Results and discussion

The absorption of frusemide was reduced by 50 per cent after phenytoin and a corresponding reduction in maximum frusemide concentration occurred. Serum and renal clearance of frusemide was unaltered by phenytoin. No significant amounts of metabolite were found by TLC, confirming that the ^{35}S-label in serum was representative of unmetabolised frusemide.

These results show that treatment with phenytoin leads to decreased intestinal absorption of frusemide, and consequently to lower peak serum frusemide concentrations. The renal response to frusemide is dose dependant and the reduction of half of the diuretic effect of oral frusemide in patients on anticonvulsant treatment[1] closely corresponds to the degree of reduction in both absorption and peak serum concentrations obtained in our patients. Malabsorption of frusemide has been described in chronic uraemia,[2] but we know of no other reports of this occurrence in other conditions.

The mechanism for this malabsorption is not clear. Phenytoin affects jejunal Na^+ pump activity,[3] and decreases gastrointestinal motility. Though our results do not indicate the mechanism, a similar reduction in folic acid absorption has been observed with phenytoin.[4] Reduced blood concentration of a drug might be due to increased metabolism; that our results are not due to the known potent stimulation of microsomal enzymes by phenytoin is clearly established by similar serum clearance values obtained in both periods. Moreover, frusemide is metabolised to only a small degree.

Diminished diuretic response to intravenous frusemide has been found in patients on anticonvulsants; this may be due to increased reabsorption of sodium observed in dogs after phenytoin administration.[5] Nevertheless, in clinical practice the effect of phenytoin on absorption is more likely to be more important. Whether other drugs have a similar effect remains to be investigated.

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[5] Koch, A, *et al*, *Physiologist*, 1972, **5**, 168.

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Renal Unit, Royal Infirmary, Glasgow G4 0SF
ADRIAN FINE, MD, MRCP, senior registrar
I S HENDERSON, BSC, MRCP, registrar
D R MORGAN, MRCP, registrar

School of Pharmaceutical Sciences, Strathclyde University, Glasgow
W J TILSTONE, PHD, MRCPATH, lecturer

Hot flushes after hypophysectomy

Menopausal flushing is said to be caused by low circulating concentrations of oestrogen or by high circulating concentrations of gonadotrophins. We have already examined these explanations and found them to be inadequate,[1] and recent studies[2 3] have cast further doubt on the oestrogen-deficiency hypothesis. If the theory of gonadotrophin excess were true then hot flushes would not occur after total hypophysectomy. We report two patients who developed typical hot flushes after surgical removal of the pituitary gland.

Case report

Case 1—After the menarche at age 12½ years, this patient had normal regular menstrual periods until her late teens, when she gradually stopped menstruating. Withdrawal bleeds were produced for a short time with oral contraceptives, but since the age of 22 she had been totally amenorrhoeic. At 28 she presented with a right homonymous hemianopia and was found at craniotomy to have a chromophobe adenoma extending through the diaphragma sellae to affect the left optic tract. The adenoma was removed transfrontally and postoperatively she received radiotherapy to the pituitary fossa. Some months later she gradually developed hot flushes which she assumed to be due to an early change of life. The flushes began with a feeling of heat spreading up the body. This sensation was followed by visible reddening of the face, neck, and forearms together with sweating of the scalp, forehead, and face. These flushes occurred up to six times a day, came on without warning, and lasted about five minutes. She did not have night sweats.

Postoperative endocrine evaluation showed hyperprolactinaemia of 22 000 mU/l (normal range 100–400 mU/l) and low circulating concentrations of gonadotrophins (LH 1 mU/l; FSH 3 mU/l), which did not rise in response to intravenous injection of 100 micrograms of gonadotrophin-releasing hormone (table). After six months of treatment with bromocriptine her prolactin concentration returned to the normal range although she remained amenorrhoeic and unresponsive to gonadotrophin-releasing hormone (see table).

Gonadotrophin-releasing hormone test in patient 1 before and after bromocriptine

Date	Bromocriptine	Prolactin (mU/l)	Gonadotrophins (mU/l)	Time after GRH (min) 0	20	60
March 1976	0	22 000	LH	1	2	2
			FSH	2	3	5
Oct 1976	10 mg daily	56	LH	1	3	4
			FSH	3	3	5

Case 2—After two normal pregnancies this patient suddenly stopped menstruating at the age of 35 and has had no periods since. When she was 50 she gradually developed hot flushes: any time of the day or night she would feel hot in the face and neck and would then have drenching sweats. The episodes lasted up to 15 minutes, and necessitated her going into a cold room. The attacks were worse in summer and after a warm drink. Two years later she had a total hysterectomy and oophorectomy with removal of an adenocarcinomatous ovarian cyst. Postoperatively the hot sweats became more frequent and intense. One year later, at the age of 53, she presented with the typical symptoms of diabetes mellitus and was found to be acromegalic. Basal growth hormone concentrations exceeded 40 μg/l and for control of her diabetes she required 60 units of lente insulin daily. She was treated by transsphenoidal hypophysectomy and histological examination showed a chromophobe adenoma. She made an uncomplicated postoperative recovery but continues to have hot flushes once or twice a day.

Postoperative evaluation showed a significant degree of hypopituitarism with basal growth hormone concentrations of 5 μg/l, a very poor adrenal response to hypoglycaemia, and increased insulin sensitivity so that her diabetes is now controlled on chlorpropamide 100 mg daily. Postoperatively her circulating gonadotrophin concentrations are LH 5 μU/l and FSH 5 μU/l (the normal values for a postmenopausal woman in our laboratory are LH 11–49 μU/l and FSH 34–148 μU/l).

Discussion

There have been anecdotal reports that flushing occurs after hypophysectomy, although usually without documentation of hypopituitarism and of low concentrations of gonadotrophins. Netter[4] has seen two women who flushed after hypophysectomy and had undetectable urinary gonadotrophins. Both he and Zarate[5] have noted flushing in women with Sheehan's syndrome.

The two patients described here have classical hot flushes despite low circulating concentrations of gonadotrophins. The theory that oestrogen deficiency causes hot flushes is strongly suspect[1–3] and these two cases provide a further argument against the already questionable concept that gonadotrophin excess plays a part in the pathogenesis of menopausal flushing.

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Department of Medicine, General Hospital, Nottingham NG1 6HA
GRAHAM MULLEY, MB, MRCP, clinical research fellow
J R A MITCHELL, MD, FRCP, professor of medicine
R B TATTERSALL, MD, MRCP, consultant physician