Hypersensitivity reaction with intravenous GnRH after pulsatile subcutaneous GnRH treatment in male hypogonadotrophic hypogonadism

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Summary: Chronic pulsatile subcutaneous administration of low doses of gonadotrophin releasing hormone (GnRH) is an effective therapy for men with hypogonadotrophic hypogonadism. Hypersensitivity reactions to GnRH are rare.

We wish to report hypersensitivity reactions with intravenous GnRH after low dose subcutaneous pulsatile GnRH treatment in two men with hypogonadotrophic hypogonadism due to suprasellar disease.

Introduction

Hoffman & Crowley found that low dose pulsatile gonadotrophin releasing hormone (GnRH) administered at a frequency similar to the frequency of luteinizing hormone (LH) pulsations in normal men could normalize both pituitary and gonadal function and initiate early pubertal changes in men with idiopathic hypogonadotrophic hypogonadism over a 3 month period¹. Since that time numerous studies have confirmed these results.^{2,3}

Another subgroup of the hypogonadotrophic category, acquired GnRH deficiency due to suprasellar disease, can also benefit from pulsatile GnRH therapy.⁴ A hypersensitivity reaction to GnRH is rare and requires discontinuation of therapy.⁵ It is reported as a wheal and flare reaction resembling an urticarial allergic reaction at multiple old injection sites.

We wish to report two reactions with GnRH, one being life-threatening.

Case reports

Case 1

At the age of 13 this male patient was treated with cranial surgery for craniopharyngioma. After surgery the patient was hypopituitary and was

treated with deamino arginine vasopressin (DDAVP), hydrocortisone and thyroxine. At the age of 16 our patient still had hypogonadotrophic hypogonadism and there was no increase in circulating levels of either LH or follicle stimulating hormone (FSH) in response to releasing hormone (RH) (Relefact LHRH Hoechst, 100 µg intravenous bolus). At that time on examination we found that one testis had descended while the other was retractile and both were of prepubertal size. Since our patient primarily had suprasellar disease and did not have surgery within the fossa, we put him on a trial with pulsatile subcutaneous (s.c.) GnRH treatment with 5.0 10.0 and 2.5 µg/pulse/90 min. He initially responded with a rise in gonadotrophins, i.e. LH rose from mean 2.8 IU/l to 14.0 IU/l and FSH from 2.2 IU/l to 6.6 IU/l (normal values for LH=4.9–8.9 IU/l; FSH=3.1–6.2 IU/l), although testicular function could not be stimulated. Soon a progressive decline in LH and FSH levels occurred. The further lack of response was due either to the development of gonadotrophin deficiency or formation of antibodies. It persisted when the dose of LHRH was lowered and so the desensitization phenomenon was excluded as the cause of failure. Treatment with pulsatile GnRH was discontinued and then an acute 100 µg intravenous (i.v.) GnRH test was performed. Within minutes after administration he suffered bronchospasm and vascular collapse. He recovered upon repeated doses of 0.3 ml 1:1000 adrenaline

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Accepted: 23 September 1987

s.c., antihistamines, corticosteroids and aminophylline. There were no signs of hypersensitivity to GnRH at the site of needle puncture on the abdominal wall during pulsatile s.c. treatment. The only complaint was that during the last 20 days of pulsatile GnRH treatment he had generalized pruritus on his arms and legs without urticaria or erythema.

Skin prick testing with 1:1000 dilution of GnRH gave no reaction. Testing with 1:100 and 1:10 dilutions of GnRH gave a positive local reaction (papule, erythema, pruritus) and at this stage testing was stopped. Negative control was performed with saline. The same testing procedure was performed on another patient who was treated by pulsatile GnRH and none of the dilutions yielded a positive result, even when given intradermally.

It was concluded that the reaction was most likely anaphylactic since minute doses gave a positive result.

Case 2

A 20 year old man was found to have a suprasellar disease and to be hypopituitary. Acute 100 µg i.v. bolus GnRH test (Relefact LHRH Hoechst) was performed and a low gonadotrophin response was noted. A trial with pulsatile s.c. GnRH was started (5 µg/pulse/90 min) during which he did not complain of any hypersensitivity reaction. He had a good gonadotrophin response (LH rose from mean 1.4 IU/l to 15.0 IU/l and FSH from mean 1.4 IU/l to 4.7 IU/l), but testosterone levels remained low. Treatment with pulsatile GnRH was discontinued and an acute GnRH 100 µg i.v. test was performed. During the GnRH i.v. bolus the patient complained of malaise and pruritus localized to the abdomen where GnRH had been previously applied subcutaneously. He also noted a swelling and

redness of the skin around the needle marks, which resembled urticaria.

Skin testing to GnRH was done in a similar fashion as stated above. Skin prick testing with 1:1000, 1:100 and 1:10 dilutions of GnRH gave no reaction nor did intradermal testing with a 1:1000 dilution. Intradermal testing with 1:100 and 1:10 dilutions of GnRH gave positive local reactions. Undiluted GnRH applied intradermally also gave positive local reaction. As it was not certain whether these reactions were due to irritation of the skin, 0.5 ml of undiluted GnRH was given intravenously. Shortly after, the patient complained of malaise and a sensation of warmth in the head. There was no drop in blood pressure or change in pulse rate. No medication was given and the patient was closely observed. Twenty minutes later, he complained of intense pruritus of the skin on the abdomen where GnRH had been previously applied. Fairly large local swelling and erythema could be seen on every spot where there was a needle mark.

It was concluded that the patient was allergic to GnRH. We have reason to believe that this adverse reaction is dose-dependent as he had previously tolerated small doses when applied s.c.

Discussion

These serious reactions raise the problem of hypersensitivity to GnRH when minor or even no complaints exist during low dose s.c. GnRH administration, and of the safety of further standard i.v. GnRH testing. We suggest that prior to bolus i.v. application of GnRH after long term treatment with GnRH immunological testing is always necessary.

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