expressed psychological distress through the presentation of physical complaints²⁶; the finding of proportionately more somatic symptoms in this group was in keeping with this suggestion. The detection of psychiatric abnormalities and traits of neuroticism in the remainder may not explain the pathogenesis of the hyperventilation syndrome in these subjects. Lum claimed that anxiety may be a consequence of disagreeable and undiagnosed physical symptoms rather than a primary disorder.³

Like Garssen *et al* we found phobic symptoms in about two thirds of our patients.¹³ It is not commonly recognised that patients with phobic neuroses and disorders of panic may suffer from chronic, unstable, hypocapnic breathing, which may lead to various alarming somatic complaints.²⁷ One such phobic patient attributed all her symptoms to multiple food allergies despite evidence to the contrary. Patients attending food allergy clinics may have symptoms that are a consequence of chronic hyperventilation as Rix *et al* showed.²⁸

Inverse correlations between PACO₂ and scores of both neuroticism and psychiatric morbidity have been reported by others.¹²⁻²⁹ Neurotic patients may be easily distressed by the symptoms of transient hypocapnia, which may then lead to increased arousal, further hyperventilation, and the establishment of a chronic disorder.³⁰⁻³¹ Wrong attribution of these hypocapnic symptoms to serious organic diseases may be another factor responsible for maintaining high levels of arousal. But half our patients had scores of neuroticism in the normal range, suggesting that other mechanisms were involved. Further research is required to determine which biological and psychosocial factors predispose towards the development of this common and underdiagnosed disorder.

References

- 1 Kerr WJ, Dalton JW, Glibe PA. Some physical phenomena associated with the anxiety states and their relation to hyperventilation. *Ann Intern Med* 1937; 11:961-92.
- 2 Grossman P, de Swart JCG. Diagnosis of hyperventilation syndrome on the basis of reported complaints. *J Psychosom Res* 1984;28:97-104.
- 3 Lum LC. The syndrome of habitual chronic hyperventilation. In: Hill OW, ed.

- Modern trends in psychosomatic medicine*. Vol 3. London: Butterworths, 1976:196-230.
- 4 Marks I, Lader M. Anxiety states (anxiety neurosis): a review. *J Nerv Ment Dis* 1973;156:3-18.
 - 5 Soley MH, Shock NW. The etiology of effort syndrome. *Am J Med Sci* 1938; 196:840-51.
 - 6 Magarian GJ. Hyperventilation syndromes: infrequently recognised common expressions of anxiety and stress. *Medicine (Baltimore)* 1982;61:219-36.
 - 7 Hardonk HJ, Beumer HM. Hyperventilation syndrome. In: Vinken PJ, Bruyn GW, eds. *Handbook of neurology*. Vol 38. Amsterdam: N Holland Biomedical Press, 1979:309-60.
 - 8 Pfeffer JM. The aetiology of the hyperventilation syndrome: a review of the literature. *Psychother Psychosom* 1978;30:47-55.
 - 9 Dent R, Yates D, Higgenbottom T. Does the hyperventilation syndrome exist? *Thorax* 1983;38:223.
 - 10 McFadden ER, Lyons HA. Arterial blood gas tension in asthma. *N Engl J Med* 1968;278:1027-32.
 - 11 Szucs MM, Brooks HL, Grossmann W, *et al*. Diagnostic sensitivity of laboratory findings in acute embolism. *Ann Intern Med* 1971;74:161-6.
 - 12 Damas-Mora J, Grant L, Kenyon P, Patel MK, Jenner FA. Respiratory ventilation and carbon dioxide levels in syndromes of depression. *Br J Psychiatry* 1976;129:457-64.
 - 13 Garssen B, Van Veenendaal W, Bloemink R. Agoraphobia and the hyperventilation syndrome. *Behav Res Ther* 1983;21:643-9.
 - 14 Bass C, Cawley RH, Wade C, *et al*. Unexplained breathlessness and psychiatric morbidity in patients with normal and abnormal coronary arteries. *Lancet* 1983;i:605-9.
 - 15 Tucker WL. Diagnosis and treatment of the phobic reaction. *Am J Psychiatry* 1956;112:825-30.
 - 16 White PD, Hahn RG. The symptom of sighing in cardiovascular diagnosis: with spiographic observations. *Am J Med Sci* 1929;177:179-88.
 - 17 Bannister RG, Cunningham DJC, Douglas CG. The carbon dioxide stimulus to breathing in severe exercise. *J Physiol* 1954;125:90-117.
 - 18 Gardner WN, Bass C. A respiratory and psychiatric study of patients with symptomatic hyperventilation (including sleep). *Bull Eur Physiopathol Respir* 1984;20:92.
 - 19 Gardner WN. The relation between tidal volume and inspiratory and expiratory times during steady-state carbon dioxide inhalation in man. *J Physiol* 1977; 272:591-611.
 - 20 Juniper EF, Frith PA, Dunnett C, Cockcroft DW, Hargreave FE. Reproducibility and comparison of responses to inhaled histamine and methacholine. *Thorax* 1978;33:705-10.
 - 21 Goldberg DP, Cooper B, Eastwood MR, Kedward HB, Shepherd M. A standardised psychiatric interview for use in community surveys. *Br J Prev Soc Med* 1970;24:18-23.
 - 22 Kellner R, Sheffield BF. A self-rating scale of distress. *Psychol Med* 1973;3: 88-100.
 - 23 Eysenck HJ, Eysenck SB. *Manual of the Eysenck personality questionnaire*. London: Hodder and Stoughton Educational, 1975.
 - 24 Plum F, Swanson AG. Central neurogenic hyperventilation in man. *Arch Neurol Psychiat* 1959;81:535-49.
 - 25 Tyrer PJ. *The role of bodily feelings in anxiety*. London: Oxford University Press, 1976:95.
 - 26 Mechanic D. Social psychologic factors affecting the presentation of bodily complaints. *N Engl J Med* 1972;286:1132-9.
 - 27 Bass C, Gardner WN. Panic disorder. *Br Med J* 1983;286:1818.
 - 28 Rix KJB, Pearson DJ, Bentley SJ. A psychiatric study of patients with supposed food allergy. *Br J Psychiatry* 1984;145:121-6.
 - 29 Grossman P. Respiration, stress and cardiovascular function. *Psychophysiology* 1983;20:284-300.
 - 30 Lewis BI. Chronic hyperventilation syndrome. *JAMA* 1954;155:1204-8.
 - 31 Clark DM, Hemsley DR. The effects of hyperventilation: individual variability and its relation to personality. *J Behav Ther Exp Psychiatry* 1982;13:41-7.

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SHORT REPORTS

Intranasal calcitonin and plasma calcium concentrations in normal subjects

Various substances are absorbed by the mucosa of the respiratory system, including vasopressin, leuteinising hormone releasing hormone, insulin, and glucagon.¹⁻⁴ We have evaluated the absorption of another polypeptide hormone, calcitonin, through the nasal mucosae of normal subjects.

Subjects, methods, and results

We studied six healthy volunteers, all doctors or medical students aged 25-30, with no family history of endocrine or metabolic diseases. After an overnight fast and abstention from smoking they were studied in bed in the morning. Calcitonin was given intravenously or intranasally according to a randomised crossover design. Tests were performed twice in each patient with an interval of one week.

Human calcitonin (Cibacalcin; Ciba-Geigy) 500 µg was either administered intravenously or mixed with a surfactant, sodium glycocholate 15 mg, dissolved in 0.5 ml distilled water, and given as nose drops. Four subjects also received intranasally calcitonin 1000 µg plus sodium glycocholate 15 mg on a separate occasion. The project was approved by this hospital's ethical committee.

The figure shows the times at which blood samples were taken for plasma calcitonin and ionised calcium assay. Calcitonin concentrations were deter-

mined by radioimmunoassay with reagents supplied by Sorin-Biomedica (Saluggia, Italy). In our experience, the main characteristics of this radioimmunoassay are: sensitivity 10 pg/ml; recovery of added doses 92%; and interassay and intra-assay coefficients of variation 8.5% and 4.4%, respectively.

The figure compares the effects of intravenously and intranasally administered calcitonin and of 500 and 1000 µg calcitonin administered intranasally on plasma concentrations of calcitonin and ionised calcium. Although plasma calcitonin concentrations were consistently higher after intravenous than after intranasal administration of the same dose, calcitonin 500 µg affected plasma calcium concentrations identically whether given intranasally or intravenously. Higher plasma calcitonin concentrations accompanied the higher dose of intranasal calcitonin, but the decrease in plasma calcium concentrations did not differ between the two doses.

Severity of side effects did not differ between either the two routes of administration or the two doses given intranasally. Five subjects experienced nausea and facial flush, one with vomiting.

Comment

Administration of peptidic hormones (insulin, calcitonin) is restricted to the parenteral route as proteolytic digestion prevents administration by mouth.⁵ This is a drawback to long term treatment with peptidic hormones and limits the compliance by patients, especially when a regimen of regular daily injections is required. We therefore studied the possible efficacy of intranasally administered calcitonin in normal subjects. To evaluate both the kinetics and the short term effects of calcitonin the hormone was administered intranasally and intravenously. A fixed dose of human calcitonin,

Mean (SEM) plasma concentrations of calcitonin (above) and ionised calcium (below) after (left) intravenous (○---○) and intranasal (●—●) administration of calcitonin 500 µg to six healthy subjects and (right) intranasal administration of human calcitonin 500 µg (▲) and 1000 µg (△) to four healthy subjects.

p Values for time after administration v 0 min: * < 0.02; ** < 0.01.

Conversion: SI to traditional units—Calcium: 1 mmol/l ≈ 4 mg/100 ml.

500 µg, exerted the same effect on plasma calcium concentrations whether administered intravenously or intranasally, this despite the plasma calcitonin concentration being higher after intravenous than after intranasal administration. If we consider in addition that when doses of 500 and 1000 µg calcitonin were used the decrease in the plasma calcium concentration was the same we must assume that in man no strict relation exists between plasma concentrations of calcitonin and calcium; alternatively, it might be suggested that the doses used in this study were always maximally effective.

Calcitonin has gained popularity in the treatment of Paget's disease of the skeleton, osteoporosis, intractable osseous pain from metastases, and hypercalcaemia, although its use in these indications is debatable and of unconfirmed value. Our study indicates that calcitonin may be given intranasally under the same or other circumstances. Further improvements in the bioavailability and metabolic efficacy of intranasally administered calcitonin may be expected with the use of aerosols, which ensure that a greater surface area of the nasal and pharyngeal mucosa is reached by the active drug.

- Schrier RW, Leaf A. Effect of hormones on water, sodium, chloride and potassium metabolism. In: Williams RH, ed. *Textbook of endocrinology*. 6th ed. Philadelphia: W B Saunders, 1981:1032-46.
- Fink G, Gennser G, Liedholm P, Thorell J. Comparison of plasma levels of LHRH in men after intravenous and intranasal administration. *J Endocrinol* 1974;63:351-60.
- Pontioli AE, Alberetto M, Secchi A, Dossi G, Bosi I, Pozza G. Insulin given intranasally induces hypoglycaemia in normal and diabetic subjects. *Br Med J* 1982;284:303-6.
- Pontioli AE, Alberetto M, Pozza G. Intranasal glucagon raises blood glucose concentration in healthy volunteers. *Br Med J* 1983;287:462-3.
- Murlin JR, Gibb CBF, Romansky MJ, Steinhilber TB, Truax FL. Effectiveness of perioral insulin in human diabetes. *Am J Physiol* 1940;120:709-22.

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Characterisation of antibodies to insulin to help diagnose factitious hypoglycaemia

Spontaneous hypoglycaemia is associated with several pathological disorders, including benign or malignant tumours, diseases of hepatic, renal, or endocrine systems, and inborn errors of metabolism.¹ As many of these conditions can be diagnosed rapidly in a young adult presenting with hypoglycaemia only a few clinical conditions remain in the differential diagnosis.

We describe a case of hypoglycaemia in which the diagnoses of spontaneous reactive hypoglycaemia, insulinoma, autoimmune spontaneous hypoglycaemia, and factitious hypoglycaemia were all considered. Factitious hypoglycaemia was confirmed by specific characterisation of the antibodies to insulin that were present.

Case report

A 16 year old girl admitted to hospital as an emergency was conscious, hypothermic (32°C), and hypoglycaemic (glucose concentration 1.2 mmol/l (21.6 mg/100 ml)). At the age of 14 she had been investigated for a similar episode with an extended oral glucose tolerance test and had been diagnosed as having spontaneous reactive hypoglycaemia. Her father and sister were known to have insulin dependent diabetes (treated with soluble and isophane insulin), but neither was living at home. Although she had been asymptomatic since then, an insulinoma needed to be excluded. A prolonged 50 g oral glucose tolerance test was repeated, which again produced reactive hypoglycaemia (figure). As up to one fifth of normal subjects can develop reactive hypoglycaemia after a glucose load this finding was not considered to be diagnostically important.¹ Concentrations of insulin were reported as too high to record. A 24 hour fast followed by exercise did not produce hypoglycaemia, and an insulin stress test (0.15 U/kg) did not result in adequate hypoglycaemia and could not therefore be interpreted. As the findings of unrecordable high insulin concentrations and resistance to exogenous insulin were attributed to the presence of antibodies to insulin an insulinoma was considered to be unlikely.

Results of prolonged (five hour) oral glucose tolerance test (50 g), with C peptide and glucose measurements showing reactive hypoglycaemia at 210 minutes.

Conversion: SI to traditional units—Blood glucose: 1 mmol/l = 18 mg/100 ml.

Antibodies to insulin were investigated further by immunochemical characterisation to distinguish between spontaneous autoimmune hypoglycaemia and factitious hypoglycaemia. This investigation indicated considerable formation of antibodies to bovine insulin (68.2% binding)² and to the C peptide moiety of bovine proinsulin (64.8% binding).³ Lateral bruising was noted on both thighs, which later developed into mild lipodystrophy. Factitious hypoglycaemia was diagnosed. She did not admit to abuse of insulin and refused to return to any follow up clinics.

Comment

Although factitious hypoglycaemia is an uncommon cause of hypoglycaemia, biochemical or immunological tests that confirm the diagnosis are of great interest to the clinician. In a patient without antibodies to insulin the simultaneous presence of a low concentration of glucose, high concentration of immunoreactive insulin, and suppressed C peptide is considered to be pathognomonic of the secret use of insulin.¹ Alternatively, a species specific antibody can be used to discriminate between human and bovine insulin in the plasma.⁴ In a patient with antibodies to insulin, however, these tests are unreliable as accurate measurements of plasma insulin concentrations are impossible and C peptide concentrations may not be suppressed due to the antibody binding proinsulin containing the C peptide moiety.⁵ Neither do they distinguish between autoimmune spontaneous hypoglycaemia and factitious hypoglycaemia.¹

The specific binding characteristics of circulating antibodies to insulin, however, can be used to confirm cases of factitious hypoglycaemia. Bovine insulin differs from human insulin by only three amino acids, and the antibodies formed due to the repeated injection