marker that can be used further to investigate differences in the two main aetiological types of diabetes.

The parallel of our results for type I diabetes with those for ankylosing spondylitis is striking. In both there are strong associations with particular HLA markers and a significant increase in the proportion of non-secretors. This is further indirect evidence to support the suggestion that an infectious agent is implicated in the initiation of type I diabetes in some genetically predisposed patients. Determining the secretor state of patients who have various viral infections would be a useful first step in investigating this hypothesis. We suggest that the initial susceptibility to some viral infections might be greater in the non-immune, non-secretor host. The specific immune response to the putative infectious agent, controlled by the class II HLA DR3/4 genes, might contribute to pathogenic sequelae leading to the diabetic state.

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Quality of haemofiltration fluids: a potential cause of severe electrolyte imbalance

Haemofiltration, which requires the infusion of large amounts of electrolyte replacement solutions, is finding increasing application in general hospitals. These solutions do not have a product licence, so responsibility for their quality, safety, and efficacy is taken by the prescriber. We report a case in which the wide limits of quality control of a solution had clinical implications and discuss a survey of the limits of quality control of some commonly used haemofiltration fluids.

Patient, method, and results

A 73 year old woman was admitted to hospital because of worsening breathlessness and peripheral oedema. She had a history of two mitral valve replacements nine years and two months previously. The clinical findings were severe tricuspid regurgitation with competent aortic and mitral valves. She progressively gained weight in hospital despite diuretics and infusion of dopamine. We decided to perform further tricuspid valve surgery, and to improve her clinical state haemofiltration was performed for 48 hours before surgery.

She underwent venovenous haemofiltration with a BSM-22 (Hospal UK), with vascular access through a right internal jugular haemofiltration catheter; a Biospal SCU/CAVH filter was used. About 16 litres of haemofiltrate was obtained on each day, with a negative balance of four litres. Fluid replacement through the BSM-22 was with Hemofiltrasol-21, with 8 mmol potassium chloride added to each three litre bag. In addition, she also received two units of human plasma protein fraction for the first 24 hours, 20% mannitol 100 ml intravenously twice and frusemide 80 mg intravenously once in the second 24 hours, and spironolactone 100 mg once daily.

Her clinical state improved. To our surprise her plasma sodium concentration decreased progressively from 138 mmol/l at the start of the procedure to 133 mmol/l after 48 hours of haemofiltration. Forty eight hours after haemofiltration had stopped her plasma sodium concentration remained at 134 mmol/l. Blood glucose concentration rose from 5·2 mmol/l (random level) before treatment to 8·4 mmol/l during haemofiltration. The plasma potassium concentration, supplemented as described above, remained at 3·8 mmol/l. The serum calcium concentration rose from 2·37 mmol/l to 2·60 mmol/l. There was no appreciable change in the magnesium concentration.

We were surprised by the progressive decrease in plasma sodium concentration during haemofiltration. The Hemofiltrasol-21 bag quoted the sodium concentration as being 140 mmol/l. When a sample of this was analysed on the same flame photometer as the plasma it was found to contain 133 mmol sodium/l. This was confirmed in two other bags of the same batch.

The sodium concentration of 133 mmol/l is within the limits of quality control of Hemofiltrasol-21. We therefore investigated the limits of quality control fluids from four suppliers in this country. The limits varied widely between manufacturers—for example, the limits of quality control for sodium with one manufacturer were +3% to −3%, while with another they were +5% to −7%. Those of magnesium were +5% to −5% with one manufacturer and +13% to −13% with another. The table shows the stated concentration and the limits of some ions.

Concentration (mmol/l) of some common ions in haemofiltration fluids (figures in parentheses are limits of quality control)

Supplier	Sodium	Calcium	Magnesium	Chloride
1	142 (138-146)	2·00 (1·90-2·10)	0·75 (0·71-0·79)	103·0 (98·0-108·0)
2	140 (130-147)	1·60 (1·40-1·80)	0·75 (0·68-0·83)	100·0 (90·0-110·0)
3	135 (128-142)	1·88 (1·79-1·97)	0·75 (0·71-0·79)	106·5 (101·2-111·8)
4	135 (128-142)	1·20 (1·10-1·30)	0·75 (0·65-0·85)	103·0 (98·0-108·0)

Comment

The development of hyponatraemia in heart failure is associated with poor prognosis.[1] The wide limits of quality control applied to some ion concentrations make control of electrolyte balance during haemofiltration unpredictable and potentially hazardous, especially when large volumes are infused. Fluids from suppliers 3 and 4 are within 2% of their intended ion concentrations at the time of manufacture, though they apply wider limits of quality control at the end of the shelf life owing to the evaporation of water from polyvinylchloride bags.

Doctors must remain alert to electrolyte imbalance caused by variations in fluid constituents during large intravenous infusions. Medicinal products without a product licence are prepared as "specials," made to the clinician's specification. Until a manufacturer obtains a product licence doctors who require haemofiltration fluids should specify not only the required concentration of ions but also the acceptable limits of quality control.

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Increased cough reflex associated with angiotensin converting enzyme inhibitor cough

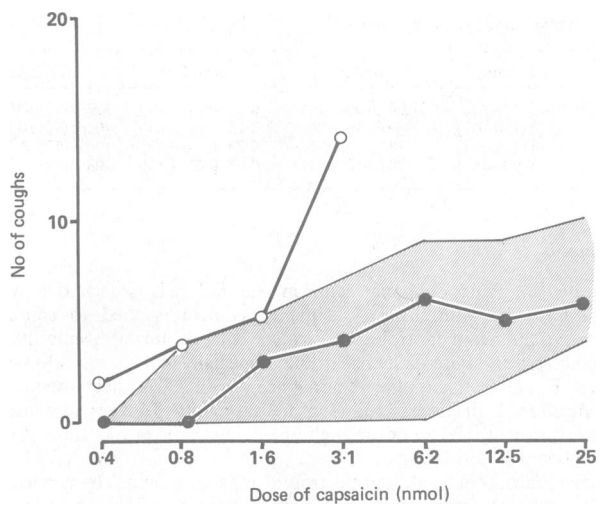
Angiotensin converting enzyme inhibitors are being used increasingly to treat hypertension and congestive cardiac failure as they are one of the few treatments that improve life expectancy in these conditions.[1] In general, these drugs are well tolerated, but recently unexpected and troublesome cough, without obvious pulmonary abnormality, has been reported in as many as 5-10% of patients taking both captopril and enalapril.[2] Until recently cough has been difficult to assess, but we have developed a method for measuring the sensitivity of the cough reflex to a standard inhaled stimulus: capsaicin (red pepper).[3] Using a modification of this method, we assessed the sensitivity of the cough reflex in five patients with cough associated with treatment with angiotensin converting enzyme inhibitors.

Methods and results

Fifty normal volunteers (21 women) (mean (SD) age 36 (18)) participated in the study, which was approved by the local hospital ethical committee. Five patients (two men) (mean age 60 (12)) had developed cough between one week and six months after starting treatment with either captopril or enalapril for hypertension (four patients) or heart failure. Two patients had stable asthma, which was being treated with inhaled steroids and β adrenoceptor agonists. In all patients cough subsided within one week of stopping treatment. Cough sensitivity to capsaicin was measured while the patients were still taking the drug and one week after treatment was stopped.

Capsaicin (0·01 M in absolute alcohol) was diluted with 0·9% saline to $1·9\times10^{-5}$ to $2·5\times10^{-3}$ M for inhalation. The subjects inhaled single breaths (0·02 ml) of 0·9% saline and all the capsaicin solutions in random order from a nebuliser controlled by a dosimeter (MEFAR, Brescia, Italy) unless the coughing became excessive. The subjects were unaware of the concentration of capsaicin in each inhalation. Coughs were recorded by a microphone connected to a mingograf recorder (Siemens-Elema AB, Solna, Sweden) running at 25 mm/s. The doses of capsaicin that caused two or more and five or more coughs were then calculated.

The figure shows the range of cough sensitivity in the 50 normal subjects. The



Ninety five per cent confidence interval (▒) of number of coughs caused by inhalation of capsaicin in 50 normal subjects and median number of coughs in five patients with cough related to angiotensin converting enzyme inhibitor during (○) and one week after stopping (●) treatment.

geometric mean (95% confidence interval) was 2·5 (1·2 to 3·8) nmol for the dose that caused two or more coughs and 7·7 (6·4 to 9·0) nmol for the dose that caused five or more coughs, and the median (range) maximum number of coughs was 7 (4 to 15). In all the patients the doses required to cause two or more coughs and five or more coughs were lower than normal (0·53 (0·38 to 0·74) nmol and 1·59 (0·75 to 3·36) nmol, respectively) and the maximum number of coughs was higher (median (range) 18 (15 to 20)) during treatment. These values returned towards normal when treatment was stopped, the doses required to cause two or more coughs and five or more coughs being 1·59 (0·75 to 3·36) nmol and 3·61 (1·32 to 9·88) nmol, respectively, and the maximum number of coughs decreasing to 8 (5 to 11).

Comment

Cough while taking angiotensin converting enzyme inhibitors may become a serious problem if the use of such drugs in patients with hypertension and heart failure continues to increase. The temporal relation between taking the drug and developing cough and the cessation of the symptom when treatment is stopped, as seen in all five of our patients, supports the diagnosis. Until now, however, diagnosis has relied on the exclusion of other causes, often by extensive investigations. This study is the first to show that cough associated with treatment with angiotensin converting enzyme inhibitors is caused by an increased sensitivity of the cough reflex. The pathogenesis of this increased sensitivity may entail persistence of inflammatory mediators in the airways. Both bradykinin and prostaglandins are potential candidates. Increased bradykinin concentrations are unlikely to be the cause as another angiotensin converting enzyme inhibitor, ramipril, did not alter the bronchoconstrictor response to bradykinin[4] and bradykinin, unlike prostaglandin D_2,[5] does not alter bronchoconstrictor responsiveness. The cough during treatment with angiotensin converting enzyme inhibitors is caused by an increased sensitivity of the cough reflex, though the cause of this remains obscure.

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Mania induced by biochemical imbalance resulting from low energy diet in a patient with undiagnosed myxoedema

We report a case which is of clinical interest because of the coincidence of two rare features—namely, the occurrence of mania in a patient with myxoedema and the precipitation of mania by biochemical abnormalities resulting from a stringent reducing diet.

Case report

A 68 year old man was referred with a three week history of overactivity, sleeplessness, and damaging household objects. One week before onset he had been seen as an outpatient and prescribed a reducing diet of only two pints (1140 ml) of whole milk a day (3·2 MJ; 760 kcal) and nothing else. A home visit was made, and he was found naked and racing around his home in ceaseless activity. In conversation he was friendly but irritable. He showed flight of ideas and pressure of speech. He made puns and jokes. There was no clouding of consciousness, and he was fully oriented. There were no paranoid ideas or hallucinations. His mood was elated, though he retained insight, which is unusual in mania, and he agreed to immediate hospital admission.

He was married with three adult children and had retired three years previously. His family described him as normally a reserved, quiet man who took his responsibilities very seriously. He had never before needed psychiatric help, but three years previously when he had had a hernia operation he had become restless and had slept badly for a few days. His sister's son suffered from manic depressive illness. The patient had been hypertensive for several years and been taking atenolol and diazoxide as maintenance treatment. (After retirement he had gained 12·7 kg in weight.) One month before psychiatric referral, however, he had been seen by a physician because of bradycardia and hypertension and it was noted that his blood pressure was 170/100 mm Hg with bradycardia considered to be due to the atenolol. This was changed to nifedipine 20 mg twice daily, and he was advised to follow the diet described above. Biochemical check immediately before starting the diet showed mild renal impairment (blood urea concentration 8·5 mmol/l (normal 3·0-6·7), plasma creatinine concentration 148 mmol/l (normal 45-120)).

Examination on admission showed dry skin, a pulse rate of 60/min, and blood pressure 130/80 mm Hg. Supinator and ankle reflexes were brisk with slow

Biochemical values on admission and at discharge

	Normal value	Value on admission	Value at discharge
Haemoglobin (g/l)	120-170	104	124
Urea (mmol/l)	3·0-6·7	11·7	8·6
Creatinine (mmol/l)	45-120	177	143
Urate (mmol/l)	<415	579	445
Alanine transaminase (IU/l)	<40	64	35
Aspartate transaminase (IU/l)	<40	155	51
Cholesterol (mmol/l)	3·6-7·8	7·7	—
Thyroxine (mmol/l)	60-160	16	31
Thyroid stimulating hormone (mU/l)	0·4-4·8	725	>25
Weight (kg)	64-73	85	78