Dose-Dependent Risks of Glucocorticoid Treatment in Classic Congenital Adrenal Hyperplasia

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Background

Congenital adrenal hyperplasia (CAH) comprises a group of rare autosomal recessive disorders characterized by a deficiency in one or more key enzymes involved in adrenal steroidogenesis.[1]

Patients with CAH experience cortisol deficiency and varying degrees of aldosterone deficiency. Loss of negative feedback from cortisol leads to upregulation of the hypothalamic-pituitary-adrenal (HPA) axis, increased adrenocorticotropic hormone (ACTH) signaling, and subsequent overproduction of androgens.[2,3]

Glucocorticoid (GC) treatment is the standard of care among patients with CAH for physiologic cortisol replacement and suppression of ACTH and adrenal androgens.[1]

Androgen suppression usually requires supraphysiologic GC doses, which confer risks that are compounded over the course of a patient's lifetime.

Dose-dependent relationships between GCs and GC-related adverse events (GCRAEs) and comorbidities have been documented in rheumatoid arthritis[4], but there is a paucity of research examining GC dose and GCRAEs among patients with CAH.

Objectives

The goal of this analysis was to examine a dose-dependent relationship between GC use and risk of GCRAEs among patients with classic CAH.

Methods

This cross-sectional study was conducted using medical and pharmacy claims from RWD Insights, an all-payer medical and pharmacy claims database between 01 January 2014 and 31 December 2021, including data for nearly 80% of the US-insured population.

Adult patients with classic CAH were selected based on diagnosis (International Classification of Disease, 9th/10th, Clinical Modification [ICD-9/10-CM] codes: 225.9, E25.0, E25.9) and treatment (continuous treatment with oral GCs).

- The index event was the first prescription of an oral GC.
- Continuous treatment was defined as 75% proportion of days covered in any calendar year in which the patient was continuously enrolled.

Patients were further required to be free of pituitary disorders and have an average daily dose of ≥10mg/day in hydrocortisone equivalents (HcE).

Eligible patients were categorized into 3 dose groups: low- (10 to <20 mg/d HcE), medium- (20 to <30 mg/d HcE), and high-dose (≥30 mg/d HcE) cohorts. See Figure 1 for complete selection criteria.

Patient characteristics (age, sex, US region, payer type) as of the index date were reported.

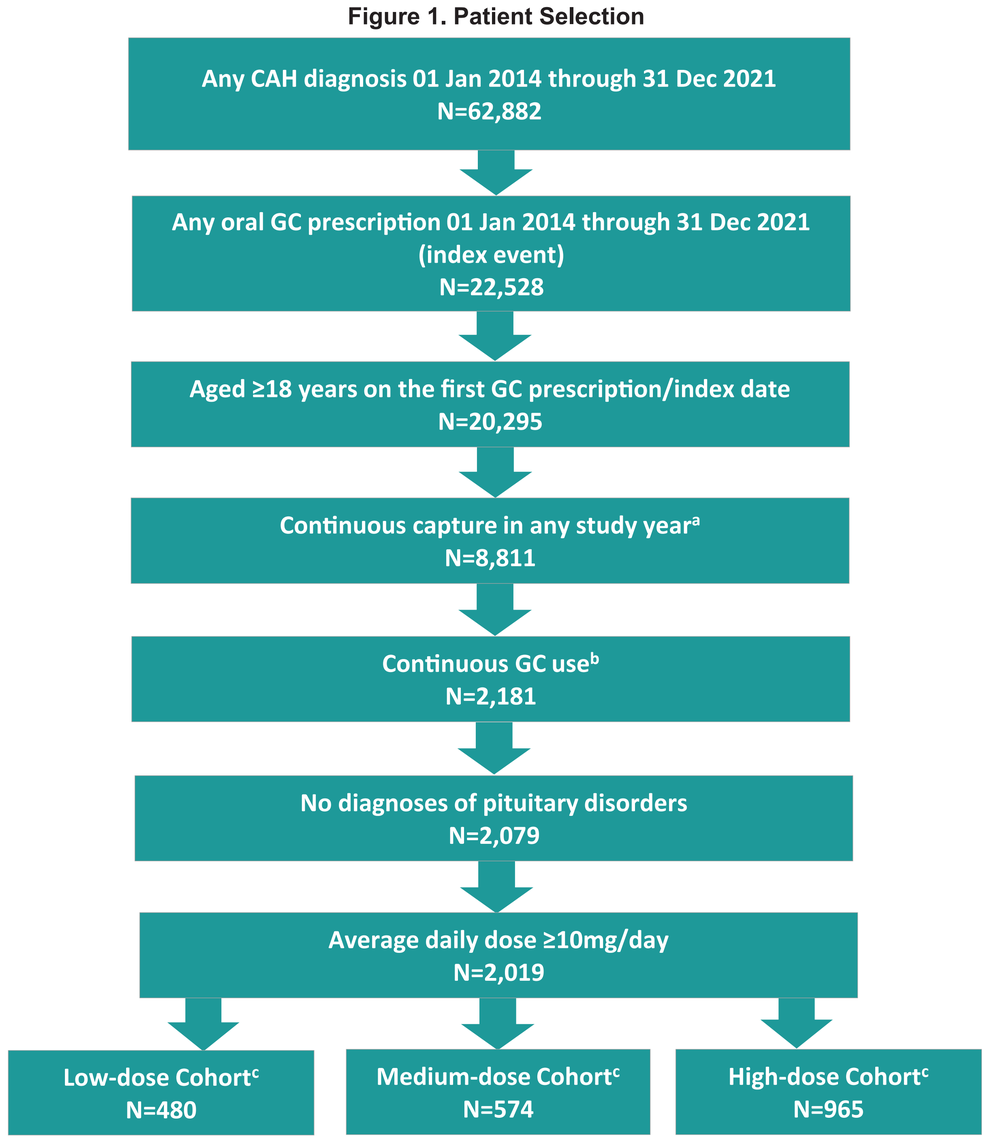
Mean and standard deviations were computed for age; number and percentages were computed for other variables.

P-values were estimated for bivariate comparisons between the low-dose and other cohorts according to Chi-square tests ($p<0.05$ was considered statistically significant).

Results

A total of 2,019 patients met the selection criteria: 480 were included in the low-dose cohort, 574 were included in the medium-dose cohort, and 965 patients were included in the high-dose cohort (Figure 1).

Figure 1. Patient Selection



CAH: congenital adrenal hyperplasia; GC: glucocorticoid

[a]Continuous capture was defined as having ≥2 prescriptions for GC on different days and ≥1 medical claim in any calendar year during the study period.

[b]Continuous use was defined as having proportion of days covered of ≥75% during a calendar year.

[c]Low-dose cohort: 10-20mg/day; medium-dose cohort: >20-30mg/day; high-dose cohort: >30mg/day

Results - cont'd

Table 1. Patient Characteristics by Dose

Patient Characteristics (N, %)	Low-dose Cohort[a] N=480	Medium-dose Cohort[a] N=574	High-dose Cohort[a] N=965
Age, mean (SD)	43.7 (16.5)	41.7 (15.7)	41.5 (16.0)
18 to 25 years	79 (16.5%)	97 (16.9%)	188 (19.5%)
26 to 35 years	102 (21.3%)	142 (24.7%)	224 (23.2%)
36 to 45 years	81 (16.9%)	126 (22.0%)	165 (17.1%)
46 to 54 years	71 (14.8%)	79 (13.8%)	158 (16.4%)
55 to 64 years	84 (17.5%)	71 (12.4%)	131 (13.6%)
65 to 74 years	51 (10.6%)	40 (7.0%)	74 (7.7%)
75+ years	12 (2.5%)	19 (3.3%)	25 (2.6%)
Sex			
Male	131 (27.3%)	177 (30.8%)	364 (37.7%)
Female	349 (72.7%)	397 (69.2%)	601 (62.3%)
US Region			
Northeast	103 (21.5%)	114 (19.9%)	203 (21.0%)
Midwest	110 (22.9%)	146 (25.4%)	237 (24.6%)
South	103 (21.5%)	121 (21.1%)	216 (22.4%)
West	164 (34.1%)	193 (33.6%)	309 (32.0%)
Payer Channel			
Medicare	87 (18.1%)	76 (13.2%)	142 (14.7%)
Medicaid	90 (18.8%)	135 (23.5%)	260 (26.9%)
Commercial	252 (52.5%)	296 (51.6%)	462 (47.9%)
Government	51 (10.6%)	67 (11.7%)	101 (10.5%)

[a]Low-dose cohort: 10-20mg/day; medium-dose cohort: >20-30mg/day; high-dose cohort: >30mg/day; SD: standard deviation

Age of patients in the low-dose cohort (44 years of age) was slightly older than in the medium and high-dose cohorts (42 years of age), mainly due to a higher proportion of patients ≥65 years of age (medium: 13.1% vs high: 10.3%).

Overall, 66.7% of patients were female (Table 1); the proportion of female patients in the low-dose cohort was higher than that in the other cohorts (low: 72.7% vs 69.2%, 62.3%).

Approximately one-half of patients across all cohorts utilized commercial insurance.

Trends were seen between increasing daily GC dose and increasing rates of GCRAEs for patients with cardiovascular (CV), gastrointestinal, and energy/sleep disorders, and infections. In general, there were no significant differences between the GCRAE rates in the low vs medium cohort (Table 2).

Table 2. GCRAE Rates by Dose Group

GCRAEs (N, %)	Low-dose Cohort[a] N=480	Medium-dose Cohort[a] N=574	P-value	High-dose Cohort[a] N=965	P-value
Psychological disorders	175 (36.5%)	199 (34.7%)	0.5454	388 (40.2%)	0.1687
Anxiety disorder	118 (24.6%)	153 (26.7%)	0.4434	294 (30.5%)	0.0196
Cardiovascular disorders	144 (30.0%)	181 (31.5%)	0.5914	354 (36.7%)	0.0118
Tachycardia	38 (7.9%)	57 (9.9%)	0.2556	131 (13.6%)	0.0016
Syncope/collapse	23 (4.8%)	35 (6.1%)	0.3545	82 (8.5%)	0.0106
Cardiomegaly	17 (3.5%)	21 (3.7%)	0.9193	57 (5.9%)	0.0547
GI disorders	172 (35.8%)	215 (37.5%)	0.5862	390 (40.4%)	0.0925
Energy/sleep disorders	174 (36.3%)	232 (40.4%)	0.1661	429 (44.5%)	0.0029
Weakness	41 (8.5%)	62 (10.8%)	0.2185	146 (15.1%)	0.0004
Bone disorders	133 (27.7%)	147 (25.6%)	0.4424	250 (25.9%)	0.4649
Infections	229 (47.7%)	300 (52.3%)	0.1406	534 (55.3%)	0.0062
Pneumonia	33 (6.9%)	51 (8.9%)	0.2302	108 (11.2%)	0.0092
Sepsis	34 (7.1%)	44 (7.7%)	0.7192	96 (9.9%)	0.0730
Cellulitis	19 (4.0%)	33 (5.7%)	0.1812	88 (9.1%)	0.0004
Bronchitis	16 (3.3%)	27 (4.7%)	0.2627	66 (6.8%)	0.0067
Other bacterial agents as cause of disease classified elsewhere	19 (4.0%)	11 (1.9%)	0.0471	31 (3.2%)	0.4650
Kidney disease	70 (14.6%)	80 (13.9%)	0.7650	138 (14.3%)	0.8853
Hypertensive chronic kidney disease	30 (6.3%)	18 (3.1%)	0.0157	37 (3.8%)	0.0397
Skin disorders	45 (9.4%)	39 (6.8%)	0.1234	67 (6.9%)	0.1034
Type II diabetes	156 (32.5%)	177 (30.8%)	0.5628	330 (34.2%)	0.5202
Hyperglycemia	24 (5.0%)	48 (8.4%)	0.0312	70 (7.3%)	0.1018

Comparisons were made between the low-dose (reference) cohort, and the medium- and high-dose cohorts, separately. [a]Low-dose cohort: 10-20mg/day; medium-dose cohort: >20-30mg/day; high-dose cohort: >30mg/day; GCRAE: glucocorticoid-related adverse event; GI: gastrointestinal

The rates of CV disorders (30.0% vs 36.7%) including tachycardia, syncope/collapse, and cardiomegaly; energy/sleep disorders (36.3% vs 44.5%), specifically weakness; and infections (47.7% vs 55.3%) such as pneumonia, sepsis, cellulitis, and bronchitis were lower in the low-dose cohort vs the high-dose cohort (all $p<0.05$).

Anxiety disorders were significantly higher in the high-dose cohort compared to the low-dose cohort ($p=0.02$). Harasymiw et al, recently reported that anxiety disorders were significantly more prevalent in children, adolescents and young adults with CAH vs peers without CAH in Medicaid and commercial insurance samples.[5]

Using average adult body surface area of 1.79mg/m^2, a low dose is considered to be approximately physiologic (5.6-11.2mg/m^2/d), and a high dose is considered to be supraphysiologic (>17.3mg/m^2/d).[6]

Limitations

- Due to the cross-sectional nature of this study, causal relationships cannot be determined between the exposure (dose intensity) and outcome of interest (GCRAEs).
- Medications were based on pharmacy fills and not evidence of actual consumption by the patient.
- The use of clinical codes to identify CAH does not delineate between actual disease or rule-out diagnoses; however, combining diagnosis codes with GC use increased the chances of currently identifying patients with classic CAH.
- Many diagnoses, such as obesity disorders, are not routinely coded as they do not impact billing.

Conclusions

- This study examined the dose-dependent relationship between GC exposure and GCRAE risk and found significant differences between the low-dose and high-dose groups for CV disorders, energy/sleep disorders, anxiety, and infections.
- Our findings suggest that supraphysiologic exposure confers greater GC-associated risk than approximate physiologic exposure.
- Given the cumulative risks of lifelong exposure to supraphysiologic GC doses in classic CAH patients, these results highlight the need for steroid-sparing therapies in this population.

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