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DESENSITIZING TREATMENT IN ALLERGY TO SYNTHETIC CORTICOTROPHIN: STUDY OF THREE CASES*

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The increasing use of ACTH therapy over the last few years has again brought to light the problem of allergic reactions to preparations of animal origin (bovine and porcine) which have gradually become more and more frequent (14).

Synthesis, therefore, of a molecule with corticotrophin activity, i.e. 1-24-corticotrophin and tetracosactide (Synacthen®), was received with enthusiasm. One of the many advantages of synthetic corticotrophin, compared with the natural form, is the lack of protein impurities and the almost complete absence of antigenicity. In fact, the end chain of 15 aminoacids which gives ACTH of animal origin its antigenic properties, is lacking in tetracosactide. Nevertheless, a few rare cases have still shown an allergic reaction to 1-24-corticotrophin, both in the simple form and in the more frequently used depot form (Synacthen® Depot Ciba), in which the molecule is adsorbed on a zinc-phosphate complex in order to produce a delayed effect (1, 2, 3, 4, 5, 6, 8, 9, 10, 15).

To our knowledge, however, there is no mention in the literature of specific desensitizing treatment in cases of allergy to tetracosactide which would thus enable patients to continue ACTH therapy without any untoward effects. In our opinion,

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therefore, it is worth while reporting on three cases which came to our attention and in which specific desensitizing therapy was performed. In the first 2 cases the therapy was highly successful, thus enabling the patients (2 women) to continue treatment with Synacthen Depot without untoward effects. The third patient decided to suspend treatment.

CASE REPORTS

Case 1

The first patient, a 27-year-old woman, affected by multiple sclerosis, had been on Synacthen Depot treatment for about 2 years (1 mg injected i.m. monthly). Prior to treatment the patient had never been exposed to any form of ACTH. In July 1970 an injection of Synacthen Depot induced paresthesia to the face and when the injection was repeated the following August it immediately induced Quincke's edema to the face, with widespread urticaria, chest pain, severe malaise and faintness. As soon as the patient came to our attention allergological tests were carried out; both skin tests and the Prausnitz & Küstner test (13) (carried out with Synacthen, Synacthen Depot, with zinc-phosphate alone and with natural ACTH (porcine and bovine)), were negative. The passive cutaneous anaphylaxis test on the guinea-pig according to Ovary (7), used to detect IgG₁₋₃₋₄ antibodies, was strongly positive with Synacthen Depot. Since the patient needed to continue therapy with this particular drug (because of the nature of the disease), it was decided to attempt specific desensitizing treatment using Synacthen Depot, given first intradermally and then subcutaneously over a period of 34 days. A total of 28 injections was given, starting with a dose of $1 \cdot 10^{-6}$ mg, and gradually increasing to 1 mg. All the doses were well tolerated and, after just over 1 month of treatment, the patient was able to tolerate an intramuscular injection of 1 mg of Synacthen Depot with no untoward reaction (9). The patient continued therapy every 15 days, without any reaction, until December 1972 when therapy was suspended due to an improvement in the patient's condition. Five months later, however, the disease reappeared and the patient was given an i.m. injection of Synacthen Depot. Within minutes paresthesia to the face and hands was evident, together with flushing of the face, congestion of the eyes, vomiting and hypotension. These reactions disappeared completely following intravenous injection of cortisone and antihistaminic drugs. Specific desensitizing treatment was recommended, beginning with 0.05 mg of the drug given by intradermal injection, and reaching a dose of 1 mg within one and half months. During the second cycle of treatment all the doses were tolerated, with the exception of one which induced widespread erythema of the skin, paresthesia, stomach cramps and nausea; all of which, however, disappeared following intravenous injection of cortisone and antihistaminic drugs. Since July 1973, the patient has been given a 1 mg i.m. injection of Synacthen

Depot every 20 days. As a precautionary measure an i.m. injection of antihistamine (chlorphenilamine maleate) is always given before Synacthen Depot.

Case 2

The second case was also a young woman, aged 21 years and affected by multiple sclerosis, who had been on tetracosactide depot (Synacthen Depot) treatment for 2 years. This patient had never been exposed to natural ACTH treatment. In December 1971, an i.m. injection of 1 mg Synacthen Depot induced Quincke's edema to the face and also widespread irritation. Fifteen days later an intradermal skin test with natural ACTH (porcine), performed for prophylactic purposes by the patient's general practitioner, induced widespread urticaria and Quincke's edema to the face. As soon as the patient came to our attention skin tests were carried out which were highly positive, both for natural corticotrophins (porcine and bovine) and for tetracosactide (normal and depot). Negative results were obtained for the zinc-phosphate complex alone which is contained in Synacthen Depot. The passive cutaneous anaphylaxis test on guinea-pigs (according to Ovary (7)) showed only one slightly increased $\text{IgG}_{1-3,4}$ level. The results of the lymphocyte transformation test *in vitro* were insignificant.

Since the patient needed to continue ACTH therapy, specific desensitizing treatment was carried out using simple Synacthen at first; this was followed by Synacthen Depot. Treatment was first administered intradermally, then subcutaneously, and finally intramuscularly. From an initial dose of 1.25×10^{-27} mg, dosage was gradually increased until, after 80 injections over a period of three and a half months, subcutaneous injections could be given of 0.25 mg tetracosactide (1 vial of Synacthen). The next step in the treatment was 0.25 mg tetracosactide depot injected subcutaneously, and after 10 such injections it was possible to give a complete phial (1 mg) of Synacthen Depot by i.m. injection. It can be seen that the time taken for desensitization was almost 4 months with a total of 90 injections. An i.m. injection of an antihistaminic drug (chlorphenilamine maleate) was usually given prior to administration of the therapy. Nevertheless, on two occasions a slight edema of the glottis was observed together with urticaria, and on another two occasions urticaria alone was seen. These adverse reactions, however, disappeared following intravenous injection of cortisone or antihistaminic drugs.

The patient has now been receiving 1 mg of Synacthen Depot regularly every 10 to 15 days since May 1972 without any adverse reaction.

Case 3

The third patient, a 41-year-old woman, had been suffering from bronchial asthma since she was 21 years old. She had been receiving Synacthen Depot treatment, but could not remember when she started the treatment. The last i.m. injection of the drug had induced anaphylactic shock. Skin tests and passive transfer, according to Prausnitz & Küstner (13), were highly positive, both with

natural ACTH (bovine or porcine) and with 1-24-corticotrophin in the normal form (Synacthen) and in the depot form (Synacthen Depot). But negative results were obtained in these tests for the zinc-phosphate complex alone which is contained in Synacthen Depot. In this patient too, specific desensitizing treatment began with 1.25×10^{-25} mg Synacthen given intradermally. After one month it was possible to give an intradermal injection (39th injection) of 0.20 ml of the drug (0.024 mg) without adverse reactions. It was then decided to give 0.40 ml (0.05 mg) by subcutaneous injection, but this was followed by severe adverse reactions with malaise, cutaneous erythema, a feeling of precordial constriction and uterine cramp. These symptoms only disappeared following cortisone, antihistaminic drugs, sympathomimetics and aminophylline. After this episode the patient refused to continue treatment and it was accordingly suspended.

DISCUSSION

Desensitizing treatment may be useful, or even very necessary, in patients affected by chronic diseases in which ACTH is the *only possible alternative to cortisone*, as for example, in the patients under examination here. There is no doubt that desensitizing treatment is possible, (and we have already shown this for other drugs, e.g. Pyramidon (11) and penicillin (12)), provided that graduated doses of the drug are used, either daily or every other day. Antihistaminic drugs should preferably be administered each time, and once the therapeutic dose has been reached it should be maintained with two-monthly, or, at the maximum, monthly doses. The lowest dose with which to commence treatment should be the lowest quantity of the drug capable, when injected intradermally, of inducing a positive reaction with a weal and erythema. It is imperative that treatment of this kind should be scrupulously carried out at a fully-equipped hospital, even if it is done in the out-patients' department.

SUMMARY

Three cases of allergy to synthetic corticotrophin (tetracosactide-depot) were submitted to specific desensitizing treatment using graduated doses of the drug. Therapy was completely successful in two patients, whilst the third suspended treatment.

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