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Nafarelin in the Treatment of Endometriosis

Dose Management

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Key Words

Endometriosis

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Abstract

Nafarelin, a [gonadotropin-releasing](#) hormone agonist, has been shown to be effective in the treatment of endometriosis. The standard dosage is 200 µg bid intranasally. Side effects most commonly include those associated with estrogen deprivation. By assessing estrogen status, the standard dosage can be manipulated to minimize these side effects and increase patient compliance.

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Introduction

Nafarelin acetate, a synthetic analog of the decapeptide gonadotropin-releasing hormone (GnRH), has been commercially available since 1990 for the treatment of endometriosis. Estradiol concentrations in the range of 10-20 pg/ml typically result in the regression of endometriosis lesions. However, they also may be associated with loss of trabecular bone mineral, vasomotor symptoms and atrophy of secondary sexual characteristics. On the other hand, estradiol concentrations > 60 pg/ml are often associated with the growth of endometriosis lesions [1].

By altering the dosage of nafarelin, on the basis of estradiol concentration, we sought to maintain suppression made evident by symptoms of recurrence and lessen the associated vasomotor symptoms and atrophy of secondary sexual characteristics.

Material and Methods

Twenty-three consecutive women with laparoscopically proven endometriosis were treated with nafarelin acetate (Syntex, Palo Alto, Calif., USA) for pain relief, starting at the usual dosage of 200 µg bid intranasally.

Nafarelin was begun during the follicular phase of the menstrual cycle between cycle days 2 and 4. Baseline height and weight was recorded at the initial visit. Body surface area (BSA) was determined from a nomogram [2]. After 4 weeks of therapy, all patients returned for follow-up which included a pelvic examination, serum estradiol level and assessment of side effects or recurrent symptoms. Serum estradiol was measured using a commercially available radioimmunoassay (RIA) kit (Coat-A-Count Estradiol, DPC, Los Angeles, Calif., USA) with a detection limit as low as 10 pg/ml. The interassay and intraassay coefficients of variation were 8.1 and 7.0% respectively, when the mean estradiol level was 50 pg/ml.

Dosage was either increased to 200 µg tid intranasally if the estradiol level was > 60 pg/ml and symptoms persisted (i.e. pelvic pain, or vaginal bleeding). Dosage was decreased to 200 µg/ml qd alternating with 200 µg bid intranasally, if the estradiol level was < 20 pg/ml and if the patient complained of symptoms associated with estrogen deprivation. All patients finished a 6-month course of treatment.

Data was analyzed using Student's t test, χ^2 analysis and Fisher's exact test where appropriate. Differences were considered significant for $p < 0.05$.

Results

Twenty-three women were treated for pain relief secondary to endometriosis. The mean age of these women was 33.7 years (± 5.1 SD). The mean weight was 63.2 kg (± 11.1 SD), mean height was 165.7 cm (7.2 SD) and mean BSA was 1.69 (± 0.14 SD).

Patients were divided according to serum levels of estradiol obtained after 4 weeks of therapy. Thirty percent of the women had serum estradiol levels < 20 pg/ml. Twenty-six percent of the women had serum estradiol levels between 20 and 30 pg/ml, while the remaining 43% had serum estradiol levels > 30 pg/ml. Patient characteristics

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Table 1. Characteristics of women based on serum estradiol levels after four weeks of therapy
Characteristics

Serum estradiol levels

Six women had maintained their dosage despite the low levels of serum estradiol. These women were asymptomatic in terms of estrogen deprivation and pelvic pain.

; 30 pg/ml

> 30 pg/ml

13

33.1 $\pm$ 5.2 63.3 $\pm$ 11.2 165.7 $\pm$ 8.2 1.69 $\pm$ 0.14

Cases Age

Weight, kg Height, cm BSA

10

34.3 $\pm$ 5.1NS

63.0 $\pm$ 10.8NS

165.6 $\pm$ 6.1NS

1.70 $\pm$ 0.15NS

NS = Not significant by Student's t test.

that might have an influence on serum estradiol level and dosage were examined. Table 1 illustrates that there were no demonstrable differences in patients characteristics among women in terms of age, height, weight and BSA.

Three of the 10 women (30%) whose serum estradiol levels were > 30 pg/ml increased their dosage to 200 µg tid intranasally. All 3 women had pelvic pain and breakthrough bleeding as well as serum estradiol values exceeding 60 pg/ml. During the 6 months of therapy, these women were evaluated on a monthly basis. Two of the 3 women increased the dosage to 200 µg qid

intranasally based on serum estradiol levels exceeding 60 pg/ml along with complaints of pelvic pain and/or breakthrough bleeding.

Serum women continued on the same dosage, since they had no complaints of pelvic pain or vaginal bleeding. However, all 7 women did experience some hot flashes.

Seven of the 13 women (54%) whose serum estradiol level was < 30 pg/ml had decreased their dosage to 200 µg/ day. All 7 women had serum estradiol levels < 20 pg/ml and complained of symptoms of estrogen deprivation (hot flashes and vaginal dryness). Three of the 7 patients (43%) had reduced their dosage to 200 µg every other day in the remaining months of therapy. In these 3 patients serum estradiol levels remained < 30 pg/ml until the end of therapy.

Discussion

In this study, 10 of the 23 women either increased or deduced their dosage after the first month of therapy. Levels after the first month of treatment have been reported < 28 pg/ml at dosages > 400 µg/day [3]. Individual variation has also been reported in a smaller study using varying dosages of nafarelin [4]. In this small sample, heterogeneity in circulating estradiol levels could not be explained on the basis of height, weight, BSA or age.

In treated women whose estradiol levels were < 30 pg/ ml, alteration of dosage is crucial not only to relieve the hot flashes but other sequelae of estrogen deprivation, namely reductions in bone density. In one particular study, low doses of nafarelin (200 µg/day) were associated with constant bone mineral measurements, whereas high doses (400 µg/day) revealed significant decreases in bone mineral content [5]. Prompted by the desire to modify risks, several series of pilot studies have explored the addition of progestins to the regimen [6].

There are other potential side effects that may or may not be associated with estrogen deprivation, such as short-term memory loss. One study revealed 56% of the patients using nafarelin at 200 µg bid intranasally reported some form of short-term memory loss [7].

Cost of medication is also a factor and those women who decrease their dosage based on serum estradiol levels, would be able to cut the expense in half.

In those women with high circulating levels of estradiol after 4 weeks of therapy, the delivery system allows one to adjust the dosage up or down with relative ease. The dosage can be increased to 200 µg bid alternating with 200 µg tid intranasally if serum estradiol levels exceed 60 pg/ml. In these cases, compliance is an issue as well and many women may benefit from a depot product.

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