JPPT | Case Report

Rectal Metyrapone for Treatment of Hypercortisolism in an Infant with McCune-Albright Syndrome

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Infantile Cushing syndrome is an infrequent yet potentially fatal manifestation of McCune-Albright syndrome, for which there are few safe treatments available. Ketoconazole is limited by potential hepatotoxicity in this population. Metyrapone may be an effective treatment, but it may not be tolerated when given orally. An infant with McCune-Albright syndrome presented with severe Cushing syndrome. Oral metyrapone resulted in feeding refusal, and ketoconazole caused an increase in liver enzymes; however, she was successfully treated with metyrapone given rectally. The patient avoided a feeding tube, and her serum cortisol concentration was lowered to a safe level. Metyrapone given per rectum may be a safe and effective alternative to oral metyrapone in treating young children with Cushing syndrome.

ABBREVIATIONS ACTH, adrenocorticotropic hormone; ALT, alanine aminotransferase; MAS, McCune-Albright Syndrome

KEYWORDS Cushing syndrome; McCune-Albright syndrome; metyrapone; rectal administration

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Introduction

In 1936[1] and 1937,[2] Donovan James McCune and Fuller Albright et al, respectively, independently described a syndrome consisting of precocious puberty, fibrous dysplasia of bone, and café-au-lait patches. The classic clinical triad was later noted to be associated with multiple endocrinopathies. McCune-Albright syndrome (MAS) is the result of a postzygotic somatic activating mutation in the guanine nucleotide–binding protein, alpha-stimulating activity polypeptide 1 gene,[3] which encodes for the alpha subunit of a G protein that is common to multiple hormone receptors, including luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, adrenocorticotropin hormone (ACTH), corticotropin-releasing hormone, and growth hormone–releasing hormone receptors. Manifestations may include peripheral precocious puberty, hyperthyroidism, growth hormone excess, cortisol excess, and/or hypophosphatemic rickets. Because of the mosaic nature of this disease, the clinical severity is extremely variable and is related to the number of tissues involved. Cortisol excess is thought to be an uncommon feature of MAS, with a prevalence of 7.1% in one large case series.[4] This form of hypercortisolism affects both adrenal glands and always presents in infancy, usually with symptoms of linear growth failure and Cushingoid facies. Hypertension, nephrocalcinosis, hyperglycemia, and hirsutism may occur. The activating mutation in the GNAS gene affects the adrenal fetal zone more significantly than mature adrenal tissue, and some patients experience spontaneous resolution of Cushing syndrome in early childhood.[4,5] For this reason, bilateral adrenalectomy with glucocorticoid and mineralocorticoid replacement is no longer used as a treatment.

There are no guidelines for the medical management of infantile Cushing syndrome in this context, although hypercortisolism is historically associated with a higher risk of death in MAS patients;[4] this is mainly attributed to sepsis resulting from severe immune suppression and adrenal crisis following adrenalectomy. Both ketoconazole and metyrapone have been used off-label in children with Cushing syndrome. Ketoconazole is an imidazole antifungal agent that blocks both the first (via CYP11A1) and final (via CYP11B1) steps of cortisol biosynthesis.[4] Its use is limited by its potential to cause hepatotoxicity,[3] of which there have been several case reports in children.[6,7] Metyrapone is an oral adrenal enzyme inhibitor acting solely at the final step of cortisol synthesis.[8] It has been shown to be effective in some cases of MAS-related Cushing syndrome;[3,5,9] however, disadvantages include poor tolerability,[5] gastrointestinal upset, overproduction of adrenal androgens secondary to increased ACTH, and minor inhibitory effects on aldosterone synthase (CYP11B2), leading to a buildup of the aldosterone precursor 11-deoxycorticosterone, which possesses mineralocorticoid activity.[10] Adrenolytic agents, such as mitotane (used in the treatment of adrenal carcinoma), are rarely used in children, because the side effect profile includes central nervous system toxicity, leukopenia, and failure to thrive secondary to abdominal pain, vomiting, and anorexia.[11]

Case Report

Our patient, a white female, was born at 37 + 2 weeks' gestation and weighing 2.5 kg, after intrauterine growth restriction was noted at 35 weeks. At birth, she was noted to have mild hypotonia but no dysmorphic features or unusual skin findings. She presented at age 1 month for evaluation of tachycardia. Initial investigations revealed sinus tachycardia and hyperthyroidism, with a suppressed thyroid-stimulating hormone concentration of 0.03 milli–international units per liter (normal range for age, 0.8–8.0 mIU/L), an elevated free T4 of 23.3 pmol/L (normal range, 11–22 pmol/L), and a free T3 of 8.5 pmol/L (normal range, 3.3–6.0 pmol/L). Initial ALT was elevated at 96 U/L (normal range, 5–50 U/L), and thyroid antibodies were negative. At age 8 weeks, the patient started treatment with methimazole at an initial dosage of 0.3 mg/kg/day. At this time, several café-au-lait patches were noted on her head, torso, and buttock.

The physical features of Cushing syndrome became apparent in our patient, and they included slow linear growth, Cushingoid appearance, and mild hirsutism. At this time the patient did not have signs of precocious puberty or fibrous dysplasia. A diagnosis of MAS was considered, and an endocrine workup was performed. Results were consistent with constitutive activation of the ACTH receptor, and they included an afternoon cortisol concentration of 797 nmol/L, a morning cortisol concentration of 753 nmol/L following a 1-mg dexamethasone suppression test, and an undetectable ACTH at a cortisol concentration of 724 nmol/L. At age 2.5 months, a 24-hour urinary free cortisol was 455 mcg/m^2/day (normal range, < 70 mcg/m^2/day).

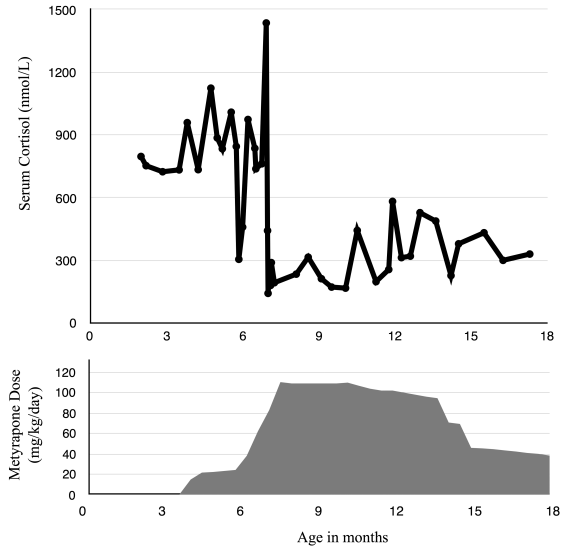
The patient was started on trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii* prophylaxis. Because of concerns about the hepatotoxicity of ketoconazole in the context of potential liver involvement in MAS,[3,4] and case reports describing the successful use of metyrapone in infants with Cushing syndrome,[5,9] oral metyrapone was chosen as the initial agent. The dose (30 mg orally twice a day, with a plan to slowly titrate up) was determined by the literature[5,9,12] and consultation with colleagues. Unfortunately, oral administration of the medication resulted in extreme distress, gagging, dyspnea, and inability to feed orally. One of the authors sampled the contents of the metyrapone capsule and described a burning sensation when it was applied to mucous membranes. Attempts were made to increase tolerability with a 1:10 solution of metyrapone in simple syrup and water flushes; however, these were unsuccessful. Poor feeding following metyrapone administration has been reported previously[5] and has led to feeding aversion and insertion of nasogastric or gastrostomy tubes in some patients.

A brief trial of ketoconazole (dosage, 2–2.6 mg/kg/day) followed, but this was discontinued after 6 weeks because of increasing liver enzymes (ALT concentration increased from 70 to 131 U/L) and a continued increase in serum cortisol concentration, from 733 to 886 nmol/L. After an unsuccessful trial of oral metyrapone, followed by intolerance to ketoconazole, a trial of metyrapone given rectally was suggested. This route of delivery has not been described previously in the literature as a treatment for Cushing syndrome, but there is a small study in which rectal metyrapone was used as part of a modified metyrapone test in children.[13]

Metyrapone suppositories were attempted several times, but unfortunately this led to discomfort as well as inconsistent dosing due to melting and defecation. The mother of the infant tried several other methods before coming up with the successful delivery method of using a calibrated syringe and a portion of a nasogastric tube. The brand of tube Med-RX Ref 54-5036R (5 Fr) was preferred because it had a softer edge when cut to length. Metyrapone is available through Health Canada's Special Access Program as a liquid-filled gelatin capsule at a strength of 250 mg (HFA Pharma, Paris, France). According to the manufacturer, 520 mg of fill liquid contains 250 mg of metyrapone. Using the average of 12 serial weights to determine an average weight per volume, it was determined that each 0.05 mL of capsular liquid weighed approximately 57 mg. Therefore, the initial dose of 30 mg approximated 0.06 mL of capsular liquid (0.06 mL = 32.8 mg). The capsule was placed in a 3-mL polypropylene syringe, with the plunger used to hold the capsule in place. The gelatin capsule was then punctured using an 18-G blunt needle, and the liquid was withdrawn into a 1-mL syringe. After drawing up the medication, approximately 12 cm of tubing was attached over the needle point. The tube was primed with undiluted drug solution, and then the baby's rectum was stimulated by inserting the tube (approximately 3–4 cm) and waiting 2 minutes to allow for the passage of any feces. The volume of drug to be administered was then slowly pushed. Initially, the drug was administered in 0.05-mL aliquots with pauses of 2 to 3 minutes between pushes, but eventually, with larger doses and increased comfort levels, the dose was pushed in 0.15-mL aliquots at 2-minute intervals.

Although unconventional, this treatment was effective in reducing the patient's cortisol to near-normal concentrations. The initial dose was 30 mg twice daily (14 mg/kg/day). This was gradually increased during the course of 6 weeks to 120 mg every 6 hours (110 mg/kg/day). The dose was titrated with a goal of a predose serum cortisol concentration between 200 and 400 nmol/L. The patient continued to take 120 mg every 6 hours, with stable predose cortisol concentration, for 5 months. Her Cushingoid features gradually resolved, and she began to demonstrate catch-up linear growth. Just before her first birthday she tolerated a wean in her medication to 120 mg three times daily (70 mg/kg/day), and a month later the dosage was weaned to 120 mg twice daily (45 mg/kg/day). Twelve months

Figure. The patient's serum cortisol concentration and per rectum metyrapone doses.



after starting treatment, the patient began to show spontaneous resolution of Cushing syndrome. She was able to discontinue metyrapone completely at age 18 months. The Figure illustrates the titration of per rectum metyrapone doses and the effect on predose cortisol concentrations.

Discussion

Treatment for patients with infantile Cushing syndrome is extremely limited. Metyrapone has been shown to be effective in case reports,[5,9,12] but it is complicated by poor oral tolerability; therefore, rectal administration was considered. The pharmacokinetic profile of drugs may differ significantly when administered rectally as opposed to orally. The rate and extent of absorption are dependent on both surface area for absorption, and therefore the volume of drug administered, as well as the presence of feces in the rectum and interruption of absorption by defecation.[14,15] The product formulation may also affect absorption rates; alcohol and water bases result in rapid absorption compared with typical suppository bases.[15] It is generally accepted that most drugs, when given rectally, do not reach the same concentrations as the same drug administered orally.[15] However, for high-clearance drugs, such as metyrapone, this may be partially balanced because the venous blood supply to the lower rectum connects directly with the systemic circulation, effectively bypassing hepatic first-pass metabolism. Therefore, the intent was to titrate the dose to the desired effect based on serum cortisol concentrations, which proved to be a viable approach. In the end, the rectal dose required was similar (per kilogram of body weight) to the oral dosing reported in a previous case report.[12] An initial rectal dosage of 100 mg/kg/day divided every 6 hours would be a reasonable starting dosage for future cases with the intent to titrate to effect.

In our patient, treatment with metyrapone per rectum has allowed her to achieve normal cortisol concentrations while avoiding the development of feeding aversion, thereby enhancing quality of life.

ARTICLE INFORMATION

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