Hypokalemia associated with mifepristone use in the treatment of Cushing’s syndrome

Sai Katta¹, Amos Lal¹, Jhansi Lakshmi Maradana¹, Pruthvi Raj Velamala¹ and Nitin Trivedi²

¹Department of Internal Medicine, Saint Vincent Hospital at Worcester Medical Center, Worcester, Massachusetts, USA and ²Department of Endocrinology, Diabetes, and Metabolism, Saint Vincent Hospital at Worcester Medical Center, Worcester, Massachusetts, USA

Summary

Mifepristone is a promising option for the management of hypercortisolism associated with hyperglycemia. However, its use may result in serious electrolyte imbalances, especially during dose escalation. In our patient with adrenocorticotropic hormone-independent macro-nodular adrenal hyperplasia, unilateral adrenalectomy resulted in biochemical and clinical improvement, but subclinical hypercortisolism persisted following adrenalectomy. She was started on mifepristone. Unfortunately, she missed her follow-up appointments following dosage escalation and required hospitalization at an intensive care level for severe refractory hypokalemia.

Learning points:

- Mifepristone, a potent antagonist of glucocorticoid receptors, has a high risk of adrenal insufficiency, despite high cortisol levels.
- Mifepristone is associated with hypokalemia due to spill-over effect of cortisol on unopposed mineralocorticoid receptors.
- Given the lack of a biochemical parameter to assess improvement, the dosing of mifepristone is based on clinical progress.
- Patients on mifepristone require anticipation of toxicity, especially when the dose is escalated.
- The half-life of mifepristone is 85 h, requiring prolonged monitoring for toxicity, even after the medication is held.

Background

Adrenocorticotropic (ACTH)-independent macro-nodular adrenal hyperplasia (AIMAH) is a rare cause of Cushing’s syndrome (1). AIMAH is characterized by autonomous production of cortisol bilaterally from benign, hyperplastic, and macro-nodular enlargement of the adrenal glands (1). Although bilateral adrenalectomy results in the cure of the disease, the procedure requires hormonal supplementation for survival. Unilateral adrenalectomy in AIMAH, particularly with the removal of the larger adrenal gland, has shown to effectively improve clinical and biochemical features (2). We present a rare case of AIMAH with reversal of subclinical Cushing’s syndrome following unilateral adrenalectomy.

If there is a recurrence of hypercortisolism after surgery, however, such as with our patient, medical management may be considered (3). Mifepristone is a non-selective steroidal glucocorticoid receptor antagonist, usually considered safe for management of hypercortisolism, especially in patients with hyperglycemia. We present a rare case of life-threatening mifepristone toxicity, highlighting the importance of close monitoring of patients on therapy.
Case presentation
A 57-year-old Caucasian woman was incidentally found to have bilateral adrenal enlargement on abdominal imaging performed for elevated liver enzymes. She had a 10-year history of type 2 diabetes mellitus. Her glycemic control progressively worsened despite metformin and insulin glargine. Furthermore, significant weight gain occurred without overt cushingoid features.

Hormonal studies of the incidental adrenal adenomas showed an elevated 8:00 h cortisol, which was non-suppressible after 1 mg of dexamethasone. She had low DHEAS and ACTH levels, which were consistent with autonomous production of cortisol from the adrenal(s). A 24-h urinary free cortisol and midnight salivary cortisol were normal.

Adrenal venous sampling revealed elevated bilateral cortisol production; however, the cortisol level in the left adrenal vein was significantly higher than the right. Given her biochemical features without overt features of Cushing’s syndrome, the patient was diagnosed with AIMAH leading to subclinical Cushing’s syndrome. She underwent left adrenalectomy because the nodule on the left side measured 4 cm in diameter. A few weeks after adrenalectomy the patient’s insulin requirement came down significantly, and her HbA1C decreased from 8.2 to 6.3%. In addition, her serum cortisol, DHEAS, and ACTH also normalized.

A few months after surgery, however, she started gaining weight, which was associated with a rise in HbA1C and non-suppressible cortisol following low-dose dexamethasone. Mifepristone was started at 300 mg, then escalated to 600 mg daily and later to 900 mg daily over 3 months. The patient did not comply with scheduled follow-up. A few weeks after adrenalectomy the patient’s insulin requirement came down significantly, and her HbA1C decreased from 8.2 to 6.3%. In addition, her serum cortisol, DHEAS, and ACTH also normalized.

A chest CT with pulmonary embolism protocol showed no evidence of pulmonary embolism, but present was bilateral predominantly perihilar airspace disease, consistent with an infectious/inflammatory process versus cardiogenic pulmonary edema/congestive heart failure, given the symmetrical perihilar distribution and the additional presence of small bilateral pleural effusions.

An echocardiogram showed an ejection fraction of 60–65%, with mild concentric left ventricular hypertrophy. The transmirtal spectral Doppler flow pattern was normal for her age. Transmitral E velocity and Doppler E/e’ ratio were suggestive of normal left ventricle filling pressures. The left ventricular wall motion was normal.

Cardiac catheterization showed no angiographically evident coronary artery disease.

Treatment
1. Mifepristone was held and dexamethasone was started.
2. Potassium was adequately repleted.
3. Symptoms and volume overload were managed with IV diuresis.

Outcome and follow-up
In summary, the patient presented with volume overload, hypokalemia, metabolic alkalosis and elevated

Investigation
Following is the tabular summary (Table 1) of the laboratory results of the patient at the time of presentation. Laboratory results are significant for severe hypokalemia. There was an expected elevation in serum cortisol and serum thyrotropin levels.

The chest x-ray showed question of flash pulmonary edema, multifocal pneumonia, and trace effusions bilaterally.

| Blood parameters                  | Normal ranges | Patient results |
|-----------------------------------|---------------|----------------|
| WBC (×1000/µL)                    | 3.9–11.0      | 9.0            |
| Hemoglobin (g/dL)                 | 11.5–15.0     | 11.9           |
| Hematocrit (%)                    | 34.0–44.0     | 35.3           |
| Platelets (×1000/µL)              | 150.0–450.0   | 161            |
| Sodium (mEq/L)                    | 134–144       | 142            |
| Potassium (mEq/L)                 | 3.6–5.6       | 2.6            |
| Chloride (mEq/L)                  | 96–109        | 97             |
| Bicarbonate (mEq/L)               | 20–32         | 30             |
| Blood urea nitrogen (mg/dL)       | 5–26          | 9              |
| Creatinine (mg/dL)                | 0.5–1.5       | 0.75           |
| Blood glucose (mg/dL)             | 65–99         | 153            |
| Calcium (mg/dL)                   | 8.3–10.0      | 9.1            |
| Magnesium (mg/dL)                 | 1.6–2.6       | 1.3            |
| Phosphorus (mg/dL)                | 2.5–4.5       | 2.1            |
| Cortisol (µg/dL)                  | 2.3–19.4      | 190.4          |
| TSH (µU/mL)                       | 0.45–4.5      | 8.62           |
| Free T4 (ng/dL)                   | 0.7–1.7       | 0.89           |
| Creatine kinase (U/L)             | 24–173        | 224            |
| CKMB (ng/mL)                      | 0.0–5.3       | 1.6            |
| Troponin (ng/mL)                  | <0.030        | <0.030         |
| Pro-BNP (pg/mL)                   | <125          | 2067           |

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thyrotropin levels, all consistent with mifepristone toxicity. Mifepristone was held at the time of discharge. She was followed up as an outpatient 2 weeks after discharge. Mifepristone was discontinued. A repeat potassium level was normal. She was managed for diabetes with dulaglutide, insulin degludec and metformin. She was monitored with periodic follow-up visits to look for specific signs of Cushing's syndrome.

**Discussion**

Medical management of ACTH-independent Cushing's syndrome includes steroidogenesis inhibitors and glucocorticoid receptor antagonists. Steroidogenesis inhibitors, which include ketoconazole, metyrapone and etomidate, are frequently used off-label in clinical practice for medical treatment of Cushing's syndrome. Ketoconazole and metyrapone are commonly used for long-term therapy. Etomidate is specifically used in the acute setting for cortisol induced psychosis. Chronic use of ketoconazole and metyrapone is limited due to liver toxicity and androgen excess respectively (4, 5). Furthermore, metyrapone is not readily available. Glucocorticoid receptor antagonists include mifepristone and a new drug under development – relacorilant. Relacorilant, a non-steroidal highly selective glucocorticoid receptor antagonist, is currently in a phase 3 trial, the GRACE study, for management of patients with Cushing's syndrome with either diabetes mellitus/impaired glucose tolerance or hypertension.

Given the elevated liver enzymes, mifepristone seemed a better option for our patient as an on-label agent for hyperglycemia induced by hypercortisolism.

We used mifepristone (RU 486) as a non-selective steroidal glucocorticoid and progesterone receptor antagonist. Mifepristone at low doses blocks the action of progesterone and has been traditionally used for medical termination of pregnancy. However, when used in high doses, mifepristone acts as competitive antagonist to glucocorticoid receptors (4, 6). The affinity of mifepristone at higher doses to glucocorticoid receptors is 18 times higher than cortisol (7). This action of mifepristone is utilized for treating patients with Cushing's syndrome. Mifepristone was approved by the FDA in 2012 to treat endogenous Cushing's syndrome associated with hyperglycemia due to hypercortisolism and type 2 diabetes or glucose intolerance and for individuals who are not candidates for surgery or had recurrence after surgery. Recommended dose incrementation is 300 mg in 2 to 4-week intervals up to 1200 mg, based on tolerability and clinical response. The approximate average cost of the medication is $15,639 for 30 tablets of 300mg, which rises to $46,917 and $62,556 for 30 tablets of 900mg and 1200mg respectively.

Given its competitive antagonist action, mifepristone disinhibits the negative feedback of glucocorticoids on ACTH and CRH secretion, leading to excessive cortisol production. It has no effect on mineralocorticoid receptors. Thus, the high levels of cortisol secondary to 11-β HSD2 enzyme saturation (8) causes excessive stimulation of mineralocorticoid receptors, resulting in hypertension, hypokalemia and volume overload. Mifepristone dose titration is essentially based on clinical improvement, as there is no specific biochemical parameter to monitor improvement. Thus, its clinical efficacy and toxicity is based on clinical monitoring. The main toxicities from overstimulation of the mineralocorticoid receptors include weight gain, hypertension, and hypokalemia (9). Hypokalemia can potentially result in life-threatening arrhythmias, muscle weakness and rhabdomyolysis.

Mifepristone toxicity manifests with features of mineralocorticoid excess as well as adrenal insufficiency (10). Clinicians should be cautious about the signs of adrenal insufficiency like generalized weakness, fatigue, hypoglycemia, and hypotension. The biochemical diagnosis can be difficult given the high ACTH and cortisol levels (11). Adrenal insufficiency is managed with discontinuation of mifepristone and starting high-dose glucocorticoids (12). Dexamethasone does not stimulate mineralocorticoid receptors, and it is usually recommended to treat mifepristone-induced adrenal insufficiency with a dose of 1 mg for 400 mg of mifepristone (4, 12). The duration of dexamethasone therapy should be made after taking into consideration the long half-life of mifepristone (up to 85 h) (12). Due to progesterone antagonism, patients treated with mifepristone may also develop endometrial hyperplasia; therefore, monitoring with vaginal ultrasound is recommended for long-term therapy (12).

Mifepristone's effects were carefully studied in the SEISMIC study, (13) a 24-week, multi-center trial in which mifepristone was given daily to patients with Cushing's syndrome at dose ranges of 300–1200 mg daily. The outcome showed dose-dependent improvement in glucose metabolism in patients with pre-diabetes and overt diabetes mellitus as well as a decrease in diastolic blood pressure in patients with hypertension. The common side effects reported in this trial were nausea, headache, joint pain, vomiting, psychosis, and hypokalemia. It was interesting to note that the side effects were not dose

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related and most side effects except for headache and hypokalemia resolved with time. The majority of patients with hypokalemia required treatment with potassium supplementation and/or spironolactone (1, 13). The findings of the SEISIMIC trial underscore the need for close clinical observation and biochemical testing to look for mifepristone adverse effects – especially during dose escalation.

Analysis of the SEISIMIC study showed that serum cortisol and ACTH levels might help to identify patients at high risk of developing hypokalemia (14). It therefore might be beneficial to start prophylactic mineralocorticoid receptor antagonist or potassium supplementation in high-risk patients (14). Co-administration of strong CYP3A4 inhibitors can increase mifepristone levels, so appropriate dose reduction of mifepristone may be necessary to avoid toxicity (10). In addition, it is imperative to educate the patients about the side effects and the importance to comply with scheduled clinic visits and biochemical testing. Physicians also need a reminder system to stay in touch with such patients if compliance is a problem. Our patient missed her office appointment and laboratory testing following dose escalation, which is the main reason we were unable to pick up the development of hypokalemia to provide timely management. Given the long half-life of mifepristone (85 h), it took approximately 3 weeks for our patient to recover from its toxicity.

Clinical trials of mifepristone use are of relatively short duration and mainly focused on the improvement of features of Cushing’s syndrome. The effect of mifepristone on improving survival of patients with Cushing’s syndrome is unknown. Furthermore, the long-term effect of unopposed mineralocorticoid receptors, especially on the cardiovascular system, also remains unknown.

Relacorilant, a non-steroidal highly selective glucocorticoid receptor antagonist, is currently in a phase 3 trial, the GRACE study, for management of patients with Cushing’s syndrome with either diabetes mellitus/ impaired glucose tolerance or hypertension.

In summary, although mifepristone provides substantial improvement of endogenous Cushing syndrome, significant and life-threatening toxicity may occur. Thus, periodic clinical and laboratory work-up must be performed after mifepristone therapy is started.

Funding
This case report did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent
A written informed consent has been obtained from the patient for publication of the submitted article.

Author contribution statement
Dr Katta, Dr Lal and Dr Maradana are the residents of the ICU team who took care of the patient. Dr Velamala is the resident who participated in the outpatient care of the patient. Dr Trivedi is the endocrinologist who was consulted during her ICU stay.

Acknowledgements
Our sincere acknowledgments to Dr Joel Popkin, who assisted us with writing the revised manuscript.

References
1 Lacroix A. ACTH-independent macronodular adrenal hyperplasia. Best Practice & Research. Clinical Endocrinology & Metabolism 2009 23 245–259. (https://doi.org/10.1016/j.beem.2008.10.011)
2 Debillon E, Velayoudom-Cephise FL, Salenave S, Caron P, Chaffanjon P, Wagner T, Massoutier M, Lambert R, Benoît M, Young J, et al. Unilateral adrenalectomy as a first-line treatment of Cushing’s syndrome in patients with primary bilateral macronodular adrenal hyperplasia. The Journal of Clinical Endocrinology & Metabolism 2015 100 4417–4424. (https://doi.org/10.1210/jc.2015-2662)
3 Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A & Endocrine Society. Treatment of Cushing’s syndrome: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism 2015 100 2807–2831. (https://doi.org/10.1210/jc.2015-1818)
4 Fleseriu M. Recent advances in the medical treatment of Cushing’s disease. F1000Prime Reports 2014 6 18–18. (https://doi.org/10.12703/P6-18)
5 Tritos NA & Biller BM. Advances in medical therapies for Cushing’s syndrome. Discovery Medicine 2012 13 171–179.
6 Yuen KCJ, Williams G, Kushner H & Nguyen D. Association between mifepristone dose, efficacy, and tolerability in patients with Cushing syndrome. Endocrine Practice 2013 21 1087–1092. (https://doi.org/10.4158/EPI15760.OR)
7 Pozza C, Grazialedo C, Giannetta E, Lenzi A & Isidori AM. Management strategies for aggressive Cushing’s syndrome: from macroadrenomas to ectopics. Journal of Oncology 2012 2012 685213. (https://doi.org/10.1155/2012/685213)
8 Sharma ST & Nieman LK. Cushing’s syndrome: all variants, detection, and treatment. Endocrinology and Metabolism Clinics of North America 2011 40 379–91, viii. (https://doi.org/10.1016/j.ecl.2011.01.006)
9 Castinetti F, Conte-Devolx B & Brue T. Medical treatment of Cushing’s syndrome: glucocorticoid receptor antagonists and mifepristone. Neuroendocrinology 2010 92(Supplement 1) 125–130. (https://doi.org/10.1159/000314224)
10 Nguyen D & Mizne S. Effects of ketoconazole on the pharmacokinetics of mifepristone, a competitive glucocorticoid receptor antagonist, in healthy men. Advances in Therapy 2017 34 2371–2385. (https://doi.org/10.1007/s12265-017-0621-9)
11 Yuen KCJ, Moraitis A & Nguyen D. Evaluation of evidence of adrenal insufficiency in trials of normocortisolemic patients treated with mifepristone. *Journal of the Endocrine Society* 2017 1 237–246. (https://doi.org/10.1210/js.2016-1097)

12 Johansen S & Alloio B. Mifepristone (RU 486) in Cushing's syndrome. *European Journal of Endocrinology* 2007 157 561–569. (https://doi.org/10.1530/EJE-07-0458)

13 Fleseriu M, Biller BM, Findling JW, Molitch ME, Schteingart DE, Gross C & SEISMIC Study Investigators. Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. *Journal of Clinical Endocrinology & Metabolism* 2012 97 2039–2049. (https://doi.org/10.1210/jc.2011-3350)

14 Moraitis A & Nguyen D. SUN-460 anticipating hypokalemia in patients With ACTH-dependent Cushing syndrome treated with mifepristone: utilization of cortisol and ACTH levels to identify at-risk patients. *Journal of the Endocrine Society* 2019 3(Supplement 1) SUN-460. (https://doi.org/10.1210/js.2019-SUN-460)

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**Received in final form** 16 September 2019

**Accepted** 20 September 2019