

and 7). Even such simple measures as traction for a fracture (case 1) or a suction drain (study 2) can easily be disturbed while moving along narrow corridors or into lifts.

The incidence of serious effects due to intrahospital movement in critically ill patients (study 1) was much higher than that previously seen during ambulance transport of similar patients.⁵ This may be partly due to a willingness to move patients within hospital who would be considered too moribund to subject to an ambulance journey. It is probably due also to less thorough preparation and less adequate maintenance of treatment during movement. In the ambulance study every possible care was taken to stabilize the patient and then maintain treatment throughout the journey. When simply wheeling a patient along a corridor it is tempting to imagine that there is less opportunity for misfortune and that a few minutes gap in treatment will do no harm. The results of study 1 suggest that in critically ill patients this is untrue; their movement within hospital may be as hazardous as an ambulance journey, and it should be seriously considered whether they need to be moved at all. Adequate preparation is essential and every possible care should be taken to maintain treatment and forestall "accidents" during the move. Such patients should not be consigned to the care of non-medical or inexperienced staff.

Experience of both ambulance transport and moving patients within hospital suggested that patients recovering from a recent operation and anaesthetic more often showed cardiovascular effects of movement, but the results of study 2 provide no evidence to support this hypothesis, all 70 patients showing remarkable stability. Weller also observed only minor effects of moving patients after cardiopulmonary bypass.⁷ Only two of

the seven very ill patients affected by movement (study 1) were recovering from an operation. Provided adequate care is taken postoperative patients do not seem to be particularly vulnerable to movement.

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Cushing's Syndrome and Pituitary-Adrenal Suppression due to Clobetasol Propionate

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Summary

Widespread application of clobetasol propionate resulted in suppression of the hypothalamic pituitary axis in four patients. Three patients showed Cushingoid features and developed symptoms of adrenocortical insufficiency on withdrawal of clobetasol.

Introduction

Features of Cushing's syndrome due to topical corticosteroid application are rarely recorded¹ except in children² and patients with advanced liver disease.³ Transient pituitary-adrenal suppression has been reported, especially when percutaneous absorption has been enhanced by polyethylene occlusion.⁴⁻⁷ Thus our interest was stimulated when we saw three patients who developed gross Cushingoid signs after using the potent new topical corticosteroid,⁸ clobetasol (Dermovate), particularly

as it has been claimed to have little systemic effect.⁹ We examined the pituitary-adrenal status of these three patients and one other.

Methods

Serum cortisol levels were measured using Murphy's competitive protein binding technique,¹⁰ slightly modified. The normal range at 9 a.m. is 138-442 nmol/l (5-16 µg/100 ml). On the insulin tolerance test¹¹ all patients experienced hypoglycaemia of less than 1.67 mmol/l (30 mg/100 ml), which is an adequate stimulus for maximal rise in serum cortisol levels.¹¹ Tetracosactrin tests were also performed.

Case 1

In July 1973 this 53-year-old woman first used clobetasol cream, which controlled her chronic severe psoriasis (covering 10% of her body surface) better than any other topical agent. She applied 300 g/week for the next year. By this time she was floridly Cushingoid with a moon face, hirsuties of the forehead, buffalo hump, truncal obesity, and wasted limbs and hypertensive (blood pressure 180/100-110 mm Hg). Widespread cutaneous atrophy was also present. She was admitted to hospital for investigation of her pituitary-adrenal status while clobetasol was continued. Serum cortisol levels were consistently less than 27.6 nmol/l (1 µg/100 ml) and there was no rise in response to the stress of hypoglycaemia induced by the insulin tolerance test. The long tetracosactrin test was normal with cortisol levels of 414 nmol/l (15 µg/100 ml) at 24 hours and a peak of over 690 nmol/l (25 µg/

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100 ml) at 48 hours. Full blood count, erythrocyte sedimentation rate, glucose tolerance test, chest x-ray picture, and urinary calcium excretion (300 mg/24 h) were normal.

She was weaned from clobetasol cream to a weaker topical corticosteroid and after 10 days suffered symptoms of adrenocortical insufficiency, with a fall in blood pressure, malaise, nausea, abdominal pain, and postural hypertension. The electrocardiogram (E.C.G.) showed inversion of the T-waves of the left chest leads. All these features were reversed rapidly by oral administration of dexamethasone 500 µg. She was supported with daily depot tetracosactrin injections for four days, but two weeks after stopping clobetasol she became erythrodermic with pustulation. Thereafter she progressed well despite unmeasurable serum cortisol levels for a fortnight. A second insulin tolerance test five weeks after withdrawal showed a small increase in serum cortisol to a peak of 124 nmol/l (4.5 µg/100 ml), which suggested the pituitary-adrenal axis had begun to recover. Symptoms of adrenocortical insufficiency then became more severe again so we managed her on suboptimal replacement therapy with weekly injections of depot tetracosactrin 0.5 mg. One month later her Cushingoid appearance was regressing, the skin atrophy had improved, and her psoriasis had virtually cleared. Serum cortisol became normal 16 weeks after stopping clobetasol. Seven months after withdrawal a third insulin stress test produced a satisfactory rise in serum cortisol.

Case 2

This 64-year-old man developed chronic plaque psoriasis over 15% of his body surface in February 1971. A trial of clobetasol ointment for unsightly hand lesions proved so successful that the patient obtained 200 g/week from his general practitioner to treat his whole body surface. Ten weeks later, when his psoriasis had changed to an unstable, gyrate, pustular pattern, his face had become moon shaped, and he complained of easy bruising related to atrophy of the skin. He was admitted to hospital for investigation of his pituitary-adrenal status. Clobetasol was continued. Serum cortisols at 9 a.m. were consistently less than 27.6 nmol/l (1 µg/100 ml), and the adrenal glands responded to plain tetracosactrin 250 µg with a rise to 469 nmol/l (17 µg/100 ml) in 30 minutes (normal). His response to insulin stress was grossly abnormal with a rise in serum cortisol to only 97 nmol/l (3.5 µg/100 ml). He was weaned to a more dilute topical corticosteroid and his serum cortisol levels became normal after seven weeks. He was discharged home for a fortnight but nine weeks after stopping clobetasol his psoriasis again became pustular, extensive, and he experienced symptoms of adrenocortical insufficiency with lethargy, postural dizziness, and upper abdominal tightness. His serum cortisol levels at 9 a.m. remained between 55 and 97 nmol/l (2.0 and 3.5 µg/100 ml) at 10 weeks. These levels became normal (207-221 nmol/l (7.5-8.0 µg/100 ml)) 18 weeks after stopping clobetasol.

Case 3

This 63-year-old man had suffered from psoriasis over 20% of his body surface for seven years when he began using clobetasol 100 g/week. After eight months he had become obviously Cushingoid with a round face, striae in the groins, wasted limbs, and truncal obesity. He was admitted to hospital for investigation and continued application of clobetasol. The serum cortisol levels were less than 1 µg/100 ml. The adrenal glands themselves responded normally to depot tetracosactrin with serum cortisols reaching 483 nmol/l (17.5 µg/100 ml). The insulin tolerance test, however, produced a very small rise in serum cortisol to 110 nmol/l (4.0 µg/100 ml). There was also evidence of hepatocellular damage, with ascites, oedema, and abnormal liver function. Liver biopsy showed periportal fibrosis and he admitted to drinking half a bottle of spirits daily.

He was weaned from clobetasol ointment to a weaker topical corticosteroid over five weeks. Withdrawal provoked no overt symptoms of adrenocortical insufficiency, but blood pressure fell and the E.C.G. showed transient widespread flattening of the T-waves, as in case 1. There were no electrolyte abnormalities at this time. His psoriasis flared up but never pustulated; it had settled by the time of discharge to a moderately extensive and scaly guttate eruption. Three weeks after stopping clobetasol his serum cortisol levels were normal at 221 nmol/l (8 µg/100 ml). Five months later a second insulin tolerance test showed a low normal serum cortisol of 179 nmol/l (6.5 µg/100 ml) with an impaired rise in serum cortisol to 359 nmol/l (13.0 µg/100 ml).

Case 4

This 65-year-old man presented with a one-month history of wide-spread (50% of body surface) flexural and plaque psoriasis. This failed to respond to inpatient treatment with betamethasone ointment 0.1% for two weeks, so applications of clobetasol ointment 200 g/week were begun. His psoriasis cleared dramatically within 10 days. Because of our previous experience serum cortisols were measured and found to be consistently less than 27.6 nmol/l (1 µg/100 ml) on successive days. An insulin tolerance test was not performed because of his poor general health. His psoriasis became pustular but later settled on a dilute topical corticosteroid. He had no signs or symptoms of adrenocortical insufficiency but his serum cortisol levels were abnormally low for 10 weeks.

Discussion

Our data agree with those of Tan and Samman¹² in indicating that clobetasol applied without occlusion may exert systemic effects far beyond those of other preparations. Clobetasol treatment was accompanied in our four patients by profound and sustained reduction in serum cortisol levels, which were sufficient in three patients to cause symptoms and signs of adrenocortical insufficiency when the topical steroid was withdrawn. Investigation with insulin tolerance and tetracosactrin tests suggested that suppression had taken place at pituitary-hypothalamic rather than adrenal level. Recovery, as measured by return of 9-a.m. cortisol levels to normal, took from 3-18 weeks in three patients, but the patient with the most profound suppression (case 1) required suboptimal replacement treatment for seven months after withdrawal. The patient who used clobetasol for only 10 days (case 4) took 10 weeks to achieve normal serum cortisol levels.

Adrenocortical insufficiency was not the only problem of clobetasol withdrawal; rebound activation of psoriasis with pustulation was seen in cases 1, 2, and 4.¹³ Fortunately the unstable psoriasis settled with rest and local measures. Spectacular skin atrophy with epidermal pallor and thinning, prominence of subcutaneous veins, and ecchymoses regressed gradually after three to four months when dilute topical steroids were substituted. Telangiectasia, capillary blushing, and striae were comparatively inconspicuous.

Walker *et al.* measured serum cortisols in patients who had applied clobetasol for two to four weeks⁹ and found low levels in only two out of six patients using 100-180 g/week. They did concede, however, that serum cortisol is a less sensitive index of pituitary-adrenal suppression than the insulin tolerance test. Munro and Clift¹⁴ found transient abnormalities in insulin tolerance in three patients using the weaker betamethasone valerate 0.1% (Betnovate) 25-100 g/week. Tolerance became normal in two to five months when the amount of ointment used was halved. Other topical corticosteroids used in similar quantities with polyethylene occlusion produced only transient suppression of plasma cortisol levels. Hendrikse and Moolenaar¹⁵ found suppressed serum cortisols in six patients using 15-50 g betamethasone valerate 0.1% under polyethylene occlusion after two and a half years. In these patients, however, insulin tolerance was normal.

Thus, clobetasol seems to have stronger systemic effects than any other topical steroid, which might be owing to increased percutaneous absorption, slow elimination from the body, or the intrinsic potency of the clobetasol molecule. Data about the metabolism of clobetasol is not yet available. Delayed elimination from the body was a likely contributory factor in the patient who was cirrhotic (case 3). Our conclusions that the widespread application of clobetasol propionate is equivalent to systemic steroid administration in its effects on the pituitary-adrenal axis and psoriasis seem inescapable.

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Removal of Abnormal Clone of Leukaemic Cells by Splenectomy

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Summary

A patient with chronic myelocytic leukaemia positive for the Philadelphia (Ph¹) chromosome underwent splenectomy in the "terminal phase" of his disease. Chromosomal analysis of a marrow aspirate obtained during the operation showed nothing abnormal. Material from the spleen, however, showed the absence of a C chromosome and the presence of a "marker" chromosome in all metaphases examined. The patient did well for almost three years after splenectomy, and serial cytogenetic studies of marrow specimens showed the Ph¹ chromosome to be the only significant abnormality. Six months before death from recurrent blastic transformation aneuploidy was found in a marrow specimen. Subsequently additional abnormalities, including cells with two Ph¹ chromosomes, were detected. The karyotypic abnormalities found in the splenic specimen, however, never recurred.

Introduction

Chronic myelocytic leukaemia (C.M.L.) is usually characterized by the Philadelphia (Ph¹) chromosome in cells of myeloid origin. With rare exceptions¹ this is a constant feature, being found in overt disease, during excellent clinical and haematological remissions, and in the terminal stages. Ph¹-positive cells may become established in the spleen^{2,3} and other extramedullary sites.⁴

In some patients the Ph¹ chromosome is the only karyotypic abnormality detectable throughout the course of the disease. Additional cytogenetic abnormalities, however, may appear as the patient enters the terminal stage. These include changes in the number of chromosomes, the appearance of "marker" chromosomes, and the presence of cells containing two Ph¹ chromo-

somes.^{5,6} Occasionally such aberrations appear before any clinical or haematological deterioration is apparent; if so, they are of serious prognostic import. There is an increasing body of evidence that haematological deterioration and death in C.M.L. results from the proliferation of one or more increasingly abnormal clones of leukaemic cells, and that the karyotypic abnormalities seen in the terminal phase constitute overt evidence of this process.

We report the case of a patient who underwent splenectomy in the "terminal phase" of C.M.L. and whose subsequent course suggested that this procedure eliminated the abnormal clone of cells responsible for his deteriorating haematological condition.

Case Report

A 32-year-old black steel worker was diagnosed in March 1968 as a case of C.M.L. after bleeding profusely following a tooth extraction. His W.B.C. was $247 \times 10^9/l$ (65% neutrophils, 2% lymphocytes, 1% eosinophils, 2% basophils, 12% myelocytes, 17% promyelocytes, 1% myeloblasts); platelets were $110 \times 10^9/l$; and haemoglobin was 11 g/dl. His spleen extended 17 cm below the costal margin and he had subcutaneous nodules 2 cm in diameter in both thighs. Appearances on bone marrow and splenic biopsy were consistent with the diagnosis; no fibrosis was seen in the biopsy specimen. Aspiration of the subcutaneous nodules yielded myelocytes and normoblasts. Leukocyte alkaline phosphatase score was zero. Chromosomal analysis of bone marrow cells revealed the Ph¹ chromosome but no other abnormalities.

The patient was included in a comparative study of mitobronitol and busulphan. His initial treatment was with mitobronitol, which decreased the W.B.C. and spleen size but caused pronounced thrombocytopenia requiring transfusions. He was then treated with busulphan from July to November 1968. This induced a good remission except for the development of recurrent thrombocytopenia. The haemoglobin and W.B.C. became normal and the spleen impalpable. Subsequently he received maintenance therapy with mitobronitol. His course was complicated by thrombocytopenia, which required frequent discontinuance of the drug or reduction of the dose, producing wide fluctuations in the W.B.C. Nevertheless, the haemoglobin remained normal, the spleen was not felt, and differential counts showed no blasts or promyelocytes.

In February 1970 recurrent splenomegaly was noted and mitobronitol was abandoned. Treatment with cytarabine, carmustine, busulphan, and cyclophosphamide failed to re-establish stable control; modest numbers of blasts and promyelocytes appeared in the peripheral blood, the haemoglobin fell to 11-12 g/dl, and the spleen increased in size. Blasts in a marrow aspirate, however,

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