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How Safe Is Glucocorticoid Treatment In Graves' Orbitopathy?

Marcocci C, Watt T, Altea MA, Rasmussen AK, Feldt-Rasmussen U, Orgiazzi J, Bartalena L. Fatal and non-fatal adverse events of glucocorticoid therapy for graves' orbitopathy: a questionnaire survey among members of the European Thyroid Association. Eur J Endocrinol 2012;166:247-53. Epub November 4, 2011.

SUMMARY

Background

The use of high-dose glucocorticoid therapy is well established for the treatment of severe autoimmune diseases, such as systemic lupus, multiple sclerosis, and graft-versus-host rejection. For approximately 25 years, it has also been used to treat severe forms of Graves' ophthalmopathy, and at present, it is in fact the preferred method of treatment in Europe. There is some suggestive evidence that intravenous (IV) administration is superior to oral treatment with glucocorticoids. The adverse effects of these two methods of treatment need, therefore, to be analyzed with great care. This was the purpose of the present article, which is based on a questionnaire survey among the members of the European Thyroid Association (ETA).

Methods and Results

The questionnaire was sent to all ETA members, including many nonclinicians; 128 members responded, 115 of whom were using glucocorticoids to treat Graves' ophthalmopathy. Of these 115 respondents, 72% of them use IV methylprednisolone. Once-weekly infusion was preferred by 60% of the physicians, but others chose to treat up to three times per week. In 80% of the cases, the mean dose of infused steroid was 0.5 to 1 g and the total amount varied between 4.5 g and a maximum of 12 g. The duration of the infusion was not specified. For the oral route, most clinicians used a fixed initial dose between 40 and 75 mg of prednisone per day. Tapering of the treatment was started after 2 weeks, and patients were treated on average for 3 months. The mean total dose was 2.4 g.

The percentage of adverse effects was much higher with the oral treatment than with IV administration (82% vs. 39%), but with the IV treatment, the rate of fatal adverse events was very high. With the oral treatment, nonfatal adverse effects were cardiovascular events, three cerebral vascular events, and increases in liver enzymes to four times above normal values; the remaining side effects were hyperglycemia, weight gain, facial changes and others. Nevertheless, 2 patients who were orally treated died of cerebrovascular events.

Of the IV-treated patients, 32 suffered from side effects, 27 of which were severe — cardiovascular (10), cerebrovascular (5), acute liver failure (3), autoimmune encephalitis (1), and liver enzymes more than four times above normal. Seven patients died, 4 of acute liver failure, 2 of a cerebrovascular events, and 1 of pulmonary embolism. Three of them had no comorbidities.

Conclusions

Intravenous glucocorticoid treatment of Graves' ophthalmopathy is the preferred treatment in Europe. The adverse side effects were less frequent than with the oral treatment, but more severe, since several lethal complications were reported, even among young and middle-aged persons with no other comorbidities. With the exception of one case, the deceased patients received a large total dose of glucocorticoids, exceeding 8 g. Oral treatment is not devoid of lethal adverse effects, since 2 lethal cases, due to cerebrovascular events, have been reported, including one 32-year-old patient with no comorbidities who initially received 60 mg per day and a total dose of 2.3 g. The authors suggest that IV treatment should not exceed a total dose of 8 g, that glucocorticoids should be given as a slow infusion, and that not more than one infusion per week should be performed.

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ANALYSIS AND COMMENTARY

Over a very short period, two articles appeared on this subject. The article under discussion reflects the results of a questionnaire addressed to many well-known European thyroidologists. It probably includes the majority, if not all, of the severe adverse effects of this treatment, but we do not know the time span over which these observations were reported. The second open question concerns the frequency of these adverse effects, since the article reports the percentage of endocrinologists who have seen adverse effects, but it does not state the frequency of these events as compared with the total number of patients treated by each individual endocrinologist. The largest study on the topic, including more than 800 subjects, states a frequency of less than 1% (1). This is important to realize, particularly in relation to the article being reviewed in the next article in this issue of *Clinical Thyroidology* by Jerry Hershman (2). This article is a careful evaluation of the hepatic immune status before treatment. No adverse effects were observed even though treatment was given as an IV pulse.

Yet hepatic adverse effects are not the only complications. In the European study, nine lethal cases are reported, four due to acute liver failure, four to a cerebrovascular event, and one to pulmonary embolism. It is particularly important to realize that from the two patients who died while undergoing oral treatment, one had no comorbidity and died at the age of 32 years from a cerebrovascular event. Three patients who died while undergoing IV treatment had no preexisting comorbidities.

The recommendations of the European survey cannot lead to ultimate answers, since they are based on common sense rather than on scientific data. Nevertheless, it is probably wise to remember that this treatment should be reserved for severe cases of Graves' ophthalmopathy, that the total IV dose should not exceed 8 g, that the infusion should not be more frequent than once a week, and that the glucocorticoid should be given as an infusion over 1 hour or more. In addition, clinical and biochemical surveillance is strictly indicated.

— Albert G. Burger, MD

References

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2. Wichary H, Gasińska T. Methylprednisolone and hepatotoxicity in Graves' ophthalmopathy. Thyroid 2012;22:64-9. Epub October 26, 2011.