Observations on oral betamethasone-17-valerate in the treatment of idiopathic steatorrhoea

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EDITORIAL COMMENT Clinical remission in three patients with idiopathic steatorrhoea was achieved with Betnovate without getting corticosteroid side-effects or adrenocortical suppression.

The efficacy of corticosteroids in the treatment of idiopathic steatorrhoea has been repeatedly demonstrated (Adlersberg, Colcher, and Drachman, 1951; Adlersberg, 1955; Mackay and Volwiler, 1955; Moeschlin and Meyer, 1961; Frič, Bednář, Niederle, and Lepšik, 1963). The limiting factor in their use has been the threat of side-effects (Badenoch, 1960).

A number of adults with idiopathic steatorrhoea are not gluten-sensitive (French, Hawkins, and Smith, 1957), hence the choice of therapy in such patients is between severe dietary restriction and corticosteroid therapy.

McKenzie and Atkinson (1964) showed that topical betamethasone - 17 - valerate (Betnovate, Glaxo) is 400 times more active than betamethasone itself, judged by the production of skin vasoconstriction. Oral Betnovate appears less active than betamethasone as judged by its effect on the plasma cortisol level nevertheless it seems effective when administered in cases of ulcerative colitis and Crohn's disease (Gill, Otaki, Daly, and Spencer-Peet, 1965).

This paper reports our initial observations on the effect of oral Betnovate in three cases of idiopathic steatorrhoea.

METHODS

The clinical condition and chemical status of three patients were assessed before and during treatment with Betnovate.

FAECAL FAT This, by the method of Van de Kamer, ten Bokkel Huinink, and Weyers (1949), was determined from two three-day collections. The normal is less than 6 g. daily.

VITAMIN A ABSORPTION This was studied by the method of Paterson and Wiggins (1954). Normal is a rise of more than 500 units/100 ml.

URINE XYLOSE The results, determined by the method of Roe and Rice (1948), were expressed as the percentage of the oral dose excreted in the five hours following administration. Normal is more than 25%.

PLASMA IRON The normal range for men is 80-175 µg./100 ml. and for women 60-160 µg./100 ml., using Ramsay's (1958) method.

PLASMA VITAMIN B₁₂ The method was based on that of Spray (1955) and Matthews (1962) using *Lactobacillus leishmanii*. The normal range is 150-900 µg./ml.

PLASMA FOLIC ACID Plasma folic acid activity was determined with *Lactobacillus casei*. Normal range is 5-25 µmg./ml.

PLASMA CORTISOL Plasma cortisol was determined by the method of Spencer-Peet, Daly, and Smith (1965). Normal range is 5-26 µg./100 ml.

ADRENOCORTICAL RESPONSIVENESS This was assessed by estimating the plasma cortisol level before and 30 min. after intramuscular injection of synthetic β^{1-24} corticotrophin (Synacthen)¹. A normal response is a rise of between 7.5 and 27.5 µg./100 ml. after 30 minutes (Wood, Frankland, James, and Landon, 1965).

CASE HISTORIES

CASE 1 In Mrs. H., aged 54, idiopathic steatorrhoea was diagnosed in 1946, and a gluten-free diet was started in 1956. Following a relapse in 1961 she was treated with prednisolone. In 1963 a jejunal biopsy showed subtotal villous atrophy (Fig. 1). In May 1965 she was admitted with megaloblastic anaemia. After treatment with haematinics the prednisolone was slowly reduced. The patient relapsed in October 1965. Steatorrhoea was severe with five or six stools daily. Betnovate 2 mg. daily was begun. In four days bowel actions had fallen to one daily and the stools appeared normal. She was able to take a normal diet without symptoms.

¹Ciba Laboratories Ltd., Horsham, Sussex.

FIG. 1. Patient Mrs. H. Jejunal biopsy. Subtotal villous atrophy. Haematoxylin and eosin $\times 100$.

On reassessment after 31 days of Betnovate therapy the patient felt completely well and the daily bowel action appeared normal. However, there were still chemical abnormalities so the dose of Betnovate was increased to 3 mg. per day.

At a second reassessment after 95 days of treatment the improvement had been maintained. There was one bowel action daily and the stool appeared normal. Her diet was full and varied. The steatorrhoea was further reduced, but the plasma vitamin B₁₂ level had fallen. There were no signs of hypercorticism and a Synacthen test showed that although the plasma cortisol level at 10 a.m. was subnormal there was a significant rise after 30 minutes.

Details of the main findings are shown in Table I.

CASE 2 Mrs. D., aged 60, had had episodes of diarrhoea and weight loss in childhood and early teens. In 1952, after a gynaecological operation, diarrhoea returned. Weight loss and severe diarrhoea led to her investigation at another hospital in 1963. Defective glucose, xylose, and fat absorption were present with villous atrophy of the jejunal muco, and idiopathic steatorrhoea was diagnosed. She was given a gluten-free diet which produced a notable improvement. However, a few months before being referred to us she resumed a normal diet. In June

TABLE I
INVESTIGATIONS ON MRS. H., AGED 54, BEFORE AND DURING BETNOVATE THERAPY

Test	Date		
	19 October 1965	24 November 1965	25 January 1966
	Before Betnovate Therapy	Betnovate for 31 Days	Betnovate for 95 Days
Stools per day	5-6	1	1
Body weight (lb.)	133½	130	135½
Blood pressure (mm. Hg)	130/90	125/80	138/80
Haemoglobin (g./100 ml.)	12.2 (84%)	13.0 (89%)	12.1 (83%)
E.S.R. (Westergren) (mm.)	20	10	4
Faecal fat (g. per day)	27.2	10.2	7.7
Xylose absorption (%)	9	10	30
Vitamin A absorption (i.u.)	130 to 250	84 to 210	84 to 294
Plasma proteins (g./100 ml.)	Total = 6.0 (albumin = 3.1)	—	Total = 6.7 (albumin = 3.7)
Plasma folic acid	Folic acid i.m. 15 mg./week	11.5	50
Plasma vitamin B ₁₂ (μg./ml.)	Vitamin B ₁₂ i.m. 190	190	90
Plasma iron (μg./100 ml.)	74	100	62
Plasma cortisol before Synacthen (μg./100 ml.)	23.3	17.0	2.8
Plasma cortisol 30 min. after Synacthen (μg./100 ml.)	25.0	35.7	14.2
Plasma cortisol 60 min. after Synacthen (μg./100 ml.)	20.0	41.3	19.3
Betnovate (mg./day)	—	2	3

1965 when she first attended she had had several bouts of diarrhoea. She complained of fatigue, postprandial faintness, and morning urgency with five or six fluid offensive stools a day.

She was admitted in September 1965. A lactose tolerance test produced a rise of blood glucose in excess of 20 mg./100 ml. and did not cause diarrhoea. Synacthen stimulated normal adrenal activity. The patient was discharged to take 2 mg. of Betnovate daily. Three days later she was passing only two normal stools a day despite a normal diet.

In November after 53 days of treatment with 2 mg. of Betnovate she was admitted for reassessment. The improvement had been maintained, and the patient said she had not felt so well for a year and could now eat 'loads of bread'. There was still some chemical evidence of malabsorption, but faecal fat was only 5.7 g. per day. A second reassessment took place after 120 days. The only abnormality detected was a low plasma folic acid level. Synacthen produced a normal adrenocortical response. There were no signs of hypercorticism. Treatment was continued with 2 mg. of Betnovate daily.

Details of the main clinical and laboratory findings are shown in Table II.

TABLE II

INVESTIGATIONS ON MRS. D., AGED 53, BEFORE AND DURING BETNOVATE THERAPY

Test	Date		
	10 September 1965	2 December 1965	3 February 1966
	Before Betnovate Therapy	Betnovate for 57 Days	Betnovate for 120 Days
Stools per day	5-6	1	1
Body weight (lb.)	109	117½	118
Blood pressure (mm. Hg)	120/80	120/85	120/80
Haemoglobin (g./100 ml.)	13.2 (91%)	13.4 (92%)	14.3 (98%)
E.S.R. (Westergren) (mm.)	30	5	5
Faecal fat (g. per day)	14.0	5.7	3.1
Xylose absorption (%)	22	21	50
Vitamin A absorption (i.u.)	85 to 250	105 to 294	126 to 798
Plasma proteins (g./100 ml.)	Total = 6.0 (albumin 3.8)	—	Total = 6.5 (albumin 3.4)
Plasma vitamin B ₁₂ (μg./ml.)	—	330	230
Plasma iron (μg./100 ml.)	25	61	71
Plasma cortisol before Synacthen (μg./100 ml.)	10.9	13.6	9
Plasma cortisol 30 min. after Synacthen (μg./100 ml.)	25.0	29.7	23.8
Plasma cortisol 60 min. after Synacthen (μg./100 ml.)	21.5	33.5	28.5
Betnovate (mg./day)	—	2	2

CASE 3 Mr. H., aged 53, began to have symptoms of idiopathic steatorrhoea in January 1962 and the diagnosis was confirmed by jejunal biopsy (Fig. 2). There was a satisfactory response to prednisolone but when the dose was reduced to 7.5 mg. the steatorrhoea relapsed. The patient was reassessed and the prednisolone reduced more slowly, but at 9 mg. daily a second relapse occurred.

He was readmitted in March 1965. There were two bulky, pale and urgent stools a day. The plasma cortisol level at 10 a.m. was 1.5 μg./100 ml., indicating pituitary-adrenal suppression. Prednisolone withdrawal was completed and the patient discharged on 2 mg. of Betnovate daily.

After 44 days of treatment he had gained weight, passed one formed stool each day, and was taking a normal diet.

After 98 days of treatment the remission continued. The plasma cortisol level at 10 a.m., and response to Synacthen were normal.

The patient was planning to return to Ireland and refused admission for reassessment. Believing himself to have returned to normal health he failed to keep an outpatient appointment in November to renew his supply of Betnovate. After omitting Betnovate for 19 days he was admitted at his own request in relapse. There was no evidence of adrenocortical failure. He was once more

FIG. 2. Patient Mr. H. Jejunal biopsy. Subtotal villous atrophy. Haematoxylin and eosin $\times 100$.

passing two bulky pale stools daily and his body weight had fallen. Although he had received 204 days of Betnovate treatment before he stopped taking the tablets, his Synacthen response was normal.

Betnovate treatment was restarted and the patient left for Ireland. Details of the main findings are given in Table III.

DISCUSSION

Glyn and Fox (1961) showed betamethasone to be about seven times more potent than prednisolone. Topical Betnovate is very much more potent than topical betamethasone, but their relative systemic potencies, and hence the relative systemic potency of Betnovate and prednisolone, are not yet fully known.

The results presented here suggest that Betnovate has a good therapeutic effect in idiopathic steatorrhoea, with little tendency to produce side-effects on low, but efficacious doses. It may be that in order to correct the malabsorption completely a severe case may need more than 3 mg. a day with a correspondingly greater possibility of side-effects. If such cases are made symptom-free with small doses, and the mal-

TABLE III

INVESTIGATIONS ON MR. H., AGED 53, BEFORE AND DURING
RELAPSE AFTER BETNOVATE WITHDRAWAL

Test	Date		
	8 March 1965	29 July 1965	1 December 1965
	Relapse during Prednisolone Reduction	Betnovate for 98 Days	No Betnovate for 19 Days
Stools per day	2	1	2
Body weight (lb.)	115	129½	—
Blood pressure (mm. Hg)	100/65	125/75	120/70
Haemoglobin (g./100 ml.)	12.4 (85%)	15.1 (104%)	12.4 (85%)
E.S.R. (Westergren) (mm.)	4	7	20
Faecal fat (g. per day)	6.7	—	25.5
Xylose absorption (%)	11.0	—	9
Vitamin A absorption (i.u.)	84 to 250	—	84 to 315
Plasma vitamin B ₁₂ (µg./ml.)	180	—	155 120
Plasma iron (µg./100 ml.)	108	—	69
Plasma cortisol before Synacthen (µg./100 ml.)	—	11.5	10.4
Plasma cortisol 30 min. after Synac- then (µg./100 ml.)	—	20.8	28.2
Plasma cortisol 60 min. after Synac- then (µg./100 ml.)	—	16.9	26.7
Betnovate (mg./day)	—	2	—

absorption of specific substances is corrected by supplementary treatment, the dose of Betnovate may be kept below that at which side-effects appear. More time is needed to assess fully the risk of side-effects with small oral doses of Betnovate, but on the doses used here none of the patients developed moon face or any other side-effect.

The Synacthen test provides a simple means of checking adrenal responsiveness during cortico-steroid therapy. Patient 1 showed a normal response to Synacthen after 31 days of Betnovate in a dose of 2 mg. daily. After a further 63 days of 3 mg. daily the initial plasma cortisol level was subnormal but the response to Synacthen was in the normal range. Patient 2 showed a normal response after 120 days of treatment. Patient 3 had an impaired response before Betnovate was begun, but after 98 days of Betnovate therapy Synacthen responsiveness had returned to normal.

A study of the effect of Betnovate on the plasma cortisol level (Otaki and Daly, to be published) showed that it caused less depression than its parent compound betamethasone. The absence of side-effects noted here with Betnovate, and its relatively slight depressing effect on adrenal responsiveness,

may be due to its being comparatively poorly absorbed, or to its having a less marked systemic effect for metabolic reasons. This is at present under investigation.

If Betnovate is poorly absorbed, its beneficial effects in idiopathic steatorrhoea and in ulcerative colitis and Crohn's disease (Gill *et al.*, 1965) are presumably due to a surface effect. This does not appear to be the only method by which steroids act on the gut because Almy (1951) obtained good results with A.C.T.H. and Moeschlin and Meyer (1961) with intravenous prednisolone.

These preliminary observations appear to indicate that Betnovate is a promising new addition to the therapy of steatorrhoea, for it shows a dissociation between its therapeutic action on the intestine and its suppressive effect on the pituitary adrenal axis.

SUMMARY

A satisfactory clinical remission was induced in three cases of idiopathic steatorrhoea using not more than 3 mg. daily of oral Betnovate (betamethasone-17-valerate). Two patients were gluten-sensitive but all three patients were able to take a normal diet. Moderate chemical steatorrhoea persisted in one patient in whom vitamin A absorption failed to improve. In two patients the plasma vitamin B₁₂ level fell during treatment. There was no evidence of steroid side effects after treatment for 95 to 204 days. Betnovate did not lead to adrenocortical suppression as judged by the Synacthen stimulation test but the response was reduced in one patient. Betnovate appears to be suitable for the long-term treatment of idiopathic steatorrhoea but supplementary vitamin therapy may be necessary in some cases.

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