Long-Term Care Updates

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Cushing syndrome in the older adult population: a review of guidelines and newer treatments

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Introduction

Cortisol, commonly known as the "stress hormone" regulates many physiological and psychological processes in the body. Cortisol is a glucocorticoid released by the adrenal gland and regulated by the pituitary gland. It regulates the body's stress response and plays a central role in metabolism; however, persistently high or dysregulated cortisol activity can lead to serious illnesses.[1] Hypercortisolism, also known as Cushing syndrome, is a serious condition that occurs when the body produces too much cortisol over a long period of time. Persistent excess cortisol disrupts the body's natural rhythm of cortisol production and can lead to high blood sugar, high blood pressure, depression, and weight gain.[2] Patients with Cushing syndrome may also experience changes in physical appearance: weight gain in the upper body, rounded face and extra fat on the upper back and collarbone, purple-red stretch marks on the abdomen and underarms, acne, and hair growth.[3] However, a study conducted by Qiao et al., discovered that older patients may present with different signs and symptoms of hypercortisolism. Older patients with Cushing syndrome had significantly lower body mass index, were more likely to have muscle wasting, and women were less likely to have hirsutism. More medical comorbidities were observed in older patients than younger patients. Older patients appeared to have a more catabolic appearance compared to the increased weight gain seen in younger patients with Cushing syndrome.[4]

There are two different types of Cushing syndrome, endogenous Cushing syndrome and exogenous Cushing syndrome. The type of disease is based on the source of excess cortisol. In endogenous Cushing syndrome, the source of excess cortisol is inside the body, often a tumor or nodule. With exogenous Cushing syndrome, the source of excess cortisol is outside the body, often medications like steroids.[2] There are limited pharmacological treatments available for Cushing syndrome; however, newer agents have demonstrated effectiveness in the treatment of endogenous Cushing syndrome. First line treatment for endogenous Cushing syndrome is surgery to remove the tumor or nodule causing cortisol production. Second line treatment options are pursued if surgery is not an option or was not curative. These options would include radiation therapy to remove the tumor or nodule, or newly approved medications.[5]

Novel Drug Approvals (January 2025)

Brand	Generic	Indication	Mechanism of Action	Dosage Form
Datroway	Datopotamab deruxtecan-dlnk	Breast cancer	Trop-2 directed antibody and topoisomerase inhibitor conjugate	Intravenous injection
Symbravo	Meloxicam; rizatriptan	Migraine treatment	NSAID (meloxicam); 5-HT 1B/1D receptor agonist (rizatriptan)	Oral tablets
Journavx	Suzetrigine	Moderate to severe acute pain	Sodium channel blocker	Oral tablets

Levoketoconazole

Levoketoconazole is a cortisol synthesis inhibitor approved in 2021 for treatment of endogenous hypercortisolism.[6] Levoketoconazole inhibits three key enzymes involved in the synthesis of cortisol and testosterone which include CYP11A1, CYP17A1, and CYP11B1.[7] Contraindications to levoketoconazole include cirrhosis, acute liver disease, liver function tests greater than three times the upper limit of normal, recurrent symptomatic cholelithiasis, prolonged QTc interval, history of torsade's de pointes, ventricular tachycardia, ventricular fibrillation, and coadministration with sensitive substrates of CYP3A4. The recommended initial adult dosing for levoketoconazole is 150mg twice daily. The dose is titrated by 150mg every two to three weeks based on cortisol levels and tolerability to a maximum dose of 1.2g/day in two equally divided doses. Prior to initiating the first dose, an electrocardiogram (ECG) should be obtained as well as before each dose increase. There is no standard duration of therapy; in most patients, the medication is continued indefinitely once the dose is stable.[6]

Clinical studies have shown that twice daily levoketoconazole treatment can lead to sustained improvement in urinary free cortisol while also improving glycemic control in patients with diabetes. The SONICS clinical trial evaluated the effectiveness of levoketoconazole by measuring mean urinary free cortisol (mUFC) normalization in 94 patients with confirmed Cushing syndrome.[6] Patients were initiated on 150mg twice daily and the dose was titrated until mUFC normalization or a maximum dose of 600mg twice daily. A 6-month maintenance phase followed once patients' doses were stabilized. The primary outcome was the proportion of responders at the end of this maintenance phase. Seventy-seven of the 94 patients advanced to the maintenance phase of the study and of the 77 patients, 81% had mUFC normalization by the end of the dose titration. Of the original 94 patients, 30% were considered responders at the end of the 6-month period (95% CI 0.21-0.40; p = 0.0154). The SONICS trial also evaluated prespecified adverse events including liver toxicity, QT prolongation, and adrenal insufficiency. Only 3% of patients experienced these prespecified adverse events during the trial.[8] A subanalysis was completed to evaluate the efficacy of levoketoconazole in patients with or without diabetes. The subanalysis found that 46% (p=0.006) of patients with diabetes and 36% (p=0.0209) of patients without diabetes experienced mUFC normalization at the end of the maintenance phase. It was also discovered that a 0.7% decrease in mean hemoglobin A1c (HbA1c) was observed in patients with diabetes (p = 0.031), and a 0.2% decrease in patients without diabetes (p = 0.003). Mean fasting blood glucose was decreased by 18.5mg/dL in patients with diabetes (p = 0.046) and 8.1mg/dL in patients without diabetes (p = 0.044). The subanalysis results demonstrated that treatment with levoketoconazole produced an improvement in glycemic control which was more pronounced in patients with diabetes.[9]

Special considerations are warranted for geriatric patients initiating levoketoconazole. Geriatric patients are more likely to have hepatic impairment; those with liver disease should avoid taking levoketoconazole. Hepatotoxicity has been reported in patients receiving levoketoconazole and liver enzymes should be evaluated in all patients taking the medication, regardless of history. Patients who have an irregular heart rhythm or are taking a QT-prolonging agent (including certain antidepressants, antiarrhythmics, and some calcium channel blockers) should also avoid levoketoconazole as it can prolong QT interval, resulting in cardiac arrhythmias. Risk factors for QT prolongation include age over 65 years, structural heart disease, kidney impairment, and loop diuretic use. Levoketoconazole should also be avoided in patients who are taking medications that are sensitive substrates to CYP3A4 including antipsychotics, lovastatin and simvastatin, and some antiseizure medications such as phenobarbital and phenytoin. Because levoketoconazole is metabolized by CYP3A4, concomitant CYP3A4 inducers or inhibitors can affect its concentration in the body.[6]

Serious adverse effects of levoketoconazole include adrenocortical insufficiency or hypocortisolism, hepatotoxicity, and QT prolongation. Common side effects include erythema, bruising, hemorrhaging, and gastrointestinal effects. Patients should be monitored at baseline and throughout treatment to prevent adverse reactions. In addition to monitoring ECG, serum potassium and magnesium levels are recommended prior to initiation and throughout treatment to prevent QT prolongation. Liver function enzymes and bilirubin should be obtained at baseline and throughout treatment to monitor for hepatotoxicity.[6]

Mifepristone

Mifepristone blocks the effect of cortisol at the glucocorticoid receptor, antagonizing its effects on glucose metabolism while increasing the amount of circulating cortisol. At high doses, mifepristone is used for the treatment of hyperglycemia occurring secondary to hypercortisolism in patients with endogenous Cushing syndrome and type 2 diabetes or glucose intolerance. Mifepristone is contraindicated in patients who are pregnant; take lovastatin, simvastatin, or CYP3A4 substrates with narrow therapeutic ranges; and in women with a history of unexplained vaginal bleeding, endometrial hyperplasia, or endometrial carcinoma. Mifepristone has a boxed warning for pregnancy termination as lower doses of the medication block the effects of progesterone. Patients of childbearing potential must use effective contraception during therapy and for one month after the last dose. The recommended initial adult dose of mifepristone is 300mg once daily. The dose can be increased in 300mg increments every two to four weeks based on tolerability and symptom control. Although the maximum daily dose is 1200mg, a maximum of 600mg is recommended in patients with renal impairment or mild to moderate hepatic impairment. Like levoketoconazole, there is no standard duration of therapy with mifepristone. The medication is typically continued indefinitely once patients are established on a stable dose.[10] Although it has been approved for over a decade, recent evidence in type 2 diabetes has resulted in increased consideration of the mifepristone.

The SEISMIC study evaluated the change in area under the curve (AUC) for glucose on a 2-hour oral glucose tolerance test and change in diastolic blood pressure from baseline. Fifty patients with endogenous Cushing syndrome with type 2 diabetes, impaired glucose, or hypertension were enrolled. Patients were initially given mifepristone 300mg per day, with 300mg dose titrations up to 1200mg by week 10 to reach significant clinical improvement. Among the patients with diabetes, 60% had a reduction in AUC of 25% or greater by week 24 of treatment ($p < 0.0001$). Among the patients with hypertension, 38% had a reduction in diastolic blood pressure of 5mmHg or greater by week 24 of treatment ($p < 0.05$). The study found additional benefits in the patients with diabetes including a 1.1% reduction in HbA1c by week 24. Seven out of 15 patients had their diabetes medications reduced while taking mifepristone and 5 out of 12 patients using insulin had their daily dose of insulin reduced by at least half.[11] Overall, mifepristone produced significant and clinical metabolic improvement in patients with Cushing syndrome.

More recently, the CATALYST clinical trial was a phase 4, two-part, multicenter trial. Part 1 was a non-interventional trial to determine the prevalence of hypercortisolism in patients with difficult to treat type 2 diabetes. Part 2 was an interventional, prospective, double-blind placebo-controlled randomized clinical trial to assess the safety and efficacy of mifepristone in lowering HgA1c in the identified patients. Patients were initiated on 300mg of mifepristone once daily with food and advanced to 600mg once daily at week 4. Participants could remain on this dose for 24 weeks of the study or increase to 900mg once daily. The change in HgA1c was evaluated from baseline to week 24.[12] A total of 136 patients were enrolled in the treatment phase. Upon analysis, individuals treated with mifepristone demonstrated a decrease in HgA1c from baseline of 1.47% compared with 0.15% for placebo ($p < 0.0001$). The safety profile of mifepristone in the study was consistent with the medication's labeling and no new side effects or adverse events were identified.[13]

Several contraindications, warnings, and precautions are pertinent to consider in geriatric patients before initiating mifepristone. Patients with irregular heart rhythm or cardiovascular disease should use caution when taking mifepristone. Mifepristone may prolong QTc interval and should be used with caution in patients taking other QT-prolonging agents. Mifepristone does not reduce serum cortisol concentrations which can cause activation of the mineralcorticoid receptor in cardiac tissues; thus, it is recommended to use with caution in heart failure or coronary vascular disease. Mifepristone should also be avoided in patients taking lovastatin, simvastatin, or other CYP3A4 substrates with a narrow therapeutic range as concentrations of the CYP3A4 substrate or mifepristone can be altered. Mifepristone should be avoided with systemic corticosteroids due to its antagonizing effects at the glucocorticoid receptor. Patients on corticosteroid treatment for long-term management of serious conditions or illnesses, such as immunosuppression following transplantation, should not take mifepristone. [10]

Serious adverse effects of adrenal insufficiency, bleeding, hypokalemia, and QT prolongation may be seen with mifepristone. Additional side effects include abnormal thyroid function tests, peripheral edema, fatigue, neuromuscular and skeletal pain, and dyspnea. Patients should be monitored throughout treatment to prevent serious adverse side effects. An ECG should be obtained at baseline and before each dose increase to monitor for QT prolongation. Serum potassium and magnesium should be obtained prior to initiation and throughout therapy to monitor for hypokalemia.[10]

Conclusion

Evidence supporting the use of levoketoconazole and mifepristone in patients with hypercortisolism has initiated a discussion of different treatment options outside of surgery. These therapies have shown benefit in controlling cortisol production and managing comorbid chronic disease states. It is essential to consider a patient's health and medication history before initiating either treatment, and to follow the monitoring protocols to prevent serious adverse events. This is especially vital in geriatric patients as these patients may be more vulnerable to adverse events. While levoketoconazole and mifepristone present promising alternatives for managing hypercortisolism, careful patient selection, thorough monitoring, and consideration of individual factors are crucial to ensure safety and efficacy.

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