High-dose inhaled corticosteroid use in childhood asthma: an observational study of GP prescribing

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ABSTRACT

Inhaled corticosteroids are effective and safe treatments for childhood asthma in standard doses, yet at high dosages they may be associated with adverse events and suboptimal outcomes; add-on therapy is, therefore, recommended to minimise their use. We quantified prescribing of high-dose inhaled corticosteroids and add-on therapy in children in July 2003 and found that high-dose inhaled corticosteroids were prescribed to 10% of children aged 5–11 years and 6% of under-5's who were treated for asthma. Add-on therapy was lacking for almost half of these individuals. Some children were receiving treatment not in accord with current licences and evidence-based recommendations and, as such, may be at risk of adverse outcomes.

Keywords

asthma; child; database; pharmacoepidemiology; prescriptions, drug.

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INTRODUCTION

Asthma is a common childhood disease that is managed mainly in the community and principally treated with inhaled corticosteroids. Inhaled corticosteroids have an excellent efficacy and safety profile in standard doses,[1] but concerns exist about the safety of high doses in children[2,3] and evidence exists showing improved asthma control in terms of symptoms, exacerbations and health status with add-on therapy.[4] The 2003 UK British Thoracic Society (BTS) asthma guidelines[5] — which, in contrast to previous consensus-based iterations of guidelines, uses an explicit evidence-based methodology recommended by the Scottish Intercollegiate Guideline Network — recommends use of the lowest effective inhaled corticosteroid dose.

The maximum recommended dose for children aged under 5 years is 400 mcg/day of beclomethasone or equivalent, and in children aged from 5 years to under 12 years is 800mcg/day. Doses above 800mcg/day in children are not licensed. Although previous guidelines had mandated higher doses of inhaled corticosteroids, receipt of higher doses should occur only in exceptional circumstances and under expert supervision after other options, such as add-on therapy, have been attempted.

Both over-use of high-dose inhaled corticosteroids and under-use of add-on therapy in children requiring more treatment than low-dose inhaled corticosteroid treatment alone may lead to adverse outcomes in children with asthma, in terms of asthma control achieved and in treatment-related adverse effects. The aims of the present study were therefore to quantify GP prescribing for children with asthma in the UK, with specific focus on the prescribing of high doses of inhaled corticosteroids and the use of add-on therapy, and to investigate whether the level of high-dose inhaled corticosteroid use was sufficient to justify widespread auditing of childhood asthma prescribing patterns to identify at-risk children.

METHOD

Data were taken from the Doctors' Independent Network database,[6] which stores routine clinical and prescribing data from UK electronic patient records.

Data is anonymised and the database conforms to the UK's Data Protection Act.

The evidence based BTS asthma guidelines recommend that in children aged under 5 years the dose of inhaled corticosteroid should not exceed 400 mcg/day, and in children aged 5 to under 12 years the dose should not exceed 400 mcg/day unless the patient remains uncontrolled after the addition of add-on therapy (initially long-acting β-agonists followed by trials of other therapies) and the dose of inhaled corticosteroid should never exceed 800 mcg/day without referral to a respiratory pediatrician. For the purposes of daily dose assessment, inhaled corticosteroid doses are calculated as 'beclomethasone diproportionate equivalent doses', with 1:1 equivalence of budesonide to beclomethasone and 2:1 equivalence of fluticasone to beclomethasone. For the purposes of this study, high-dose inhaled corticosteroids equated to >400 mcg/day on the latest prescription; add-on therapy included any long-acting β-agonist preparation, leukotriene-receptor antagonist, oral theophylline, or inhaled chromone prescription in the 6-month period spanning the latest inhaled corticosteroid prescription.

De-identified prescribing data including issued prescriptions (including the corticosteroid molecule prescribed) and dosing instructions were collected. The data analysis plan was specified a priori. Descriptive statistics were used to calculate means and 95% confidence intervals (CIs) for percentages of patients receiving high and unlicensed doses of inhaled steroids and for the percentages of patients receiving add-on therapy.

RESULTS

A database of 111 764 patients who were aged under 12 years was used: 39 184 patients were under 5 years and 72 580 aged from 5 years to under 12 years (hereafter referred to as the 5–11 age group). Of these, 894 (2.3%) of the under-5s and 4141 (5.7%) of the 5–11 year olds had a diagnosis of asthma and received treatment using inhaled corticosteroids in the preceding 12 months. The dosing instructions enabled a daily dose calculation for 788 of those patients aged under 5 years and for 3544 of the 5–11 year olds; these formed the main groups used in this study.

'High-dose' prescribing (>400 mcg/day) occurred in 44 of the under-5s (5.6%, 95%CI = 4.3 to 6.9%) and 353 of the 5–11 year olds treated for asthma (10.0%, 95% CI = 9.0 to 11.0%). Of those who were prescribed high-dose inhaled corticosteroids, 63.6% (95% CI = 49.4 to 77.8%) of the under-5s and 46.7% (95% CI = 41.5 to 51.9%) of the 5–11 year olds were not co-prescribed add-on therapy (Table 1).

Inhaled corticosteroid doses exceeding 800 mcg/day day (equating to over double the recommended maximum dose) were prescribed to 31 of the 788 under-5s (3.9%, 95% CI = 2.6 to 5.2%), and to 175 of the 3544 patients in the 5–11 year age group who were treated for asthma (4.9%, 95% CI = 4.2 to 5.6%).

Analysis of the steroid molecule prescribed showed that although beclomethasone was the most commonly used treatment overall, for those patients prescribed >800 mcg/day, fluticasone predominated (Table 2).

How this fits in

Asthma is a common chronic disease of childhood and outcomes remain sub-optimal. Inhaled corticosteroids, the principal treatments for persistent asthma, have an excellent safety and efficacy profile in low doses but safety concerns exist for high-dose use, and add-on therapy is recommended before high-dose use. UK prescribing records in 2003 showed some children may be receiving excessive and inappropriate therapy and so may be exposed to steroid-related side-effects. Auditing of childhood asthma prescribing and clinical review of those receiving high-dose inhaled corticosteroid treatments is needed.

DISCUSSION

This study describes GP asthma prescribing in children within a large UK clinical database in June 2003. At this

Table 1. High-dose inhaled corticosteroid (>400mcg/day) and add-on therapy use in children treated for asthma.

Treatment	Aged <5 years (*n* = 44)	Aged 5–11 years (*n* = 353)
High-dose inhaled corticosteroids no add-on (%)	28 (63.6)	165 (46.7)
High-dose inhaled corticosteroids plus long-acting β-agonist (%)	13 (29.5)	152 (43.1)
High-dose inhaled corticosteroids plus leukotriene receptor antagonist (%)	3 (6.8)	33 (9.3)
High-dose inhaled corticosteroids plus xanthine (%)	0 (0)	3 (0.8)
High-dose inhaled corticosteroids plus chromone (%)	0 (0)	0 (0)

Table 2. Inhaled corticosteroid prescribing by molecule in all children receiving inhaled corticosteroids for asthma and in children prescribed unlicensed doses (>800 mcg/day).

Inhaled corticosteroid	% of total inhaled corticosteroid use by molecule		% of unlicensed dose (>800 mcg/day) corticosteroid use molecule	
	Aged <5 years	Aged 5–11 years	Aged <5 years	Aged 5–11 years
Beclomethasone	77	63	3	12
Budesonide	7	15	19	6
Fluticasone	16	23	78	83

time an extensive body of well-publicised research had questioned the safety and efficacy of high-dose inhaled corticosteroid use in paediatric asthma and emphasised the use of add-on therapy at an early stage in children uncontrolled on standard doses.

We observed that 4.5% of all children were prescribed inhaled corticosteroids for the treatment of asthma. Ten per cent of children aged 5–11 years who were treated with inhaled corticosteroids were receiving high doses; a slightly lower proportion of those aged under 5 years (5.6%) also appeared to be receiving high-dose corticosteroid treatments. Very high and unlicensed doses of inhaled corticosteroids were recommended to 1 in 20 of the 5–11 year old patients and 1 in 26 of the under-5s; fluticasone was the main drug associated with high-dose prescribing. Add-on therapy was lacking in half of the patients prescribed >400 mcg/day, and unlicensed use of long acting β-agonists was the commonest form of add-on therapy in the under 5s. Evidence-based treatment as summarised in the BTS guidelines specifies that no child should receive over 400 mcg/day of inhaled corticosteroid without having had sequential trials of add-on therapy (initially long acting β–agonists, followed by leukotriene-receptor antagonist chromone or slow-release theophylline), and that the only recommended add-on therapy in children aged under 5 years is a leukotriene-receptor antagonist.

Our results indicate that prescribing for childhood asthma in the UK in 2003 was not always consistent with current best practice or with license; some children were prescribed doses of corticosteroid that risked life-threatening adrenal suppression, and some children failed to receive add-on therapy associated with fewer symptoms, less exacerbations and lower exogenous corticosteroid exposure.

The limitations of this study include its cross-sectional nature, thereby providing information on only one point in time. In addition, we cannot be certain that add-on therapies had previously been trialled in all patients studied as, due to patients moving between general practices, full information from birth was not present for all individuals. Prescribing instructions were not clear for some 14% of children and we could not determine whether the original prescription for those on whom we did have data was ordered by a GP or a paediatrician. To combat this we took the approach that as the repeat prescription was issued by the GP, final responsibility for the prescribing advice should lie with him or her. The strength of this study is that it accessed data from large numbers of representative subjects in a large well-validated clinical database. The prescribing information held in the database is accurate and likely to reflect what was actually occurring in real-world UK practice at the time of the survey.

CONCLUSION

This study highlights the over-use of high-dose inhaled corticosteroids, the under-use and inappropriate use of add-on therapy, and the use of very high and potentially dangerous doses of inhaled corticosteroids in a minority of children. Further research is needed to assess the changes in prescribing patterns over time and in response to new evidence and new guidelines.

There is a need for further pharmacovigilance studies to monitor the trends in prescribing patterns for childhood asthma to assess adherence to best practice. We recommend that GPs audit high-dose inhaled corticosteroid and add-on therapy prescribing in children to identify children at risk of adverse outcomes.

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Ethics committee

Ethical approval was retrospectively gained from the Optimum Patient Care Ethics Committee

Competing interests

Mike Thomas has no shares in pharmaceutical companies; either through his role at the University of Aberdeen or personally has received grants, honoraria or educational support from the following pharmaceutical companies as well as the UK NHS R&D programme and Asthma UK: Altana, AstraZeneca, GlaxoSmithKline, Ivax, Merck, Sharpe and Dohme, Novartis, Schering Plough, Trinity Pharmaceuticals, Viatris. Steve Turner has no shares in pharmaceutical companies, but received a £300 bursary to travel to the American Thoracic Society from GlaxoSmithKline. Dave Leather is Director of Medical Affairs for GlaxoSmithKline UK and holds shares in the company. He receives no funds from any other companies or institutions. David Price has no shares in pharmaceutical companies; either through his role at the University of Aberdeen or personally has received grants, honoraria or educational support from the following pharmaceutical companies as well as the UK NHS R&D programme: Altana, AstraZeneca, GlaxoSmithKline, Ivax, Merck, Sharpe and Dohme, Novartis, Schering Plough, Trinity Pharmaceuticals, BI, Viatris.

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