Prevention of Premenstrual Exacerbation of Hereditary Coproporphryia by Gonadotropin-Releasing Hormone Analogue

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A 20-year-old Japanese female needed frequent hospitalization due to premenstrual exacerbation of hereditary coproporphryia (HCP). Intranasal buserelin acetate, a gonadotropin-releasing hormone analogue, was given to suppress her menstrual cycles. Her porphyric symptoms subsided dramatically as she became amenorrhoeic. Urinary excretion of porphyrin derivatives fell significantly. She has been free from recurrent attacks, but suffers a minor porphyric attack once in 5 years. However, borderline osteopenia secondary to hypoestrogenism has been noted. Although these analogues are potent in suppressing estrogen-induced porphyric symptoms, due precautions should be taken to avoid bone demineralization in the long-term use. (Internal Medicine 38: 365–368, 1999)

Key words: buserelin, luteinizing-hormone releasing hormone analogue, porphyria

Introduction

Hereditary coproporphryia (HCP) is an inherited metabolic disorder caused by a reduced bioactivity of the key enzyme coproporphyrinogen oxidase, the sixth enzyme in the heme biosynthetic pathway (1). Premenstrual exacerbation is a clinical burden in patients with HCP as well as in those with acute intermittent porphyria (AIP) (1, 2). Endocrine manipulation with oral contraceptives (3), progestins or androgens (4) has been employed in some cases. Intravenous use of heme derivatives is also useful to prevent cyclical attacks in acute porphyrias (5, 6). Anderson and colleagues introduced agonistic analogues of gonadotropin-releasing hormone (GnRH) to prevent such attacks in 1984 (2). Some reports have described the usefulness of these products (7–13). However, the clinical experience has been limited exclusively to patients with AIP, and in only one patient with variegate porphyria (10). We report a case of HCP showing a remarkable suppression of premenstrual exacerbation with treatment by buserelin (D-Ser[TBU]⁶-des-Gly-NH₂¹⁰) acetate, a GnRH analogue. We also discuss the possible adverse events in the long-term use of these analogues.

For editorial comment, see also p 307.

Case Report

A 20-year-old Japanese woman was admitted to our hospital in December 1992, for premenstrual pain in the abdomen and the extremities. The early course of her medical history had been described previously (14, 15). Briefly, porphyria was recognized at age 15 years. Her urinary samples and those of her father demonstrated excess porphobilinogen (PBG), but those of her mother did not. She had been misinterpreted as suffering from AIP (14). Intravenous hematin brought dramatic relief of her acute porphyric symptoms. She needed two more series of hematin infusion in February and March 1993, respectively. It was burdensome, expensive, and also potentially hazardous to continue hematin treatment (15). Buserelin acetate, one of the GnRH analogues was thus commenced to prevent recurrent attacks in April 1993 with the patient's informed consent. Since then, her urinary excretion of PBG, coproporphyrin and δ -aminolevulinic acid (ALA, data not shown) fell significantly (Fig. 1). Mild hot flushes were noted to be a climacteric symptom. GnRH provocation test (100 μ g i.v.) revealed almost complete suppression of both follicle stimulating hormone (4.4 to 5.7 IU/L, peak value at 120 minutes) and luteinizing hormone (1.8 to 5.8 IU/L, peak value at 30 minutes) in August 1993. She has been amenorrhoeic for 5 years with a minor porphyric attack on one occasion. Even when she suffered from acute gastroenteritis and acute hepatitis due to cytomegalovirus infection in August 1997, and diclofenac sodium, one of the porphyria-inducing agents, was accidentally given

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Figure 1. Clinical course and urinary excretion of porphyrin derivatives.

on this instance, she remained asymptomatic. However, the urinary excretion of porphyrin derivatives rose significantly. Urinary excretion of ALA was also mildly elevated from 3.0 to 7.6 mg/day. The dosage of buserelin was carefully tapered from 900 to 150 µg daily without recurring symptoms. In July 1996, the correct diagnosis of HCP was established by high performance liquid chromatography analysis of her urine and fecal sample (15). Further, a deletion mutation was demonstrated on her coproporphyrinogen oxidase gene as described elsewhere (16). In September 1997, her bone mineral density determined by X-ray bone densitometer QDR 4500 (Hologic Inc., Waltham, MA) was revealed to be 0.811 g/cm², which was 80% of the mean of age-matched females (17). Hypercholesterolemia with borderline hypertension was also noted.

Discussion

HCP is an inborn metabolic disorder resulting from a reduced bioactivity of coproporphyrinogen oxidase (1). The prevalence of the disease is lower than that of AIP. Among 612 porphyrics reported in Japan by 1993, 145 had AIP, and 23 had HCP (18). Prevalence of HCP was estimated to be two per million in Denmark (19) and 15 per million for AIP in Sweden (20). Clinical symptoms as well as treatment of HCP resemble those of AIP.

Although hematin is a potent therapeutic agent for acute porphyric attacks (5, 6), it brings symptomatic relief only tem-

porarily (15). It is essential to carefully avoid the precipitating factors for the patients, because the disease is essentially a life-long process. After the first report by Anderson and colleagues (2), 18 cases with acute porphyrias have been treated with GnRH analogues (Table 1). Like most cases with AIP (2, 7–13) or variegate porphyria (10), we observed a good response in this case. Thus, patients with HCP may be an additional indication for the treatment with the GnRH analogues.

GnRH analogues have an inhibitory effect on reproductive function through pituitary desensitization when administered repeatedly (21). Both follicle stimulating hormone and luteinizing hormone were completely suppressed in our case four months after the commencement of the agent. The implications of sex steroids in the pathogenesis of clinical porphyria remain controversial. Oral contraceptive agents have been used to prevent cyclic attacks of porphyria (3, 4). However, progesterone has been thought to increase heme catabolism (22), and synthetic progesterone induces clinical porphyria (23). Estrogen is generally believed to have only a weak action on porphyrin biosynthesis (24, 25). In this context, a lower progesterone secretion in response to pituitary suppression may lead to decreased porphyrin secretion. In fact, urinary excretion of porphyrin derivatives fell significantly after the introduction of intranasal buserelin in the present case. The clinical symptoms were also ameliorated with no further premenstrual exacerbation, except for one minor attack in five years. It should be noted that GnRH analogues did not normalize porphyrin

Table 1. LH-RH Analogues for Acute Porphyrias

Author	Year	Analogue	Route	No. of cases	Porphyria	Reference
Anderson, KE	1984	[D-His[ImBzl] ⁶ , Pro ⁹ -NET]GnRH	s.c.*	1	AIP [@]	2
Anderson, KE	1986	[D-His[ImBzl] ⁶ , Pro ⁹ -NET]GnRH	i.n.**	4(3) ^{##}	AIP	7
Semon, C	1986	buserelin	i.n.	1	AIP	8
Norman, RJ	1988	[D-Trp ⁶ , Pro ⁹ -NET]GnRH	s.c.* [#]	1	AIP	9
Bargetzi, MJ	1989	buserelin	i.n.	2	AIP, VP ^{@@}	10
Herrick, KEL	1990	buserelin	i.n.	7	AIP	11
Anderson, KE	1990	[D-His[ImBzl] ⁶ , Pro ⁹ -NET]GnRH	s.c., i.n.	6(2) [#]	AIP	12
Bode, H	1992	buserelin	i.n.	1	AIP	13
present report	1999	buserelin	i.n.	1	HCP [§]	—

*subcutaneous, **intranasal, #originally described merely as "injected", ##Numbers in parentheses indicate those of original cases, @acute intermittent porphyria, @@variegate porphyria, §hereditary coproporphyria.

excretion in most cases (8–13). Clinical improvement was observed without a decrease in the porphyrin excretion in those cases. Actually, the urinary porphyrin derivatives are still higher than normal with the buserelin treatment in our case. The clinical course of porphyria is variable and spontaneous remission occurs frequently (1, 26). The exact mechanism by which GnRH analogues bring about clinical remission of porphyria remains to be elucidated.

One must be careful that the initial agonistic action of the analogues may lead to a deterioration of the porphyric symptoms. Fortunately, this condition did not occur in the present case. Hot flushes were her only symptom. Nevertheless, borderline osteopenia secondary to hypoenestrogenism was observed four and a half years after the initiation of buserelin treatment. Progressive bone loss due to bone demineralization must be carefully monitored, and proper therapeutic intervention should be considered in the long-term use of these agents.

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