CPSP
CANADIAN PAEDIATRIC SURVEILLANCE PROGRAM

Adrenal suppression

PROTOCOLS

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Background

Glucocorticoid (GC) therapy is used in the treatment of a variety of disorders secondary to its anti-inflammatory effects and immunosuppressive activity. These disorders include: asthma, malignancy, nephrotic syndrome, inflammatory bowel disorder, arthritis, and vasculitis. While the efficacy of GCs has been well established, there can be potentially serious side effects. Among them is hypothalamic-pituitary-adrenal (HPA) axis suppression, which is clearly proven but under-recognized. The incidence of adrenal suppression (AS) has not been established. While a low-dose ACTH stimulation test is considered to be the best test for diagnosis, a first morning cortisol level is more practical and frequently ordered by physicians as an investigation for AS. Unfortunately, this test has very limited predictive power in differentiating between normal and impaired HPA function. AS can be associated with significant morbidity, including adrenal crisis and even death. More than 60 recent cases of AS are described in the literature; these have been associated with hospitalizations and prolonged ICU admissions.

GCs exert negative feedback control at the level of the pituitary gland and the hypothalamus, which leads to decreased cortisol secretion. Factors influencing the development of AS include the type, dose, timing, duration and method of delivery of GC therapy, and individual differences in GC metabolism.

Adequate cortisol production is critical during physiologic stress, such as illness or surgery. AS may go undetected until a stress precipitates an adrenal crisis. This can be prevented by recognition of children at risk and administration of higher doses of GCs during times of stress. A tapering regimen may also facilitate the recovery of the adrenal axis and prevention of symptoms in an individual with AS.

Evidence for AS is mostly in the setting of inhaled corticosteroids (ICS) for the treatment of asthma, as they are the mainstay of asthma therapy. A retrospective survey of tertiary care consultant paediatricians and adult endocrinologists in the United Kingdom showed that from an initial 2,912 questionnaires, 33 patients receiving ICS for asthma met the diagnostic criteria for adrenal crisis. Twenty-eight of the patients were children. Asthma affects 15.5% of Canadian children aged 4-11 years, putting a high proportion of our children at risk of AS from asthma therapy. The risk of AS along with other often feared side effects of ICS may cause parents and physicians to be hesitant to appropriately treat childhood asthma. Poorly controlled asthma can lead to decreased physical activity and ultimately increased weight and its associated morbidities and public health burden. Similarly, children receiving asthma therapy with undetected AS may have decreased activity secondary to the symptoms of AS (e.g., fatigue and generalized malaise). An understanding of the risk of AS in children treated with GCs will be helpful in counselling families about ICS therapy. Ultimately, guidelines for screening and treating AS should alleviate fears associated with the condition and lead to improved asthma management.

Anticipated significance and impact for patients

Given the morbidity associated with AS and the potential for intervention and treatment of those affected, it is crucial to understand which children are at risk of this serious complication of GC therapy. Based on the results of this surveillance study, screening guidelines can be developed to identify and treat children with AS prior to the development of symptoms or adrenal crisis. In the setting of asthma management, an approach to detection and treatment of AS in children may improve outcomes and lessen the comorbidities associated with inadequately controlled asthma. The implementation of screening guidelines will prevent morbidity, mortality and costly hospitalizations in our paediatric population. The CPSP provides the ideal format to estimate the frequency and morbidity of this condition in Canada.

Method

Through the established methodology of the CPSP, over 2,500 paediatricians and paediatric subspecialists will be actively surveyed on a monthly basis to report new cases of symptomatic adrenal suppression. For each initial monthly report, participants will be asked to complete a detailed clinical questionnaire to ensure that the case definition is met.

Objectives

1) To estimate the national incidence of paediatric adrenal crisis and symptomatic adrenal insufficiency due to AS in association with GC treatment, diagnosed by Canadian paediatricians.
2) To describe the clinical features of AS at diagnosis and to document burden of illness.
3) To identify characteristics of children with symptomatic AS.
4) To generate awareness among paediatricians of the frequency of AS and associated morbidity in children on GC therapy.

Adrenal suppression (continued)

Case definition

Report any new patient less than 18 years of age treated with any form of GC therapy with evidence of adrenal suppression (AS) defined as:

- Adrenal crisis, an acute critical illness out of proportion in severity to the current illness and manifested by any of the following:
  - hypotension/shock
  - decreased level of consciousness/lethargy
  - unexplained hypoglycemia or hyponatremia
  - seizure
  - death

OR

- Symptomatic* adrenal insufficiency with supportive biochemical evidence

* Signs/symptoms can include anorexia, weakness, fatigue, lethargy, fever, gastrointestinal symptoms (nausea, vomiting, constipation, diarrhea, abdominal pain), morning headache, hypoglycemia, myalgia, arthralgia, psychiatric symptoms, and growth failure.

Exclusion criteria

Adrenal insufficiency unrelated to GC therapy, including adrenocorticotropic hormone (ACTH) deficiency due to hypothalamic or pituitary gland abnormalities, and primary adrenal disorders, such as:

- Congenital adrenal hyperplasia
- Autoimmune adrenalitis or polyglandular syndromes
- Adrenal hypoplasia congenita
- ACTH resistance syndromes
- Metabolic disorders (adrenoleukodystrophy, peroxisome biogenesis disorders, cholesterol metabolism, mitochondrial disorders)
- Infectious disorders (sepsis, tuberculosis, fungal infections, viral infections)
- Infiltrative/destructive causes (hemorrhage, amyloidosis, sarcoidosis, metastases)
- Drugs inhibiting steroid biosynthesis (e.g., ketoconazole, etomidate, suramin, aminoglutethimide, metyrapone)

Duration

April 2010 to March 2012

Expected number of cases

The maximum expected number of cases is 30 per year.

Ethical approval

Research Ethics Board, Children's Hospital of Eastern Ontario, University of Ottawa

Analysis and publication

The investigators will analyse the data promptly and report any significant findings to the CPSP. Quarterly reports and an annual report will be distributed to all participants. Data will be presented as a scientific abstract at national and international paediatric and/or endocrinology meetings and submitted for publication to a peer-reviewed paediatric and/or endocrinology journal.

Bibliography

Todd GRG, Acerini CL, Ross-Russell R, et al. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child* 2002;87:457-61

Tordjman K, Jaffe A, Trostanetsky Y, et al. Low-dose (1 microgram) adrenocorticotrophin (ACTH) stimulation as a screening test for impaired hypothalamo-pituitary-adrenal axis function: sensitivity, specificity and accuracy in comparison with the high-dose (250 microgram) test. *Clin Endocrinol (Oxf)* 2000;52:633-40

(A full bibliography is available from the principal investigators or the CPSP office.)