

THEODORE C. FRIEDMAN, MD, Ph.D.

Surgical Versus Medical Treatment for Cushing Disease, the New and the Old

Classically Cushing disease, which is a tumor in the pituitary gland causing high ACTH and subsequently high cortisol, has been treated surgically. Once the diagnosis of Cushing disease is made, the surgeon identifies the tumor often based on a high resolution MRI scan and removes the tumor. According to the literature, the cure rate for surgical treatment of Cushing disease is about 80%, although Dr. Friedman has found that in the patients that are more mild that he specializes in treating, cure rate might be a little bit lower. After surgery, the patient is placed on hydrocortisone replacement and usually within 6 months to a year, the patient can be off hydrocortisone replacement and the patient's health has returned. Therefore pituitary surgery has the advantage of permanently curing patients with Cushing disease.

However, there is still a percentage of patients with Cushing disease that are uncured and also some that either do not want to go to surgery or for other reasons Dr. Friedman elects not to send to surgery at the current time. For these patients medical treatment for Cushing disease is a possibility. There are several medicines that can be used to lower cortisol levels or block its action. Dr. Friedman uses medical treatment for patients that either do not want or cannot have pituitary surgery. He also has another important indication for using medical treatment and if the tumor is not seen on MRI the patient could be treated medically until the tumor is seen on MRI with the idea that when a tumor is seen on an MRI the cure rate is much higher. Another indication for medical treatment for Cushing disease is if Dr. Friedman is unsure of the diagnosis and wants to figure out how much of the patient's symptoms are due to high cortisol and how much is due to other problems.

Dr. Friedman has frequently used a medicine called ketoconazole, which blocks cortisol symptoms with the adrenal gland. Ketoconazole is FDA-approved for treating fungal infections, so its use for Cushing disease is considered off-label. Dr. Friedman has found that ketoconazole is quite effective at lowering cortisol, especially in those mild and even episodic patients. As Cushing's syndrome is a problem with high cortisol at night, Dr. Friedman usually gives them ketoconazole at nighttime. He would often give 2 doses of 200 mg each at 8 PM and 10 PM and the patient's cortisol at night will be much lower. Patient will often have improved sleep and this can often lead to having more energy during the day as well as possibly decrease in the weight gain associated with Cushing's syndrome. Dr. Friedman could add back a small amount of hydrocortisone in the morning to prevent the low cortisol symptoms sometimes associated with Cushing's syndrome, as often patients have high cortisol at night and low cortisol during the day. He often gives 5 to 10 mg of hydrocortisone in the morning and finds that this is quite effective. The patient is warned about adrenal insufficiency and told to stop the ketoconazole and take extra hydrocortisone if adrenal insufficiency occurs.

The main side effect of ketoconazole is increased liver function tests. Ketoconazole has classically been used in patients with very high cortisol, especially those with ectopic ACTH syndrome and has been used in a high dose up to around 1200 mg a day. If ketoconazole is given at 400 mg a day, increased liver function tests are rare and is reversible. Dr. Friedman

monitors liver function tests at baseline and every 3 months in patients on ketoconazole. If the liver function tests are off, the ketoconazole has to be stopped. The other side effects of ketoconazole is that it does interact with a fair number of other medicines including a cholesterol medicines and can occasionally lead to a long QT interval in the EKG.

In February of 2012, the FDA recently approved a new medicine for Cushing's syndrome called Korlym and this agent is very promising for treatment for Cushing's syndrome. As a disclosure, Dr. Friedman is on the advisory committee for Corcept that manufactures Korlym and has been assisting the company in their efforts to treat patients with Cushing's syndrome with Korlym. Korlym works as a glucocorticoid receptor antagonist in that it blocks the action of cortisol at the receptor. Cortisol and ACTH levels actually go up, as the cortisol does not work in the receptor.

Dr. Friedman did have some experience with this medicine when it was called RU-486 in the early 1990s when he was doing his fellowship at NIH and was one of the first doctors to use this in patients with Cushing's syndrome. However, since then there has been much more experience with this glucocorticoid receptor antagonist and we have much more information on dosing. In general, the initial dose is 300 mg once a day and the highest dose used is 1200 mg a day. At these, dosage adrenal insufficiency is fairly uncommon. Dr. Friedman thinks the low incidence of adrenal insufficiency is due to the fact that the mineralocorticoid hormone aldosterone is increased as the glucocorticoid receptors are blocked. Aldosterone can compensate for some of the adrenal insufficiency symptoms such as low blood pressure and high pulse. In a recent trial of 50 patients with rather severe Cushing's syndrome, the rate of adrenal insufficiency was about 10%.

The main complication from taking Korlym is endometrial buildup and vaginal bleeding in women. This is because Korlym also blocks progesterone receptor and patients on the medicine have unopposed estrogen with no progesterone. The unopposed estrogen leads to endometrial buildup, which can then cause vaginal bleeding and at times require a hysterectomy. Patients need to be carefully monitored for this side effect and one solution is to stop the Korlym every 6 months and have the women undergo a period, which would then prevent the vaginal buildup. Other side effects were rare and include nausea, fatigue, low potassium, joint pain, edema and dizziness. Again, the advantage of this medicine is that it is FDA-approved for Cushing's syndrome. This drug is now available for Dr. Friedman's patients.

Another drug that had some promise for Cushing's syndrome was actually turned down by the FDA called Pasireotide (SOM230). This medicine is a somatostatin analog (increased binding to the somatostatin-5 receptor that was thought to decrease ACTH symptoms and can possibly even shrink the pituitary tumor. However, this drug gave an unacceptable high rate of diabetes, as somatostatin inhibits insulin secretion. It is possible that there may be other somatostatin drugs used for Cushing's syndrome in the future but none are available at this moment.

The medicine cabergoline has also been used in some cases with Cushing's syndrome; however, the percentage of patients that have lower cortisol on this drug is much less than the ketoconazole. There are older drugs that also block cortisol including metyrapone and aminoglutethimide; however, these are hard to obtain in the United States. Another drug called mitotane destroys the adrenal tissue. This drug is very hard to tolerate, as it does cause a lot of

nausea and is also infrequently used in Cushing's syndrome, although it is used for adrenal cancers.

To summarize, surgical treatment for Cushing's syndrome would be the best option in most patients. The medical treatment with either ketoconazole or Korlym is also an option in certain patients. For more information about Dr. Friedman's practice go to www.goodhormonehealth.com.