RATIONAL TESTING
Investigating secondary hyperhidrosis
A N Paisley, H M Buckler

Excessive sweating can be due to menopause or drugs but can also result from neoplastic and neurological disease and endocrine or metabolic disorders

A 52 year old woman presented to her general practitioner with a three month history of excessive and distressing chest and facial sweating. This occurred both day and night (often requiring changes of the bed clothes), and at times was associated with facial flushing. She was otherwise well, her weight was stable, and there was no important medical history. Her menstrual cycle had been regular until three years previously but since then had become more erratic, and she had not had a period for 12 months.

What is the next investigation?
Hyperhidrosis (excessive sweating) affects 2.8% of the population. Secondary hyperhidrosis tends to present in adulthood and occurs both during waking and sleeping, unlike primary (idiopathic, essential) hyperhidrosis. Although hyperhidrosis can be due to menopause or drugs, it can also result from underlying medical conditions. The differential diagnosis is similar to that of night sweats and includes infectious or febrile illnesses, neoplastic and neurological disease, endocrine or metabolic disorders, and drugs (box). A full medical history should be taken to ensure no underlying cause is missed, and examination should include assessment of thyroid status and evidence of lymphadenopathy, hepatomegaly, or splenomegaly. A therapeutic trial of withdrawing or reducing any possible contributing drugs should also be considered.

Hyperhidrosis, hot flushes, and night sweats are commonly associated with the menopause, which occurs at a median age of 51 years. Sweating and flushing occur in up to 51% of women before menopausal transition, 35-50% during perimenopause, and 30-80% after the menopause.

Episodes typically start with an unpleasant sensation or sudden onset of a sensation of heat in the face and upper chest, which quickly becomes generalised. It lasts for a few minutes and is associated with profuse perspiration and sometimes palpitations. These flushes are thought to be due to thermoregulatory dysfunction, initiated at the level of the hypothalamus by oestrogen withdrawal. Although sweating in a woman of menopausal age is common, clinicians should not immediately conclude that it is only due to menopausal hot flushes. Measuring gonadotrophins (luteinising hormone and follicle stimulating hormone) and oestriadiol can be helpful. Raised luteinising hormone and follicle stimulating hormone with a low oestradiol concentration confirm menopausal status. In perimenopause, some menstrual bleeding may still be occurring, and luteinising hormone, follicle stimulating hormone and oestriadiol may be normal, or only follicle stimulating hormone may be raised. If there is any doubt about perimenopausal status, blood tests should be repeated in the first few days after the onset of menstrual bleeding, when follicle stimulating hormone is likely to be raised.

Thyroid function is an important investigation as hyperthyroidism can lead to sweating and to menstrual irregularities with oligomenorrhoea. This should be evident with a low concentration of thyroid stimulating hormone in the context of a raised free thyroxine (fT4) or free triiodothyronine (fT3).

Full blood count should be done to look for any underlying haematological disorder, in particular a lymphoproliferative or myeloproliferative disorder. Lymphoma is the most common malignancy associated with night sweats, with around 25% of patients with Hodgkin’s disease experiencing low
LEARNING POINTS

Hyperhidrosis can result from underlying medical conditions, menopause, or drugs. Clinicians should not immediately conclude that sweating in a woman of menopausal age is due to menopausal hot flushes. Patients can present with menopausal symptoms some time after they have completed the menopause.

Initial investigations should include gonadotrophin and oestradiol concentrations to confirm menopausal status, thyroid function tests looking for evidence of hyperthyroidism, and a full blood count to help exclude an underlying haematological disorder.

Outcome

In this patient, gonadotrophin concentrations were high (follicle stimulating hormone 56 IU/l, luteinising hormone 44 IU/l, with oestradiol 46 pmol/l), compatible with a postmenopausal state. Because of the severity of her night sweats, it was important to exclude sinister causes. No other features in the history suggested other disease. Examination was entirely normal, as were results of a full blood count and thyroid function tests. It is important to remember that patients can present with menopausal symptoms some time after they have completed the menopause.

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REFERENCES


LESSON OF THE WEEK

Proton pump inhibitors and acute interstitial nephritis

S Ray,1 M Delaney,2 A F Muller1

Proton pump inhibitors are an important iatrogenic cause of acute kidney injury

Since the introduction of omeprazole in 1989, proton pump inhibitors (PPIs) have become one of the most widely prescribed classes of drugs. A community database of patients who have had any renal function tests in our region shows a prescription rate of 8% (C Farmer, personal communication, 2010). Proton pump inhibitors are associated with a range of side effects including hip fracture, Clostridium difficile infection, and hyponagenaemia.1-3 Sporadic case series have implicated them as a potential cause of acute interstitial nephritis leading to acute kidney injury.4-6

In southeast England during 2007 and 2008, we examined 210 kidney biopsies and found six cases of acute interstitial nephritis that were strongly associated with PPIs either by temporal association with the injury or response to stopping the drugs. These patients had biopsies because renal function was declining, the cause was uncertain, and screening for acute kidney injury was negative. The table summarises five of the six cases of acute interstitial nephritis associated with PPIs (one patient did not consent to be included), and we present two of the cases.
Acute interstitial nephritis related to proton pump inhibitors (PPIs)

### Renal function

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<th>Patient</th>
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<th>Creatinine (µmol/l)</th>
<th>eGFR</th>
<th>Creatinine (µmol/l)</th>
<th>eGFR</th>
<th>Creatinine (µmol/l)</th>
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</table>

eGFR=estimated glomerular filtration rate, calculated by the modification of diet in renal disease formula (ml/min/1.73 m²).

*1-12 months.
†No steroids.

### Case 1

A 70 year old woman was referred by her general practitioner in April 2008 with deteriorating kidney function. She presented with malaise and tiredness. Her medical history included hypertension. She was taking lisinopril (for 15 years), domperidone, and omeprazole. She had not used antibiotic or non-steroidal anti-inflammatory drugs (NSAIDs) recently. Omeprazole was first prescribed in December 2007.

Physical examination, including blood pressure, was normal. Urinalysis confirmed a trace of blood and protein. Screening for acute kidney injury (antinuclear antibodies, antineutrophil cytoplasmic antibodies, complement factors, C3 and C4, and serum and urine electrophoresis) was negative. Proteinuria (urinary protein:creatinine ratio) was 15 mg/mmol (normal range 3-14 mg/mmol). Kidney function was assessed by plasma creatinine (µmol/l) and estimated glomerular filtration rate (table; patient 1). An ultrasound scan showed normal sized, non-obstructed kidneys.

Kidney biopsy confirmed normal glomeruli and patchy tubulo-interstitial lymphocytic infiltrates. An allergic-type drug reaction was diagnosed. In view of the temporal association of omeprazole ingestion and acute kidney injury, the omeprazole was stopped. Lisinopril and domperidone were continued. She was treated with oral prednisolone at 30 mg daily for four weeks and tapered to cessation at three months. Kidney function improved but it did not return to pre-PPI levels.

### Case 2

A 60 year old woman was referred by her general practitioner with chronic kidney disease stage 4 in February 2008. She gave a two month history of fatigue and thirst. Her medical treatment consisted of betahistine, citalopram, omeprazole, and tramadol. She had no history of recent antibiotic or NSAID use. Omeprazole was first prescribed in February 2005 for gastritis and used intermittently until January 2007, and then consistently until presentation. Kidney function was normal during November 2006, but at presentation the creatinine concentration was 196 µmol/l (eGFR 23 ml/min/1.73 m²). Physical examination was unremarkable and urinalysis confirmed 1+ protein and a trace of blood. Screen for acute kidney injury was negative. Proteinuria measured by protein:creatinine ratio was 108 mg/mmol (normal range 3-14 mg/mmol), equivalent to approximately 1 g/day. Proteinuria in the non- nephrotic range supported a non-glomerular aetiology. Kidney function results are summarised in the table (patient 2). Ultrasound scan was normal.

Renal biopsy confirmed normal glomeruli and focal lymphocytic tubulitis consistent with an acute tubulointerstitial nephritis. Omeprazole was discontinued on 19 March 2008 and prednisolone was started at 30 mg daily, tapered for four months, and then discontinued. Kidney function improved but did not return to normal.

### Discussion

About 15% of patients admitted to hospital with acute kidney injury will eventually be diagnosed with acute interstitial nephritis. Most cases are due to an idiosyncratic reaction to certain drugs, including penicillins and NSAIDs. Since the first case report of acute interstitial nephritis provoked by proton pump inhibitors was published in 1992, all drugs in the PPI class have been associated with reports of acute kidney injury. The mechanism of renal injury is not fully understood but is thought to involve an immune component. In vitro lymphocyte stimulation tests show response to selected drugs and rapid return of disease on inadvertent rechallenge. The standard treatment involves withdrawing the drug and steroids (depending on the degree of acute kidney injury and clinical assessment).

In the cases presented, the deterioration in kidney function was temporally associated with treatment with PPIs, stopping PPIs led to an improvement in kidney function, and the biopsy findings were consistent with an allergic-type acute tubulo-interstitial nephritis. Although these findings are insufficient to show causation, due to possible confounding factors (such as the use of other drugs), our data combined with other case reports are highly suggestive. In our renal unit, PPIs were the leading likely cause of acute interstitial nephritis. Omeprazole was discontinued on 19 March 2008 and prednisolone was started at 30 mg daily, tapered for four months, and then discontinued. Kidney function improved but did not return to normal.

The incidence of acute interstitial nephritis related to PPIs remains uncertain, but it is thought to be relatively uncommon. During a 22 month period, we identified six cases of acute interstitial nephritis associated with PPIs, proved by biopsy, in a renal centre serving a population of 1.1 million people. An earlier study in the United Kingdom reported eight cases in a four year period.
Medicines and Healthcare products Regulatory Agency reporting scheme in the UK (www.mhra.gov.uk/Onlineservices/Medicines/Druganalysisprint/index.htm) found 74 cases of acute interstitial nephritis related to PPIs between 1992 and December 2009. The condition is likely to be considerably under-reported because of a lack of awareness of the condition, the non-specific nature of the symptoms, and attributing decline in kidney function to other conditions.

Although the incidence of acute kidney injury induced by proton pump inhibitors is likely to be low (even accounting for under-reporting), it is important to consider it in the differential diagnosis of kidney disease. Acute interstitial nephritis induced by PPIs is an iatrogenic cause of kidney injury that can be wholly or partially reversed in most patients, avoiding the development of chronic kidney disease and its deleterious sequelae.

The relative infrequency of kidney function testing and the non-specific symptoms of this condition suggest that a high index of suspicion is needed. If a decline in renal function is noted, PPIs should be considered as a cause and stopped. They can often be replaced with lifestyle measures, antacids, and ranitidine (which is very rarely associated with acute interstitial nephritis). PPIs are not without risks and should always be appropriately prescribed.

Contributors: SR reviewed the results of all renal biopsies in the study period and the notes of those identified with interstitial nephritis and drafted the paper. MD and AFM devised the study protocol, reviewed all of the results, and contributed to the final version of the paper. AFM is guarantor.

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ANSWERS TO ENDGAMES, p 677. For long answers go to the Education channel on bmj.com

PICTURE QUIZ
A case of progressive breathlessness

1 The cardiac magnetic resonance image shows widespread thickening of the pericardium of up to 6 mm (figs 3 and 4). Normal pericardial thickness is 2 mm. The signs detected by echocardiography indicate constrictive haemodynamics, consistent with a diagnosis of constrictive pericarditis.

2 Given the patient’s history of fever and weight loss, infection is the most likely cause of his constrictive pericarditis. The insidious onset suggests a chronic infection such as tuberculosis. Therefore, the most likely aetiology is tuberculous pericarditis.

3 The hepatomegaly and abnormal results on liver function tests are caused by hepatic congestion secondary to right sided heart failure.

4 Antituberculous treatment is imperative. First line drugs currently used to treat tuberculosis are rifampicin, isoniazid, pyrazinamide, and ethambutol given for the first two months, followed by rifampicin and isoniazid for the following four months; a total of six months of treatment. Some patients may require a pericardectomy if the constriction remains haemodynamically significant despite antituberculous treatment.

ON EXAMINATION QUIZ
Gastro-oesophageal reflux disease in children
Answer D is correct.

STATISTICAL QUESTION
Confounding in case-control studies
Answers a, b, c, and d are all true.