

SURVEY OF ADRENAL CRISIS ASSOCIATED WITH INHALED CORTICOSTEROIDS IN THE UNITED KINGDOM

Todd GRG, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D. *Arch Dis Child*. 2001;87:457–461

Purpose of the Study. This is a report from a national survey performed in the United Kingdom that looks at the frequency of acute adrenal crisis associated with the use of inhaled corticosteroids (ICS).

Methods. A questionnaire was sent to pediatricians and adult endocrinologists. The question was asked as to whether or not they had ever encountered cases of acute adrenal crisis thought to be associated with the use of inhaled corticosteroids used to treat asthma. Those who had such an experience were subsequently contacted and given a more detailed questionnaire. Information was requested regarding the patient's age, sex, height, growth, weight, details of the clinical presentation, acute serum cortisol levels and results of hypothalamic-pituitary-adrenal (HPA) axis function. Information on the dose, duration of treatment, device, days of prednisolone used in the past year, and asthma severity. The respondents were also asked whether or not they thought the symptoms were attributable to asthma. Specific criteria were set up for the diagnosis of adrenal crisis.

Results. Only the results of the pediatric patients will be presented here. A questionnaire was sent to 2912 physicians of which only 709 (24%) were returned. A total of 55 (1.9%) indicated one or more cases of adrenal crisis. Thirty-three patients met the criteria of which 28 were children. The average age of the children was 6.4 years (range: 3.3–10). There were 17 boys in the group. Twenty-three of the 28 children presented with hypoglycemia. Adrenal insufficiency was believed to contribute to the death of 1 child. Five had insidious onset of symptoms such as lassitude, weakness, nausea, and dizziness. In most of the patients there was no obvious precipitating factor for the crisis. Twenty-five of the children had abnormal HPA axis function as determined by a short synacthen stimulation test. One child was on budesonide (AstraZeneca, Wilmington, DE), one was on budesonide and fluticasone, and the remainder were on fluticasone (GlaxoSmithKline, Research Triangle Park, NC). The duration of treatment with the ICS was 1.7 years. The average dose of fluticasone was 980 $\mu\text{g}/\text{day}$ (range: 500–2000). In retrospect, 3 thought that their patients did not have asthma. Five had probable asthma, but were overtreated with ICS attributable to other concurrent lung disorders. The duration of oral corticosteroid use in the past year was <21 days.

Conclusions. The frequency of acute adrenal crisis associated with ICS use is greater than previously thought. The dose of ICS used was within the recommendations of the British Guidelines on Asthma Management. The vast majority of the reactions occurred with fluticasone (94%) which accounts for only 10% of the total prescribed ICS in the United Kingdom. The high lipophilicity of fluticasone is offered as a possible reason for higher absorption via the lung. The longer elimination half-life and possible accumulation may also account for continuous suppression of adrenal function. Caution with the use of >400 $\mu\text{g}/\text{day}$ of fluticasone was advised by the authors along with an assessment of HPA axis function when an ICS is used for >1 year.

Reviewer's Comments. I had the pleasure to see this data at a national meeting. I also listened to a number of asthma specialists who were surprised and concerned. The concern was the rarity of ICS-precipitated adrenal crisis in this country. No one in the audience had any reports of adrenal

crisis in their practices. The authors point out that this has been a rare event; however, a substantial number of children on fluticasone did experience problems. Just as soon as we put to bed the issue of growth suppression and ICS, the possibility of HPA axis suppression awakens us. Those at risk were on a specific ICS that has unique properties that may allow for absorption. The take-home message is one of vigilance. For those on high doses of ICS for long periods of time, be aware of the possibility of adrenal suppression. Perhaps, even for the rare event, an additional education message should include the signs and symptoms of adrenal crisis. Perhaps this is even something to include on those asthma emergency action plans.

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RISK OF HOSPITALIZATION RESULTING FROM UPPER GASTROINTESTINAL BLEEDING AMONG PATIENTS TAKING CORTICOSTEROIDS: A REGISTER-BASED COHORT STUDY

Nielsen GL, Sorensen HT, Mellemkjoer L, et al. *Am J Med*. 2001;111:541–545

Purpose of the Study. The authors assessed the risk of hospitalization for upper gastrointestinal bleeding among patients using systemic corticosteroids, accounting for the use of other drugs that may increase the risk of bleeding.

Study Population and Methods. The authors conducted a population-based cohort study in North Jutland County, Denmark. Data on the use of corticosteroids, nonsteroidal antiinflammatory drugs, aspirin, and anticoagulants during 1991–1995 were obtained from a countywide prescription database. All hospitalizations attributable to upper gastrointestinal bleeding were identified through the Hospital Discharge Registry. The observed numbers of patients with gastrointestinal bleeding in various exposure categories among corticosteroid users were compared with the expected number based on the North Jutland population who did not receive prescriptions for any of the drugs under study.

Results. A total of 45 980 patients accrued 18 379 person-years of corticosteroid use. There were 109 hospital admissions for gastrointestinal bleeding among corticosteroid users, compared with 26 expected, yielding a relative risk of 4.2 (95% confidence interval [CI]: 3.4–5.0). Among corticosteroid users who did not use other drugs associated with gastrointestinal bleeding, the relative risk was 2.9 (95% CI: 2.2–3.7). The relative risk decreased further to 1.9 (95% CI: 1.4–2.5) when current corticosteroid usage was compared with former usage.

Conclusions. We observed an increased risk of hospitalization because of upper gastrointestinal bleeding among patients prescribed corticosteroids, especially among those who use other medications. Confounding from the underlying disease may also have contributed to the observed increase in risk.

Reviewer's Comments. It seems that I'm using oral corticosteroids less for asthma, but more for chronic rhinosinusitis and urticaria/angioedema. This study reminds us to consider the additive risks of gastrointestinal bleeding in corticosteroid treated patients who are also taking nonsteroidal antiinflammatory drugs and/or anticoagulants or who have other comorbid predisposing conditions.

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Frederick E. Leickly
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