Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Risk of adrenal insufficiency with inhaled corticosteroids

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A Canadian observational study found that the use of inhaled corticosteroids at high doses appears to be a significant independent risk factor for adrenal insufficiency. This adds to the evidence that prompted MHRA warnings on this issue and reminds prescribers to follow the clinical guidance on COPD and asthma on the appropriate use of high doses of inhaled corticosteroids.

Overview and current advice

The NICE-accredited BTS/SIGN guideline on the management of asthma recommends inhaled corticosteroids (ICS) at step 2, as the first-choice regular preventer therapy for adults and children with asthma. The dose of ICS should be titrated to the lowest dose at which effective control of asthma is maintained.

The NICE guideline on the management of chronic obstructive pulmonary disease (COPD) recommends the use of an ICS in a combination inhaler with a long-acting beta agonist (LABA), as an option for the treatment of adults with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required, and who have an FEV₁ <50% predicted.

The Medicines and Healthcare products Regulatory Agency (MHRA) has previously highlighted that prolonged use of high doses of ICS (as with the use of oral corticosteroids) carries a risk of systemic side effects, including adrenal suppression or crisis. The MHRA (as the Committee on Safety of Medicines (CSM)) has issued warnings about the use of high-dose ICS, particularly in children, and in relation to fluticasone. Children prescribed ICS should have their growth monitored annually (although isolated growth failure is not a reliable indicator of adrenal suppression).

Evidence to date that ICS are associated with adrenal insufficiency has come from case reports and one observational study performed in the UK.

See the NHS Evidence topic pages on COPD and on asthma for a general overview of these conditions. The NICE Pathway: chronic obstructive pulmonary disease brings together all related NICE guidance and associated products on this condition in a set of interactive topic-based diagrams. ‘High-dose inhaled corticosteroids in asthma’ is a topic included in the latest update of the QIPP document; Key therapeutic topics - Medicines management options for local Implementation. The NICE quality standard for asthma includes a quality statement that ‘People with asthma receive a structured review at least annually’. Such reviews include adjustment of treatment (considering...
stepping up if the person has had poor control or stepping down if the person has had good control since the last annual review).

New evidence

A Canadian observational study has re-examined the link between the use of ICS and adrenal insufficiency. A cohort of 368,238 users of respiratory medications was formed using a province wide registry (mean age 49.2 ± 27.5 years, range 1-108). Both asthma and COPD patients were included in the cohort.

Within the cohort, 392 cases of adrenal insufficiency were identified using coding for hospital discharge diagnosis (mean age 67.9 ± 18 years). The authors completed a nested case control analysis. For each case, up to 10 controls matched on age and cohort year of entry were randomly selected.

Cases had more severe respiratory disease as well as a higher number of prescriptions for respiratory drugs, antibiotics and cumulative doses of oral corticosteroids than controls.

Exposure to any ICS in cases and controls was identified and converted to fluticasone equivalences because, the authors state, fluticasone accounts for more than 75% of ICS prescriptions in Canada. This was categorised according to the defined daily dose of the most recent prescription as high (fluticasone 1000 microgram per day or higher), moderate (fluticasone 500-999 microgram per day) and low (less than 500 microgram per day). Usage was further categorised as current, recent, past or no use, dependant on when the last prescription for ICS was dispensed in relation to the index event. Exposure was then further defined in terms of defined daily dose and cumulative dosages among current and recent users of ICS. Exposure to oral corticosteroids was adjusted for by taking into account the number of prescriptions or the cumulative dose of oral corticosteroids in the time period used to define exposure to ICS.

The study found that there was no statistically significantly increased risk of adrenal insufficiency with current use of ICS overall (odds ratio [OR] 1.22, 95% confidence interval [CI] 0.85 to 1.70). However, patients whose most recent prescription had been for a high dose of ICS had a greater risk of developing adrenal insufficiency than controls (OR 1.84, 95% CI 1.16 to 2.90), as did those with the highest cumulative dosage of ICS over the preceding year (OR 1.90, 95% CI 1.07 to 3.37). Risk of adrenal suppression in relation to current high dose ICS use appeared higher among patients with COPD. However, this must be interpreted with caution due to the reduced sample size available for this sub-analysis.

Observational studies, such as this one, can only suggest an association not prove causation and are prone to confounding. In addition the authors acknowledge several limitations including the diagnosis of adrenal insufficiency not being formally validated, residual confounding due to disease severity (although attempts were made to adjust for this), and the fact that the life-time cumulative exposure to ICS or oral corticosteroids could not be investigated due to the nature of the registry database. Furthermore, any differences in risk between individual ICS agents was not investigated.

In terms of beclometasone equivalent doses, the divisions used by these investigators would be: high, 2000 micrograms/day or more; moderate, 1000–1998 microgram/day; and low, less than 1000 micrograms/day. The BTS/SIGN guidance on asthma recommends use of 2000 micrograms/day or more beclometasone equivalent only at Step 4 or Step 5. At Step 3 the advice is to increase the dose to 800 micrograms/day beclometasone equivalent if this has not been done already, and at Step 2 the recommended dose is 200–800 micrograms/day beclometasone equivalent. In COPD, the licensed dose of fluticasone (as Seretide 500 Accuhaler) is 1000 micrograms (2 puffs) per day. The licensed dose of budesonide (as Symbicort 400/12 Turbohaler) is 800 micrograms (2 inhalations) per day (equivalent to 800 micrograms beclometasone or 400 micrograms fluticasone per day).
Commentary

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The MHRA and CSM recommend use of a ‘steroid treatment card’ in patients who require prolonged treatment with high doses of inhaled corticosteroids (ICS). The latest version of the BTS/SIGN guideline on the management of asthma also recommends the use of ‘a steroid alert card’ in children on high doses of ICS. However, it is not clear when a card should be issued as there is no guidance as to what dose of ICS increases the risk of adrenal suppression and other side effects.

This large observational study provides further evidence that patients on high doses of ICS (1000 micrograms or more of fluticasone/day - equivalent to 2000 micrograms of beclomethasone) may be at increased risk of adrenal insufficiency. The study attempted to minimise the effects of potential confounding factors such as use of oral corticosteroids. An additional finding was that patients with COPD were more at risk than those with asthma. Although the authors claim there is limited prior evidence, there are three studies from the UK that have shown that up 20% of patients taking doses of more 1500 micrograms/day of beclomethasone may have evidence of adrenal insufficiency.

These findings are of concern for UK prescribers as high dose inhaled corticosteroids inhalers (either alone or in combination with a long-acting beta agonist) are very frequently prescribed. There is also evidence gathering that much of this use may be inappropriate as, while many patients may have their dose of inhaled steroid ‘stepped up’, this may not be ‘stepped down’ again. Checking inhaler technique and/or the use of a spacer device may improve the delivery of the steroid resulting in lower doses still achieving control of symptoms. High doses are also currently used to treat COPD even though there is evidence that lower doses can be equally effective. This study now provides further support for the recommendation of a specific ICS treatment card to alert prescribers (and patients) to the potential dangers of high dose ICS.

Study sponsorship

No details were given of the sponsorship of this study.

References

6. NHS Business Services Authority, February 2013
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