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PREDNISOLONE IN THE TREATMENT OF BRONCHIAL ASTHMA

By

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The present observations on the treatment of bronchial asthma with Prednisolone were made during a period of one year. They concern two types of cases; patients suffering from status asthmaticus of acute onset, who were treated for periods of 10 to 15 days, either on one or several occasions, and patients with chronic forms of status asthmaticus who were treated continuously for periods of three to six months.

This report also contains the results of investigations designed to detect the effects of Prednisolone therapy on the metabolism of carbohydrates, water and electrolytes. Some of the results of our investigation have already been published (5-6): the present is the completion and extension of the work.

CLINICAL INVESTIGATIONS

Material and methods.

80 patients were studied. Some of these were out-patients, and some were in-patients of the Clinica Medica of Bologna. Their ages ranged from 10 to 60 years. The majority were between 30 and 40 years of age.

All the cases presented in severe status asthmaticus of

bronchial origin. That is, they had the typical clinical picture of severe bronchospasm and cough, together with a typical history of bronchial asthma. Cases of chronic bronchitis or left heart failure in which there was an element of bronchospasm were not included. The patients had all been under observation for varying periods of time. It was therefore possible to divide them into two groups, acute and chronic, according to whether their presenting symptoms had developed during the previous day or two, or had been present continuously for weeks or months.

Some of the patients had already been treated with ACTH or Cortisone, but none with Prednisolone. In all cases routine antiasthmatic measures including bronchodilator drugs and specific desensitization had given poor results.

All of the 80 patients in the present series were treated with Prednisolone alone. In the 60 acute cases the Prednisolone alone treatment lasted 10 days with doses of 30 mg. pro die for the first two days, then 20 mg. pro die for three days, 15 mg. pro die for two days, then 10 to 15 mg. pro die as maintenance dosage. In 15 of these patients this schedule was repeated 3 to 7 times at intervals.

In the group of 20 chronic cases the symptoms were sufficiently severe to warrant continuous maintenance treatment. An initial dosage of 20 to 30 mg. pro die was given until marked clinical improvement was attained, then progressively lower doses were tried to ascertain the lowest dosage (found to vary between 5 and 15 mg. per day) capable of maintaining the improvement.

The subjective and objective symptoms of the patients of the first (acute) group were noted each day, with particular attention to the respiratory system. Urine out-put, body weight, blood pressure and vital capacity were measured daily. In addition the "apnoea time"—*that is, the time for which the patient could maintain voluntary apnoea*—, was measured daily. The same observations were made on the patients in the second (chronic) group, when the treatment was started and repeated at intervals of 10 to 15 days.

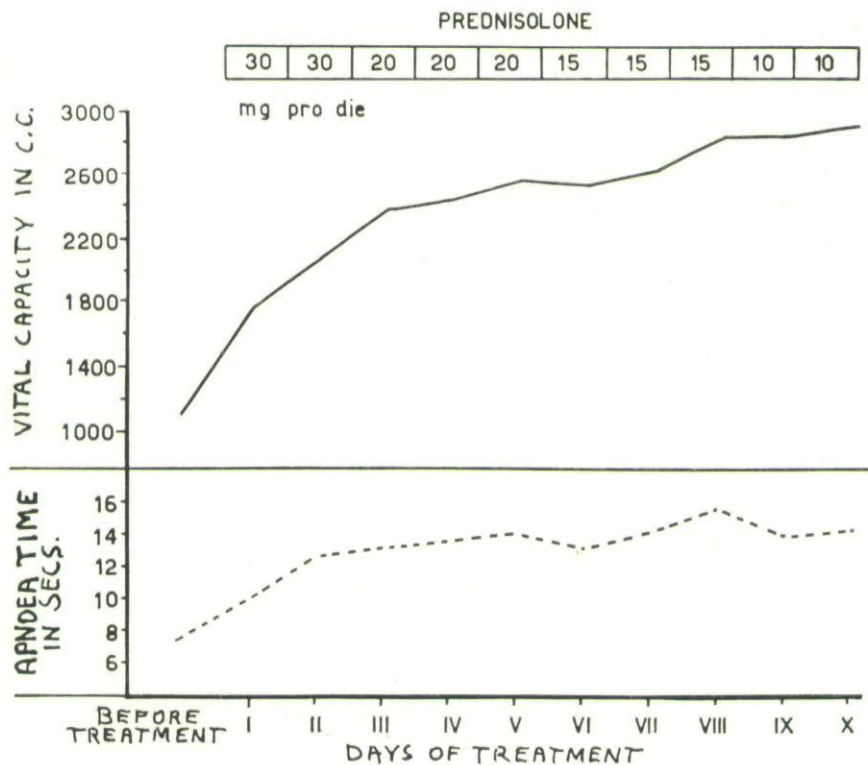


Fig. 1.

Vital capacity and Apnoea time during Prednisolone treatment.

RESULTS

Acute group: 80 % of the patients noted slight subjective improvement after only 12 hours from start of therapy; little or no objective improvement was noted at this time. The first sign of objective improvement appeared between 24 and 48 hours from the start of the therapy, and this response reached its maximum 3 or 4 days from the start. The improvement was assessed by clinical examination and by measuring the vital capacity and apnoea time. The mean of our results is shown in Fig. 1.

In 55 of the 60 cases a complete remission of the status

asthmaticus was observed within 4 days and was maintained for the period of the treatment. These patients reacted variably to the interruption of the therapy: in some asthma reappeared after three to ten days, in others it reappeared only after 30 to 60 days. A few patients had remissions lasting even longer, up to ten months.

The treatment succeeded in interrupting the current attack but did not appear to influence the ultimate course of the disease. In 30 patients the therapeutic cycle was repeated and no sign of intolerance were noted. In the remaining 5 cases therapy had to be interrupted between the third and the fifth day, because in three cases the patients complained of intense headache, agitation and insomnia, and in two cases gastralgia and profuse sweating occurred.

The doses of Prednisolone employed are summarized in Table 1.

TABLE 1

No. of cases	Days 1-2	Days 3-4-5	Days 6 to 10
19	30 mg	20 mg	10 mg
41	30 mg	20 mg	15 mg
Total 60			

Chronic group: in 20 patients with chronic status asthmaticus, once having ascertained the minimum therapeutic maintenance dosage (2.5 to 15 mg. pro die), this dosage was continued for periods from 4 to 6 months in each case. During this period these patients enjoyed a state of health which permitted them to work in moderation. In each patient the dosage was maintained constant, because every attempt to decrease it, caused a reappearance of the asthmatic symptoms, with an intensity inversely proportional to the amount of Prednisolone used. The doses of Prednisolone employed are summarised in Table 2.

During the treatment of these chronic cases, the tolerance of these patients to Prednisolone was generally good; in

2 patients, however, mild peripheral oedema was noted and the fleshy parts of the face acquired a slightly pasty consistency. These side-effects were of a mild nature and disappeared a few days after the treatment was suspended.

TABLE 2

No. of cases	Initial days 1-2	Doses days 3-4-5	Maintenance dose	Period of treatment days
5	30 mg/day	20 mg/day	10 mg/day	150
10	30 "	20 "	10 "	180
4	30 "	20 "	7.5 "	120
1	30 "	20 "	2.5 "	180
Total				
20				

CONCLUSIONS

From the above results the following conclusions were drawn:

a) Prednisolone was given in acute asthma in an initial dosage of 30 mg. pro die for two days; over the following week this was gradually reduced to a maintenance dosage which varied from 20 to 15 mg. pro die. This treatment proved effective in 55 patients out of 60, eliminating asthmatic symptoms generally between the 3rd and the 4th day of treatment.

b) In these cases in which treatment was repeated (3 to 7 times), after periods of rest which varied from 5 to 30 days, no appreciable change in sensitivity to the compound occurred, and in particular no tachyphylaxis was observed.

c) In treating chronic cases, we were able to determine the minimum dosage of hormone necessary to obtain a therapeutic effect. This minimum dosage:

- 1) varies from patient to patient.
- 2) remains constant for an individual patient.
- 3) permitted out patients to perform a moderate amount of work.

In our opinion this minimum dosage of Prednisolone represents replacement of a hormone which these patients lack and which is necessary to prevent the appearance of hypersensitization phenomena. We consider that this dosage of Prednisolone exercises a physiological function of which the organism is no longer capable.

METABOLIC INVESTIGATIONS

Some observations were made on carbohydrate, water and electrolyte metabolism in patients treated with Prednisolone in doses of 30 mg. pro die the first two days, 20 mg. pro die the following three days and 15 mg. pro die the following three days.

CARBOHYDRATE METABOLISM

Material and Methods. In 20 patients whose carbohydrate metabolism was previously ascertained to be normal, the Himsworth test (glucose and insulin) was performed before and after 8 days of Prednisolone treatment. The Himsworth test was performed according to the author's original paper (2). In certain patients whose periods of treatment with Prednisolone were considerably longer, this test was repeated at regular intervals over a period of 30 to 60 days.

RESULTS

a) After treatment, the fasting blood sugar level increased in 11 cases, remained unchanged in 6, decreased in 3; the mean values varied from 0.85 % to 0.92 gm. %. No pathological changes were observed.

b) The insulin sensitivity, as expressed by the curve of Himsworth test, increased in 13 cases, did not vary in 5 cases and decreased in 2 cases. In Fig. 2 we have represented the averages of the individual values and in Fig. 3 the behaviour of all the curves as a whole.

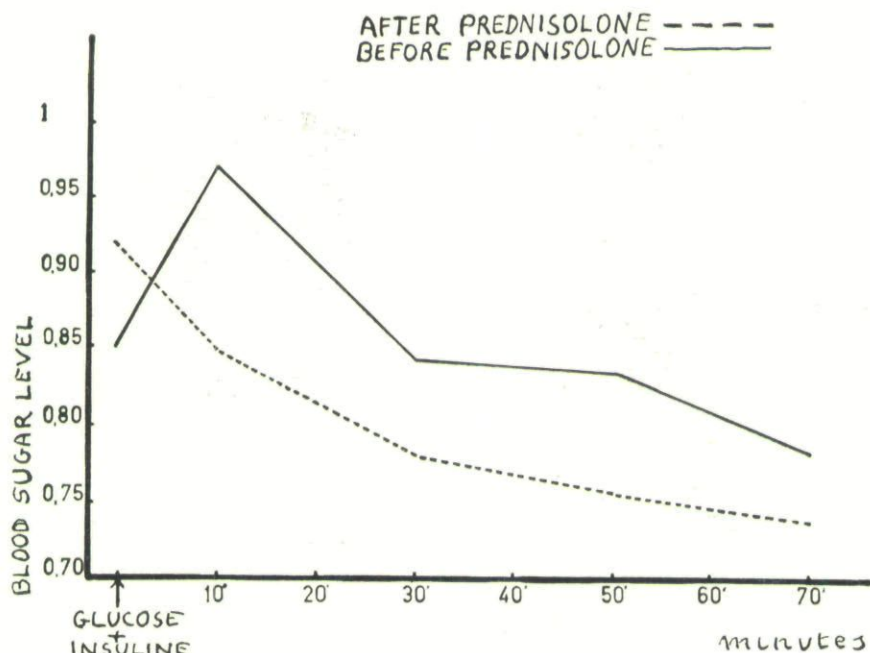


Fig. 2.

Himsworth test before and after Prednisolone treatment.

c) In 10 of the 11 cases in which the fasting blood sugar level rose, an increased insulin sensitivity was also observed.

d) In some patients observations were repeated every 8 days for a period of one or two months and these results did not modify the preceding data.

COMMENT

From the above it seems evident that Prednisolone modifies the carbohydrate metabolism very little when given in therapeutic doses. The fasting blood sugar value was slightly raised and this fact is worthy of note because it was observed in most cases. The increase in insulin sensitivity was more marked, indicating increased glycogen storage (1). We believe that these phenomena and the metabolic phenomena of cortisone have the same explanation: the hyperglycemia is probably

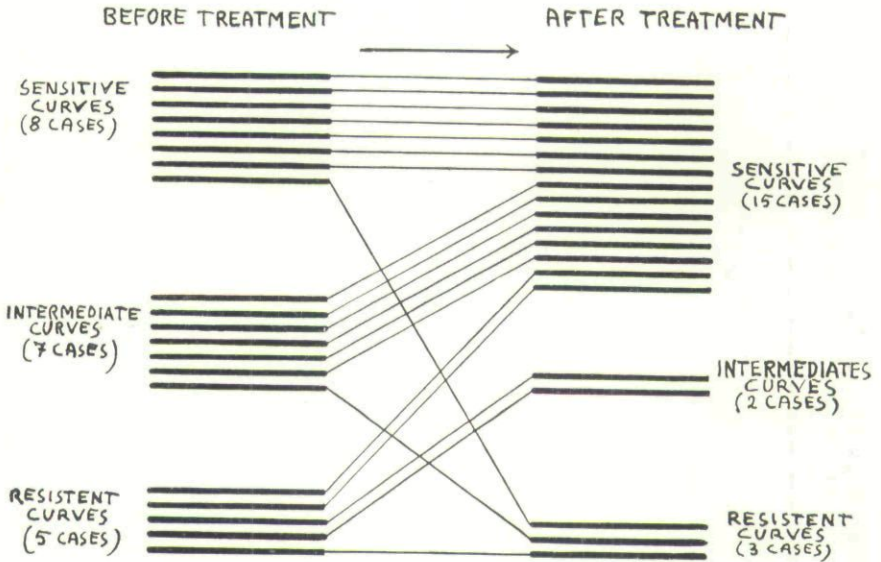


Fig. 3.

Insulin sensitivity, according to Himsworth test, before and after Prednisolone treatment.

caused by inhibition of carbohydrate oxidation, by glyconeogenesis from protein, and by an increased intestinal carbohydrate absorption. The small extent of the variations observed was probably due to the small dosages of Prednisolone used. The increased sensitivity toward insulin, as evidenced by comparison of the average curves of the Himsworth test, is caused by the adrenocortical hormones which stimulates glycogenesis (1).

Generally speaking, Prednisolone produces hyperglycemia, thereby being hyperglycemic or anti-insulinic. On the liver, however, it has a similar action to insulin, increasing glycogen deposition. Its action therefore results in a general increase in carbohydrate metabolism.

A quantitative comparison of the effects of Cortisone and Prednisolone on carbohydrate metabolism cannot be made on the present results. However, Prednisolone can be used in much lower dosage than Cortisone and carbohydrate meta-

bolism is much less affected by this therapy than it is by Cortisone therapy.

METABOLISM OF WATER AND SALTS

Material and Methods. 30 patients who received an 8-days course of Prednisolone therapy were studied. In this period a free diet was permitted. Urine output was measured daily. Before and after the 8-days treatment the following were estimated:

1) serum sodium by Müller's method (4), 2) serum potassium as described by Kramer and Tisdal (3), 3) total body extra-cellular water (by determination of the sodium-thiocyanate diffusion space), 4) renal plasma flow, 5) glomerular filtration rate, 6) tubular reabsorption and excretion (by the clearance of sodium thiosulfate and paraminohippuric acid).

RESULTS

Urine output. This was measured daily for 15 to 20 days in 25 patients. The average output showed a slight but constant increase during the first 3 or 4 days of treatment, but

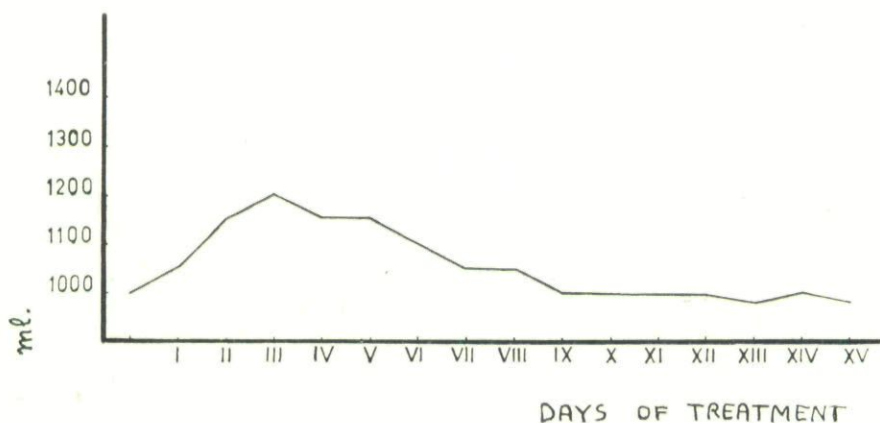


Fig. 4.

Urine output (ml) in 24 h. during Prednisolone treatment.

returned to the original values on the 7th or 8th day. In no case was a decrease of urine output observed. The arithmetic means of the daily values are shown in Fig. 4.

EXTRA CELLULAR H_2O BLOOD Na, K

Values were determined before and after the 8-days treatment in 10 patients and showed no significant variations either of individual or of average values.

Renal function. In 6 patients these tests were performed before starting treatment and on the 3rd and 8th day of treatment. On the 3rd day both tubular reabsorption and glomerular filtration increased, particularly the latter, accounting for the slight increase in urine output observed. On the 8th day a slight decrease in glomerular filtration had balanced the two factors again (both remaining above normal) and the urine output returned to its original value. Renal plasma flow increased slightly in 2 cases. The maximum tubular excretion capacity did not vary to a degree worthy of note.

COMMENT

From the above it is obvious that the metabolism of water and salts was not significantly altered after 8 days of Prednisolone treatment at therapeutic doses. The equilibrium of this metabolism was altered to a slight degree, however, as evidenced by the slight increase of diuresis during the first day of treatment.

Renal function tests showed that this compound produces alterations similar to those of Cortisone. The initial increase of tubular reabsorption occurring with Prednisolone is accompanied by an increase in glomerular filtration. The dual nature of the response avoids an antidiuretic phase, but the fact that the changes in filtration rate, which may be compensatory, are greater than those in tubular reabsorption, leads to a diuresis on the 3rd or 4th day. The initial sodium and water retention caused by Cortisone can only be explained by a more

powerful action of Cortisone, at therapeutic doses, on the tubules, than that of Prednisolone at therapeutic doses. This action of Cortisone is so much stronger that it can be compensated only later by an increased glomerular filtration on the 5th or 6th day. We wish to emphasize that the above compensation requires normally functioning glomeruli and vessels, and might be impossible in a pathological kidney. It may be concluded from the above that Prednisolone influences the metabolism of water and salts through an action on kidney function qualitatively similar to that exercised by Cortisone, but much less in intensity at the considerably smaller dosage required therapeutically. We have not attempted to evaluate quantitatively the difference in action of the two compounds. Prednisolone used in therapeutic doses, does not significantly disturb the equilibrium of water and electrolyte metabolism so long as the organs which regulate this metabolism are intact.

SUMMARY

Prednisolone was given to 60 patients suffering from acute asthma, in an initial dosage of 30 mg. pro die, which was gradually decreased to 15 mg. pro die. In 55 of the patients a complete remission of the status asthmaticus was observed within 4 days.

In the group of the 20 chronic cases an initial dosage of 20 to 30 mg. pro die was given until marked improvement was attained; then progressively lower dosages were given to the minimum capable of maintaining the improvement (from 2.5 to 15 mg. pro die.).

The Himsworth test was performed before and after 8 days of Prednisolone treatment in 20 patients. The fasting blood sugar level was slightly increased, the insulin sensitivity was more marked indicating increased glycogen storage.

30 patients were studied after 8 days of Prednisolone therapy. In 15 of them the urine output showed a slight but constant increase during the first 3 or 4 days, then returned to original value on the 7th or 8th day.

The extracellular water, the blood Na and K measured in 10 patients showed no significant variation.

In 6 patients renal function was tested before the Prednisolone treatment and on the 3rd and 8th day. On the 3rd day tubular reabsorption and glomerular filtration increased; on the 8th the glomerular filtration decreased slightly, but remained above normal. Renal plasma flow increased slightly in 2 cases. The maximum tubular excretion capacity did not vary.

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