LOG NO. 9

CORTROPHIN ZINC
References


CORTROPHIN® ZINC
Stiefel Certification Zinc Hydrolysate Suspension S.S.F.

COMPOSITION - An aqueous suspension of purified corticotropin (ACTH) with zinc hydrolysate for therapeutic action. It is available in two strengths: 40 USP units of ACTH per cc, 110 mg of zinc per cc, which preserves therapeutic ACTH activity for a period of from one to three days, depending upon individual patient requirements, and 20 USP units of corticotropin per cc, 110 mg of zinc content per cc, which provides therapeutic ACTH activity for a period of from one to two days, depending upon individual patient requirements. Each strength contains 1.0% ethanol (preservative) and sodium metabisulfite with NaCl adjusted with HCl and NaOH. This is a fine suspension which floes readily through a 20-38 gauge hypodermic needle. It should be given (subcutaneously) to avoid any possible local reaction.

PROPERTIES: This product exerts primarily corticotropin in a form which provides sustained action of the hormone, causing the adrenal cortex to release its adrenal steroids in physiological proportions over a longer period of time than would be the case with corticotropin in larger amounts in other forms. This period of activity ranges from 7 to 14 days depending upon the patient's requirements and upon the strength administered. The response is conditioned by the functional integrity of the adrenal cortex, a highly active gland would respond dramatically, while an inactive adrenal cortex would respond less, particularly at first. This response helps to compensate for defects or deficiencies of corticosteroids and other hormones vital for the successful maintenance of body functions. The production of compressed fluid hormones is clinically the most significant, for if it is the aspect of therapy that promotes clinical responses to so many diseases, and which enables the tissues and the body as a whole to meet serious stress.

Adequate therapy usually produces the following desirable general changes: Temperature, if elevated, usually returns to normal within 6 to 18 hours. Pain is abolished within a short time and becomes an index of the reversibility of the disease under treatment. Fatigue develops a sense of well-being and of normal activity, bordering on euphoria. Fibrogenic proliferation and inflammatory processes are blocked.

Test of Adrenocortical Activity: One of the requisites to successful corticosteroid therapy is functioning adrenal cortex. The functional capacity of the adrenal cortex causes clinical responses. A reduction in the number of circulating corticosteroids is considered to reflect increased secretion of adrenal steroids and indicates a possible relation to corticosteroids. Normal subjects respond to an adequate dose with at least 50 per cent fall in circulating corticosteroids. The test known as the Zonks test is applied in the diagnosis of Addison's disease, as a test of adrenal reserve pre-and post-operatively, to determine the patient's ability to react to stress.
In rheumatoid arthritis, dosage in general has been 40 to 60 units per day until control is achieved, then reduced to 20 to 40 units every other day to maintenance. If it has been possible in some cases to reduce the dosage even further.

In drug sensitivity, dosage has been 20 to 40 units per day until symptoms are controlled. This dosage has also been employed in the treatment of gouty arthritis.

In acute lupus erythematosus, dosage has averaged 40 to 60 units or more per day to gain control of the symptoms with antifebrile treatment possible in some cases with 30 units every other day. However, any of these patients have relatively high dosage requirements, even during maintenance treatment, and in these cases the maximum dosage seems to be particularly helpful in satisfactory control of the disease.

In anticonvulsant therapy, including status epilepticus, 60 units a day were required for control, and 40 units twice a week is some instances provided successful maintenance.

In psychostimulants and psychomotor disorders, the initial dosage prescribed is 40 units per day, maintenance may be achieved with 40 units twice a week.

In pulmonary emphysema, initial dosage has been 40 units per day, reduced to 20 units per day or every other day for maintenance.

These changes are, of course, subject to the physician to follow. As with other corticosteroid preparations, either the patient or the disease at some period or the dosage may be adjusted to the needs of the particular patient being treated.

CONTAMINATION—The use of corticosteroids is contraindicated in Addison's disease. Tolerable, acute, subacute or occasional bacterial, fungal, or virus infections, including staphylococcal or other skin or internal conditions. Papel, fever, allergic reactions, local or systemic conditions, including lupus, and other is not known to be affected, the patient's weight, or some other condition, may be added to the product of the particular patient being treated.

INDICATIONS—The product should not be used in patients with a history of previous reactions to any form or component of one who is known to be allergic to any form or ingredient of the product.

PRECAUTIONS AND SIDE EFFECTS—The product contains corticosteroid hormones by the lowest or other and corticosteroid to be used. It is of course, subject to the physician to follow. As with other corticosteroid preparations, either the patient or the disease at some period or the dosage may be adjusted to the needs of the particular patient being treated.

The following precautions have been employed: 40 units twice a week.

In dermatologic disorders, lupus erythematosus, alergic pro-

nons, and so on, dosage has been 40 units every two to four days. Maintenance dosage in some cases has been achieved with 40 units once a week.

In dermatologic disorders, lupus erythematosus, alergic pro-

nons, and so on, dosage has been 40 units every two to four days. Maintenance dosage in some cases has been achieved with 40 units once a week.
and complications compared with other corticosteroid preparations, the possibility of overdosage exists must be borne in mind.

Corticosteroids will produce the same type of side effects as corticosteroids and these include: Cushing's syndrome, appetite or suppressed, acid-base disturbances, suppression of adrenals, electrolyte imbalances, adverse reactions, weight changes, hypertension, edema, bleeding or purpura, diaphoresis, weaks, weakness of the skin, delayed healing, constipation, pancreatitis, increased intracranial pressure, convulsions, and bradycardia. Venous changes such as polycythaemia rubra in an increased incidence for Reye's syndrome have been reported. The incidence, type and severity of intracranial reactions usually related to the dose and duration of therapy. For example, prolonged use of corticosteroids may also cause growth suppression, reversible with withdrawal in children, delayed wound healing, or posterior subcapsular cataracts in adults.

Susceptible individuals may become sensitized to traces of proteins that accompany corticosteroids so that subsequent injections given after intervals of several years may give rise to hypersensitivity phenomena ranging from mild urticaria to anaphylactic shock. The first signs of developing hypersensitivity may be localized itching or itching from the injection site. This product should not be used in patients with a history of previous reactions to any form of corticosteroid or who are known to be allergic to products of animal origin.

It may be used in traumatic therapy in certain infectious diseases provided such infections are adequately controlled by appropriate antibiotics or chemotherapeutic agents. It may be terminated if the anti-inflammatory effects of corticosteroids may mask signs of infection and such patients should be carefully observed. While corticosteroids will usually not increase the requirements for controlled diabetes, when the drug is used in such patients, they should be observed closely for evidence of increased hyperglycemia or glycosuria. Periodic determinations of blood glucose during prolonged therapy are advisable.

PACKAGING—The product should be refrigerated. Available in ampoules containing 40 U.S.P. units of corticosteroid (ACTH) per ampoule. Each ampoule is filled with 20 U.S.P. units of corticosteroid per ml; in 4-ml containers of 40 U.S.P. units of corticosteroid with a sterile syringe and needle pack.

CAUTION Federal law prohibits dispensing without prescription.
This drug has been evaluated by the following Panels:

1. Panel on Drugs Used in Endocrine Disturbances
2. Panel on Drugs Used in Rheumatic Diseases
3. Panel on Anti-Infective Drugs
4. Panel on Drugs Used in Respiratory Disturbances
5. Panel on Drugs Used in Allergy
6. Panel on Drugs Used in Dermatology

Evaluations follow:

Panel on Drugs Used in Endocrine Disturbances

GENERAL STATEMENT

This statement summarizes the opinion of the Panel about the use of ACTH in the treatment of endocrine diseases, specifically hypopituitarism and steroid-induced pituitary adrenal suppression.

The members of the Panel are in general agreement that ACTH is a useful substance in the differential diagnosis of primary versus secondary adrenocortical insufficiency and, for that matter, useful in diagnostic tests of adrenocortical disease in general. In fact, the Panel believes that this is the major usefulness of ACTH. The Panel also agrees that, in spontaneous hypopituitarism and certainly persistent pituitary-adrenocortical suppression by corticosteroids, the treatment of choice is not ACTH, but rather corticosteroids. This is especially true of acute situations. The principal reason for the choice of corticosteroids over ACTH is that ACTH may have only limited capacity to stimulate adrenocortical response for the first few days of treatment. In the treatment of hypopituitarism, ranging the dose of ACTH is more difficult than standardization with corticosteroids, and the Panel further feels that the dose often recommended by the manufacturer may be too large.

1. The study of several standard reference works on the treatment of endocrine diseases does not reveal a single instance in which the administration of ACTH was recommended as the treatment of choice for hypopituitarism.

2. Environ et al. (10) studied a patient with longstanding hypopituitarism to whom they gave ACTH in doses up to 66 mg/day. Over a 10-day period, the metabolic changes were described as "minimal." These workers found no alteration in carbohydrate or nitrogen metabolism over the period of study. Although this study might be criticized on the grounds that it was early and the preparation of ACTH was possibly, and even probably, less pure than are the ordinary therapeutic preparations now available, the validity of the authors' conclusion is supported by the fact that definite increases in urinary steroid values were observed when this preparation of ACTH was given. The important point, allowed to above, is that ACTH may indeed be very useful for diagnostic purposes in subjects with hypopituitarism of long duration but that, during the first days and perhaps weeks of ACTH administration to such patients, very little metabolic effect is to be expected until the adrenals have been stimulated to the point of a fairly normal response to ACTH.

3. The ACTH doses often recommended for hypopituitarism may be too high, and it is the Panel's opinion that the adrenal response is hard to predict and therefore hard to control in a given patient. Fifty units of ACTH daily, as often recommended, may
It is surprising to the Panel that no mention is made of diagnostic uses of ACTH for adrenal or pituitary disease. In the opinion of the Panel, this is the major indication for ACTH. The Panel feels that all the manufacturers' package inserts ought to indicate clearly that, when ACTH is used therapeutically, it should never be relied on until the adrenocortical response has been carefully validated by the response of urinary or plasma corticosteroid values to the administration of a standardized ACTH test. There are several protocols for standard ACTH tests that rely on the increase in plasma or urinary corticosteroids for definitive diagnosis.

It should be emphasized, in the opinion of the Panel, that hypothalamic-pituitary suppression will occur as a result of ACTH administration, owing to the stimulation of a high rate of destruction of endogenous adrenocortical steroids. In addition, there is some evidence that ACTH may itself inhibit pituitary release of ACTH. In the insert, therefore, the statements about the preservation of normal pituitary-adenal function if ACTH is used, rather than steroids, should be very much tempered. It follows that, in the patient who has received prolonged treatment with corticosteroids, ACTH does little, or may actually impair the return of endogenous ACTH production.

DOCUMENTATION:
Panel on Drugs Used in Rheumatic Diseases

1. Rheumatoid arthritis.

EVALUATION: Effective, but . . . .

COMMENTS: Corticosteroid preparations may be used as adjunctive therapy for short-term administration to tide the patient over an exacerbation. However, when the patient with rheumatoid arthritis is given sustained steroid therapy, it becomes increasingly difficult to withdraw the drug. "Temporary" treatment is effective in suppressing the symptoms of rheumatoid arthritis, but difficult to limit, and after prolonged administration the dangerous side effects of steroids will appear. (See General Comments.)

DOCUMENTATION:


II. Acute lupus erythematosus.

EVALUATION: Effective, but . . . .

COMMENTS: Corticosteroid preparations are effective in the therapy of acutely ill 111 patients, where they may be lifesaving, and probably effective in the maintenance and control of most systemic manifestations. In the control of lupus nephritis, although the proper dosage and time of administration have not been firmly established, steroids may be effective. In nephritis, neither ACTH and cortisone, are not the drugs of choice. The Panel recommends the use of the term "systemic lupus erythematosus," instead of "acute lupus erythematosus."

DOCUMENTATION:


III. Polyarteritis and periarteritis nodosa.

EVALUATION: Possibly effective.

COMMENTS: Although there is short-term and long-term improvement after treatment with corticosteroids, follow-up studies after 4 to 5 years show no particular benefit.

DOCUMENTATION:

GENERAL COMMENTS
See general statements on corticosteroid and corticotrophin preparations.

Approved by
Chairman

GENERAL STATEMENTS ON CORTICOSTEROID AND CORTICOTROPHIN PREPARATIONS

Systemic glucocorticoids and corticotrophin are effective in the acute control of the symptoms and signs of rheumatoid arthritis, systemic lupus erythematosus, and rheumatic fever. These preparations will also control the acute arthritic symptoms of scleroderma and some of the acute symptoms of necrotizing arteritis and polymyositis.

In other classes of drugs approaches the anti-inflammatory potency of the adrenal cortical steroids. Of the several forms available (prednisone, am痕迹hase, triamcinolone, etc.), none is clearly "better" than the others in regard to anti-inflammatory potency. Parenteral glucocorticoids should be used for systemic effect only when the patient is unable to tolerate oral medication.

In the long-term maintenance of rheumatoid arthritis, the hazards of continued treatment with glucocorticoids or corticotrophin often outweigh the advantages of disease suppression. When they are used, they should be adjuncts and not the sole therapy. In the treatment of sclerodermatous (progressive systemic sclerosis), the lack of effect of visceral manifestations and the probable hazard of accelerated renal involvement in so great a length of time of these agents should be avoided. In systemic lupus erythematosus, the benefits of the treatment outweigh the hazards, and maintenance therapy with these agents may be the procedure of choice. It should be stressed that some patients with SLE do not need steroids, and in some situations, patients surviving for years with SLE. In necrotizing arteritis, the evidence is inconclusive and no statement can be made in regard to the benefits as contrasted with the hazards. In polymyositis, the reduction in the serum enzymes that can be achieved with steroids is believed to be due to the suppression of the myositis process and its attendant destruction of muscle. Chronic administration is justified in active disease. In acute rheumatic fever, with carditis, treatment beyond 3 months is not required, and it that period the benefits may outweigh the hazards. In pustular arteritis, as in rheumatoid arthritis, the hazards of continued treatment often outweigh the advantages of disease suppression. In addition, the risk of a flareup of the pustules after steroid withdrawal is great. In uncomplicated amyloidosis, glucocorticoids and corticotrophin should not be used in long-term management.

A general rule for all long-term treatment with these agents is that the smallest possible dose be used to control a given symptom or sign, and when the agent is reduced, it must be reduced gradually. At this time, the only exception is chronic high-dose steroid therapy for the nephritis of systemic lupus, which some believe to have advantages outweighing the hazards; there is not complete agreement on this.


In all patients receiving long-term therapy with systemic glucocorticoids or corticotrophin, one must anticipate and expect the development of the following undesirable events which are generally dependent on the dose used and characteristic of the Cushinglead state:

1. Osteoporosis and spontaneous fractures. This has not been modified by high protein or calcium intake, by physical exercise, or by the administration of anabolic steroids.

2. The development of a peptic ulcer, more commonly seen when salicylates are administered concurrently, but also seen when salicylates are not administered. A peptic ulcer may develop slowly and present as catastrophic bleeding or perforation.

3. Decreased resistance to infection and decreased ability to counteract and localize infection. These effects result in altered patterns of response to infection, making them difficult to recognize and diagnose.

4. Impaired wound healing and thin, fragile skin.

5. In rheumatoid arthritis an increased frequency of generalized necrotizing arteritis.

6. Decreased carbohydrate tolerance, making latent diabetes overt.

7. Rises in blood pressure and fluid retention, particularly with corticotrophin, cortisone, and hydrocortisone.

8. An increasing tendency to development of aseptic necrosis of bone, especially of the femoral head.

9. The development of posterior subcapsular cataract is not uncommon. Also, long-term use of systemic steroids may give rise to increased intraocular pressure.

10. The development in varying degree of steroid myopathy, and loss of muscle mass, possibly seen more frequently with the 9-alpha-fluorogluocorticoids.

11. In children suppression of growth with chronic administration of glucocorticoids and corticotrophin, even at low doses as well as the other untoward events outlined.

12. One may anticipate adrenal unresponsiveness after sustained administration of glucocorticoids. During periods of stress, increased amounts of glucocorticoids may be required. Administration of corticotrophin will increase adrenal size and lead to an adrenal which will respond to exogenous corticotrophin but also will lead to suppression of the pituitary and thus, during stress, the adrenal glands may be unresponsive. Both adrenal and pituitary suppression are almost invariably temporary, and function will ultimately return within varying periods after withdrawal.

Many of these effects are the more threatening because the agents cannot be abruptly withdrawn, for two reasons: one, the temporary suppression of pituitary-adrenal responsiveness, and two, the near certainty of sharply increased activity of the underlying connective-tissue disease.
BIBLIOGRAPHY

1. Osteoporosis and spontaneous fractures.
   (a) Clinical state:

(b) Incidence of preventive treatment:

2. Peptic ulcer, perforation and hemorrhage.

3. Increased resistence to infection and ability to counteract and localize infection.

4. Impaired wound healing, thin fragile skin, and edema.

5. Increased frequency of generalized necrotizing arteritis.

6. Altered carbohydrate tolerance.

7. Fluid retention.

8. Aseptic necrosis.
   (a) Osteonecrosis:

   (b) Rheumatoid arthritis and lupus erythematosus:
9. Subcapsular cataracts.


10. Steroid myopathy.


13. Increased renal involvement in scleroderma.


15. Hypertension.


17. Congenital abnormalities.

General Statements on Corticosteroids

The parenteral administration of corticosteroids in patients with intact adrenal cortical function leads to the increased endogenous production of cortisol, corticosterone, and weak androgens (6). Because corticosteroids can be given only parenterally, its use is associated with all the inconveniences of parenteral therapy.

Adrenocorticosteroid hormone is clinically available in four formulations. The aqueous preparation is relatively short-acting, and is in part inactivated locally when given subcutaneously or intramuscularly (1). There is little justification for giving aqueous corticosteroid intravenously for therapeutic reasons (15). Because there is local inactivation of aqueous corticosteroid, delayed-release varieties of corticosteroid have been devised. These include preparations combined with zinc, in gelatin, and in carbocyclic/cellulose suagluc. The effect of the cortexgluc apparently lasts longer than that of the gelatin preparation (2). For survey considerations, however, these three preparations can be considered by type.

There are three circumstances within this clinical area in which adrenocorticosteroid hormone is used with somewhat greater frequency than in the other disorders: in long-term treatment of rheumatoid arthritis, in the short-range treatment of acute gout, and in the attempted prevention of the adrenocorticosteroid suppression associated with the use of oral corticosteroid agents.

The virtues claimed for adrenocorticosteroid hormone in the treatment of rheumatoid arthritis in comparison with orally administered steroids included reduction in the frequency of gastric symptoms (17) and a decrease in ease of withdrawal (13). Nonetheless, Goodman and Gilman's conclusions seem valid here: "there is no substantial evidence that any therapeutic benefits can be attained with ACTH that cannot be attained with appropriate doses of currently available steroids." (6).

Experience with rheumatoid arthritis suggests that the dose of adrenocorticosteroid hormone, given once daily in a delayed-release form, should be sufficient to increase the urinary excretion of 17(OH)CS for 24 hours to 15-30 mg, measured by the Bayh-Diller method (25-27). The determination of adrenocorticosteroids and cortisol in plasma e.g. a test for adrenocorticosteroid hormone effect is not satisfactory (26). Most (25) suggests beginning with 20 units of corticosteroid daily in the treatment of rheumatoid arthritis, and then altering the dose according to the urinary excretion of 17(OH)CS. If doses larger than those specified above are used, steroid complications are more likely to ensue.
INDICATIONS

1. Adjunctive therapy in certain infectious diseases, provided such infections are adequately controlled by appropriate antibiotics or chemotherapeutic agents.

EVALUATION: Effective, but...

COMMENTS: If increased levels of corticosteroids are desired when treating an infectious disease process, they should be obtained by administration of corticosteroids, not by administration of ACTH. Adrenal responsiveness to ACTH cannot be guaranteed and the high steroid levels desired are a difficult to maintain properly with ACTH.

The following should be included in the "contraindications" and "precautions" sections: "Latent or questionably healed tuberculosis or even tuberculin reactivity is a relative contraindication to the use of ACTH, but it may be used if covered with an effective antituberculosis regimen. ACTH may mask signs of infection during treatment. If this is suspected, measures should be taken to make a diagnosis and appropriate antibacterial therapy should be vigorously pursued."

DOCUMENTATION: See attached background information.

Chairman
The effectiveness of antituberculous drugs is neither enhanced nor lessened by steroid hormone administration. Many physiologic changes, however, can be brought about in the inflammatory process by the use of these hormones, which result in lesions or constitutional manifestations of illness.

Steroid therapy can dramatically abolish or lessen the constitutional manifestations of illness, such as fever, malaise, and anorexia, and add to the comfort of the acutely ill patient. The reversible component of the tuberculous pulmonary lesion, namely inflammation and granulomatous change, is quickly diminished, leaving only the destroyed anatomy for reflection in the chest x-ray. At present, the role of steroid therapy in pulmonary tuberculosis must be regarded as minor from a therapeutic viewpoint, and its use should be highly individualized.

Currently accepted indications for corticosteroids in active tuberculosis are: overwhelming or life-threatening pulmonary tuberculosis not responding satisfactorily to an appropriate chemotherapy regimen; tuberculous meningitis with subarachnoid block or impinging block; endobronchial tuberculosis in children; and, rarely, to aid in controlling otherwise uncontrolled or unavoidable drug hypersensitivity reactions. The use of steroids in tuberculous meningitis, especially when block is present, has become traditional; this attitude is clearly based on clinical impression and not controlled trials.

Active tuberculosis is a contraindication to the use of corticosteroids unless an effective antituberculous drug regimen to which the bacilli are susceptible is concurrently used.

Latent or questioned healed tuberculosis or even tuberculoid reactivity in a tuberculin-positive individual is a relative contraindication to the use of corticosteroids, but they may be used in this situation if covered with an effective anti-tuberculosis regimen.

If corticosteroids are administered to patients with active or latent tuberculosis, continued close observation should be maintained; chest x-rays and sputum bacteriology should be obtained frequently. The antituberculous drugs should be continued at least briefly after the corticosteroids are stopped.

Rebound fever, joint pains, and transient chest radiographic worsening may occur after steroid withdrawal, and hypersensitivity to one or more of the anti-tuberculosis drugs may be unmasked after discontinuation of corticosteroids.

Because of the possibility of dissemination of fungal infection, the use of corticosteroids is contraindicated when the primary, tuberculous infection is complicated by fungal infection or cannot reliably be distinguished from a pure fungal infection.

Corticosteroids may be administered to patients with severe acute or chronic infection only if appropriate antibacterials are given concurrently in amounts adequate to control the infection. The antibacterials should be continued at least briefly after the corticosteroids are stopped.

Corticosteroids may mask some signs of infection, and in some new infections may appear during their use. If this is suspected, measures should be taken to make a diagnosis and appropriate antibacterial therapy should be vigorously pursued.

Corticostereoid (ACTH) and Corticosteroids in Tuberculosis and Infectious Diseases

I. ACTH and corticosteroids have been used to manage the clinical manifestations and complications of tuberculosis. Their effectiveness in tuberculosis is not antituberculous.

A. To inhibit fibrosis: ACTH and corticosteroids prevent or suppress inflammation (26,30,37,45,46,67) and suppress the formation of fibrous tissue (30).

1. Pleural effusion: some studies (20,42,45,51) find that these drugs reduce pleural fluids and others (27,34) find that they do not. Most studies agree, however, that these drugs cause a more rapid clearing of pleural effusions than in patients treated only with antituberculous chemotherapy (21,18,16,92).

2. Pericardial effusion: one article suggests that ACTH and corticosteroids are beneficial in pericardial tuberculosis (62).

3. Pulmonary paracardial disease: two reports (33,60) show no significant inhibition of paracardial fibrosis and destruction, as determined by pulmonary function; one other found improvement, although no long term functional measurements were made (64). In a fourth report, the steroid-treated group was significantly improved in one respect at 6 months (3).

B. To relieve severe toxicity in pulmonar, for advanced, and hopeless peritoneal tuberculosis, particularly in those showing poor response to standard therapy (9,21,34,38,59,61,69).

C. To treat tuberculous meningitis: When ACTH or corticosteroids are used concomitantly with effective antituberculous chemotherapy, the cerebrospinal fluid pressure, cell count, and protein all promptly fall with both subjective and objective clinical improvement in the patient (2,4,10,12,31,58,73). The corticosteroid for use of ACTH or corticosteroids in tuberculous meningitis vary among observers; clinical judgment must be used to decide on concurrent or change dosage in this type of therapy. A variety of dosage schedules have been recommended for treating tuberculous meningitis (4,5,10,31,58).

D. To hypothermia patients with allergic reactions to isoniazid, PAS, streptomycin or other antituberculosis drugs: ACTH and/or corticosteroids have been used (14,17,41,60).

E. To treat endobronchial tuberculosis: ACTH and corticosteroids added to effective antituberculous chemotherapy provide rapid regression of the endobronchial lesion (22). Also, in laryngeal tuberculosis these drugs seem to accelerate clearing of the lesion (38).

F. To prevent bronchectasis: In children with primary tuberculosis presenting larinar or segmental shadows, ACTH and corticosteroids have been recommended (20).

G. In pulmonary tuberculosis in general: Rapid improvement in the patient's general condition, with reduction of fever, weight gain, and accelerated clearing of pulmonary lesions, has been reported (7,15,36,37,70). Various dosage 21:advices have been recommended for patients with pulmonary tuberculosis (28-30,37,43,46,53).

II. Expected effects of ACTH and corticosteroids in tuberculosis include the following:

A. "Rebound" fever, joint pains, and transient chest radiographic worsening may occur following steroid withdrawal (19,71).
C. Tissue calcifications may possibly be aggravated by ACTH or corticotrocid administration in suspected but not proved tuberculous meningitis (2). For this reason, when active pulmonary infection is present, fungal infections of tuberculoises or ACTH is contraindicated (52, 64).

D. Active tuberculoses may be made worse by the use of ACTH or corticotrocid in the absence of effective anti-tuberculous therapy; with few exceptions, ACTH and corticotrocid are contraindicated in active tuberculosis in the absence of effective anti-tuberculous therapy (18, 34, 48, 50, 67, 73).

E. Reactivation of healed, contiguously healed, or latent pulmonary tuberculoises has been reported during, after, and presumably due to ACTH and/or corticotrocid therapy (53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64). Published information concerning the length of time corticotrocid is safe to give to patients with tuberculosis is incomplete.

In the presence of healed tuberculososes, ACTH and corticotrocid should be administered with caution (1, 73), the status of the pulmonary lesions observed closely by frequent x-rays (1, 73), and bacteriologic examination (18) of the sputum is mandatory before tuberculous therapy is given if arterial disease is found (72).

F. Because ACTH and corticotrocid may mask the symptoms and signs of infections and facilitate the progression of infections, they must be used with caution; an antibacterial agent to which the infecting organism is responsive should be started concurrently (56, 63, 64). ACTH and corticotrocid should be slowly reduced in dosage (34, 43) and discontinued at least 3 days before specific antituberculosis or anti-infectious therapy ceases (36). In any signs or symptoms of bacterial infection occur while ACTH or corticotrocid are being administered, every effort should be made to diagnose and treat the infection (36). There is no consensus as to whether the ACTH or corticotrocid should then be stopped rapidly, tapered slowly, continued in similar dosage with specific antibacterial therapy, or continued in higher dosage with concurrent specific antituberculous therapy.

BIBLIOGRAPHY


12. Drukker, J.C. and J.B. Partners. Military tuberculosis with meningitis complicated by severe skin necrosis and amputal block, both conditions completely reversed by treatment with cortisone. Trans. 16th VA-AF Conf. on Chemotherapy, p. 120, 1957.


INDICATIONS

I. Bronchial asthma.

EVALUATION: Effective, but ... .

COMMENTS: See General Comments.

DOCUMENTATION: See General bibliography.

II. Pulmonary emphysema.

EVALUATION: Effective, but ... .

COMMENTS: Corticotropin has no effectiveness in modifying the pathologic processes of pulmonary emphysema; the structural damage to the alveoli is irreversible. Corticotropin can, however, provide considerable benefit in those cases where bronchospasm or bronchial edema plays a significant role in the over-all symptom complex. This is especially true when they are used in conjunction with other measures to improve bronchial toilet and thereby improve the respiratory status of a given patient.

The use of corticotropin is somewhat more hazardous in patients with pulmonary emphysema than in other patients. Patients with chronic pulmonary insufficiency are more prone to develop peptic ulcer with or without the added risk of corticotropin; extra precautions should be taken, therefore, when these agents are used in this type of patient.

DOCUMENTATION: See General bibliography.

GENERAL COMMENTS

The Panel subscribes to the view that the therapeutic usefulness of corticotropin preparations has largely been supplanted by the advent of the corticosteroid compounds. The advantages of the latter are that they are more easily administered on a long-term basis and have more predictable effects. Patients treated for a long time with a foreign protein derivative run a risk of developing hypersensitivity reactions, which is unnecessary. The Panel doubts that it is desirable to advocate the use of an injectable product for the management of chronic diseases when more acceptable, oral preparations (which accomplish the same end) are available.


Panel on Drugs Used in Allergy

INDICATIONS

1. Drug sensitivities.

EVALUATION: Effective.

COMMENTS: ACTH should be reserved for intractable sensitivities not manageable by other means. Severe, life-threatening reactions, such as anaphylaxis, require the administration of epinephrine and other standard measures.

DOCUMENTATION:


II. Bronchial asthma.

EVALUATION: Effective.

COMMENTS: ACTH should be reserved for intractable asthma not manageable by other means.

DOCUMENTATION:


Allergy Panel - General Statement for ACTH Preparations

The Panel feels that the source of the ACTH protein should be stated in each package insert or on the label. This may be important when a patient has an allergy to protein of one animal origin but not to that of another. The undesirable preparation may be avoided only if its origin is stated.

In the opinion of the Panel, dosage recommendations should be very general and emphasis should be placed on patient response as a guide to proper doses. Specific dosage schedules are of little value when one is faced with the variable nature of any patient's capacity to respond. Furthermore, specific dosage recommendations may be harmful in some circumstances. Standard textbooks should be referred to where specific advice is needed regarding management of any given disease. The package insert should merely serve as a reminder and general guide.

The same remarks apply to the "Precautions" and "Side Effects" sections. These should either provide a complete list of all possible side effects or note the general types of problems that may result. The Panel favors the latter position.

The package insert should include a warning that anti-inflammatory effects resulting from ACTH administration may mask acute inflammatory reactions of any origin. Corticosteroid replacement is preferable to ACTH during such periods of stress.

It is evident that there are no absolute contraindications to the administration of ACTH preparations. All contraindications are relative to the need for ACTH therapy. All contraindications, such as tuberculosis, should be managed in the appropriate manner when ACTH is administered.

* The general introductory paragraphs of the package insert imply unwarranted clinical advantages for ACTH preparations. There is ample evidence that ACTH depresses the pituitary and the hypothalamus both directly and indirectly, and therefore, has no advantage over corticosteroids.

* The paragraph is used only when appropriate to the insert.
Indications

I. For the treatment of such dermatologic disorders as atopic dermatitis, seborrheic psoriasis.

Evaluation: Effective, but . . . .

Comments: Because of the dangers involved in using foreign proteins systematically in humans and because of the poorly controlled dose-response with ACTH, this type of therapy has nearly been replaced by the safer and more efficient corticosteroids. Current dermatologic therapy utilizes systemic and/or topical steroids.

Documentation:

II. For the treatment of acute lupus erythematosus.

Evaluation: Effective, but . . . .

Comments: Because of the dangers involved in using foreign proteins systematically in humans and because of the poorly controlled dose-response with ACTH, this type of therapy has nearly been replaced by the safer and more efficient corticosteroids. Current dermatologic therapy utilizes systemic and/or topical steroids.

The company should define acute lupus erythematosus. The Panel feels that the insert should indicate use in systemic lupus erythematosus only.

Documentation: None applicable.

III. For the treatment of polyarteritis and periarteritis nodosa.

Evaluation: Effective, but . . . .

Comments: The Panel feels that this is an effective form of therapy, but see the General Comments Section.

Documentation: None applicable.

IV. For the treatment of pemphigus vulgaris.

Evaluation: Effective.

Comments: The Panel feels that this is effective therapy in this condition.

Documentation: None applicable.

General Comments

I. Because of the dangers involved in using foreign proteins systematically in humans and because of the poorly controlled dose-response with ACTH, this type of therapy has nearly been replaced by the safer and more efficient corticosteroids. Current dermatologic therapy utilizes systemic and/or topical steroids.
Symptomatic aerodigestive
Leukemia (not manageable by other means)
Berylliosis.
Furnishing or disseminated pulmonary tuberculosis when there is a response to treatment with corticosteroids.
Aspiration pneumonia.
8. HEPATITIS AND LIVER DISEASES.
Acquired (autoimmune) hemolytic anemia.
Secondary adrenal insufficiency in adults.
Erythropoietic (FSC anemia).
Secondary adrenal insufficiency in children.
Neoplastic diseases.
9. NEUROISCHECTOMY.
For palliative management of:
Leukemia and lymphoma in adults.
Acute leukemia of childhood.
To induce a diuresis or a remission of proteinuria in the next 1 to 2 days or to establish remission without uremia of type or that due to lupus erythematosus.
To tide the patient over a critical period of the disease in:
Ulcerative colitis.
Regional enteritis.
12. Miscellaneous.
Tuberculosis meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculosis chemotherapy.
CONTRAINDICATIONS—When any of the following conditions are present, corticosteroids should not be administered:
Scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, hypersensitivity, or sensitivity to proteins derived from porcine source.
Tuberculous meningitis or encephalitis within the indication section when they are accompanied by primary adrenocortical insufficiency or adrenal suppression. 
Intravenous administration of corticosteroid for treatment of conditions requiring immediate action may be contraindicated.
WARNINGS—Chronic administration of corticosteroids has been shown to lead to irreversible effects which are not reversible. Corticosteroids may cause changes in the signs and symptoms of chronic disease without altering the natural course of the disease. This product should not be administered for treatment until adrenocortical responsiveness has been verified with the route of administration which will be utilized during the period of corticosteroid therapy. A rise in urinary and plasma corticosteroid levels provides direct evidence of such a loss of effect. Prolonged administration of corticosteroids increases the risk of hypercortisolism. While the action of corticosteroids may be that of an estrogen, adrenal androgens, and corticosteroids may be used with caution in patients with diabetes, alcohol, pyrogenic infections, or any condition with a tendency to produce hyperglycemia. Growth and development of children and infants on prolonged corticosteroid therapy should be carefully observed.
ADVERSE REACTIONS
Fluid and Electrolyte Disturbances
Sodium retention.
Fluid retention.
Potassium loss.
Musculo-skeletal
Muscle atrophy.
Steroid myopathy.
Vertebral compression fractures.
Aseptic necrosis of femoral and humeral heads.
Pathological fractures.
Gastrointestinal
Peptic ulcer with possible perforation and hemorrhage.
Pancreatitis.
Dermatologic
Impaired wound healing.
This fragile skin.
Increased sweating.
Suppression of skin test reactions.
PERIPHERAL AND CENTRAL NERVOUS SYSTEM
Hypertension.
Dizziness.
Headache.
Vertigo.
Acute cardiovascular disease.
Peripheral neuritis.
Increased intracranial pressure with papilledema, (brain tumor or cancer) usually after treatment.
Endocrine
Menstrual irregularities.
Misperception disorders in normal subjects.
Secondary adrenocortical and pituitary unresponsiveness, partial or complete.
Decreased carbohydrate tolerance.
Metabolic
Increased insulin requirement.
Intravenous or oral hypoglycemic agents in diabetics.
Ophthalmic
Posterior subcapsular cataracts.
Increased intraocular pressure.
Glaucoma with possible damage to optic nerve.
Cataracts.
Metabolic
Negative nitrogen balance due to protein catabolism.
Allergic reactions
Especially in patients with allergic responses to proteins manifesting as urticaria, urticarial, and shock, skin reactions.
Malignancies
Malignancies.
Prolonged ACTH may result in antibodies and loss of stimulatory activity.
DOSAGE AND ADMINISTRATION—Standard tests for verification of adrenocortical responsiveness to corticosteroids may be used. All patients should be started on a low dosage of corticosteroids and the dosage should be increased gradually until the appropriate maintenance dose is reached. Dosage schedules should be readjusted at intervals to prevent possible drug toxicity. The test should utilize the route of administration proposed for treatment. Following verification dosage schedules, dosage may be adjusted according to the disease under treatment and the general medical condition of each patient. Frequent evaluation of renal function and determination of the creatinine load by determination of the severity of the disease, plasma and urine corticosteroid levels, and the functional status of the patient. Only gradual change in dosage should be attempted after full drug effects have become apparent.
Dosage of adrenocorticosteroids is used to control the symptoms of the disease in non-adamant cases. A lower maintenance dosage may be used in some cases.
PACKAGES—This product contains technological and other materials and its atroxa such as:
Corticosteroids.
Dextrose.
Benzyl alcohol.
Packaging
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Corticosteroids may produce Cushing's syndrome and its atroxa such as:
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