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The Toxicity of cortisone

Byron Peterson
University of Nebraska Medical Center

THE TOXICITY OF CORTISONE

by

Byron Peterson
University of Nebraska College of Medicine

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FOREWORD

This thesis does not represent a complete review of the world literature on the toxicity of Cortisone. It does represent a review of the available American literature and some foreign articles to which English translations are available.

In many instances in the present literature, the authors have arrived at a certain conclusion when using A.C.T.H. and attributed the same results to Cortisone without actually testing Cortisone in the same project. Also in many case reports, the patient had been receiving both A.C.T.H. and Cortisone.

These two types of references have not been used in the bibliography for this thesis.

Tuberculosis was among one of the first diseases in which the use of Cortisone was found to be dangerous. C. G. Popp, et al[65] report the case of a sixty-four year old white female who had been released from a tuberculosis sanitorium as a case of arrested tuberculosis. She was then treated with a dose of 800 mgm Cortisone the first day, 200 mgm the second, and 500 mgm the third, and then 200 mgm for a total of 4000 mgm. The patient became febrile and very toxic. A chest X-ray at this time revealed a far-advanced bilateral tuberculosis.

E. Q. King, et al[66] report a similar case in a thirty-nine year old white female. The patient received numerous pre-treatment diagnostic roentgenograms which revealed nothing. After receiving 100 mgm Cortisone daily for several months, the patient developed an acute fulminating tuberculosis and died.

Leo Fred, et al[66] report the same type of case in a fifty-eight year old white male in whom sputum exams revealed nothing. The patient was placed on Cortisone therapy and then developed a cough and hemaptysis. Sputum was then found to be positive for tubercle bacilli.

Eugene F. Traut, Jerome Ellman[67] report a case of tuberculosis in a thirty-seven year old colored lady in whom previous roentgen examinations had revealed nothing. R. F. Kleinschmidt, and J. Johnston[46] report a similar case.

A. A. Doerner, et al[18] report the case of a fourty-four year old white female with an old tubercle lesion. After receiving 100 mgm of Cortisone for one and one-half months, the patient developed a tuberculous meningitis and died.

Spain, D. M. and Malomut, N.[72] report an experiment in which a group of guinea pigs were inoculated with tubercle bacilli. A portion of the group was given Cortisone. This portion was made worse as evidenced by mortality and distribution of lesions at autopsy.

C. LeMaistre, Ralph Tompsett[56] report a similar experience in an experiment with guinea pigs.

Duodenal ulcers are a second disease which it was soon found are affected adversely by Cortisone.

R. I. Lubin, et al[38] reports two cases, both in females and both receiving over 200 mgm of Cortisone daily in which duodenal ulcer perforation following 100 mgm of Cortisone daily.

Other cases of perforated duodenal ulcers are reported by Thornton H. Davis and M. Zeller[71]; J. C. Beck, et al; D. V. Habif, et al.[50]

D. J. Ingle, et al[20] conducted á study on the affect of Cortisone on the anatomy and physiology of rats. Among other findings, twenty-one of the rats receiving Cortisone developed duodenal ulcers, while none of the rats in the control group exhibited them.

S. J. Gray, J. A. Benson, R. W. Reifenstein, and H. M. Spero[6] conducted a controlled study on humans. One hundred to one hundred-sixty milligrams of Cortisone per day were administered intra-muscularly to the following patients:

Six patients with normal stomachs

One patient with a duodenal ulcer

One patient with a healed duodenal ulcer

After the evening meal a Levine tube was inserted and

continous twelve hour aspiration was instituted. Diet, etc. was kept as uniformly constant as possible.

They reported a rise in the gastric secretion of hydrochloric acid in all patients varying from 100%-300% with a mean increase of 208%. The rise varied from patient to patient. In some patients the increase appeared in seven days, in others not until twenty-one days.

Along with this study, these authors report four case histories of duodenal ulcers following Cortisone, two of which succumbed to gastric hemorrhage.

Soon after Cortisone was produced in amounts large enough to be used widely, it was noticed that Cortisone intensified the severity of Diabetes Mellitus in patients with that disease. Boland and Headley report such a case in 1949. Other cases are reported by S. S. Fajans, et al,[32] William Geller, et al,[47] J. Brown, et al.[51]

E. H. Kass, et al[15] report the case of a patient with glycosuria but a low blood sugar level. They expressed the belief that Cortisone lowered the renal threshold in some instances. J. Conn, E. Louis, B. Wheeler[7] [21] report a similar case and expressed the same conclusion.

Randall G. Sprague,[22] Selvan Davison,[35] both individually report cases of patients with glycosuria and hyperglycemia.

C. Long, et al[33] in a study on rats found that the glycosuria of partially depancreatized rats became worse under Cortisone. Kobernick and More[30] observed the development of a diabetic state associated with lipemia and hydropic changes in the islet cells of rabbits after receiving twenty mgm of Cortisone daily. D. J. Ingle

produced diabetes in rats spontaneously by feeding them five to ten mgm of Cortisone daily. In another study conducted in 1951 the same author[20] noted that in rats fed on high fat diet, few developed glycosuria. Kinsell, et al,[37] in reporting two cases of Cushingoid syndrones, noticed that when his patients were fed a mixed diet the Cushingoid manifestation appeared. When the same patients were fed a high fat, high protein, low carbohydrate diet, the Cushingoid manifestions regressed.

D. J. Ingle[20] observed that the rats on high fat diets developed lipemias that resulted in clouding of the corneas. D. Adlersberg, L. Schufer, and S. Drachman[25] carried out an extensive study in regards to hypercholesterolemia in long term Cortisone therapy. They found that in patients who had recieved Cortisone for a long period of tiem, 88% developed hypercholesterolemia while in s horter courses only 26% developed it. B. L. Baker, et al[7] in reporting a study of the effect of Cortisone on liver structure, state that it is responsible for an increased amount of fat in the liver. H. Steinberg, et al[43] report the case of a fourteen year old white male receiving Cortisone for rheumatic fever over a period of fourty-three days. On admission to the hospital, the patient had no hepatomegaly. During the course of hospitalization he developed an hepatomegaly which extended below the umbilicus. It regressed to a non-palpable position within thirteen days after stopping Cortisone. Punch biopsies during the time of enlargment revealed large intracytoplasmic fat droplets.

Along with the changes in carbolydrate and fat metabolism produced by Cortisone there is also a change in nitrogen metabolism. D. J. Ingle[20] noted that all of the rats given Cortisone in his study developed a negative nitrogen balance. Thorn, et al[19]

observed a 58% increase in urinary nitrogen excretion in a patient of theirs. J. Conn, E. Louis, and B. Wheeler[21] noticed an increase in urinary nitrogen in three cases of normal adults receiving Cortisone. O. H. Pearson[54] studied six patients with lymphomatous tumors. All exhibited negative nitrogen balances during Cortisone therapy. Sidney H. Ingbar, et al[9] found an increased filtration of uric acid in four normal patients receiving Cortisone. F. L. Engel[11] believed, as a result of his experiments, that the formation of uric acid was decreased in rats by this drug.

L. W. Kinsell, et al[37] observed in studies on fourteen patients that if sodium intake was limited, edema did not develop. Other authors have also observed sodium retention as a result of Cortisone.[3, 22, 53, 9, 35, 54, 36.]

L. P. Eliel, et al[10] found a marked depression of muscle potassium. Selvan Davison[35] observed muscle weakness in his patients. An increased excretion of potassium was reported by Davison as well as others individually.[9, 10, 22, 31, 54, 36.]

J. L. Baake[3] believes that Cortisone is an antagonist to other physiological hormones. As proof, he cites the loss of libido, amenorrhea, etc. observed in patients. M. F. Costello,[36] in his study on sixty patients receiving Cortisone, cites the loss of libido as one of the major enitities. Cases of Cushings syndrome which regressed after treatment with Cortisone was interrupted are reported by J. Dean Robinson[69]; Kinsell, et al.[37]

C. W. Thorn, et al[19] found that long continued Cortisone depressed the activity of the thyroid gland as evidenced by ioding uptake. Eugene F. Traut[67] reports a slowed iodine uptake and the development of a thyroiditis in a patient receiving 100 mgm of Cortisone daily. Cases of hirsuitism developing while receiving Cortisone therapy have been cited by J. L. Baake,[3] M. F. Costello,[36]

and Henry G. Kupperman and Harry Bortfeld.[62] D. J. Ingle[20] observed that all of the rats receiving Cortisone had a higher incidence of infection than did the controls. William A. Antopal[14] gave Cortisone to mice and found they would not gain but lost body fat while the controls were gaining on the same diet. He also gave Cortisone to one group of mice, then subjected them to wet and cold enviroments. All of this group died while mice not receiving Cortisone exposed to the same conditions survived. George H. Schen[17] found that high temperature increased the toxicity of Cortisone in mice.

It has been noted by several investigators that Cortisone had an inhibitory effect onthe healing of wounds, fractures and lacerations.

D. M. Spain, et al[18] experimented on fourty mice. They induced experimental wounds and studied the time required for healing in mice receiving Cortisone as compared with those which did not receive Cortisone. They concluded that Cortisone depressed the rate and ability of healing. However, they found no evidence of lysis on existing tissue. They also injected carbon particles into the peritoneal cavity of a control group and a group receiving Cortisone. They then studied phagocytes from intraperitoneal smears. They found that the phagocytes from the mice receiving Cortisone did not contain as much carbon as those from mice not receiving Cortisone. Charles Ragan, et al[29] repeated the same type of experiment in rabbits. Other authors[13] showed the same result in experimental ocular lesions. Other experiments with the same results were reported by B. L. Baker, and W. L. Whitaker,[7] A. Rubin, et al[42] and M. F. Costello.[36]

R. S. Spiers[57] noted an eosinophilopemia in mice following Cortisone. The same result has been reported by G. W. Thorn,[19] and J. L. Baake.

C. G. Fraser, et al,[44] believe that doses of Cortisone exceeding 25 mgm/day with normal adrenals can cause adrenal insufficiency. They report a fatal case of insufficiency following 100 mgm/day. D. J. Ingle, and Mason,[34] D. J. Ingle, and E. C. Kendall[28] performed experiments on rats and found that Cortisone caused a decrease in size of rat adrenals and that the amount of decrease in size was directly related to the time and size of dose of Cortisone. Other instances of adrenal insufficiency following Cortisone therapy in patients have been reported by J. L. Baake,[3] and M. J. Costello.[36]

H. Heilman, and Kendall,[55] J. Higgins, R. Woods and Benton,[49] each group in separate experiments, found that Cortisone inhibited the growth of mouse lymphosarcomas and rhabdomyosarcomas. However, it was found that growth started again as soon as Cortisone was stopped and that after long continued therapy, the tumors became refractory to treatment and progressed. O. H. Pearson, et al[54] selected six patients with lymphomatous tumors. They found that Cortisone depressed the activity of lymphomatous tumors, Hodgkins, lymphatic leukemia, etc. as judged by the disappearence of enlarged lymph nodes, lowering of fever, etc. However, all but two regressed after treatment was discontinued.

David Grob, et al[40] report eight cases of myasthenia gravis treated with Cortisone. Cortisone caused the patients to relapse to the point where they would not respond to neostigmine. These authors also report the onset of one case of myasthenia gravis in a woman, sixty-five, while receiving 100 mgm/d for one month and 50 mgm/d for one month.

Other isolated cases of Herpes Zoster,[61,60] urticaria,[34] malignant hypertension,[70,45] and thromboembolism,[48] have been reported and attributed to Cortisone.

Hans Selye[23] reports an experiment in which he did a unilateral nephrectomy on rats and fed them high salt diets. Post-mortem exams revealed inflammatory vascular lesions and edema in the brain. C. W. Caster,[12] et al gave normal rats Cortisone and on post-mortem found widespread chromatalysis and vacuolation throughout the thalamus.

There have been a great number of different types of mental disturbances attributed to Cortisone. These changes include insomnia, depression, euphoria, pessimism, tremors, drowsiness, convulsions, paresthesias, intellectual depression, psychosis, apprehensiveness,&suicidal intention.[1,2,3,4,5.]

J. L. Baake,[3] in reviewing cases of Cortisone toxicity, found that euphoria occured in approximately 9%-38% of patients and depression in 35% of the patients receiving Cortisone.

SUMMARY:

It has been shown that the administration of Cortisone to a person with tuberculosis or a history of tuberculosis is very dangerous, in that the drug may reactivate the infection.

Several cases of perforated gastric ulcers, after or during Cortisone treatment, have been cited, along with a careful study by S. J. Gray, et al[6] in which they showed that the gastric acidity and pepsin content were greatly increased by Cortisone.

It has been shown also that Cortisone is an insulin antagonist and that diabetic patients require an increased amount of insulin while receiving Cortisone. Also cases have been reported in which

Cortisone induced a temporary diabetes mellitus which disappeared after cessation of therapy. There is some evidence that a high fat, high protein, low carbohydrate diet, may oppose the development of a diabetic state. It was found, however, that on high fat diets all patients had high blood fat contents. One group observed that in patients receiving Cortisone, over a long period of time on mixed diets, 88% developed hypercholesteralemia, and on shorter periods fewer developed hypercholesteralemia.

It has been shown by one group of investigators that Cortisone may cause a deposit of intracytoplasmic fat in the liver cells. This is believed to account for the hepatomegaly which sometimes occurs during Cortisone therapy.

Several groups have reported negative nitrogen balances during Cortisone therapy, as well as sodium retention with edema. Other observers have reported muscle weakness and an increased potassium excretion while receiving Cortisone.

Many groups have reported a loss of libido, amenorrhea, Cushingoid Syndromes, development of diabetic states, decreased iodine uptake, and hirsuitism as evidence that Cortisone is an antagonist to the physiological hormone balance.

Other investigators have concluded, as a result of their observations, that the ability to gain weight and the general body resistance is decreased by Cortisone. It has been shown, as a result of experiments, that Cortisone decrease the ability of the body to mend fractures and lacerations.

A few cases of eosinophilopemia have been reported. Many cases of adrenal insufficiency have been reported as a result of long term Cortisone administration. One group showed that in

rats, the degree of insufficiency was directly related to the size of the dose and the length of time that it was administered.

Cortisone also depresses the activity of lymphomatous tumors, Hodgkins disease, and lymphatic leukemia as judged by the disappearence of enlarged lymph nodes, fever, and signs of mediastinal compression. However, these diseases soon become refractory to the drug and regress.

Cortisone will cause myasthenia gravis to become refractory to treatment.

Cortisone has been blamed for a great many mental disturbances; most serious of which are psychoses, depressions with suicidal intentions, and convulsions. Other mental changes attributed to Cortisone are euphoria, insomnia, pessimism, tremors, and apprehensiveness.

CONCLUSIONS:

1. Cortisone is contraindicated in patients with active tuberculosis or in cases of arrested tuberculosis.
2. Cortisone is contraindicated in patients with duodenal ulcers or a history of duodenal ulcers.
3. Cortisone is contraindicated in patients who show signs of mental disturbance.
4. Cortisone should be used with caution in diabetic patients. The patient should be warned that it will increase his insulin requirement.
5. The Sodium intake must be limited during therapy with Cortisone.

6. Patients receiving Cortisone must receive high protein diets to compensate for the negative Nitrogen balance.
7. The Potassium in the diet must be supplemented because of the increased excretion of Potassium during the therapy.
8. Cortisone should be used with caution in patients in which an increase in body fluids would be dangerous such as cardiac decompensation, brain concussion, etc.
9. During and after the use of Cortisone, signs of adrenal insufficiency should be watched for. Dosages of Cortisone should be reduced gradually to allow the adrenal glands to assume an increasing role in supplying Cortisone to the body.
10. Elective surgery should not be done until fourteen days after the patients last dose of Cortisone. If emergency surgery is necessary, a large dose of Cortisone should be given before surgery and the patient should be watched carefully for shock as a result of adrenal insufficiency.
11. Cortisone is contraindicated in patients with fractures, serious lacerations, ulcerations, and serious infections.
12. The dosage of Cortisone should be decreased or stopped in patients showing manifestations of hormonal imbalance.
13. Cortisone should be used with caution in patients in cachetic states.
14. Cortisone is contraindicated in patients with myasthenia gravis.

15. When hepatomegaly develops during Cortisone therapy, fatty infiltration of the liver must be considered in the differential diagnosis.

16. If glycosuria develops during Cortisone therapy, a lowered renal threshold must be considered as well as the onset of diabetes mellitus.

17. In patients showing Cushingoid manifestations during short term Cortisone therapy, it would be worthwhile to feed them high protein, high fat, and low carbohydrate diets.

18. The use of Cortisone in conjunction with other therapy should be further investigated in the treatment of lymphomatous tumors.

19. In patients on whom long term Cortisone therapy was anticipated, the effect of hypercholesterolemia should be weighed against any benefits to be derived.

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