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Anticipating Hypokalemia in Patients With ACTH-Dependent Cushing Syndrome Treated With Mifepristone: Utilization of Cortisol and ACTH Levels to Identify At-Risk Patients

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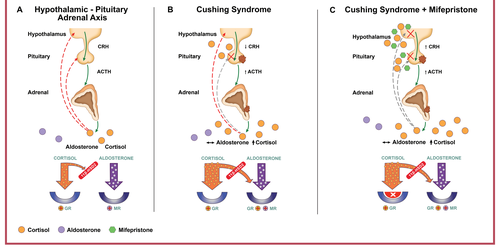
INTRODUCTION

- Hypokalemia (potassium level <3.5 mEq/L) is commonly seen in patients with Cushing syndrome (CS, also referred to as hypercortisolism)[1,2] (**Figure 1**)
- Mifepristone is a competitive glucocorticoid receptor (GR) antagonist approved to treat hyperglycemia associated with endogenous hypercortisolism of all etiologies[3]
- In some patients, mifepristone use can exacerbate hypokalemia[4] due to the mineralocorticoid effects produced by the rapid and significant increase in cortisol levels that result from the loss of negative feedback of the hypothalamic-pituitary-adrenal (HPA) axis (**Figure 1**)

Figure 1. Effect of Mifepristone on the Pathophysiology of Hypokalemia in Hypercortisolism



(A) In healthy individuals, glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) activity are maintained within normal range. 11β-hydroxysteroid dehydrogenase (11β-HSD2), a cortisol-metabolizing enzyme, shields MR from cortisol binding. (B) In CS, high circulating cortisol levels can overwhelm 11β-HSD2, allowing cortisol to bind to the MR, leading to hypokalemia. (C) Mifepristone, a competitive GR antagonist, increases ACTH and cortisol levels, which can exacerbate the "spill-over" effect of MR activation by excess cortisol. Loss of negative feedback is shown by grayed-out arrows and red Xs.

ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.

- Correction of hypokalemia is required prior to initiating mifepristone and potassium levels must be closely monitored during treatment[3]
- Guidance to help clinicians identify patients who may be at greater risk for developing hypokalemia during mifepristone therapy and who may benefit from prophylactic treatment (eg, mineralocorticoid antagonists, potassium replacement) is limited
- In SEISMIC, a pivotal, phase 3 trial evaluating the use of mifepristone in the treatment of patients (N=50) with endogenous hypercortisolism, hypokalemia occurred in 44% of patients[4]
- SEISMIC data were analyzed to investigate potential associations between cortisol and adrenocorticotropic hormone (ACTH) levels and the development of hypokalemia following initiation of mifepristone treatment

SEISMIC STUDY – BACKGROUND

DESIGN

- 24-week, open-label, prospective, multicenter, phase 3 trial[4]
  - Patients were enrolled at 17 US centers from January 2008 to January 2011
- Patients received a single daily 300-mg dose of mifepristone, with dose increases to 600 mg/day on Day 14, 900 mg/day at Week 6, and 1200 mg/day at Week 10[4]

PATIENT POPULATION

- Adults (N=50) with confirmed endogenous CS who had associated impaired glucose tolerance/type 2 diabetes mellitus (n=29) or hypertension (n=21)[4]
  - Endogenous hypercortisolism was defined as elevated urinary free cortisol on at least two 24-hour collections and elevated late night salivary cortisol and/or lack of suppression with dexamethasone
- Inclusion/exclusion criteria and study results, including baseline characteristics of the overall study population, have been published previously[4]

ANALYSIS OF HYPOKALEMIA RISK

METHODS

- Data from 47 patients with ACTH-dependent CS enrolled in SEISMIC were analyzed retrospectively to identify:
  - **Early-onset hypokalemia** (occurring within the first 2 weeks of mifepristone treatment during doses of 300 mg/day)
  - **Late-onset hypokalemia** (occurring after 2 weeks of mifepristone treatment during dose escalation >300 mg/day)
- The risk of experiencing at least one episode of hypokalemia (potassium level <3.5 mEq/L) was evaluated using stepwise multivariable logistic regression and single-variable logistic regression models
- To determine cut-off values for baseline serum cortisol and 2-week ACTH levels that best differentiate patients at high risk for early-onset and late-onset hypokalemia, points on the receiver operating characteristic (ROC) curve that would balance sensitivity and specificity were considered

EARLY-ONSET HYPOKALEMIA (WITHIN FIRST 2 WEEKS OF TREATMENT)

- Independent factors evaluated for potential association with early-onset hypokalemia included total serum cortisol, ACTH, and potassium levels at Day 1
- The proposed cut-off value of 750 nmol/L (27 µg/dL) for baseline serum cortisol provided a high level of sensitivity to detect early-onset hypokalemia and a low false-positive rate

LATE-ONSET HYPOKALEMIA (AFTER DOSE ESCALATION)

- Factors evaluated for potential association with late-onset hypokalemia included total serum cortisol at Day 1 and ACTH and potassium levels at Day 1 and Day 14
- The proposed cut-off value of 112 pg/mL for Day 14 ACTH provided a high level of sensitivity to detect future hypokalemia and a low false-positive rate

RESULTS

ASSOCIATION BETWEEN SERUM POTASSIUM AND LEVELS OF SERUM CORTISOL AND ACTH

- Patients with potassium levels <3.5 mEq/L had, higher total cortisol and ACTH levels on the same study day vs those with levels ≥3.5 mEq/L (**Figures 2** and **3**)

Figure 2. Comparison of Mean Total Cortisol for Patients With Serum Potassium Levels <3.5 mEq/L vs ≥3.5 mEq/L

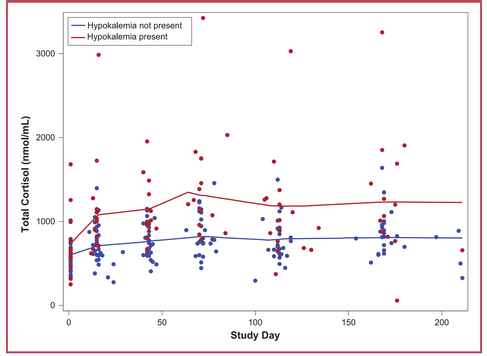
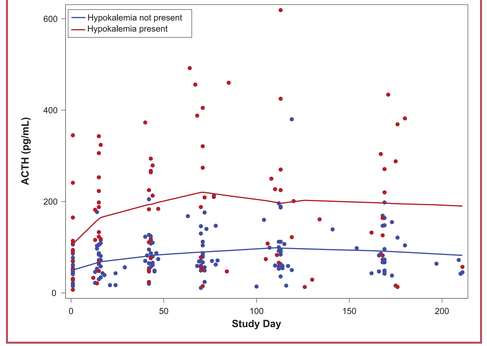


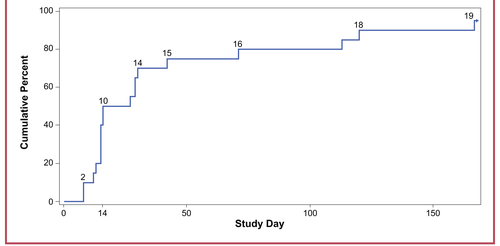
Figure 3. Comparison of Mean ACTH for Patients With Serum Potassium Levels <3.5 mEq/L vs ≥3.5 mEq/L



OVERALL INCIDENCE OF HYPOKALEMIA

- Nineteen patients (40.4%) developed hypokalemia at least once
  - Of these 19 patients, 10 (52.6%) developed hypokalemia by Day 14 (ie, early-onset hypokalemia) (**Figure 4**)

Figure 4. Time (Days) to First Event for Patients With ACTH-Dependent CS Who Developed Hypokalemia (potassium <3.5 mEq/L) (n=19)



EARLY-ONSET HYPOKALEMIA (WITHIN FIRST 2 WEEKS)

- Early-onset hypokalemia was significantly related to baseline serum cortisol levels (*P*=0.0155)
  - Baseline serum cortisol levels >750 nmol/L (>27 µg/dL) were associated with a 6.8-fold increase in the occurrence of early-onset hypokalemia vs patients with cortisol ≤750 nmol/L (≤27 µg/dL) (58.3% [7/12 patients] vs 8.6% [3/35 patients], *P*<0.0011) (**Table 1**)

Table 1. Patients With Early-Onset Hypokalemia by Total Serum Cortisol Level at Day 1

n (%)	No Early Hypokalemia (n=37)	Early Hypokalemia (n=10)	Total (n=47)
Total serum cortisol ≤750 nmol/L	32 (86.5)	3 (30)	35 (74.5)
Total serum cortisol >750 nmol/L	5 (13.5)	7 (70)	12 (25.5)

LATE-ONSET HYPOKALEMIA (AFTER DOSE ESCALATION)

- Late-onset hypokalemia was significantly related to 2-week ACTH levels (*P*=0.0032)
  - At 2 weeks, ACTH levels >112 pg/mL (>25 pmol/L) were associated with a 5.6-fold higher risk of late-onset hypokalemia vs patients with ACTH ≤112 pg/mL (≤25 pmol/L) (*P*<0.0001) (**Table 2**)

Table 2. Patients With Late-Onset Hypokalemia by ACTH Levels After 2 Weeks of Treatment With Mifepristone

n (%)	No Hypokalemia (n=30)	Hypokalemia (n=16)	Total (n=46)
ACTH ≤112 pg/mL	26 (86.7)	4 (25)	30 (65.2)
ACTH >112 pg/mL	4 (13.3)	12 (75)	16 (21.7)

- Nine (19.1%) of the 47 patients experienced severe (potassium ≤2.5 mEq/L) or recurrent hypokalemia
- High ACTH levels (>112 pg/mL [>25 pmol/L]) at the Day 14 visit were also associated with a greater risk of severe or recurrent hypokalemia (77.8% [7/9] vs 22.2% [2/9]) (**Table 3**)

Table 3. Patients With Late-Onset Hypokalemia or Late-Onset Severe/Recurrent Hypokalemia, by ACTH Levels After 2 Weeks of Treatment With Mifepristone

n (%)	No Hypokalemia (n=30)	Non-Severe Hypokalemia (n=7)	Severe or Recurrent Hypokalemia (n=9)	Total (n=46)
ACTH ≤112 pg/mL	26 (86.7)	2 (28.6)	2 (22.2)	30 (65.2)
ACTH >112 pg/mL	4 (13.3)	5 (71.4)	7 (77.8)	16 (34.8)

CONCLUSIONS

- Analysis of the SEISMIC study data show that serum cortisol and ACTH levels may be useful in identifying patients at risk for developing hypokalemia while using mifepristone
  - Serum baseline cortisol levels >750 nmol/L (>27 µg/dL) were associated with a significantly higher occurrence of early-onset hypokalemia
  - ACTH levels >112 pg/mL (>25 pmol/L) obtained 2 weeks after starting treatment with mifepristone 300 mg were associated with a significantly higher occurrence of late-onset or recurrent hypokalemia upon dose escalation
- To identify patients at high risk of developing hypokalemia following mifepristone initiation, serum cortisol levels should be measured prior to starting mifepristone
  - If serum cortisol is >750 nmol/L (27 µg/dL), prophylactic therapy with mineralocorticoid antagonists should be initiated concurrently with mifepristone
- To identify patients at high risk of developing hypokalemia following an increase in the dose of mifepristone, morning ACTH levels should be measured 2 weeks after starting mifepristone
  - If ACTH levels are >112 pg/mL (>25 pmol/L), prophylactic treatment for hypokalemia with mineralocorticoid antagonists should be initiated or intensified before the dose of mifepristone is increased

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DISCLOSURES

AGM, DN: Employees, Corcept Therapeutics.

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