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PROPERTIES AND THERAPEUTIC USES OF SOME CORTICOSTEROIDS WITH ENHANCED TOPICAL POTENCY

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SUMMARY

Amongst the advances made by steroid chemists has been the development of corticosteroids with exceptional topical activity. The use of such compounds in treating skin diseases is well known. More recently the effects of these compounds has been investigated on other body surfaces, particularly the mucous membranes lining the gut, the bronchi and nasal passages. Hopefully to demonstrate some separation of topical anti-inflammatory activity from systemic glucocorticoid effects. Their use in the gut has been disappointing as no useful separation of these effects has been observed. However, the administration of some of these steroids by inhalation to treat bronchial asthma or intra-nasally for rhinitis has recently been shown to be of therapeutic benefit and to demonstrate some separation of effects within the glucocorticoid function. Betamethasone-17-valerate and beclomethasone-17,21-dipropionate appear to demonstrate greater separation than two esters of dexamethasone which are also available as aerosols. Some of the properties of these four steroids have been investigated in man and are described.

INTRODUCTION

Amongst the advances made by steroid chemists during the last two decades was the development about twelve years ago of corticosteroids with exceptional anti-inflammatory potency on human skin. These compounds were produced by forming 16,17 acetonides or 17 and/or 21 esters from orally active anti-inflammatory glucocorticoid steriods such as triamcinolone and betamethasone. Although these corticosteroids are widely used in treating skin disease, their use on other body surfaces has, until recently, been limited. Betamethasone-17-valerate given by mouth was investigated in the treatment of four patients with Crohn's disease and ten patients with ulcerative colitis by Morton Gill[1] and his colleagues in London in 1965. These patients either had a recurrence of symptoms when treatment with prednisolone was reduced, or they had developed corticosteroid side effects of sufficient severity to make the withdrawal of prednisolone essential. These workers concluded that doses of betamethasone-17-valerate from 2 mg to 8 mg daily for periods of one to thirteen months controlled symptoms as effectively as 40 mg of prednisolone, and that no side effects associated with corticosteroid therapy were seen, including a normal response of the Hypothalamic-Pituitary-Adrenal (H.P.A.) axis to stress. However, plasma cortisol levels observed in some patients were below "normal" values. These findings were challenged in 1967 by Friedman and his colleagues [2] also in London. They investigated the absorption of betamethasone-17-valerate in normal subjects by measuring its effect on adrenal function, and in patients with ulcerative colitis its use as a treatment was correlated with studies of adrenal function. In seven normal subjects adrenal suppression was noted when the dose reached 8 mg a day, and three of these subjects experienced dyspepsia before this dose level was reached. In twenty-seven patients with ulcerative colitis who received a dose of 8 mg a day the clinical effect was indistinguishable from the placebo, and adrenal suppression was noted in three out of the ten patients in which this was studied. They concluded that oral betamethasone-17-valerate was not a satisfactory treatment for ulcerative colitis. No further work with this or any other topically active steroid on the mucous membrane lining the gut has subsequently been reported. The same steroid was used locally in the treatment of rhinitis by Czarny and Brostoff in 1968 [3]. Good control of symptoms, particularly in allergic rhinitis, at a daily dose of 0·4 mg without adrenal suppression being noted [3, 4].

Recently, good control of symptoms without corticosteroid side effects have been reported following the use of inhaled beclomethasone dipropionate in asthma [5–9] and similar findings have been noted with inhaled betamethasone-17-valerate [10, 11]. Beclomethasone dipropionate has also been shown to be of value in allergic and perennial rhinitis when given intra-nasally [12, 13].

Four corticosteroids (beclomethasone dipropionate, betamethasone-17-valerate, dexamethasone-isonicotinate and dexamethasone-sodium-phosphate) are presently available in pressurised aerosols for the treatment of bronchial asthma. This paper reports of some of the properties of these corticosteroids in man. They are considered under four headings:—

1. Topical anti-inflammatory activity on skin.

2. Effects on the H.P.A. axis following administration of the drugs by inhalation.
3. Effects on fasting blood glucose.
4. Effects on circulating white blood cells.

METHODS

1. *Topical anti-inflammatory activity on skin*

Assays based on the effects of compounds with unusually high topical potency on various experimental inflammatory lesions produced on human skin were soon abandoned in favour of the vasoconstriction assay method described by McKenzie[14]. This test is based on the occurrence of intense vasoconstriction and blanching after alcoholic solutions of corticosteroids with special topical activity are placed under occlusion on intact human skin. The degree of blanching is assessed visually, usually by two observers working independently and the results are expressed as simple whole numbers relative to those obtained with a standard steroid such as fluocinolone-16,17- acetonide.

A modification of the method described by McKenzie was used in this study, in which the steroid was placed on a smaller (8 mm square) demarcated area and each site was occluded separately.

2. *The effects of inhaled beclomethasone dipropionate, betamethasone-17-valerate, dexamethasone-21-phosphate and dexamethasone-21-isonicotinate on H.P.A. function*

Twelve subjects aged from twenty-four years to thirty-nine years were divided into four groups of three. Varying doses of beclomethasone dipropionate and betamethasone-17-valerate were each given to two of these groups and dexamethasone-21-phosphate and dexamethasone-21-isonicotinate were given to the other two groups at their recommended doses. The methods for determining plasma cortisol and urinary 17-oxogenic steroids have already been described [15].

3. *The effects of beclomethasone dipropionate, betamethasone-17-valerate, dexamethasone-21-phosphate and dexamethasone-21-isonicotinate on fasting blood glucose and circulating white blood cells.*

Six healthy human subjects aged from nineteen years to twenty-nine years took part in this study and in that of circulating white blood cells.

The effects of two inhaled doses (500 μg and 2 mg) of beclomethasone dipropionate and betamethasone-17-valerate were compared with two inhaled doses (0·5 mg and 0·9 mg) of dexamethasone-21-phosphate and two inhaled doses (0·5 mg and 1·25 mg) of dexamethasone-21-isonicotinate. Dexamethasone 2 mg by mouth was given as a positive control and a placebo as a negative control.

For assessing the effects on fasting blood glucose, the subjects starved from 8.00 p.m., took their doses of steroid at 11.45 p.m. and reported for a sample of blood to be taken at 8.45 a.m. the following morning. Blood glucose was estimated by the method described by Werner, Rey and Wielinger[16].

In the white cell study, blood samples were taken at 9.00 a.m. The doses of steroid were then given and second blood samples taken five hours later. A total and differential white cell count and, for greater accuracy, an absolute eosinophil count were carried out on each sample.

RESULTS

1. *Vasoconstriction assays*

The results are summarised in Table 1. Beclomethasone dipropionate had the greatest activity of the steroids tested and beclomethasone monopropionate, a possible metabolite of beclomethasone dipropionate, was also highly active with an assay value identical with that of betamethasone-17-valerate. Dexamethasone-21-isonicotinate and dexamethasone-21-phosphate were much less active.

2. *H.P.A. function*

Figures 1 and 2 show that no important effects on 9.00 a.m. plasma cortisol values following inhalation of beclomethasone dipropionate and betamethasone-

Table 1. Topical potency of various corticosteroids in man

Steroid	Skin Blanching Activity (McKenzie's Method) Relative Potency Fluocinolone-16,17-Acetonide = 100
Cortisol	0·1
Cortisol-21-Acetate	1·0
Triamcinolone	0·01
Triamcinolone 16,17 Acetonide	100·0
Fluocinolone-16,17-Acetonide	100·0
Betamethasone	0·8
Betamethasone-17-Valerate	360·0
Dexamethasone	0·8
Dexamethasone-21-Isonicotinate	8·0
Dexamethasone-21-Phosphate	6·0
Beclomethasone	0·8
Beclomethasone-17-Propionate	360·0
Beclomethasone-17,21-Dipropionate	500·0

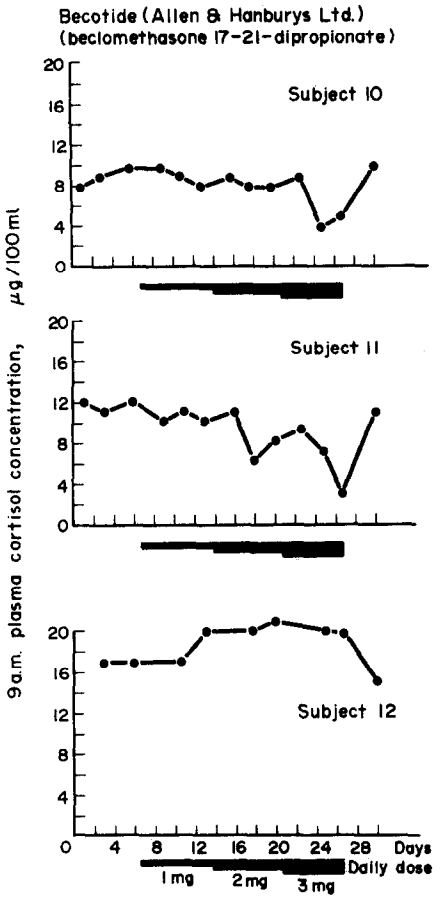

Fig. 1. The effect on 9.00 a.m. plasma cortisol values of inhaling increasing doses of beclomethasone-17,21-dipropionate in excess of the therapeutic range (300 μg–600 μg daily).

17-valerate are noted until the daily dose reaches 3 mg. In contrast, dexamethasone-21-phosphate and dexamethasone-21-isonicotinate given by inhalation at therapeutic doses recommended by the manufacturers rapidly caused large falls in the plasma cortisol levels in all subjects in much the same way as orally administered dexamethasone (Figs. 3 and 4).

3. *Blood glucose levels*

None of the steroids given by inhalation had an effect on fasting blood glucose levels. Individual results are given in Table 2.

4. *White blood cells*

Figures 5 and 6 show the results obtained. A significant ($P < 0{\cdot}05$) increase in neutrophils and a reduction in lymphocytes and eosinophils occurred after each dosage regimen.

DISCUSSION

The results of the vasoconstriction assays and the effects on 9.00 a.m. plasma cortisol values presented in this paper enable these four steroids to be divided into two groups. Beclomethasone dipropionate and betamethasone-17-valerate both have exceptional anti-inflammatory potency on human skin and are relatively less active when administered by inhalation or by mouth; dexamethasone-21-phosphate and dexamethasone-21-isonicotinate are poorly active on skin and as active as dexamethasone as systemic steroids. The basic reasons for the different orders of vasoconstrictor activity of these steroids is not known, but it is noteworthy that the less active compounds are distinctly more polar than the others and might, therefore, penetrate the skin less readily. Alternatively, the steroid receptors which mediate the vasoconstriction may be set in a non-polar environment which allows a better fit with the less polar compounds.

9.00 a.m. plasma cortisol values are not affected by beclomethasone dipropionate or betamethasone-17-valerate until doses in excess of 2 mg a day are inhaled. This finding is in agreement with other work on the effects of beclomethasone dipropionate on the H.P.A. axis [15] and in asthmatic patients [17]. As the usual dose of beclomethasone dipropionate and betamethasone-17-valerate necessary to treat bronchial asthma lies between 300 μg and 600 μg daily, there is a clear separation between the therapeutic doses of beclomethasone dipropionate and betamethasone-17-valerate and the doses necessary to affect the H.P.A. axis. On the other hand both the dexamethasone esters cause a rapid fall in plasma cortisol values at doses within the therapeutic range for those compounds.

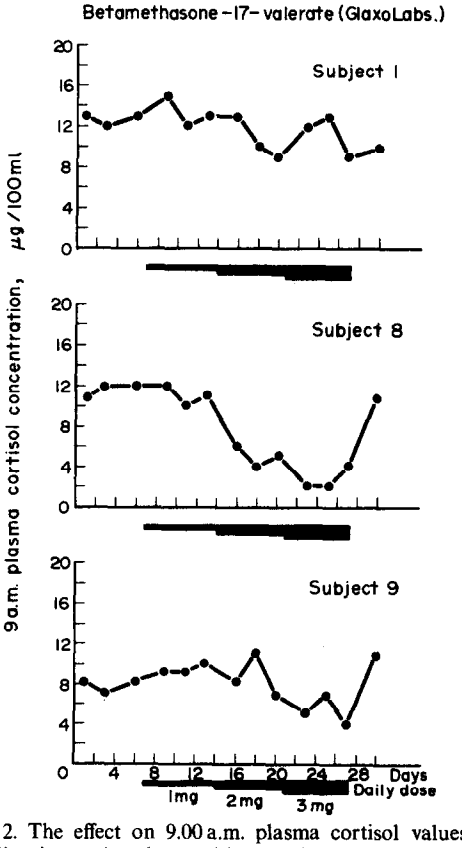

Fig. 2. The effect on 9.00 a.m. plasma cortisol values of inhaling increasing doses of betamethasone-17-valerate in excess of the therapeutic range (300 μg–600 μg daily).

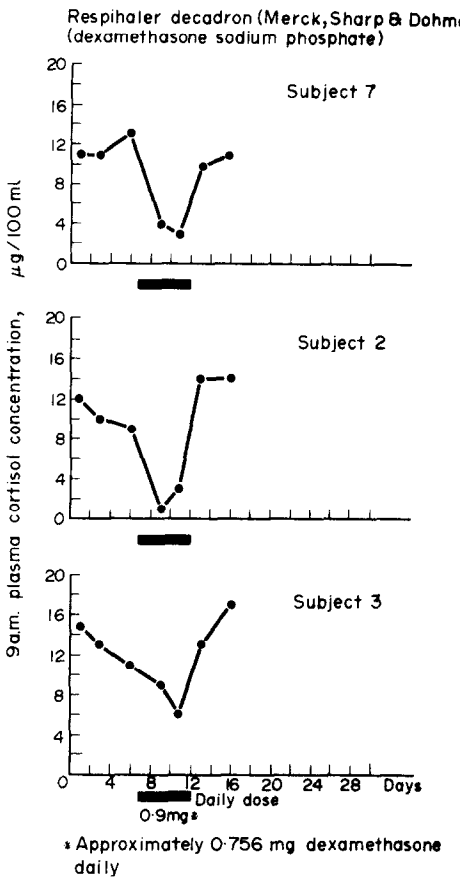

Fig. 3. The effect on 9.00 a.m. plasma cortisol values of inhaling therapeutic doses of dexamethasone–sodium-phosphate.

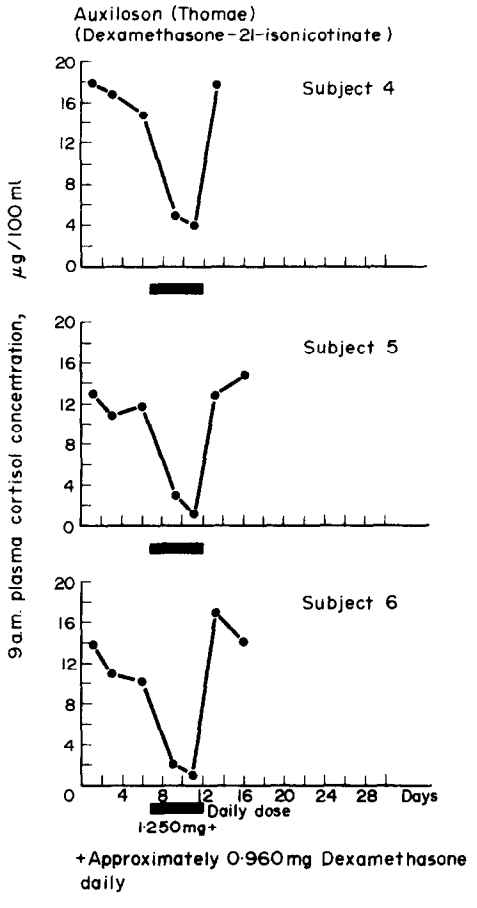

Fig. 4. The effect on 9.00 a.m. plasma cortisol values of inhaling therapeutic doses of dexamethasone-21-isonicotinate.

As the greater part of any drug administered by inhalation is deposited in the mouth and pharynx from whence it is subsequently swallowed [18], the effect of oral beclomethasone dipropionate and betamethasone-17-valerate on adrenal function is important when considering possible reasons for their selective action in bronchial asthma, oral doses of beclomethasone dipropionate in excess of 4 mg daily are necessary to suppress plasma cortisol values in normal subjects [15], despite being well absorbed if given as a microfine suspension. The drug is metabolised, probably in the liver, to inactive polar materials which are excreted *via* the bile in the faeces [19]. This metabolic barrier means that the swallowed portion of beclomethasone dipropionate in therapeutic inhaled doses cannot contribute to any observed effects on the H.P.A. axis. This conclusion is consistent with the finding that the drug when given by inhalation affects H.P.A. function at a lower dose than that required after oral administration. The effects of orally administered betamethasone-17-valerate have not been studied in detail, but the results obtained in earlier work in ulcerative colitis [1, 2] and recent work in bronchial asthma [10, 11] leave no doubt that it too has less effect on the H.P.A. axis after oral administration than after inhalation. The fate of

Table 2. Fasting blood glucose values nine hours after single doses of various steroids (means of six subjects)

Steroid	Blood glucose mg/100 ml	Change from control
1	93	+17*
2	72	−4
3	72	−4
4	78	+2
5	73	−3
6	77	+1
7	77	+1
8	76	0
9	77	+1
10	76	—

* Significantly greater than control ($P > 0.05$).

1. Dexamethasone 2·0 mg by mouth.
2. Dexamethasone-isonicotinate 1·25 mg by inhalation.
3. Dexamethasone-isonicotinate 0·5 mg by inhalation.
4. Dexamethasone–sodium-phosphate 0·9 mg by inhalation.
5. Dexamethasone–sodium-phosphate 0·5 mg by inhalation.
6. Betamethasone-17-valerate 0·5 mg by inhalation.
7. Betamethasone-17-valerate 2·0 mg by inhalation.
8. Beclomethasone dipropionate 0·5 mg by inhalation.
9. Beclomethasone dipropionate 2·0 mg by inhalation.
10. Control.

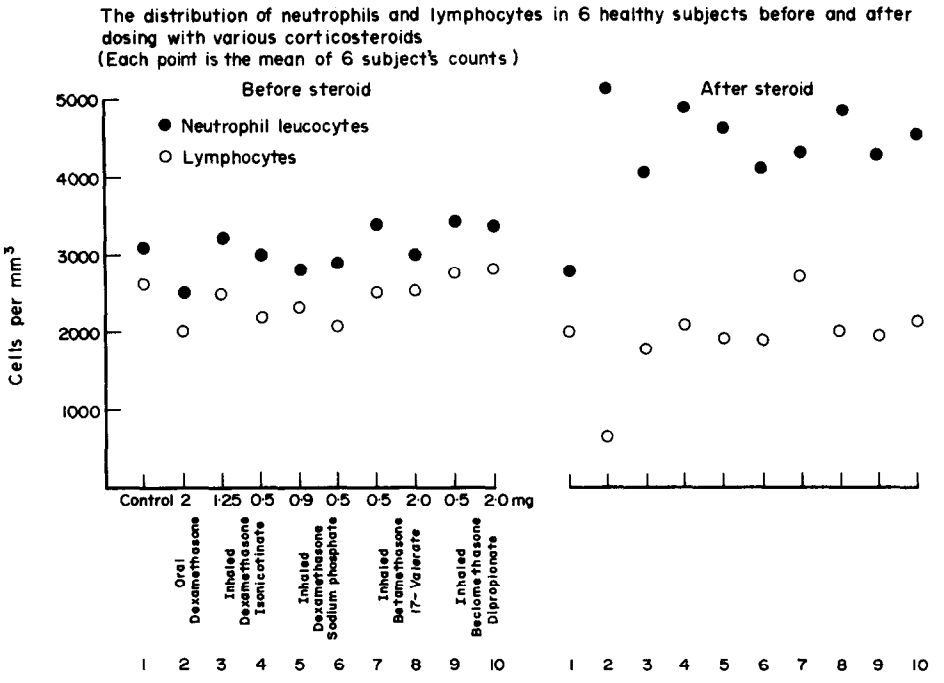

Fig. 5.

orally administered betamethasone-17-valerate has not yet been established in man.

No advantage over oral administration appears to be gained by administering either of the dexamethasone esters by inhalation. This is probably because they lack enhanced topical activity and, like hydrocortisone and prednisolone which have also been given by inhalation to asthmatic patients, they have potent glucocorticoid activity by any route of administration. Unless there is a clear separation between the anti-inflammatory dose of an inhaled steroid and the dose necessary to affect the H.P.A. axis there will be no advantage for the patient in terms of a reduction in unwanted glucocorticoid effects. High topical activity relative to systemic glucocorticoid activity appears to be important in any corticosteroid intended for use on a body surface such as the mucous membrane lining the lungs.

The effects of glucocorticoid steroids on fasting blood sugar levels in man are thought to give similar results to the measurement of liver glycogen deposition in animals. Generally, however, in man fasting blood sugar appears to be a less sensitive index of glucocorticoid activity than the H.P.A. axis, and this

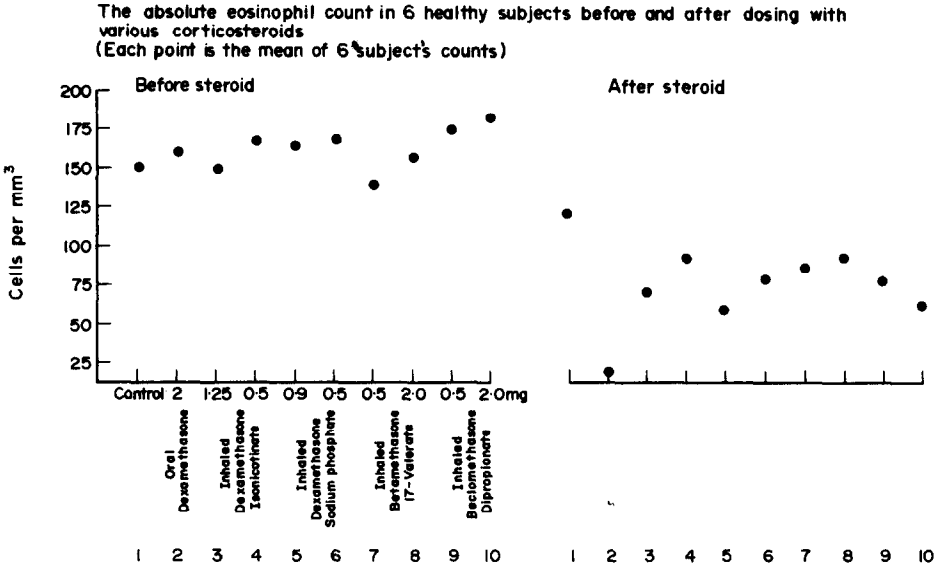

Fig. 6.

is so in the studies described. In contrast, circulating white blood cells appear to be more sensitive to glucocorticoid steroids. For example, oral dexamethasone has four to five times the anti-inflammatory activity of prednisone but about seven times the activity upon circulating white cells, particularly eosinophils [20]. This observation is consistent with the finding in these studies that all four steroids had a significant effect on circulating white cells. Neutrophil leucocytosis, lymphopenia and eosinopenia occurred at therapeutic doses of beclomethasone dipropionate and betamethasone-17-valerate and at doses well below therapeutic in the case of the two dexamethasone compounds. The likeliest explanation is simply that these cells are exceptionally sensitive to the small amounts of these steroids absorbed from the lungs. On the other hand these cells are involved in inflammatory and allergic processes in the tissues and so the observed effects on these cells may be related in some way to the anti-inflammatory action of these corticosteroids. For example, they may represent a useful shift from the blood to sites of functional demand in the tissues or following a useful anti-inflammatory effect the need for such cells may be reduced. Further work is necessary to distinguish between possible explanations of the phenomenon.

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