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THE INFLUENCE OF TREATMENT WITH INTRAVENOUS GLUCOCORTICOIDS ON HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Rozprawa na stopień naukowy doktora nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne

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Glucocorticoids (GCs) are commonly used to treat chronic diseases due to their anti-inflammatory and immunosuppressive effects. However, long-term use of glucocorticoids (GCs) can suppress the hypothalamic-pituitary-adrenal (HPA) axis, leading to glucocorticoid-induced adrenal insufficiency (GI-AI). GI-AI is a severe complication of GC therapy that may cause life-threatening adrenal crises. The risk of GI-AI is determined by various factors such as duration of GC therapy, form of administration, dose, potency of GCs, and use of medication that affects the metabolism of GCs.

According to the guidelines published by the European Group on Graves' Orbitopathy (EUGOGO), the recommended treatment for moderate-to-severe and active Graves' orbitopathy (GO) involves the administration of intravenous methylprednisolone (ivMP) pulses every 7 days for 12 consecutive weeks in total cumulative dose of 4.5 g or 7.5 g.

Early diagnosis and appropriate treatment of GI-AI are crucial due to the risk of a life-threatening adrenal crisis. So far, the published analyses have described no cases of AI in patients with moderate-to-severe and active GO treated with ivMP according to EUGOGO guidelines. However, it is important to note that these studies were conducted on a small number of patients and using one diagnostic method.

Presented doctoral dissertation includes three thematically consistent articles which evaluate the impact of ivMP treatment administered in 12 weekly pulses with a total dose of either 4.5 g or 7.5 g on the function of adrenal cortex. The analysis was performed using data obtained from 35 patients treated for moderate-to-severe and active GO according to EUGOGO recommendations. The conducted studies had the following objectives: 1) to analyze the effect of 12 weekly ivMP pulses at a cumulative dose of 4.5 g on the adrenal cortex function using a stimulation test with a synthetic analog of adrenocorticotropic hormone (ACTH) at a dose of 250 µg; 2) to assess the incidence of GI-AI during the use of 30 mg of prednisone in a gradually reduced dose following cessation of ivMP therapy; 3) to analyze the impact of 12 weekly ivMP pulses in a cumulative dose of 4.5 g or 7.5 g on the functioning of the adrenal cortex using a stimulation test with synthetic ACTH at a dose of 1 µg; 4) to provide a detailed summary of current knowledge on the epidemiology, pathophysiology, diagnosis, and treatment of GI-AI, with particular emphasis on available schemes for discontinuing chronic GC therapy.

Article number 1 aimed to analyze the impact of ivMP on adrenal function by evaluating serum, salivary cortisol, serum dehydroepiandrosterone sulfate (DHEA-S), and plasma ACTH levels. Fourteen patients received ivMP treatment (cumulative dose of 4.5 g in 12 weekly infusions) followed by oral prednisone (for 3 months). In patients with morning serum cortisol <10 μg/dl a high-dose (250 μg) ACTH stimulation test was performed. GI-AI was ruled out if the serum cortisol level was ≥18.1 μg/dl at 30. or 60. minute after ACTH administration. All patients showed normal adrenal function in the ACTH stimulation test before the 12th ivMP pulse. Following prednisone treatment, one patient was diagnosed with GI-AI. DHEA-S levels were significantly lower before the 12th ivMP pulse and after oral prednisone (p=0.015 and p=0.00002, respectively) compared to evaluation before therapy. DHEA-S levels were below the reference range in one and three patients before the 12th ivMP pulse and after prednisone therapy, respectively. For the first time, we observed decreased serum (p=0.05) and salivary (p=0.011) cortisol levels after oral prednisone therapy compared to the evaluation before therapy. Treatment with ivMP in a cumulative dose of 4.5 g affects adrenal function, causing a severe impairment of DHEA-S secretion. Additional therapy with oral GCs following ivMP can cause GI-AI.

Article number 2 for the first time evaluated the impact of ivMP pulses on adrenal reserve using a low-dose (1 μg) ACTH stimulation test. Adrenal function was assessed in 21 patients treated for moderate-to-severe and active GO with ivMP in weekly pulses in a cumulative dose of 4.5 g or 7.5 g. Serum cortisol, plasma ACTH, and serum DHEA-S levels were evaluated before the 1st and 12th ivMP pulse. We performed dynamic testing using a 1 μg ACTH stimulation test before the 12th IVMP pulse in all patients. Two patients failed to achieve serum cortisol levels ≥18.1 μg/dl at 30. and 60. minute and were diagnosed with GI-AI. They were recommended to take hydrocortisone in situations of acute stress. Both patients were reassessed within 4 to 7 weeks following treatment cessation and showed an adequate response in the low-dose ACTH stimulation test and overnight metyrapone test. We observed a statistically significant decrease in DHEA-S levels (p=0.004) before the 12th ivMP pulse compared to the baseline in all patients. Our study showed that ivMP in 12 weekly pulses may lead to GI-AI.

Article number 3 summarizes current knowledge on the management of GI-AI, including diagnostic methods and treatment schedules. This review provides detailed recommendations on GC tapering regimens. The presented summary may be considered a useful tool in daily

clinical practice, especially while facing adrenal suppression despite following recommended GC tapering regimens.

To summarize, the presented studies have shown that the use of ivMP for the treatment of moderate-to-severe and active GO in a cumulative dose of 4.5 g or 7.5 g can negatively affect the function of adrenal cortex. Additionally, the conducted research indicates that therapy with 12 weekly ivMP pulses in line with EUGOGO guidelines may cause GI-AI. Therefore, it is recommended to evaluate the function of the adrenal cortex in patients with GO after discontinuing the treatment with weekly ivMP pulses. For certain patients, it may be necessary to conduct a stimulation test using 1 μg of synthetic ACTH. Various studies have shown that the use of GCs in different forms such as oral, inhaled, local, intranasal, intra-articular, and intravenous, can result in the suppression of adrenal cortex function. It has been confirmed that even short-term therapy (less than 3 weeks) and low doses (less than 5 mg of prednisone per day) of GCs can also lead to inhibition of the HPA axis. The above reports suggest that it is important to assess the function of the adrenal cortex after completing the treatment with ivMP pulses according to EUGOGO guidelines. However, no definitive advantage of using either a 1 μg or 250 μg dose of synthetic ACTH has been proven, and recommendations on the matter are inconsistent.

Further studies, particularly prospective and comparative ones, are necessary to determine the incidence of GI-AI during ivMP therapy and the effectiveness of using 1 μg or 250 μg of a synthetic ACTH analog in the diagnosis of GI-AI.