BETAMETHASONE PHOSPHATE ORAL SOLUTION: A DERMATOLOGICAL ASSESSMENT

BY

RONALD E. CHURCH, M.D., F.R.C.P.Ed.

*Consultant Dermatologist, the Rupert Hallam
Department of Dermatology, Sheffield
Royal Infirmary*

The following is an account of the systemic use of betamethasone phosphate (16 β -methyl-9 α -fluoro-prednisolone 21-disodium phosphate) in the treatment of 62 patients suffering from a variety of skin disorders.

Betamethasone is available as the alcohol ("betnelan") and the 21-disodium phosphate ("betnesol"). Betamethasone alcohol is practically insoluble in water (approximately 0.005%), while the phosphate is freely soluble (over 30%). The tablets of the phosphate are specially formulated to produce a clear solution in water and to effervesce so that solution time is reduced. A water-soluble dye has been incorporated so that the final solution is coloured, indicating to the patient that the tablet has dissolved. The tablets are packed in moisture-proof containers containing a capsule of desiccant as they are susceptible to moisture.

Selection of Cases

Of the 62 patients included in this trial, 38 were male and 24 female. The diagnoses were as follows: pemphigus 4; systemic lupus erythematosus, 2; dermatomyositis, 1; exfoliative dermatitis and exfoliative psoriasis, 7; atopic eczema, 26; eczema and dermatitis, 16; Behcet's syndrome, 1; urticaria, 1; alopecia areata, 3; epidermolysis bullosa, 1.

Previous steroid therapy had been given to 44 patients, who were on a maintenance dose of a steroid at the start of the trial. The duration of previous steroid therapy varied, but was over a year in 30 patients, and the longest period of continual maintenance was eight years in a patient suffering from pemphigus vulgaris.

All patients who had in the past been or were suffering from dyspepsia were admitted to the trial in order to assess the effect of administration of the steroid as a solution on their dyspepsia.

Relative Potency

In patients suffering from exfoliative dermatitis, eczema, and dermatitis the relative potency of steroids can be assessed objectively and fairly accurately, as once the patient has had the maintenance dose reduced to the lowest controlling dose a further slight reduction—for example, of 1 or 2 mg. of prednisolone—is rapidly followed by a relapse in the skin eruption.

During the past year the effects of transferring patients from maintenance doses of prednisolone, enteric-coated prednisolone, betamethasone, and triamcinolone to betamethasone phosphate and back to the previously used steroid have been observed. In many cases this switch has been effected on more than one occasion, and the results of individual cases have remained remarkably constant. The following results were obtained:

1 mg. betamethasone as phosphate was equivalent to 10 mg. prednisolone in 8 cases, 12.5 mg. in 5, 15 mg. in 4, and 20 mg. in 6.

1 mg. betamethasone as phosphate was equivalent to 10 mg. enteric-coated prednisolone in 3 cases, 12.5 mg. in 1, 15 mg. in 1, 20 mg. in 6, and 30 mg. in 1.

1 mg. betamethasone as phosphate was equivalent to 1 mg. betamethasone alcohol in 11 cases, to marginally over 1 mg. in 8, to 1.5 mg. betamethasone alcohol in 6, and was less effective than 1 mg. in 1.

1 mg. betamethasone as phosphate was equivalent to 4 mg. triamcinolone in 1 case.

1.5 mg. betamethasone as phosphate was equivalent to 8 mg. triamcinolone in 2 cases.

Thus 1 mg. of betamethasone as phosphate was approximately equivalent to 12.5 mg. of prednisolone and 1.25 mg. of betamethasone alcohol.

The equivalent dose of enteric-coated prednisolone was spread over a wider range, but 1 mg. of betamethasone as phosphate appeared to be equivalent to between 15 and 20 mg. of enteric-coated prednisolone in most cases.

Complications of Disease

One patient suffering from dermatomyositis which was not controlled by steroid therapy died of heart-block. One patient with disseminated lupus erythematosus was psychotic only while the disease was uncontrolled, and a psychosis had occurred in a patient with pemphigus vegetans before the start of corticosteroid therapy.

A

Complications Attributable to Steroids

One patient developed diabetes mellitus and four male patients aged 20 to 40 developed moderately severe acne vulgaris while taking betamethasone phosphate.

Six patients gained between 7 and 14 lb. (3.2 and 6.4 kg.), having previously been static in weight while on other steroids, and it is notable that four of them were previously taking a maintenance dose of triamcinolone. Dyspepsia was the only other serious complication encountered, but the incidence in this series is not a true one, as those suffering from this symptom were selected for inclusion in the trial.

Three patients had long-standing dyspepsia before the start of steroid therapy, and one of these had had a perforated duodenal ulcer. Barium meals in these three showed no active ulceration. Seventeen patients developed dyspepsia for the first time on other steroids—mainly prednisolone—and 12 of these were already taking enteric-coated prednisolone for maintenance therapy. Those patients in whom dyspepsia persisted despite treatment with enteric-coated prednisolone and betamethasone phosphate were investigated further for evidence of peptic ulceration but none was found.

On betamethasone phosphate the patients' symptoms of dyspepsia have been as well controlled in most cases as on enteric-coated prednisolone (see Table), and the

Patients with Dyspepsia—Analysis of 20 Cases

Previous History	Results with Betamethasone Phosphate	
Patients on E.C. prednisolone ..	12	
Dyspepsia continued	5	No dyspepsia .. 3
		Dyspepsia less severe .. 2
No dyspepsia	7	No dyspepsia .. 5
		Redeveloped dyspepsia .. 2
Patients having dyspepsia on other steroids	5	No dyspepsia .. 2
		Dyspepsia less severe .. 3
Patients having dyspepsia prior to steroids	3	No dyspepsia .. 2
		Mild .. 1

control of the skin eruption has been much more effective. The only patient who suffered any degree of discomfort on betamethasone phosphate had been taking 25 mg. of enteric-coated prednisolone and having injections of 20 mg. of A.T.C.H. gel thrice weekly without control of his skin eruption.

Discussion

Dyspepsia is a common complication of steroid therapy (Morton, 1958; Nordin, 1960), and it has been suggested that the ulcerogenic action of oral steroids is due in part to a more powerful action on the gastric mucosa as well as to the systemic action on cellular function. This theory is supported by the relief from symptoms experienced by patients taking enteric-coated prednisolone.

The disadvantage of enteric coating is the variability in effectiveness from patient to patient, so that relapses may occur on substitution. Also, the small dose of 2.5 mg. per tablet may necessitate swallowing a large number of tablets. In the small series of dyspeptics reported here administration of betamethasone phosphate solution controlled their symptoms as effectively as enteric-coated tablets, with the advantage of more effective control of the skin eruption.

The administration of betamethasone phosphate as a solution eliminates the possibility of slow or poor disintegration of a tablet, and the fact that the drug is freely soluble in water probably allows more rapid absorption. The volume of fluid taken with the drug may speed the gastric emptying-time and the larger surface of the intestine makes it the optimum site for absorption.

These physical factors may therefore be responsible for the two features which this trial suggests. Firstly, the increased efficiency of the phosphate over the relatively insoluble alcohol may be due to better absorption. Secondly, the diminished incidence of dyspepsia may be due to rapid passage through the stomach, rapid absorption, and the absence of any local high concentration of steroid which might be produced in the vicinity of a tablet disintegrating slowly in the stomach.

Summary

Sixty-two patients suffering from various skin diseases have been treated with betamethasone phosphate administered as an oral solution.

It was found that 1 mg. of betamethasone as phosphate was approximately equivalent to 12.5 mg. of prednisolone, 1.25 mg. of betamethasone alcohol, and between 15 and 20 mg. of enteric-coated prednisolone.

Dyspepsia was as well controlled as with enteric-coated tablets, and it is suggested that administration of the drug as a solution may be responsible for this and for its greater efficiency than betamethasone tablets.

I am grateful to Dr. I. B. Sneddon for allowing me to include patients under his care in this trial; to Mr. F. W. Tea'her, of Glaxo Laboratories, for much technical advice; and to Glaxo Ltd. for generous supplies of betamethasone phosphate ("betnesol").

REFERENCES

- Morton, E. V. B. (1958). *Proc. roy. Soc. Med.*, **51**, 317.
Nordin, B. E. C. (1960). *Brit. J. Derm.*, **72**, 40.

Preliminary Communications

Immunological Relationship Between Pernicious Anaemia and Thyroid Disease

Achlorhydria is a cardinal feature of Addisonian pernicious anaemia and also occurs in a high proportion of patients suffering from spontaneous hypothyroidism (Tudhope and Wilson, 1962). It is conceivable that the impairment of gastric acid secretion in both these conditions may be based on immunological mechanisms. This has been investigated by testing the sera of such patients and of patients suffering from Hashimoto's thyroiditis for antibodies against mucosa and against thyroid by the technique of complement fixation.

Clinical Material.—The following cases were included in the present study:

14 untreated patients diagnosed consecutively as suffering from Addisonian pernicious anaemia and 27 treated cases currently maintained on cyanocobalamin; 77 patients with untreated or treated spontaneous hypothyroidism; 44 untreated cases of Hashimoto's thyroiditis, the majority of whom were euthyroid; and 100 hospital control patients suffering from a range of other diseases excluding D.L.E. and hepatitis.

METHODS

The technique of complement fixation (C.F.) adopted was after the method of Donnelley (1951). Saline extracts were prepared from mucosa taken from body of stomach, pyloric antrum, and jejunum in patients undergoing partial gastrectomy for duodenal ulcer and from colonic mucosa taken proximal to an area of diverticulitis at colectomy. Saline extracts were also prepared from human thyrotoxic glands at the time of partial thyroidectomy and from human foetal liver obtained within three hours of death. Each tissue was homogenized with four volumes of calcium-magnesium buffer of pH 7, centrifuged at 3,000 r.p.m. for 15 minutes, and small aliquots of the supernatant were stored at -20°C . The optimum dilution of antigen was determined by chessboard titration with known positive sera; the highest concentration that was not anti-complementary was used. Sera were stored at -20°C . and inactivated for 30 minutes at 56°C . before testing. Complement (C^1) preserved in Richardson's salt solution (Burroughs Wellcome) was titrated in the presence of antigen. The haemolytic system consisted of a 2% sheep-cell suspension sensitized with five minimum haemolytic doses of haemolytic serum. The test was done in "perspex" trays, 3 drops of each reagent being measured from pipettes cut to deliver 30 drops/ml. Serum and antigen were incubated for one hour at 37°C . with two minimum haemolytic doses of C^1 , the haemolytic system was added, and incubation was continued for a further one and a quarter hours. The results were read visually, taking 50% haemolysis as the end-point. Serum controls were done routinely and known positive and negative sera were included in each batch of tests. All sera were initially screened at dilutions of 1:4, 1:8, 1:16, and 1:32. Sera giving titres greater than or equal to 1:32 were titrated again in doubling dilutions from 1:4 to 1:512.

C.F. tests were also carried out using hog intrinsic factor (Lederle) as antigen component. Serum gamma-