therefore advisable to prevent recurrent or prolonged hypophosphataemia in any patient with chronic renal disease. This is particularly important in patients on maintenance haemodialysis, as the near universal use of phosphate-free dialysate fluid produces a fall in the plasma phosphate concentration, and after dialysis the patient may be hypophosphataemic. The measurement of the postdialysis phosphate concentration is obviously important, but it is more usual to measure the predialysis concentration. This study shows that the predialysis concentration of phosphate is all the clinician needs to know, as it bears a simple and constant relation to the postdialysis value.

Patients, methods, and results

Thirty-eight patients on haemodialysis (Meltec multipoint 1.5 m² for 4 hours or Meltec multipoint 1.0 m² for 6 hours) were dialysed with a dialysate fluid containing 1.5 mmol/l (6 mg/100 ml) of calcium and no phosphate with a blood flow rate of at least 160 ml/minute. Plasma phosphate was measured by the Technicon SMA method immediately before and after each dialysis session. A total of 52 predialysis and postdialysis plasma samples were examined with the patients in the non-fasting state and the mean change in plasma phosphate was 0.93 ± 0.66 mmol/l (2.9 ± 2.0 mg/100 ml).

Relation between initial plasma phosphate concentration and fall in concentration during dialysis.

Conversion: SI to traditional units—Phosphate: 1 mmol/l $\approx$ 3.1 mg/100 ml.

An additional 17 samples were obtained before and after dialysis from patients who had fasted for 12 hours before starting haemodialysis, and then remained fasting throughout the dialysis session. In this fasting group the mean change in plasma phosphate concentration was 1.12 ± 0.66 mmol/l (3.47 ± 2.0 mg/100 ml) (no significant difference between the groups on *t* testing). There was also no significant difference in the change in plasma phosphate that occurred in the patients dialysed with a 1.5 m² or 1.0 m² dialyser.

There was a correlation between the initial plasma phosphate concentration and its fall which occurred during a dialysis session ($r = 0.88$; $P < 0.001$). The mean regression line for these data was $\Delta[\text{PO}_4] = 0.7 \times [\text{PO}_4]_i - 0.4$ (see figure). From this equation it was possible by simple manipulation to be able to predict the postdialysis phosphate concentration from any predialysis phosphate concentration: $[\text{PO}_4]_p = 0.4 + 0.3 \times [\text{PO}_4]_i$.

Comment

The result of this study clearly shows that the reduction in the plasma phosphate concentration during dialysis regimens occurs most predictably. It depends primarily on the initial plasma phosphate concentration, as the two different dialysers used in this study did not seem to influence the fall significantly; nor did the dietary intake of phosphate just before or during haemodialysis. The clinician can therefore safely use the predialysis plasma phosphate concentration to prevent subclinical phosphate depletion developing in patients on dialysis. If the lower limit of the normal range of phosphate is 0.8 mmol/l (2.5 mg/100 ml), as in our own laboratory, it can be calculated that the predialysis concentration should be no lower than 1.33 mmol/l (4.1 mg/100 ml) if postdialysis hypophosphataemia is to be prevented. This accords well with Massry's suggestion that 1.3 mmol/l (4.0 mg/100 ml) was the minimum safe plasma phosphate

concentration necessary to prevent the development of hypophosphataemic osteomalacia.⁵

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Malabsorption of frusemide caused by phenytoin

Ahmad has reported that epileptics on chronic anticonvulsant treatment have a diminished response to frusemide, possibly owing to renal insensitivity rather than alteration in absorption, although no measurements of frusemide metabolism were made.¹ To investigate this phenomenon further, we performed frusemide absorption studies in normal volunteers both taking and not taking phenytoin. We found that malabsorption of frusemide occurred in the former.

Subjects and methods

Five healthy male volunteers aged between 21 and 30 taking no medication were studied during control conditions and after a ten-day course of phenytoin, 100 mg three times per day, the order being randomised. They were allowed unrestricted fluids and one hour after a normal light breakfast were given frusemide. All subjects had both intravenous and oral ³⁵S-frusemide (10.6 μ Ci aqueous ³⁵S-frusemide (20 mg) kindly supplied by Hoechst

Effects of phenytoin on absorption and clearance of frusemide in normal subjects

	Serum clearance (ml/min)	Absorption (%)	Maximum concentration (μ g/ml)
Control	125.1 ± 11.5	80.9 ± 6.46	2.24 ± 0.34
Phenytoin	116.5 ± 7.5	39.0 ± 5.4	1.22 ± 0.10
P	NS	< 0.01	< 0.01

NS = Not significant.

Pharmaceuticals Limited). Blood samples were taken at half-hourly intervals for four hours and one four-hour urine specimen collected. Serum and urine samples were counted in a liquid scintillation counter and the concentrations calculated from the specific activity. Thin-layer chromatography (TLC) was performed to identify significant labelling of any metabolites, and also to ensure that the starting product contained no degradation products. Serum concentration (IV) curves were plotted and the areas under curves calculated using an ICL 19045 digital computer.

The following calculations were made:

$$\text{Absorption (\%)} = \frac{\text{Area under oral curve}}{\text{Area under IV curve}} \times 100$$

$$\text{Serum clearance} = \frac{\text{Dose administered}}{\text{Area under IV curve}} \text{ ml/min.}$$

Data are expressed as mean $\pm$ SE of mean. In the statistical analysis values obtained during the control period and after phenytoin administration were compared by paired *t* test as each subject served as his own control.

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 treatment¹ 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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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	Bromo-cryptine	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. Netter⁴ has seen two women who flushed after hypophysectomy and had undetectable urinary gonadotrophins. Both he and Zarate⁵ 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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