related, the methotrexate and isosorbide mononitrate were stopped, and the doses of frusemide and amitriptyline halved. Her symptoms and postural hypotension persisted.

Following the result of the short synacthen test the patient was commenced on hydrocortisone 5 mg tid. At follow-up, her orthostatic hypotension and dizziness had resolved and her weakness and fatigue had improved. The megesterol was stopped and 6 weeks later she was symptom free with a subsequent baseline cortisol of 519 nmol/l off the hydrocortisone. In view of the symptomatic improvement and recovery in baseline cortisol a further synacthen test was not considered necessary.

Discussion

Megestrol is a synthetic progesterone most frequently used as a second-line agent in the treatment of breast cancer, endometrial cancer, hypernephromas and prostatic carcinoma. Synthetic progestagens may have beneficial effects on survival and increase appetite in patients with anorexia and advanced malignancies. In the UK over 100 000 prescriptions were written for megestrol in 1996 and it is estimated that 12 500 new patients begin treatment each year. These numbers are likely to increase with its evolving use in patients with AIDS-associated cachexia.

While side-effects of high-dose progestagen therapy such as nausea, weight gain and fluid retention are well recognised, the glucocorticoid effects of high-dose progestagen therapy, in particular their role in suppression of the HPA axis is not. Medroxyprogesterone acetate (MPA) was first noticed to have a cortisone-like effect over 30 years ago. Its effects in suppressing the HPA axis were first noticed in children receiving MPA for precocious puberty. Subsequent studies have confirmed an MPA-mediated reduction in mRNA coding for the ACTH precursor proopiomelanocortin in the pituitary. Recent studies have demonstrated a possible similar effect with megestrol acetate.

Prospective analysis of 16 cancer patients, prior to and during treatment with megestrol, showed marked suppression of serum cortisol levels and decreased levels of corticotropin during the treatment phase, consistent with...
central suppression of the pituitary-adrenal axis. These findings are supported by another recent study on patients with cachexia and AIDS. 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 levels and even doses as low as 20–40 mg/day may have some effect. One study suggests that 50% of patients treated with high-dose progestagens have biochemical evidence of HPA axis suppression. 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. 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


1 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 x 10^9/l, platelets 346 x 10^3/l, clotting screen normal, Na 151 mmol/l, K 4.7 mmol/l, urea 27.6 mmol/l, creatinine 287 mmol/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?