Higher glucocorticoid replacement doses are associated with increased mortality in patients with pituitary adenoma

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*(G Johannsson and D S Olsson contributed equally to this work)

Abstract

Objective: Patients with secondary adrenal insufficiency (AI) have an excess mortality. The objective was to investigate the impact of the daily glucocorticoid replacement dose on mortality in patients with hypopituitarism due to non-functioning pituitary adenoma (NFPA).

Methods: Patients with NFPA were followed between years 1997 and 2014 and cross-referenced with the National Swedish Death Register. Standardized mortality ratio (SMR) was calculated with the general population as reference and Cox-regression was used to analyse the mortality.

Results: The analysis included 392 patients (140 women) with NFPA. Mean ± s.d. age at diagnosis was 58.7 ± 14.6 years and mean follow-up was 12.7 ± 7.2 years. AI was present in 193 patients, receiving a mean daily hydrocortisone equivalent (HCeq) dose of 20 ± 6 mg. SMR (95% confidence interval (CI)) for patients with AI was similar to that for patients without, 0.88 (0.68–1.12) and 0.87 (0.63–1.18) respectively. SMR was higher for patients with a daily HCeq dose of >20 mg (1.42 (0.88–2.17)) than that in patients with a daily HCeq dose of 20 mg (0.71 (0.49–0.99)), P = 0.017. In a Cox-regression analysis, a daily HCeq dose of >20 mg was independently associated with a higher mortality (HR: 1.88 (1.06–3.33)). Patients with daily HCeq doses of ≤20 mg had a mortality risk comparable to patients without glucocorticoid replacement and to the general population.

Conclusion: Patients with NFPA and AI receiving more than 20 mg HCeq per day have an increased mortality. Our data also show that mortality in patients substituted with 20 mg HCeq per day or less is not increased.

Introduction

Patients with hypopituitarism have increased morbidity and mortality (1, 2). Along with factors such as young age at diagnosis, female gender, underlying pituitary disease and pituitary radiation therapy, it has been suggested that the current hormone replacement regimes may contribute to the adverse outcome (2, 3, 4, 5, 6, 7, 8).

The traditional glucocorticoid (GC) replacement dose used in patients with adrenal insufficiency (AI) is considerably higher than the estimated endogenous cortisol production rate in healthy subjects (10–15 mg/day) (9, 10). Excess GC exposure over time may contribute to an increased risk of adverse metabolic profile and
premature death (4, 11, 12, 13). Previous studies have shown increased mortality in hypopituitary patients with acromegaly using daily hydrocortisone (HC) replacement doses of ≥25 mg (12) and in patients with NFPA with daily HC doses of ≥30 mg (13). HC clearance depends largely on body weight and a weight-adjusted GC replacement dose has therefore been suggested (14). Zueger et al. demonstrated that body weight-adapted HC doses of ≥0.35 mg/kg are associated with increased mortality (4).

Our group has, in a previous study, shown that patients with hypopituitarism and AI using a daily hydrocortisone dose ≥20 mg per day had a worse cardiometabolic risk profile than hypopituitary patients without GC replacement therapy (11).

The aim of this study was to investigate the impact of GC dose on mortality in a large and unselected population of NFPA patients. Our main hypothesis was that patients receiving daily HC doses higher than 20 mg have the worst outcome.

**Subjects and methods**

**Study design**

This was a cohort study including all patients treated or followed for NFPA in the western region of Sweden between Jan 1, 1997 and Dec 31, 2011. To be certain that all patients with NFPA from the western region of Sweden were included, we also searched the Swedish National Patient Register (Patient Register). The Patient Register achieved a national coverage in 1987 and contains information from every patient visit within the Swedish hospital system using a unique identification number.

Medical charts for all patients were manually reviewed to ensure that the diagnosis of NFPA was correct and in order to collect information on medical history and clinical characteristics, including hormonal replacement therapy. In total, 405 patients with a confirmed NFPA were identified. Of these, 13 patients were excluded due to GC treatment for non-endocrine diseases (ten of these patients were identified. Of these, 13 patients were excluded due to GC treatment for non-endocrine diseases (ten of these patients were identified. Of these, 13 patients were excluded due to GC treatment for non-endocrine diseases (ten of these patients died during the study period). Thus, 392 patients were included in the final analysis.

For each patient start of follow-up was defined as either the time point when NFPA was diagnosed or the start of the study (January 1, 1987). All patients were followed to Dec 31, 2014 or until death. Current replacement therapy was defined as the treatment the patients received at their last clinical visit before the end of study. Information on mortality was obtained from the Swedish National Cause of Death Register.

Secondary AI was diagnosed according to local clinical practice. The majority of patients have, however, been diagnosed and followed at Sahlgrenska University Hospital, using morning serum cortisol measurements and a Synacthen test. If inconclusive, these tests were followed by an insulin tolerance test.

For patients with secondary AI, and not receiving HC (7 female, all receiving cortisone acetate), a HC equivalent (HCEq) dose was calculated (15, 16). Patients with GC replacement were divided into three groups according to their daily HCEq dose (<20, 20 or >20 mg/day). The patients were also grouped according to their daily HCEq dose per kg body weight (≤0.25, >0.25–0.30 and >0.30–0.55 mg/kg/day).

**Ethics**

The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden, and by the National Board of Health and Welfare, Sweden.

**Statistics**

Person-years at risk were calculated from study inclusion to death, or end of study, and stratified according to gender, 5-year age groups and 1-year calendar periods. The expected number of deaths for each stratum was calculated using the general Swedish population for every calendar year and 5-year age group as reference. The observed number of deaths among patients with NFPA was compared to that expected by standardised mortality ratios (SMRs). Ninety-five percent confidence intervals (CIs) were calculated assuming a Poisson distribution of the observed numbers. Subgroup analyses for absolute daily HCEq dose and daily HCEq dose per kg were performed. SMRs for non-overlapping subgroups were compared to each other (17).

Multivariable Cox-regression models were used to calculate hazard ratio (HR) of mortality, adjusted for: age at the start of the study, gender and treatment with radiotherapy, as well as absolute- or weight-adjusted HCEq dosage. HR was also calculated for patients with secondary AI and compared to patients with intact hypothalamic–pituitary–adrenal function. The level of significance was set to P<0.05. IBM SPSS (version 24) and STATA SE (version 14) software was used to perform the statistical analyses.
Table 1 Characteristics of patients with non-functioning pituitary adenoma included in the study.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n=392)</th>
<th>Without GC (%)</th>
<th>With GC (%)</th>
</tr>
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<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>252 (64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>140 (36)</td>
<td></td>
<td></td>
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<tr>
<td>Age at diagnosis, years, mean ± s.d.</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Men, mean ± s.d.</td>
<td>58.7 ± 14.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, mean ± s.d.</td>
<td>58.9 ± 13.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypopituitarism, n (%)</td>
<td>313 (80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes insipidus, n (%)</td>
<td>46 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormonal replacement, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- None</td>
<td>75 (19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Levothyroxine</td>
<td>272 (69)</td>
<td></td>
<td></td>
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<tr>
<td>- Glucocorticoids*</td>
<td>193 (49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Sex steroids</td>
<td>186 (47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Growth hormone</td>
<td>160 (41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean follow-up time, years (range)</td>
<td>12.7 (0.1–28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient-years at risk in the study</td>
<td>4961</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment with surgery, n (%)</td>
<td>287 (73)</td>
<td></td>
<td></td>
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<tr>
<td>Treatment with radiotherapy, n (%)</td>
<td>78 (20)</td>
<td></td>
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</tbody>
</table>

Patients treated with glucocorticoids due to non-endocrine chronic disorders were excluded (n=13).

*Includes replacement with hydrocortisone (n=186) and cortisone acetate (n=7).

Results

Patient characteristics

In total, 392 patients with NFPA were included in the analysis, 252 men and 140 women (Table 1). The mean age at diagnosis was 58.7 ± 14.6 years and the mean follow-up time was 12.7 ± 7.2 years. Of the 392 patients, 287 (73%) underwent surgical treatment, of whom 76 (19%) also received pituitary radiation therapy. Two patients received treatment with radiation therapy alone, and the remainder (n=103, 26%) did not receive any targeted therapy for their NFPA.

The prevalence of growth hormone, levothyroxine, sex hormones and anti-diuretic hormone replacement therapy in the cohort are shown in Table 1. The number of patients with any form of hypopituitarism was 313 (80%). Secondary AI was recorded in 193 patients (49%). The vast majority received HC (n=186) and the remainder received cortisone acetate (n=7). The mean ± s.d. daily HCeq dose was 20 mg ± 6 and the mean HCeq dose per kg was 0.25 ± 0.09. The most common dosing frequency of GC replacement was BID (n=159), followed by OD (n=27) or TID (n=7).

Mortality

In the whole group of 392 patients, 106 deaths were recorded. The most frequent cause of death in all subgroups was diseases of the circulatory system (ICD-10 Chapter 9) (Table 2). Only two patients died due to infectious diseases (ICD-10 Chapter 1). Patients with secondary AI had an SMR similar to that for patients...
without, 0.88 (95% CI: 0.68–1.12) and 0.87 (95% CI: 0.63–1.18) respectively. Also, when separately analysing women, there was no difference in SMR between patients with and without secondary AI, 1.01 (95% CI: 0.60–1.59) and 0.86 (95% CI: 0.50–1.38) respectively. SMR for patients with an HCeq dose of >20 mg per day was higher (1.42; 95% CI: 0.88–2.17) than that for patients with a daily HCeq dose of 20 mg (0.71; 95% CI: 0.49–0.99) (P = 0.017) (Table 3). Furthermore, SMR was also higher for patients receiving a daily HCeq dose of >0.30–0.55 mg/kg (1.56; 95% CI: 1.01–2.30) compared to patients receiving a daily HCeq dose of >0.25–0.30 mg/kg (0.65; 95% CI: 0.37–1.06) (P = 0.011).

Internal analyses were also performed in order to adjust for confounding factors. Cox-regression, adjusted for age at the start of study, gender and radiotherapy, showed that patients receiving a daily HCeq dose of >20 mg had a significantly increased mortality compared to patients without GC replacement (HR: 1.88; 95% CI: 1.06–3.33; P = 0.032). In contrast, patients with a daily HCeq dose of 20 mg and patients with <20 mg had mortality similar to patients without GC replacement (Fig. 1A). These results were consistent for weight-adjusted doses where patients receiving >0.30 mg/kg of daily HCeq had an increased mortality (HR: 1.97; 95% CI: 1.13–3.41; P = 0.016) (Fig. 1B) compared to patients without GC replacement. Neither treatment with radiotherapy, nor gender had a significant effect on mortality. The HR for women was 1.5 (95% CI: 0.92–2.63) in the Cox-regression investigating the total daily HCeq dose and 1.4 (95% CI: 0.86–2.34) in the Cox-regression investigating the weight-adjusted dose.

**Discussion**

In this study on an unselected population of 392 NFPA patients, we have shown that daily HC replacement doses above 20 mg or 0.30 mg/kg in patients with secondary AI were associated with increased mortality compared to patients with lower doses and to patients without secondary AI. Patients with NFPA with daily doses of ≤20 mg had, however, a mortality risk comparable to patients without GC replacement and to the general population.

This study is the first to show that daily HC doses already at >20 mg or >0.30 mg/kg are associated with increased mortality. Previous studies have shown that patients with secondary AI receiving higher GC replacement doses conferred an independent risk of death in studies conducted among patients with acromegaly (>25 mg/day) and NFPA (>30 mg/day) (4, 12, 13). Zuiger et al. reported increased mortality with a RR of 4.0 (95% CI: 1.07–14.85) for patients receiving daily HC.
The previously demonstrated excess mortality in patients with AI has been mainly attributable to cardiovascular, respiratory and infectious diseases as well as cancer (1, 2, 24). It is likely that the degree of AI is of importance for outcome and that patients who are completely insufficient may be more vulnerable to intercurrent illness, whereas patients with partial ACTH deficiency may be over-treated under normal unstressed conditions using conventional replacement doses (25). Hence, inadequate treatment of hypocortisolism remains a significant cause of death during stressful events and intercurrent illness in patients with hypopituitarism (26). A possible explanation for the poor outcome in patients with AI receiving overly high doses of GC replacement is that excess GC exposure over time induces independent risk factors for cardiovascular disease such as diabetes mellitus, hypertension and obesity (27, 28, 29).

A major strength of this study is the unselected cohort of patients diagnosed with NFPA within the same geographical area. To the best of our knowledge, this is the first study where SMR was compared between patients on different GC replacement doses in a cohort of patients without a high inherent excess mortality such as acromegaly or craniopharyngioma. In addition, the follow-up period was extensive with a mean observation time of more than 10 years. Also, patients were not only compared to the general population, but also to a group with the same underlying pituitary disease without GC replacement. Furthermore, all patients with high doses of GC due to non-endocrine diseases were excluded from the analysis. The limitations of this study are its retrospective design and that cumulative GC exposure over time was not available. Additionally, due to the limitations of the study size, effects of gender and radiotherapy on mortality cannot be ruled out.

In conclusion, we can show that NFPA patients with secondary AI with a daily HCeq replacement dose already higher than 20 mg or 0.30 mg/kg have an increased mortality both when compared to patients with HCeq doses ≤20 mg per day and in comparison with the background population. Our study also shows that daily replacement doses of 20 mg HCeq or less do not result in any premature mortality. Previous studies together with our data highlight the importance of using replacement treatment that results in a physiological cortisol exposure to prevent an excess mortality.

Declaration of interest
D S O has been a consultant for Sandoz, Ipsen, Novartis and Pfizer. A G N has received lecture fees from Shire and Pfizer. G J has received speaker’s honorarium from Eli Lilly, Merck Serono, Novartis, Novo Nordisk, Pfizer, Otsuka and Shire and has been a consultant for Astra Zeneca, Merck Serono, Pfizer and Shire. C H, T H, E A, T S and O R have nothing to disclose.

Funding
This study was sponsored by the Swedish federal government under the ALF agreement on medical training and research. The sponsors did not take part in any manner in the design and conduct of the study, in the collection, management, analysis and interpretation of data, or in the writing and the decision to submit the manuscript.

Author contribution statement
All authors took part in the design of the study. C H and D S O performed the patient selection process. C H and D S O have reviewed all the patient medical records. All authors contributed to the data interpretation and analysis and in writing and revision of the report. All authors are responsible for the integrity of the data and accuracy of the analysis, and all approved the final report.

Acknowledgements
The authors would like to express our gratitude to the staff at the Centre for Endocrinology and Metabolism at the Department of Endocrinology at Sahlgrenska University Hospital and to The National Board of Health and Welfare for their excellent collaboration.
References
16 Boland EW. Antihypertensive effects of hydrocortisone (free alcohol), hydrocortisone acetate, and cortisone (free alcohol) as compared with cortisone acetate: results of oral administration in patients with rheumatoid arthritis. British Medical Journal 1952 1 559–564. (doi:10.1136/bmj.1.348.559)

Received 27 April 2017
Revised version received 3 June 2017
Accepted 8 June 2017