Respiratory and psychiatric abnormalities in chronic symptomatic hyperventilation

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Abstract

Many physicians believe that the hyperventilation syndrome is invariably associated with anxiety or undiagnosed organic disease such as asthma and pulmonary embolus, or both. Twenty one patients referred by specialist physicians with unexplained somatic symptoms and unequivocal chronic hypocapnia (resting end tidal P_{CO_2} $\leq$ 4 kPa (30 mm Hg) on repeated occasions during prolonged measurement) were investigated. All but one complained of inability to take a satisfying breath. Standard lung function test results and chest radiographs were normal in all patients, but histamine challenge showed bronchial hyper-reactivity in two of 20 patients tested, and skin tests to common allergens were positive in three of 18. Ventilation-perfusion scanning was abnormal in a further three of 15 patients studied, with unmatched perfusion defects in two and isolated ventilation defects in one. None of the 21 had thyrotoxicosis, severe coronary heart disease, or other relevant cardiovascular abnormalities. Ten of the 21 patients were neurotic and suffered from chronic psychiatric disturbance characterised by anxiety, panic, and phobic symptoms. The remainder had no detectable psychiatric disorders but reported proportionately more somatic than anxiety symptoms.

Severe hyperventilation can occur in the absence of formal psychiatric or detectable respiratory or other organic abnormalities. Asthma and pulmonary embolus must be specifically excluded.

Introduction

The hyperventilation syndrome remains largely unrecognised in clinical practice despite numerous reports since the original description in 1937.[1] This may be due to a lack of widely accepted, unequivocal diagnostic criteria based on objective measurements. Apart from tetany, which is rare, symptoms and signs are diverse and non-specific, providing an unsatisfactory basis for diagnosis.[2] Lum claimed that spot measurements of PA_{CO_2} in the normal range can be consistent with the diagnosis,[3] which suggests that hypocapnia may occur at other times. This assumption may not always be justified. Hyperventilation is a physiological term implying arterial hypocapnia and should be objectively documented before a diagnosis is made. Because of these uncertainties the hyperventilation syndrome has been diagnosed in patients with little in common, usually according to the bias of the doctor concerned.

Factors that initiate and sustain the hyperventilation syndrome are obscure. It has been said to represent a non-specific manifestation of anxiety[4] or be synonymous with Da Costa's syndrome and other functional cardiovascular disorders.[5 6] Lum suggested that it is a habit disorder with exaggerated thoracic breathing.[3]

Organic diseases can cause hyperventilation and hypocapnia[7 8] but can also coexist with the hyperventilation syndrome. Many physicians believe that the hyperventilation syndrome is always secondary to undiagnosed organic diseases.[9] Certainly, it should not be diagnosed until relevant organic disorders have been excluded. Asthma,[10] pulmonary embolus,[11] and parenchymal lung disorders are known causes of hyperventilation. They may not be obvious clinically or after standard investigations and may require specialised procedures for detection.

Anxious and non-retarded depressed patients have appreciably lower PA_{CO_2} than normal people,[12] and agoraphobia with avoidance behaviour may become established after an initial episode of hyperventilation.[13] We previously found both hypocapnia and high rates of psychiatric morbidity in patients with chest pain and normal coronary arteries.[14] It has not, however, been established whether symptomatic hyperventilation—that is, the hyperventilation syndrome—can occur in the absence of both organic and psychiatric disorder.

A collaborative study between a chest physician and a psychiatrist was devised to explore three of the most common suggested causal factors. We determined the prevalence of formal psychiatric disorders, hypersensitive bronchi suggestive of asthma, and abnormalities on ventilation-perfusion scanning suggestive of disordered lung parenchyma or pulmonary embolus in a group of patients with proved chronic hypocapnia but without obvious organic diseases.

Patients and methods

We studied 29 consecutive patients referred by specialist physicians with a diagnosis of the hyperventilation syndrome, based on presenting complaints after clinical assessment and basic investigations had failed to show any obvious underlying organic condition. Symptoms included chest pain, dyspnoea, and inability to take a satisfying breath or "air hunger."[15] Many patients did not have conspicuous overbreathing, but some had obvious sighing or panting respiration[14 16]; only one had tetany.

Diagnostic criteria for the hyperventilation syndrome are imprecise. The practice of basing the diagnosis on symptom checklists is unreliable[2] and equivalent to diagnosing diabetes on the basis of symptoms without measuring blood glucose concentrations.

For similar reasons we were reluctant to base the diagnosis of the hyperventilation syndrome solely on the results of a provocation test, which is usually regarded as positive if most of the patient's symptoms are reproduced during three minutes of forced overbreathing.[7] Not all patients are able to complete this test, which can produce equivocal results and is subject to the bias of the observer.

Hyperventilation has a precise physiological definition implying arterial hypocapnia. In patients with normal lung function it has long been accepted that end tidal (equivalent to alveolar) P_{CO_2} (PA_{CO_2}) is very close to arterial P_{CO_2}.[17] We therefore based our final selection of patients on prolonged measurements of PA_{CO_2} alone, corroborated in some subjects by measuring arterial blood gases from a brachial artery sample. In all cases these measurements agreed (table I).

End tidal P_{CO_2} was measured uninvasively by a Centronics 200 MGA (Centronics Ltd, Croydon) mass spectrometer, and samples were taken continuously with a long 1·2 mm diameter polythene catheter taped 2-4 mm inside the entrance of one nostril. End tidal readings were accepted only if obvious plateaus were present in more than three quarters of breaths over the period of measurement. Breaths without plateaus were rejected (figure). Respiratory frequency could also be obtained from this trace. We devised a protocol, which is described

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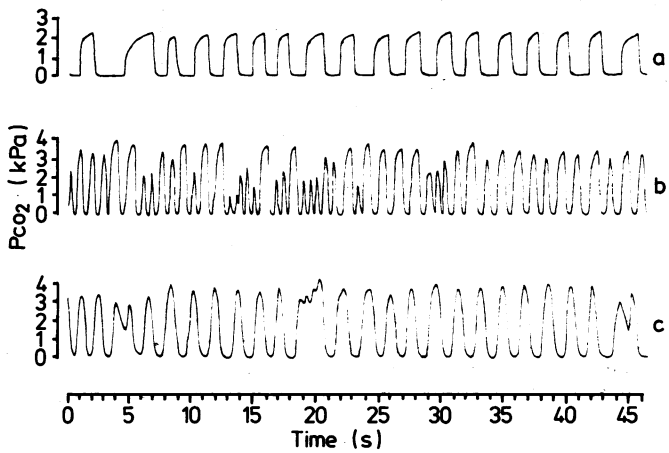
TABLE I—*Data on arterial blood gases with corresponding end tidal partial pressure of carbon dioxide in 10 patients. (Random samples)*

Case No	Age and sex	pH	$PaCO_2$ (kPa)	$PACO_2$ (kPa)	Pao_2 (kPa)	HCO_3^- (mmol/l)	Actual base excess (mmol/l)
1	37 F	7·57	2·5	2·3	16·8	18·4	−1·0
2	29 F	7·46	1·9	2·0	14·3	9·4	−9·5
3	36 M	7·49	3·1	2·5	13·9	17·2	−2·7
4	45 F	7·42	4·2	4·0	15·1	20·6	−2·4
5	43 M	7·46	4·1	4·1	11·4	22·0	−0·5
6	58 F	7·47	2·7	2·8	16·8	14·8	−6·3
7	25 F	7·50	2·7	2·7	15·2	14·2	−4·7
8	69 M	7·45	4·0	3·9	8·7	20·1	−2·6
9	45 F	7·42	4·1	4·1	11·9	19·5	−3·4
10	48 F	7·52	3·1	3·6	16·0	18·9	−1·8
Mean (SD)			24·4 (6·17)	24·0 (6·22)			

Conversion: SI to traditional units—$PaCO_2$, $PACO_2$, and Pao_2: 1 kPa ≈ 7·5 mm Hg; HCO_3^- and actual base excess: 1 mmol/l ≈ 1 mEq/l.

more fully elsewhere.[18] Resting Pco_2 measured by catheter was alternated with various everyday and laboratory methods of exertion such as exercise and voluntary overbreathing. Our inclusion criteria required that $PACO_2$ was ⩽4 kPa (30 mm Hg) for five minutes or more after the patient had been sitting quietly for at least five minutes and at a time when our previous experience would lead us to expect normocapnia. $PACO_2$ was usually low for much longer periods, and the diagnoses were rarely unequivocal. The value of 4 kPa (30 mm Hg) was determined from the past experience of one of us (WNG) with normal subjects[19] and from the results of a previous study.[14] Most of these patients had various degrees of chronic hyperventilation.



Three examples of records of a Mingograph chart recorder of Pco_2 measured continuously by mass spectrometer. In (*a*) end tidal plateaus are satisfactory with a valid measure of alveolar (and thus arterial) Pco_2. In (*b*) plateaus are present in only some breaths but a valid measure of mean alveolar Pco_2 can still be obtained. In (*c*) there are no plateaus; runs such as these were rejected.

CLINICAL INVESTIGATIONS

Extensive clinical investigations were usually performed before patients were referred. We performed further investigations to exclude less conspicuous and subclinical causes of hyperventilation (see table II). Lung function tests included chest radiographs, skin testing to common allergens, and measuring forced expiratory volume in one second, vital capacity, gas transfer, and the flow volume loop. Bronchial hyper-reactivity was excluded by histamine challenge[20]; normal was defined as a reduction of forced expiratory volume in one second of less than 20% after a doubling inhalation of histamine up to and including 4 mg/ml concentration, as previously established for our laboratory.

Serum thyroxine concentration was measured in all patients. To exclude pulmonary embolism and parenchymal lung disorders radiolabelled technetium-99m/krypton-81m ventilation-perfusion scanning was performed in 15 patients. In patients presenting with chest pain coronary artery and other cardiac diseases were excluded by coronary arteriography and echocardiography. To exclude abnormalities of the brain stem computed tomography of the brain was performed in some subjects.

PSYCHIATRIC EXAMINATION AND PSYCHOLOGICAL INVESTIGATIONS

The clinical interview schedule yielded ratings on a five point scale of the severity of each of 10 symptoms during the previous week and 12 abnormalities observed at interview.[21] A composite score of psychiatric morbidity is obtained by doubling the scores for manifest abnormalities and adding them to the scores for symptoms. A score of 13 or more is indicative of psychiatric illness; patients with such scores were designated psychiatric cases. Ratings of phobic symptoms were as follows: 0, absent; 1 phobia without limitation of activities; 2, limitation of activities to avoid the phobic situation; 3, extreme limitations of activities; 4, recurrent extreme distress during the previous week. The Kellner and Sheffield rating scale, a self administered questionnaire of 30 items covering anxiety, somatic symptoms, depression, and inadequacy, was used to rate the patient's subjective experience of distress in the previous week.[22] The Eysenck personality questionnaire was completed[23] and details of previous treatment for psychiatric illness recorded.

Results

Twenty one patients out of 29 fulfilled our criteria for hypocapnia (see table II). The mean age of these 13 women and eight men was 45·3 years (range 25-69). Mean resting $PACO_2$ based on the lowest value recorded during the protocol was 3·3 (SD 0·82) kPa (24·0 (6·1) mm Hg) (range 1·7-4 kPa (13-30 mm Hg)). The clinical provocation test for hyperventilation was not attempted in four patients with severe chronic hyperventilation, and a further eight were unable to complete it.

Unrecognised respiratory disorders were detected in five patients despite normal chest radiographs. Two patients (cases 5 and 12), with no history of asthma, had bronchial hyper-reactivity to histamine with PC_{20}s of 3·3 and 1·7 mg/ml, respectively. In both, the degree

TABLE II—*Details of investigations in patients in whom hypocapnia was diagnosed*

			Respiratory data								Psychiatric data		
Case No	Age and sex	Presenting complaints	Forced expiratory volume in one second (% predicted)	Vital capacity (% predicted)	Carbon monoxide diffusion coefficient (% predicted)	Residual volume (% predicted)	Peak expiratory flow rate (% predicted)	PC_{20} for histamine challenge (mg/ml)	Ventilation-perfusion scanning	Skin test to common allergens	Other investigations	Score in clinical interview schedule	Psychiatric cases	Phobic symptoms
1	37 F	Facial pain	117	129	91			>4	Unmatched ventilation defect	−	CT, fibreoptic broncoscopy	24	+	4
2	29 F	Palpitations	124	126	114	193		>4	Normal	+	ECG and echo	32	+	2
3	36 M	Chest pain	105	98	117			>4	Normal	−	E, A, CT, gastroscopy, cardiac biopsy	8		
4	45 F	Chest pain	104	110	129	165		>4	Unmatched perfusion defect	−	E, A	20	+	2
5	43 M	Chest pain	90	108	88			3·3	Normal	−	E, A, EEG	8		1
6	58 F	Food allergies	110	89	112	50	113	>4	Normal	−	E, A, barium meal, gastroscopy	22	+	2
7	25 F	Tetany	97	109	130			>4	Normal	−	EEG	11		1
8	69 M	Dyspnoea	119	132	90	76	86	>4	Unmatched perfusion defect	−	E, A	10		
9	45 F	Vertigo	117	120	106	106	101	>4	Normal	−		15	+	2
10	48 F	Chest pain	96	97	149			>4	Normal	−	E, A, CT, barium meal, gastroscopy	21	+	2
11	53 M	Chest pain	108	102	99			>4	Normal	−	E, A	4		
12	45 F	Chest pain	85	86	125	194		1·7		+	E, A, EEG	13	+	2
13	39 F	Chest pain	108	113	107	120	95	>4	Normal	−	E, A	13	+	
14	43 F	Chest pain	92	97	104			>4	Normal	+	E, A, EEG, barium meal, oral cholecystography	6		1
15	43 F	Chest pain	112	100				>4			E, A, CT	18	+	1
16	46 M	Chest pain	97	105	110			>4		−	E, A	6		1
17	50 F	Chest pain	123	111	122	33	124	>4	Normal	−	E, A	7		1
18	42 F	Chest pain	111	106	92						E, A	8		
19	48 M	Chest pain	122		113			>4		−	E, A	23	+	1
20	53 M	Chest pain	115	107	111	123	108	>4	Normal	−	E, A	8		
21	55 M	Chest pain	115	107	143	157		>4			E, A, barium meal	10		1

E = exercise cardiac stress test; Echo = echocardiography; A = coronary angiography; CT = computed tomography of brain.

of breathlessness was disproportionate to the physical findings. Positive skin responses to common allergens were detected in three of 18 patients tested.

Ventilation-perfusion scans were abnormal in three patients. A 37 year old woman (case 1) with extreme hypocapnia and a history suggestive of recurrent bronchitis showed patchy ventilation defects unmatched by perfusion defects. Fibreoptic bronchoscopy showed intrabronchial pus growing *Streptococcus pneumoniae* and *Haemophilus influenzae* but no endobronchial abnormalities.

In a 69 year old man (case 8) with breathlessness and sighing that began when a pacemaker was inserted six months previously the scan showed perfusion defects suggestive of resolving pulmonary embolus. Despite normal results of lung function tests and chest radiography arterial Po_2 was reduced at 8·7 kPa (65 mm Hg). Resting ventilation, increased at 14·5 l/min, was unaffected by raised inspired oxygen. These findings were unchanged after four months of anticoagulant treatment.

In a third patient (case 4) the scan showed a perfusion defect in the middle of the left lobe, but all other tests, including those of blood gases, yielded normal results apart from low Pco_2.

Serum thyroxine concentrations were normal in all as were the results of gastrointestinal, cardiac, and neurological investigations.

PSYCHIATRIC ASSESSMENT

Ten patients had evidence of psychiatric illness and were designated psychiatric cases. Most had multiple somatic and psychic symptoms of anxiety, and nine reported panic, which occurred either spontaneously, in relation to circumscribed situations such as crowds, or in response to disagreeable symptoms such as palpitations. Seven had clinical phobic neuroses with limitation of activities. Another eight reported mild phobic symptoms but without avoidance behaviour. Thus all but six of the 21 patients reported phobic symptoms of some description.

Eleven patients were designated non-cases with composite scores of 12 or less in the clinical interview schedule. They had appreciably lower mean scores of neuroticism and a shorter history of symptoms than the cases (table III).

Mean anxiety and depression scores on the Kellner scale were also considerably higher in the psychiatric cases. These findings, together with the difference in scores of neuroticism, validated the distinction between cases and non-cases. The ratio of somatic score to anxiety score, however, was greater for the non-cases (mean 1·30 (SE 0·12)) than the cases (mean 1·04 (0·05); $p = 0·09$, Mann-Whitney U test), suggesting that the non-cases reported proportionately more somatic than anxiety symptoms.

There were inverse correlations between the lowest value for $PAco_2$ and overall score in the clinical interview schedule ($r = -0·42$; $p < 0·05$), overall Kellner score ($r = -0·46$; $p < 0·05$), and score of neuroticism ($r = -0·23$; NS).

Nine of the 10 psychiatric cases had a history of treatment for psychiatric disorders; most of them were neurotic with multiple somatic complaints and had made repeated visits to both hospital outpatient departments and emergency rooms. One neurotic patient (case 6) with a six year history of multiple somatic complaints attributed all her symptoms to food allergies. She had been agoraphobic for 26 years and her resting $PAco_2$ was 3·5 kPa (26 mm Hg). In contrast, most non-cases had endured many disagreeable physical symptoms and painful investigations before a diagnosis of hyperventilation was made. All of these patients could clearly date the onset of their complaints, and six reported mild phobic symptoms, which had not led to any recent limitation of activities.

It was not ethically justifiable to undertake the more invasive or expensive clinical investigations in all subjects. Nevertheless, there were at least six patients (cases 3, 7, 11, 14, 17, and 20) in whom the most exhaustive investigations failed to show any conspicuous psychiatric or organic disturbance apart from profound hypocapnia and (in cases 7, 14, and 17) mild longstanding phobic traits. These patients were remarkable for their apparent normality.

We searched for a common unifying characteristic in these patients. The only clinical feature common to all but one was the complaint of "air hunger."

TABLE III—*Main psychiatric and other data*

	Psychiatric cases (n = 10)	Non-cases (n = 11)	Significance	
			t	p
Mean (SE) age (years)	43·8 (2·36)	46·8 (3·43)	0·73	NS
Mean (SE) duration of symptoms (months)	66·4 (13·9)	49·9 (12·6)	0·88	NS
Mean (SE) Eysenck personality questionnaire scores:				
Neuroticism	16·00 (1·12)	9·27 (0·94)	4·62	<0·001
Extraversion	12·10 (1·56)	13·55 (1·37)	0·70	NS
Psychoticism	3·30 (0·76)	3·45 (0·84)	0·14	NS
Lie score	11·50 (1·56)	10·18 (1·57)	0·60	NS
Mean (SE) Kellner scores*:				
Anxiety	18·44 (2·09)	12·70 (0·63)		<0·01†
Somatic symptoms	18·78 (1·67)	15·90 (0·80)		NS
Depression	16·78 (1·64)	12·30 (0·86)		<0·05†
Inadequacy	13·33 (1·34)	11·70 (0·65)		NS

*Only 19 patients (nine cases, 10 non-cases) completed the Kellner distress inventory.
†Mann-Whitney U test.

Discussion

The most important finding from this study is that some patients can have profound hypocapnia with no evidence of either organic or apparent psychiatric disorder. The cause of this hypocapnia is unknown. These patients could be classified as having the hyperventilation syndrome, but because of lack of consensus regarding cause, diagnosis, and classification we prefer the more descriptive term chronic hyperventilation of unknown cause.

The chronicity of hyperventilation in our patients has been characterised elsewhere[1,8] and was confirmed by repeated measurement of hypocapnia in the absence of acute episodes. Our sample was biased against patients with acute hyperventilation related to attacks of panic, but acute and chronic forms are not mutually exclusive. We used criteria for hypocapnia more stringent than those usually quoted but which reflect the current uncertainty about the normal range of $PAco_2$.

Our criteria for selection do not permit us to draw conclusions about the prevalence of organic disease in a community sample of patients with hyperventilation. In our group 19 (90%) showed normal bronchial reactions to histamine, and a further 12 out of 15 had normal ventilation and perfusion scans, suggesting that severe hyperventilation can occur in the absence of asthma, pulmonary embolus, and lung parenchymal disorder. We were unable to show that hyperventilation in the five patients with respiratory abnormalities was a consequence of their underlying lung disease, although hyperventilation has been documented in these disorders.[9,10] Nevertheless, we consider that no patient should be diagnosed as having the hyperventilation syndrome without prior investigation for evidence of asthma, pulmonary embolus, and intrinsic lung disease. Chest radiography and standard lung functoin tests can be normal in the presence of these disorders.

The ventilation defects shown by the ventilation and perfusion scan in one patient (case 1) were probably related to episodic bronchitis and considered to be a consequence rather than a cause of hyperventilation. In another (case 8) failure of ventilation to fall after the increase of inspired oxygen to 50% suggested that hyperventilation was not due to peripheral chemoreceptor stimulation by hypoxia; the most likely explanation for hyperventilation is stimulation of J receptors in the lungs.

Possible organic causes of hyperventilation include small lesions of respiratory pathways in the spinal cord, the major afferent respiratory nerves such as the vagus, the chemoreceptors or lung reflex receptors, and the medulla, pons, or higher centres.[24] These may not be detectable on a computed tomogram.

The most universally reported complaint was "air hunger," often but not always associated with a sensation of constriction in the chest. This non-specific symptom may represent the final common pathway to hyperventilation but may occur in the absence of hypocapnia.

Patients who were designated non-cases reported numerous somatic symptoms but surprisingly little anxiety. One possible explanation for this is that they tended to deny the psychological aspects of their condition.[25] Alternatively, they may have

expressed psychological distress through the presentation of physical complaints[26]; 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 a*, showed.[28]

Inverse correlations between $PAco_2$ 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.

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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 mucosas 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 determined 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,