MeReC Extra

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Inhaled corticosteroids: children are at risk from high doses

Inhaled corticosteroids (ICS) are safe and effective for the prevention of symptoms of asthma when used at the recommended doses.[1] However, prolonged treatment at high doses carries a risk of systemic side effects and has been associated with adrenal crisis, coma and even death in children.[2,3] In a recent Scottish study, 42% of children prescribed above licensed doses of fluticasone had adrenal suppression.[4] The Committee on Safety of Medicines (CSM) has advised that the paediatric licensed dosages for ICS (see **Table**) should not be exceeded.[7]

The British Guideline on the Management of Asthma[8] recommends that, in children under five years, the dose of ICS should not exceed 400mcg/day beclometasone dipropionate (BDP) or equivalent (e.g. 400mcg/day budesonide, or 200mcg/day fluticasone propionate). In children aged five to 12 years, the dose should not exceed 400mcg/day BDP or equivalent, unless the patient's asthma remains uncontrolled despite add-on therapy (initially a long-acting $ß_2$-agonist, followed by trials of other therapies e.g. a leukotriene receptor antagonist or sustained-release theophylline). In such cases the dose may be increased to 800mcg/day BDP or equivalent.[8] However, higher, unlicensed doses of ICS should only be initiated and supervised by specialists, and therapy should be reviewed regularly and titrated down to the lowest dose at which effective control of asthma is maintained.[1,2]

The Commission on Human Medicines (CHM: an amalgamation of the CSM and the Medicines Commission) recently advised that steroid treatment cards should be issued routinely for patients, including children, who require prolonged, high, unlicensed doses of ICS,[1] because they may need corticosteroid cover during an episode of stress (e.g. an operation).[2]

An observational study,[9] which looked at asthma prescribing in children in primary care (n=4,332), found that high-dose ICS (>400mcg/day BDP or equivalent) were prescribed to 6% of under-fives, and 10% of children aged 5–11 years, who were treated for asthma. Of these children, 47% of the 5–11 year olds were not prescribed add-on therapy as recommended by the British asthma guideline.[8] Even more worryingly, ICS doses exceeding 800mcg/day BDP or equivalent were prescribed to 4% of under-fives and 5% of 5–11 year olds. The authors recommended that GPs should audit high-dose ICS and add-on therapy prescribing in children to identify those at risk of adverse outcomes.[9]

Table: Maximum licensed doses of inhaled corticosteroids in children[5]

	Maximum dose	Age
Beclometasone dipropionate*	400mcg/day	*Asmabec*: 6–12 years Others: no age range stated
Budesonide	800mcg/day†	*Easyhaler*: 6–12 years *Novolizer*: 6–12 years *Pulmicort*: no age range stated *Pulmicort Turbohaler:* 12 years and under
Fluticasone propionate	400mcg/day	Over 4 years
Ciclesonide▼	Not licensed in children under 12 years	
Mometasone furoate▼	Not licensed in children under 12 years	

* Doses for CFC-free beclometasone inhalers may be different from those that contain CFCs. The maximum licensed dose of *Clenil Modulite*▼ in children (age range not stated) is 400mcg/day.[6] *Qvar* is not licensed for use in children.[2]
† However, doses above 400mcg are not recommended and should only be used under specialist supervision.

NHS NPC National Prescribing Centre

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Development of diabetes with thiazides: what are the consequences?

In the ALLHAT study, the first-line use of a thiazide diuretic, an angiotensin-converting enzyme (ACE) inhibitor, or a calcium-channel blocker (CCB) for hypertension was similarly effective in reducing the risk of major cardiovascular (CV) events.[1] However, there were significant differences between treatments for some outcomes. Notably, CCBs were less effective in preventing heart failure than thiazide diuretics, whereas development of diabetes (defined as fasting blood glucose levels [FGs] above 6.9mmol/l) was more frequent with thiazide diuretics than with CCBs.[1] When costs associated with these outcomes were factored into the NICE health-economic model, CCBs were identified as the most cost-effective option.[2] However, this analysis had many limitations, not least whether or not an elevated FG developing as a consequence of drug treatment has the same long-term health impact as diabetes developing in other circumstances.[2] A recent analysis of the ALLHAT study data provides some insight into this issue.[3]

This post-hoc subgroup analysis considered non-diabetic patients in ALLHAT who were randomised to initially receive chlortalidone (n=8,419), amlodipine (n=4,958), or lisinopril (n=5,034).[3] After two years, mean FGs were raised in all groups — by 0.47mmol/l, 0.31mmol/l and 0.19mmol/l, respectively. New incidences of diabetes were seen in all treatment groups, as would be expected as the study population aged. As diuretics increased blood glucose levels to a greater extent than the other treatments, it is not surprising that more cases of incident diabetes, when defined by a 6.9mmol/l FG threshold, were detected in the chlortalidone group. However, absolute differences between groups in incident diabetes were small (chlortalidone 9.3%, amlodipine 7.2%, lisinopril 5.6%).[3] The risk of developing diabetes was lower for lisinopril (odds ratio [OR] 0.55, 95%CI 0.43 to 0.70, P<0.001) or amlodipine (OR 0.73, 95%CI 0.58 to 0.91, P=0.008) compared with chlortalidone.[3]

Although, there was a significant association between incident diabetes at two years and coronary heart disease (risk ratio [RR] 1.64, P=0.006), the relative risk of coronary heart disease was not significant in the chlortalidone group (RR 1.46, P=0.14).[3] There was no significant association between FG changes at two years and any of the study endpoints (death, CV disease or end-stage renal disease), whether analysed for all treatments combined or for chortalidone alone.[3]

Although requiring a prospective study for confirmation, these findings support the results from the 14-year follow-up of SHEP[4] and suggest that, even if diabetes does occur during the treatment of hypertension with thiazide diuretics, this does not create any greater cardiovascular risk. It is possible that that the raised FGs that occur with thiazide diuretics arise from mechanisms that are different from those associated with diabetes in other circumstances.[3]

For the first-line treatment of hypertension:
"Thiazide diuretics or CCBs are considered by NICE as equal first-line choices for people who are black (i.e. of African or Caribbean descent, not mixed race, Asian or Chinese) or aged 55 years or older. NICE suggests that the choice between thiazide diuretics and CCBs should be made by the clinician and patient, using careful clinical judgement about the patient's risk of adverse effects and consideration of the patient's preference. **Prescribers may decide to use diuretics preferentially in view of their lower acquisition costs, unless there are good reasons to do otherwise.**"

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Grazax▼ sublingual vaccine against grass pollen allergy

An extended version of this article can be found on the NPC website (www.npc.co.uk)

Grazax▼ is a once-daily sublingual tablet containing allergen extract of grass pollen. It is licensed for adults with clinically relevant symptoms of pollen allergy who have been diagnosed with a positive skin prick test and/or specific IgE test to grass pollen.[1] It should be initiated by physicians with experience in the treatment of allergic disease. In view of the possibility of local or systemic allergic reactions when first taken, the first dose should be taken under medical supervision (20–30 minutes).[1]

There is evidence from a double-blind, randomised controlled trial that Grazax reduces rhinoconjunctivitis symptoms and medication use compared with placebo when initiated at least 16 weeks before, and continued throughout, the whole grass pollen season.[2] However, the absolute benefits appear very modest, and its clinical efficacy and cost-effectiveness have yet to be established in comparison with subcutaneous allergen immunotherapy.

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