

THE USE OF CORTICOSTEROIDS IN COMBINATION WITH ISONICOTINIC ACID HYDRAZIDE IN THE TREATMENT OF ADVANCED BILATERAL PROGRESSIVE CAVITARY PULMONARY TUBERCULOSIS

SECOND REPORT WITH DISCUSSION

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Although the picture presented by tuberculosis has been dramatically altered by the advent of drugs such as isonicotinic acid hydrazide (INH) and streptomycin, one of the gravest problems still unsolved is that of long-standing, often partially treated or untreated, pulmonary disease. In these cases, active foci surrounded by fibrosis and avascular tissue remain shielded from medical attack, while the extensive nature of the areas involved in fibrosis and cavitation preclude the possibility of surgical removal. At best they can be maintained *in statu quo* while occupying hospital beds urgently needed for the treatment of acute cases. As out-patients they are dangerous and prolific spreaders of disease.

In the series being reported on, prednisone was added to the routine treatment to determine whether in these cases, the worst of their type, the course of disease could be altered, and also to obtain information which would be of value in the treatment of pulmonary tuberculosis generally.

It was reasoned that prednisone might be of value in the following ways:

(a) By reducing inflammatory reaction (exudate, congestion and oedema) and thus allowing better access of medication to tubercle bacilli, better aeration and lung function, and improved drainage of diseased and destroyed tissues. This is of importance also in secondary sepsis.

(b) By preventing or retarding further formation of fibrous tissue.

(c) By altering the host-reaction to stress (on the assumption that stress, e.g. diet, fatigue and disease, plays an important part in the Bantu type of rapidly-advancing tuberculosis).

(d) By improving appetite and general well-being and minimizing unpleasant symptoms.

On 30 June 1956 a preliminary report was published in this *Journal*¹ on a 3 months' trial of prednisone and isonicotinic acid hydrazide in the treatment of a selected group of 23 female Bantu patients with advanced bilateral progressive cavitary pulmonary tuberculosis of poor prognosis. It was reported that 'during the period of the trial no patient died although a fatal outcome would have been anticipated in the majority of cases of this type. All patients exhibited marked clinical improvement. All but one showed satisfactory weight-gains. On independent radiological assessment no patient showed further deterioration and 5 actually showed slight improvement. All sputa remained positive for tubercle.'

The present report covers a total period of 9 months, during which the treatment of this group of 23 patients was as follows:

1. *First period of 3 months:* As in the preliminary report¹—INH (15 mg. daily per kg. body-weight) and prednisone (15 mg. daily).

2. *Second period of 3 months:* Without prednisone—INH (15 mg. per kg. daily) and Viomycin (1 g. twice weekly).

3. *Third period of 3 months:* On prednisone (30 mg. daily), INH (15 mg. per kg. daily), Dipasic (20 mg. per kg. daily) and streptomycin (1 g. twice weekly).

Prednisone was gradually 'tailed off' at the end of each period.

Throughout the period the patients received extra vitamins, extra proteins and treatment for secondary sepsis.

TABLE OF OBSERVATIONS

| | <i>At end of 1st 3-month period (15 mg.*)</i> | <i>At end of 2nd 3-month period (nil*)</i> | <i>At end of 3rd 3-month period (30 mg.*)</i> |
|--|---|--|---|
| Number of patients showing X-ray improvement | 5 | 9 | 12 |
| Number of patients showing X-ray deterioration | 0 | 3 | 4 |
| Average weight-gains (lb.) .. | 20½ | 21¾ | 35 |
| | <i>During 1st 3-month period (15 mg.*)</i> | <i>During 2nd 3-month period (nil*)</i> | <i>During 3rd 3-month period (15 mg.*)</i> |
| Number of patients having haemoptysis during the period .. | 0 | 5 | 1 |
| Number of deaths | 0 | 2 | 1 |
| Number discharged | 0 | 2 | 1 |
| <i>Side Effects</i> | | | |
| 'Moon Face' | 3 | 0 | 17 |
| Hyperglycaemia | 0 | 0 | 1 |
| Hirsutism | 0 | 0 | 1 |

* daily dosage of prednisone.

All sputa remained positive for tubercle on culture, some being occasionally negative on straight examination.

One month after the end of the trial, all the patients remaining in hospital were ambulant and in good general condition.

DISCUSSION

X-ray Changes

Changes were assessed by independent observations of a panel of 3 senior physicians. By means of numerical evaluation the sums of the monthly variations were

checked against evaluation of changes for the entire period.

During this trial it was suggested that potassium iodide might be as effective as the corticosteroids in aiding the response to INH as shown by X-ray clearing. To settle this point, a series of 18 non-selected tuberculous female Bantu patients were treated with 20 mg. of INH per kg. body-weight, and half of them were given potassium iodide and half of them prednisone. After 1 month X-ray changes were assessed by the independent panel. X-ray clearing in the prednisone group compared to the pot. iod. group was in the ratio of 13 to 8. The average weight-gain in the prednisone group was 9 lb., and in the pot. iod. group 2½ lb. Of the prednisone group, 5 showed good clearing, while of the pot. iod. group 2 showed good clearing.

Deaths

Only 3 patients had died after 9 months, 2 during the second 3-month period while not receiving prednisone. The patient who died while on treatment with prednisone, in the third 3-month period, was well a few hours before death and suddenly had a massive haemoptysis. At post-mortem she was found to have suffered a mechanical rupture of the left pulmonary vein, which was smooth and clean, showing no sign of active tuberculous infiltration, but was passing unsupported across the large cavity which occupied the upper 2/3rds of her left lung. At this, and the other autopsy done, a striking feature was the normal healthy appearance of the myocardium, and the absence of active tuberculous foci in the lungs. (Consent for an autopsy was not obtained in the 3rd case in which the patient died.)

Discharges

Two patients were discharged against medical advice; one of them was doing extremely well, and the other was in poor condition. The third patient discharged is being treated as an out-patient with INH only and is doing very well.

General Condition

As in the preliminary report,¹ patients receiving prednisone exhibited striking improvement in mood, sleep and appetite. During the second 3-month period (while not receiving prednisone) there was a general tendency toward deterioration of general condition at the end of the 3rd month. This, however, was not sudden or alarming and there was still a great improvement as compared with the condition before treatment with prednisone was begun.

Weight Gains

Although a certain proportion of the increase in weight was undoubtedly due to sodium and water retention, it was felt that the general beneficial effect of this hormone and the suppression of the disease were inductive of a healthy increase in weight. Prednisone exerts a catabolic or anti-anabolic effect in protein metabolism, thereby suppressing the synthesis of protein, but to what extent this affects normal tissue is not known. It certainly is most advisable to make extra-readily assimilable protein available to patients on prednisone therapy. During these trials 'Davein' (protein hydrolysate

with vitamin B-complex) has been given, and it was observed that, on high dosage of corticosteroids 'moon face' became more marked when the Davein was withheld and was largely reversed when it was given again.

Haemoptysis

An unexpected observation was the marked diminution in the incidence of haemoptysis. Small doses of prednisone in combination with vitamins C and K and antibiotics have, in fact, been successfully used in other cases of bleeding. It is suggested that this is due to reduction in capillary fragility and inflammation.

Carbohydrate Metabolism

All patients exhibited mild glycosuria after 10-14 days on 30 mg. of prednisone. One patient suddenly (within 24 hours) developed symptoms and signs of hyperglycaemia (fasting blood-sugar 428 mg. %). The blood-sugar curve was typical of diabetes mellitus. The patient suffered a violent reaction to only 10 units of soluble insulin, given as a test dose. Prednisone was stopped, and after 19 days the sugar content of blood and urine was normal. Prednisone was then renewed (15 mg. daily) without further untoward effects.

Hirsutism

One patient on 30 mg. of prednisone developed mild hirsutism, which has not disappeared 1 month after cessation of prednisone treatment.

Dosage

It will be noticed that a daily dosage of 30 mg. of prednisone produced more side-effects but no proportional clinical or radiological improvement. The optimum dosage for the average adult appears to be 15 mg. daily.

SUMMARY AND CONCLUSION

A 9 month's trial is described of the use of prednisone in combination with isonicotinic acid hydrazide in the treatment of a series of 23 patients (Bantu females) with advanced bilateral progressive cavitory pulmonary tuberculosis of poor prognosis.

The probable mode of action, dosage and side-effects are discussed.

Bearing in mind that these patients were all suffering from very advanced pulmonary tuberculosis it can be stated that:

1. Prednisone may safely be given to tuberculous patients with beneficial effect, provided that the tuberculous disease as well as secondary infections are adequately controlled by antibiotic therapy and chemotherapy.

2. Prednisone appears to speed up initial response to INH therapy in non-selected cases of pulmonary tuberculosis, and to be more efficacious than potassium iodide for this purpose.

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1. Handley, A. E. (1956): S. Afr. Med. J., 30, 605.