Metabolism
Clinical and Experimental

VOL 50, NO 9 SEPTEMBER 2001

PRELIMINARY REPORT

Use of Gonadotropin-Releasing Hormone Analog With Tibolone to Prevent Cyclic Attacks of Acute Intermittent Porphyria

Camil Castelo-Branco, Juan José Vicente, and Juan Antonio Vanrell

A 25-year-old woman with a 10-year history of recurrent attacks of acute abdominal pain just before menstrual periods had acute intermittent porphyria (AIP) diagnosed when she was 23.5 years old. Many acute attacks required hospitalization. Suppression of the menstrual cycle with a gonadotropin-releasing hormone analog (GnRHa; triptorelin) and tibolone administration as add-back therapy resulted in absence of acute porphyric attacks. The patient had no acute attacks over a 1-year follow-up period. This case suggests that long-term GnRHa therapy with tibolone add-back may be a therapeutic option for patients with AIP.

ACUTE INTERMITTENT porphyria (AIP) is an uncommon inherited metabolic disorder in which a disturbance of heme synthesis is caused by a deficiency of hydroxymethylbilane synthase (porphobilinogen deaminase). Symptoms may be severe and of rapid onset. Abdominal pain, tachycardia, vomiting, paralysis, mania, coma, and death can ensue. Clinical expression of the disease often occurs with exposure to factors such as sex steroid hormones and certain of their metabolites, dietary factors, and a wide variety of drugs. Some women experience exacerbations of AIP in relation to the menstrual cycle, and in a minority, disabling attacks occur with almost every cycle. Preliminary reports indicate that agonistic analogs of gonadotropin-releasing hormone analog (GnRHa) might benefit such patients[1,2], however, the related hypoestrogenism causes menopausal-type symptoms and bone loss, which limit how long treatment can be given. Treatment with a GnRHa with steroid add-back has been explored to permit long-term therapy. We present the case of a patient with AIP whose acute attacks were provoked by each menstrual cycle. Therapy with triptorelin and tibolone add-back therapy prevented these attacks.

CASE REPORT

The patient was a 25-year-old white woman with a family history of abdominal attacks and mental disorder. She presented with acute abdominal pain with no clear cause since she was teenager during almost every premenstrual period. Gynecologic evaluation revealed no abnormalities that could cause menstrual disorders. The crises increased in severity every time, and was diagnosed AIP when she was 23.5 years old. Since the diagnosis, 6 additional attacks that required hospitalization and therapy with intravenous glucose and hematin occurred in relation to the patients menstrual cycles. The laboratory tests at this time showed high levels of urinary porphobilinogen (112.46 mg/L; normal, 0 to 2 mg/L) and Δ-aminolevulinic acid (94.32 mg/L; normal, 0 to 5 mg/L). Total urinary porphyrin level was 2,550.5 μg/L (normal, 0 to 249 μg/L), of which uroporphyrins comprised 191 μg/24 h (normal, 1 to 40 μg/24 h). Finally, results of tests for porphyrins in blood and feces were normal, and coproporphyrin levels in urine were 117 μg/24 h (normal, 1 to 283 μg/24 h), distinguishing this case from acute attacks of variegate porphyria or hereditary coproporphyria.

To prevent cyclical attacks, therapy with triptorelin depot (3.75 mg intramuscularly and monthly GnRHa) to suppress menstrual cycles and tibolone (2.5 mg/d) as add-back therapy to prevent menopause-induced or-related symptoms were administered. After 1 year of follow-up, no further acute attacks occurred. Occasional episodes of dark urine were noted with high porphobilinogen (11.8 mg/L) and normal Δ-aminolevulinic acid (3.06 mg/L) levels. No menses have been noted, but no menopausal symptoms were reported. Moreover, bone mass assessed by dual x-ray absorptiometry (DPX-L system; Lunar Radiation Corp,

From the Institut Clinic de Ginecologia, Obstetricia i Neonatologia, Hospital Clinic, Faculty of Medicine, University of Barcelona, Barcelona, Spain.

Submitted June 9, 2000; accepted March 11, 2001.

Address reprint requests to Camil Castelo-Branco, MD, Institut Clinic de Ginecologia, Obstetrícia i Neonatologia, Hospital Clinic, C/ Villaroel 170, 08036-Barcelona, Spain.

0026-0495/01/5009-0001$35.00/0
doi:10.1053/meta.2001.25587

Madison, WI) remained unchanged (1.182 g/cm^2 and 1.179 g/cm^2 for basal and 1-year follow-up measurements, respectively).

DISCUSSION

Continued administration of GnRHa results in down-regulation of GnRH receptors, with resultant reduction in serum gonadotropin and ovarian steroid levels, preventing ovulation and causing a reversible state of hypogonadism. These low estradiol levels cause menopausal-type symptoms (ie, vasomotor inestability and accelerated bone loss), which limit the duration for which treatment can be given. Treatment with a GnRHa with steroid add-back has been explored to permit long-term therapy without bone loss.[3] Oral contraceptives are probably contraindicated in AIP patients, so they are not an appropriate alternative to add-back therapy. Although medroxyprogesterone has been used with success in add-back therapy for AIP,[2] progestins are inducers of hepatic heme synthesis and p450 enzymes[4]; therefore, there is no guarantee that such a therapy is safe in every patient. In addition, bone density was not measured in this study,[2] and progestins alone appear not to be a complete and effective add-back therapy.[5] Finally, estrogen therapy has been used safely as add-back in subjects treated with GnRHa.[6]

The reason we used the described regimen in this patient was to prevent unwanted effects of prolonged hypoestrogenism such as osteoporosis, vaginal dryness, and hot flashes. The long-acting GnRHa avoids cyclical ovarian steroid production and cyclical attacks, and tibolone, a noretisterone derivate with weak estrogenic, progestogenic, and androgenic activity, prevents the deleterious effects of prolonged GnRHa therapy.[7] Moreover, tibolone in subjects with demonstrated hypoestrogenism do not induce endometrial proliferation, and the patients usually remain amenorrheic[8,9]; this is another reason for electing tibolone rather than transdermal estradiol as add-back therapy. So far, the patient has been treated for 12 months. During this period, she had no menses and no further porphyric attacks and showed no adverse effects of therapy. As in the other cases reported, porphobilinogen excretion was not completely normalized during GnRHa treatment.[1,2] This regimen also provides reliable contraception. Finally, before tibolone is considered safe to administer in AIP, this drug should also be studied in experimental animals and cultured hepatocytes to determine if it has the properties of inducing hepatic heme synthesis. Careful observation of this and other cases will help determine whether the present or the previously proposed treatment modalities should be used.

REFERENCES

1. Anderson KE, Spitz IM, Bardin W, et al: A gonadotropin releasing hormone analogue prevents cyclical attacks of porphyria. Arch Intern Med 150:1469-1474, 1990

2. Bargetzi MJ, Meyer UA, Birkhaeuser MH: Premenstrual exacerbations in hepatic porphyria: Prevention by intermittent administration of an LH-RH agonist in combination with a gestagen. JAMA 261:864, 1989 (letter)

3. Stewart EA, Friedman AJ: Steroidal treatment of myomas: Preoperative and long-term medical therapy. Semin Reprod Endocrinol 10:344-348, 1992

4. Simpson ER: Cholesterol side-chain cleavage, cytochrome p450, and the control of steroidogenesis. Mol Cell Endocrinol 13:213-227, 1979

5. Lindsay P, Shaw R, Coelingh Bennink H, et al: The effect of add-back treatment with tibolone on patients treated with the gonadotropin-releasing hormone agonist triptorelin. Fertil Steril 65:342-348, 1996

6. Anderson KE: The porphyrias, in Zakim D, Boyer T (eds): Hepatology (ed 3). Philadelphia, PA, Saunders, 1996, pp 417-463

7. Taskin O, Yalcinoglu Al, Kucuk S, et al: Effectiveness of tibolone on hypoestrogenic symptoms induced by goserelin treatment in patients with endometriosis. Fertil Steril 67:40-45, 1997

8. Ginsburg J, Prelevic G, Butler D, et al: Clinical experience with tibolone over 8 years. Maturitas 21:71-76, 1995

9. Berning B, Kuijk CV, Kuiper JW, et al: Effects of two doses of tibolone on trabecular and cortical bone loss in early postmenopausal women: A two year randomized, placebo-controlled study. Bone 19: 395-399, 1996