Novel Therapeutic Approaches in Cushing's Disease: PPar-Gamma Agonists

Cushing Hastalığında Yeni Tedaviler: PPAR-Gamma Agonistleri

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Abstract

The rationale for the treatment of Cushing's disease is to normalize serum cortisol and ACTH levels, while preserving the anterior pituitary function. The treatment of choice for Cushing's disease is surgery. However, in some circumstances the patients can need further treatment modalities including reoperation, radiotherapy and medical therapy. The medical therapy for Cushing's disease is preferred in order to decrease the excessive cortisol levels prior to surgery, to decrease the complications or to control hypercortisolaemia while awaiting the full effect of radiotherapy or of the treatment of metastatic disease. Between the two groups of drugs-steroidogenesis inhibitors and centrally acting drugs-steroidogenesis inhibitors, particularly metyrapone and ketoconazole, are the preferred agents. Centrally acting drugs may be superior to steroidogenesis inhibitors in the treatment of Cushing's disease by decreasing the adrenocorticothrophic hormone (ACTH) levels and inhibiting the tumor growth. In this review we are aimed to evaluate the possible use of peroxisome proliferator-activated receptor-gamma agonists as centrally acting drugs in the treatment of Cushing's disease. *Turk Jem 2009; 13: 80-3*

Key words: Cushing's disease, PPAR-gamma agonists

Özet

Cushing hastalığının tedavisinde amaç, kortizol ve adrenokortikotropik hormon (ACTH) düzeylerini normale getirmek ve ön hipofiz fonksiyonlarını korumaktır. Cushing hastalığında ilk seçilecek tedavi cerrahidir; fakat bazı hastalarda ikinci cerrahi, radyoterapi ve medikal tedavi gerekebilmektedir. Medikal tedavi; cerrahi öncesi kortizol düzeylerini normale getirmek, radyoterapinin etki etmesinin beklendiği dönemde hiperkortizolemiyi kontrol altında tutmak ve metastatik hastalığın tedavisinde kullanılmaktadır. Medikal tedavide iki grup ilaç vardır: steroidogenez inhibitörleri ve santral etkili ilaçlar. Tedavide steroidogenez inhibitörleri daha etkili olduğu için özellikle metirapon ve ketokanazol tercih edilmektedir. Santral etkili ilaçlar ise ACTH düzeylerinde düşüş sağlama ve tümör büyümesini kontrol altına alma gibi etkilerle steroidogenez inhibitörlerine üstünlük sağlayabilir. Bu derlemede, santral etkili ilaçlardan peroxisome proliferatör aktive reseptör (PPAR) gamma agonistlerinin Cushing hastalığı tedavisindeki yerini inceleyeceğiz. *Türk Jem 2009; 13: 80-3*

Anahtar kelimeler: Cushing Hastalığı, PPAR-gamma agonistleri

Introduction

Pituitary tumors are generally benign and the morbidity of them is a consequence of hormone hypersecretion or compressive effects. Hypersecretion of prolactin, adrenocorticothrophic hormone (ACTH), growth hormone (GH), thyrotrophin-thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) leads to associated endocrinological syndromes. In some cases, the adenoma is non-functional, leading to local compression disorders. The most common cause of Cushing's syndrome is ACTH-secreting pituitary tumors. Generally, ACTH-secreting pituitary adenomas are small tumors and the hypersecretion of ACTH and cortisol leads to a debilitating course of the disease. In 90% of patients, the tumor is smaller than 10 mm, but ACTH hypersecretion and hypercortisolaemia cause obesity, insulin resistance, hyperglycemia, dyslipidemia, hypertension, diabetes mellitus, osteoporosis, coronary artery disease, psychiatric problems, which further increase the mortality (1,2).

The rationale for the treatment of Cushing's disease is to normalize serum cortisol and ACTH levels, while preserving the anterior pituitary function. The treatment of choice for Cushing's disease is surgery. However, in some circumstances the patients can need further treatment modalities including reoperation and

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radiotherapy (3-6). Although pituitary radiotherapy is effective in controlling the hypercortisolaemia, it can take several years to have its effect (7). The medical therapy for Cushing's disease is not a promising mode of therapy, however, it is needed in order to decrease the excessive cortisol levels prior to surgery, to decrease the complications, or to control hypercortisolaemia while awaiting the full effect of radiotherapy or of the treatment of metastatic disease.

The medical therapy in Cushing's disease is managed by two groups of agents (Table 1):

1. Adrenal steroidogenesis inhibitors
2. Drugs, modulating the ACTH release from the pituitary

The agents inhibiting steroidogenesis include: metyrapone, ketoconazole, mitotane, aminoglutethimide, trilostane, etomidate. The centrally acting drugs modulating the ACTH secretion and under investigation are: dopamine agonists, somatostatin analogues, cyproheptadine, ritanserine, sodium valproate and PPAR agonists.

The currently available drugs for Cushing's disease have limited efficacy with high incidence of adverse effects. Steroidogenesis inhibitors are superior to central acting drugs, and metyrapone and ketoconazole are the preferred agents. Metyrapone inhibits the conversion of 11-deoxycortisol to cortisol resulting in an increase in 11-deoxycortisol levels. Long-term metyrapone treatment may normalize the serum cortisol levels in patients with Cushing's syndrome. However, hypoadrenalism must be avoided. Increased cortisol precursors may induce hyperandrogenism and hence hirsutismus in women. In Cushing's disease, metyrapone does not lead to tumor shrinkage, but causes elevation in ACTH levels. The oral antifungal agent ketoconazole inhibits 11beta-hydroxylase and C17-20 lyase enzymes, and therefore diminishes the cortisol and sex steroid synthesis. The onset of the full effect of the drug is slow. The risk of hypoadrenalism is small, but ketoconazole has antiandrogenic effects and may cause gynecomastia and decreased libido in men. Co-administration of these drugs adds benefits in term of decreasing the adverse events. Hepatotoxicity limits the use of ketoconazole, and hirsutismus, hypertension and the risk of overtreatment leading to hypoadrenalism are the limitations of metyrapone. Moreover, both drugs do not inhibit pituitary tumor growth or ACTH secretion. Centrally acting drugs are thought to overcome this issue. In the treatment of Cushing's disease, the previous centrally acting drugs were not promising. However, new drugs in this group, such as peroxisome proliferator-activated receptor-gamma (PPAR-gamma) agonists and somatostatin analogues, have been developed.

Table 1. Medical agents for treating Cushing's syndrome

Adrenal steroidogenesis inhibitors	**Drugs modulating ACTH release from the pituitary**
Metyrapone	Dopamine agonists
Ketoconazole	Somatostatin analogues
Mitotane	Cyproheptadine
Aminoglutethimide	Ritanserine
Trilostane	Sodium valproate
Etomidate	PPAR agonists

PPAR-gamma is a member of nuclear receptor superfamily. PPAR-gamma heterodimerizes with retinoid X receptor to function as a transcription factor, binding to peroxisome-proliferating response elements (8,9). PPAR-gamma was shown to be expressed in many tissues including adipocytes, monocytes, macrophages, liver, skeletal muscle, breast, colon, and type 2 alveolar pneumocytes (10-15). Activation of PPAR-gamma leads to several effects on adipogenesis, carbohydrate and lipid metabolism, inflammation processes and cell proliferation. Animal studies support the idea that PPA- gamma behaves as a tumor suppressor gene.

Synthetic PPAR agonists include thiazolidinedion (TZD) compounds and triterpenoids. Thiazolidinedions (rosiglitazone and pioglitazone) are in clinical use for the treatment of diabetes due to their insulin sensitizing effect. Synthetic PPAR agonists are shown to inhibit the growth of many tumors including breast, prostate and colon cancer cells. Heaney et al. demonstrated immunocytochemical PPAR-gamma expression in autopsy-derived normal human pituitary tissue which were primarily restricted and co-localized with ACTH (16). However, in pituitary tumors, including ACTH secreting tumors, PPAR-gamma expression was shown to be higher than in the normal pituitary (17). PPAR-gamma ligands inhibit in vitro and in vivo corticotroph tumor growth by increasing the apoptotic pituitary corticotroph tumor cells. In rat and human corticotroph adenoma cell series, troglitazone and rosiglitazone decreased the tumor cell growth, increased the apoptosis and lowered the ACTH secretion by inhibiting POMC mRNA expression (16). In animal studies, PPAR-gamma was shown to act as tumor suppressor gene (18,19). These findings led to the hypothesis that synthetic PPAR-gamma agonists may be of value in treating corticotroph pituitary adenomas by inhibiting ACTH synthesis and secretion, and by inhibiting tumor growth. To test this hypothesis, clinical studies investigating the role of PPAR-gamma agonists in the treatment of Cushing's disease were conducted. In a small group of patients, after treatment with rosiglitazone 8 mg for 16 weeks, 4 of 5 patients had a decline in serum cortisol levels (20). In another study, rosiglitazone treatment prior to pituitary surgery in two patients failed to decrease cortisol levels in one patient and the other patient, who seemed to respond, was on concomitant ketoconazole therapy (21). Ambrossi et al. conducted the largest study on the treatment of Cushing's disease with rosiglitazone (22). Fourteen patients with active Cushing's disease were included in the study. Of the 14 patients, 7 had pituitary surgery. Rosiglitazone 8 mg/day normalized urinary free cortisol (UFC) at 30-60 days in 6 out of 14 patients with active Cushing's disease. Acute administration had no effect on plasma ACTH. Follow-up of 2 out of 6 responsive patients for 7 months, showed mild improvement in the clinical features of the disease. Immunohistochemical analysis of pituitary tumors removed from two responder and two non-responder patients showed a similar intense immunoreactivity for PPAR-gamma in about 50% of cells. They concluded that administration of rosiglitazone normalizes cortisol secretion in some, but not all, patients with Cushing's disease, at least for short periods. During the treatment period, 3 patients had glycemic improvement and increased insulin sensitivity. In two responder patients with nor-

mal insulin sensitivity at the baseline, no change was observed in insulin sensitivity after treatment. No clinical side effects were observed except for new developing hypercholesterolemia in one patient. Insulin sensitivity did not change after treatment in non-responder patients. Giraldi et al. treated 10 patients with pituitary adenoma with rosiglitazone for acute challenge and protracted treatment (23). Four patients were prior to pituitary surgery, 4 had recurrence after pituitary surgery and 2 had inadequate pituitary surgery. Acute challenge with rosiglitazone in 5 patients did not lower cortisol and ACTH levels. Among the patients treated with 4-16 mg rosiglitazone for 1,5-8 months, four patients showed a persistent reduction in urinary free cortisol levels (up to 24% of pretreatment values), achieving normalization in three. In the remaining patients, urinary free cortisol, plasma ACTH and cortisol decrements had wide, random oscillations indicating that disease activity was substantially unchanged. Although effective in a subset of patients, protracted rosiglitazone administration did not consistently restrain ACTH and cortisol secretion in patients with Cushing's disease. Except for three patients who reported subjective amelioration during rosiglitazone treatment, rosiglitazone was not well tolerated because of oedema, weight gain (2-5 kg), somnolence and increased hirsutism. Two patients complained of easy bruisability. Glycaemic control and blood pressure were stable, except for one patient who developed a hypertensive crisis. No significant change in liver function tests, lipid profile, and haemoglobin levels was observed during rosiglitazone treatment. In another study on 30 patients with type 2 diabetis mellitus treated with rosiglitazone 8mg/day for 26 weeks, pre-and post-treatment cortisol levels did not differ (24). The studies on PPAR agonist action in Cushing's disease were conducted mostly with rosiglitazone. Only one study with short duration, which investigated the effect of pioglitazone on five patients with Cushing's disease, could not find an improvement in cortisol, ACTH and urinary cortisol levels (25). Pioglitazone have both PPAR-gamma and alpha activity, which may result in the difference between the actions of rosiglitazone and pioglitazone. Rosiglitazone has a higher in vitro binding affinity for the PPAR-gamma receptor and may be more potent than pioglitaozone, although, there is no evidence that either drug is more effective biologically or clinically. The variable potency of PPAR-gamma agonist, which was used, may be another reason for the difference. Furthermore, the duration of the pioglitazone study was short.

The differences between animal and human studies may be a result of different growth potentials of the pituitary cells. The growth potential of human corticotroph cells is lower. Rosiglitazone is suggested to decrease the ACTH levels with its antiproliferative effect and therefore, a protracted treatment of rosiglitazone may be needed to suppress the ACTH secretion. As macroadenomas have a higher proliferative potential than microadenomas, rosiglitazone may be effective in macroadenomas. The antiproliferative effect of rosiglitazone, rather than its antidiabetic effect, is seen in higher doses. The differences in the drug's treatment dose may be another reason for the discrepancy between animal and human studies.

Nelson syndrome is another challenging situation with sustained elevated ACTH levels. ACTH lowering effect of TZD's are studied in this patient group. 3 patients with Nelson syndrome were treated with rosiglitazone 4mg for 1 month and then 8mg, and ACTH levels decreased in 2 patients (26). However, in 1 patient ACTH increased to its incipient levels. In another study, rosiglitazone treatment for 12 weeks failed to decrease the ACTH levels in 7 patients (27). Munir et al. also showed that rosiglitazone 12 mg/day did not change circulating ACTH levels over time in patients with Nelson syndrome (28). In these patients the pituitary adenoma was shown to express PPAR-gamma in the specimens of pituitary surgery before adrenalectomy. The authors suggested that Nelson syndrome, as an aggressive tumor, may have diminished PPAR-gamma expression.

Emery et al. suggested that the antiproliferative effect of rosiglitazone may be independent from PPAR-gamma (29). They showed that PPAR-gamma antagonism did not reverse the antiproliferative effect of rosiglitazone and pioglitazone.

In conclusion, the preferred drugs in the treatment of Cushing's disease are steroidogenesis inhibitors. However, they fail to decrease the ACTH levels and have no effect on pituitary tumor growth. Central acting drugs in order to normalize both ACTH and cortisol levels and to regress the tumor growth may be new alternatives in the medical treatment for Cushing's disease. PPAR-gamma agonists are one of the drugs in this group, as its PPAR-gamma expression was shown in corticotroph adenomas. However, PPAR-gamma agonists failed to reproduce the effect seen in vitro and in animal studies on the treatment of Cushing's disease. Higher doses than used in diabetes mellitus and longer treatment periods may be more effective in treating these patients with PPAR-gamma agonists. Further studies are needed to clarify the potency of longer treatment duration with high doses of PPAR-gamma agonists.

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