Results of investigations in the five patients

Investigation	Case 1	Case 2	Case 3	Case 4	Case 5	Normal range
Calcium concentration at presentation (corrected value; mmol/l)	3·96	3·14	3·49	3·06	2·72	2·25-2·50
Phosphate concentration at presentation (mmol/l)	0·70	0·81	0·80	1·20	0·80	0·87-1·45
Chloride concentration at presentation (mmol/l)	107	92	ND	104	107	95-105
Alkaline phosphatase activity at presentation (U/l)	158	130	150	140	150	30-140
Parathyroid hormone value (U/l)	<0·80	<0·20	0·16	<0·20	ND	0·20-0·60
Bone scan appearances	Normal	Normal	Normal	ND	ND	
Skeletal survey result	Normal	Normal	ND	ND	ND	
Histological findings	Papillary cystadeno-carcinoma	Clear cell carcinoma	Serous cystadeno-carcinoma	Clear cell carcinoma	Papillary cystadeno-carcinoma	

ND = Not done.
Conversion: SI to traditional units—Calcium: 1·0 mmol/l ≈ 4·0 mg/100 ml. Phosphate: 1·0 mmol/l ≈ 3·1 mg/100 ml. Chloride: 1·0 mmol/l = 1·0 mEq/l.

centration remained between 2·70 and 2·90 mmol/l (10·8 and 11·6 mg/100 ml) until near her death, 14 months later, when it rose sharply. She remained asymptomatic of hypercalcaemia throughout.

Comment

In none of these patients was there evidence of bone metastases. Paraneoplastic hypercalcaemia occurs in 5-10% of malignancies and has been reported in ovarian carcinoma.[1 2] Fisken *et al*, however, found that 89 out of 159 hospital inpatients with hypercalcaemia had malignant disease, but none had ovarian carcinoma.[3] Our five patients represented a high incidence in our practice, being among 70 new patients seen over 18 months. Two of the patients had clear cell carcinoma, and in the few other reports this tumour has been disproportionately represented.[1 2 4 5] The mechanism of paraneoplastic hypercalcaemia in ovarian cancer is obscure but the biochemical findings in our patients were compatible with production of a parathyroid-hormone-like substance.

Paraneoplastic hypercalcaemia due to ovarian carcinoma may be more common than previously suggested. It is an important association, since the symptoms of hypercalcaemia may be mistaken for intestinal obstruction (a common preterminal event in ovarian carcinoma), as exemplified by our case 3. Patients may also present afresh or with recurrence of disease and be found to have life threatening hypercalcaemia requiring urgent treatment.

References

1 Stewart AF, Romero R, Schwartz PE, Kohorn EI, Broadus AE. Hypercalcemia associated with gynecologic malignancies. *Cancer* 1982;**49**:4389-94.
2 Powell D, Singer FR, Murray TM, Minkin C, Potts JT. Non parathyroid humoral hypercalcemia in patients with neoplastic diseases. *N Engl J Med* 1973;**289**:176-81.
3 Fisken RA, Heath DA, Somers S. Hypercalcaemia in hospital patients: clinical and diagnostic aspects. *Lancet* 1981;i:202-7.
4 Ferenczy A, Okgaki T, Richart RM. Para-endocrine hypercalcemia in ovarian neoplasms. Report of mesonephroma with hypercalcemia and review of the literature. *Cancer* 1971;**27**:427-31.
5 Holty G, Johnston JR, Shrock ME. Paraneoplastic hypercalcemia in ovarian tumors. *Obstet Gynecol* 1979;**54**:483-7.

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Subcutaneous terbutaline and control of brittle asthma or appreciable morning dipping

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Abstract

In a pilot study two patients with brittle asthma and two with morning dipping received terbutaline or a placebo administered subcutaneously either by continuous infusion or in injections every six hours. In two patients brittle asthma was completely suppressed by terbutaline 1 mg/day given by either method. In the two others early morning dipping responded only to continuous subcutaneous infusions of terbutaline 12 mg/day.

Terbutaline administered subcutaneously may be an effective treatment in asthmatic patients who show important diurnal variations in air flow.

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Introduction

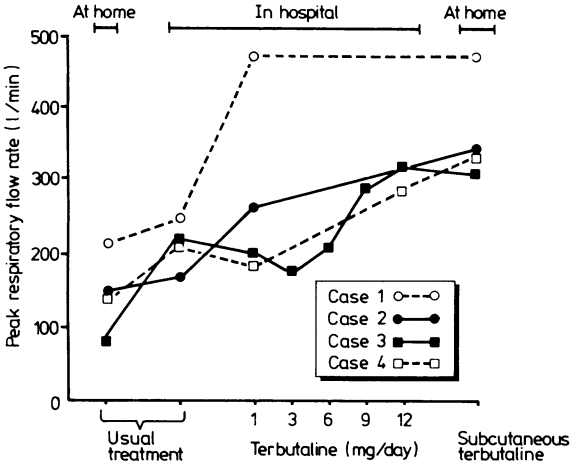
Some patients with asthma—for example, patients with brittle asthma or morning dipping[1]—show considerable changes in air flow throughout the day despite maximal treatment. In a pilot study we used subcutaneous administration of terbutaline to treat two patients with brittle asthma and two with morning dipping.

Methods

We studied one woman aged 19 and three men aged 29, 35, and 44. All had diurnal variation in peak expiratory flow rate of at least 40%

despite daily prednisolone (15, 30, 30, and 30 mg), therapeutic doses of oral theophyllines, daily nebulised salbutamol (50 mg), ipratropium bromide (2·5 mg), and high doses of inhaled steroids. Three of the patients were also taking oral β_2 agonists. The study was a double blind, placebo controlled, within patient comparison of terbutaline given in the same daily dose either by continuous subcutaneous infusion or in four subcutaneous injections, one every six hours.

Each patient was studied on three occasions in hospital. Each of the three occasions comprised a four day run in period during which the patient's usual treatment was continued and five days during which treatment was changed. During the first two periods in hospital the patient's usual oral and inhaled β_2 agonists were withdrawn after the run in period; on the first occasion the patient then received terbutaline by continuous subcutaneous infusion and placebo (saline) in four subcutaneous injections, one every six hours; on the second occasion the patient received placebo by continuous subcutaneous infusion and terbutaline in four subcutaneous injections, one every six hours. During the third period in hospital the patient's usual β_2 agonist treatment was continued during the treatment period and saline given both by continuous subcutaneous infusion and in four subcutaneous injections (double placebo). The dose of terbutaline was 14 μg/kg/day (1 mg/day for a man weighing 70 kg). The peak expiratory flow rate (best of three values) was recorded hourly and pulse rate and blood pressure every four hours throughout each period in hospital. Statistical analysis was carried out using the Mann-Whitney U test.



Mean lowest daily peak expiratory flow rate while patients were at home receiving standard treatment, in hospital and at home receiving subcutaneous terbutaline (1 mg/day in divided doses in cases 1 and 2; 12 mg/day by continuous subcutaneous infusion in cases 3 and 4).

Results

In one patient (case 1) the mean lowest daily peak expiratory flow rate rose from 254 to 474 l/min (an increase of 87% ($p<0·001$)) with divided doses (figure) and from 133 to 296 l/min (an increase of 123% ($p<0·001$)) with continuous subcutaneous infusion. Another patient (case 2) also showed an improvement in her mean daily peak expiratory flow rate both with divided doses (170-266 l/min, an increase of 57% ($p<0·02$)) (figure) and with continuous subcutaneous infusion (288 to 360 l/min, an increase of 58% ($p<0·001$)). These two patients showed no change in peak expiratory flow rate with placebo. The two other patients (cases 3 and 4) showed no change in air flow during any of the three periods in hospital. Their blood pressures and pulse rates remained unchanged throughout.

Two patients (cases 1 and 2) subsequently received subcutaneous injections of terbutaline at home every six hours. In both all oral steroid and nebulised bronchodilator treatment could then be stopped, and neither was admitted to hospital in the subsequent 36 (case 1) or 48 (case 2) weeks, though they had been admitted six and 12 times respectively in the previous year.

One patient (case 3) received serially increasing doses of continuous subcutaneous infusion of terbutaline as replacement for his oral and inhaled β_2 agonists. There was a clear improvement, related to dose, in mean lowest daily expiratory flow rate (figure). He was then sent home, and after 29 days of treatment with terbutaline 12 mg/day his asthma was well controlled, he required only occasional doses of nebulised salbutamol, and his steroid dose had been reduced from 30 to 20 mg daily. The remaining patient (case 4) was treated with 12 mg terbutaline daily by continuous subcutaneous infusion (instead of his usual β_2 agonist treatment). His mean lowest daily peak expiratory flow rate rose from 148 to 288 l/min ($p<0·001$). After 14 weeks' follow up at home he had stopped all treatment with oral steroids and aminophylline.

When receiving nebulised salbutamol two patients (cases 3 and 4) had severe tremor and tachycardia without control of their asthma, whereas terbutaline given by continuous subcutaneous infusion controlled their asthma without side effects. Another patient (case 2) initially had small haematomas at the sites of injection, but these cleared when her steroid dose was reduced.

Discussion

In all four patients terbutaline given subcutaneously improved control of asthma, both subjectively and objectively, and other treatment, notably oral steroids, could be reduced. Adrenaline concentrations are low at night in patients with nocturnal asthma,[2] and nocturnal falls in peak expiratory flow rate can be corrected with infusions of adrenaline.[3] Oral slow release salbutamol is ineffective in morning dipping,[4] although slow release aminophylline gives small improvements in morning peak expiratory flow rate.[5] This pilot study suggests that subcutaneous terbutaline, possibly acting by stimulation of β_2 receptors on smooth muscle or mast cells, or both, may prove an effective treatment in patients who show considerable diurnal variations in air flow.

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References

1 Warwick MT. On observing patterns of airflow obstruction in chronic asthma. *Br J Dis Chest* 1977;**71**:73-86.
2 Barnes P, Fitzgerald G, Brown M, Dollery C. Nocturnal asthma and changes in circulating epinephrine, histamine and cortisol. *N Engl J Med* 1980;**303**:263-7.
3 Barnes P, Fitzgerald GA, Dollery CT. Circadian variation in adrenergic responses in asthmatic patients. *Clin Sci* 1982;**62**:349-54.
4 Fairfax AJ, McNabb WR, Davies HJ, Spiro SG. Slow release oral salbutamol and aminophylline in nocturnal asthma: relation of overnight changes in lung function and plasma drug levels. *Thorax* 1980;**35**:526-30.
5 Barnes PJ, Greening AP, Neville L, Timmers J, Poole GW. Single dose slow release aminophylline at night prevents nocturnal asthma. *Lancet* 1982;i:299-301.

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ONE HUNDRED YEARS AGO We publish this week a letter from a correspondent on the practice of uncovering the head at funerals. We quite agree with him that the practice is often highly prejudicial to the health of mourners, who may have many living persons dependent upon them, and who are exposed by the custom to actual risk of life, or at least to a very great chance of being seized with temporary indispositions, which are certain to cause them unfair and needless inconvenience. The depression of spirits under which the chief mourners labour at these melancholy occasions, peculiarly predisposes them to some of the worst direct and indirect effects of chill; and even when any person is present at a burial out of respect to the deceased, with whom he has had none of the deep sympathy due to relationship or intimacy, the risk of his catching cold is considerable, as a visitor of this kind has often walked some distance or travelled in a hot carriage by rail or road. A duty of this kind is often pressed upon a medical man; and in his case the risk is great, and the result of any consequent illness often very serious. It is, however, very difficult to break old customs without giving offence; and perhaps the best thing to do, under the circumstances, is for the mourner to wear a skull-cap, or to raise his hat as little from his head as possible, as both these subterfuges appear to be conventionally permissible. (*British Medical Journal* 1884;i:1163.)