

TODAY'S DRUGS

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Tetracosactrin

This synthetic tetracosapeptide with corticotrophic activity is marketed by CIBA Laboratories Limited under the name Synacthen.

Chemistry and Pharmacology

Corticotrophin (A.C.T.H.) is secreted by the anterior lobe of the pituitary gland and is a straight-chain polypeptide consisting of 39 amino-acids. Its most important effects are those on the adrenal cortex, where it causes an increased production of cortisol (hydrocortisone) and adrenal androgens and maintains the size and weight of this gland. The biological activity of this hormone is associated with the sequence of the first 24 amino-acids in the chain, which is common to corticotrophin obtained from pigs, sheep, cattle, and man. Species differences involve only the N 25 to 33 positions. Tetracosactrin (Synacthen) is a synthetic polypeptide composed of these first 24 amino-acids and has been shown by Landon and his colleagues¹ to have a high degree of biological activity in man, 0.1 mg. being approximately equivalent to 10 international units of the natural hormone. Tetracosactrin is similar to the natural hormone in that it is destroyed in the gastrointestinal tract and is therefore only effective when given parenterally.

Corticotrophin is widely used in clinical practice for the diagnosis of various disorders of the adrenal cortex and in the symptomatic treatment of diseases, such as asthma and rheumatoid arthritis, which are known to respond to pharmacological doses of corticosteroids. As a diagnostic test it is most frequently used to confirm the diagnosis of primary adrenal failure (Addison's disease) or to assess the degree of secondary adrenal atrophy following prolonged corticosteroid therapy. Its therapeutic value depends upon the increased production of adrenal steroids which results from its prolonged systemic administration. Commercially available preparations of the natural hormone are obtained from the pituitary glands of animals and have the disadvantage that they may very occasionally cause severe hypersensitivity reaction and even death.²⁻⁴ It is not clear whether these reactions are due to contamination by foreign proteins or to species differences in the latter part of the corticotrophin molecule, but they are more likely to arise in patients with an allergic history who have been given corticotrophin in the past. However, it is only fair to point out that these preparations have been given to thousands of patients over the past ten years and the reported incidence of severe reactions is very small.

Nevertheless, there is no doubt that tetracosactrin has certain definite advantages over preparations of the natural hormone. As it is a pure substance it can be assayed by weight and is not contaminated by foreign proteins. This purity, and its shorter amino-acid sequence which is common to all known forms of corticotrophin, decrease the likelihood of hypersensitivity reactions. The main disadvantage of tetracosactrin is its short duration of action by the intramuscular route, which limits its use in therapy. Tetracosactrin is rapidly absorbed from muscle and produces its maximal steroidogenic effect within minutes of the injection, the effect of a single intramuscular injection of 0.25 mg. being over within four hours. On the other hand, it is extremely potent by intravenous infusion and as little as 3 µg./hour may produce a maximal adrenocortical response.¹

Diagnostic Uses

Tetracosactrin can be used in place of the natural hormone to assess the function and reserve capacity of the adrenal cortex. Two tests have been developed for this purpose, the adrenocortical response in both tests being measured by the

rise in plasma 11-hydroxycorticoids⁵ following administration of tetracosactrin.

In the test described by Wood and his colleagues⁶ the response is measured by the increase in the plasma 11-hydroxycorticoid level 30 minutes after a single intramuscular injection of 0.25 mg. of tetracosactrin dissolved in 1-2 ml. of saline or sterile water. The criteria for a normal response in adults are an initial plasma level of more than 5 µg./100 ml., provided that the patient has not received corticosteroids within the previous 12 hours, an increase in the plasma 11-hydroxycorticoid level of more than 7 µg./100 ml. 30 minutes after the injection, and a plasma level at 30 minutes greater than 18 µg./100 ml. irrespective of the initial level. This test is of great value in screening patients for Addison's disease in the outpatient clinic, but the adrenal stimulus is too brief to differentiate between primary adrenal failure and secondary adrenal atrophy due to treatment in patients with suspected Addison's disease who have already been started on corticosteroid therapy.

The intravenous infusion of tetracosactrin provides a greater stimulus to the adrenal glands, and in the test described by Landon and his colleagues¹ the drug is dissolved in isotonic saline or 5% dextrose and infused at a rate of approximately 0.1 mg./hour for five hours. The criteria for a normal response are a basal plasma 11-hydroxycorticoid level greater than 5 µg./100 ml., and a level at five hours within the range 36 to 60 µg./100 ml. It is doubtful, however, if even this stimulus is sufficiently prolonged to overcome the adrenal atrophy produced in some patients by prolonged corticosteroid therapy.

Therapeutic Uses

Tetracosactrin has too short a duration of action by the intramuscular route to replace the long-acting corticotrophin preparations used in the long-term treatment of disorders such as asthma, the nephrotic syndrome, or rheumatoid arthritis. The use of tetracosactrin by intravenous infusion, however, has much to commend it in the emergency treatment of acute conditions such as status asthmaticus and hypersensitivity to drugs. Allergic reactions to tetracosactrin are extremely unlikely, even in patients sensitized to corticotrophin of animal origin.¹ CIBA Laboratories recommend that it be given in isotonic dextrose or electrolyte solutions at a rate of approximately 40 µg. per hour in order to ensure a maximal adrenocortical response. It should not be added to blood or plasma, as it is apt to be inactivated rapidly by enzymes.

Presentation and Cost

Synacthen is a white solid, freely soluble in water and presented in sterile ampoules each containing 0.25 mg. tetracosactrin as lyophilized powder. As a dry powder in the ampoule, synacthen is stable indefinitely at room temperature. Prepared solutions should be used at once and any surplus discarded.

The basic N.H.S. cost of six ampoules is £3 10s.

REFERENCES

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Correction

In the "Today's Drugs" article on nalidixic acid (25 March, p. 741) the dose for children was stated to be 600 mg./kg. body weight daily, and the concentration of nalidixic acid in the suspension was quoted as 600 mg./ml. This should have read "The dose for children is calculated on the basis of 60 mg./kg. body weight daily, given in divided doses. A flavoured suspension containing 60 mg./ml is available."