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6. Baratz KH, Hattenhauer MG. Indiscriminate use of corticosteroid-containing eyedrops. *Mayo Clin Proc* 1999; **74:** 362–6.
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11. Derby L, Maier WC. Risk of cataract among users of intranasal corticosteroids. *J Allergy Clin Immunol* 2000; **105:** 912–16.
12. Cumming RG, Mitchell P. Inhaled corticosteroids and cataract: prevalence, prevention and management. *Drug Safety* 1999; **20:** 77–84.
13. Polak BCP, *et al.* Diffuse retinal pigment epitheliopathy complicating systemic corticosteroid treatment. *Br J Ophthalmol* 1995; **79:** 922–5.

Effects on the gastrointestinal tract. It has long been considered that treatment with corticosteroids might lead to peptic ulcers. Some years ago a review of the data then available suggested that since an ulcer developed in 1% of control patients not receiving corticosteroids, the 2% incidence for patients receiving corticosteroids did not warrant the prophylactic use of anti-ulcer drugs in all patients.[1] Others have found little evidence of an increased risk of peptic ulcer produced by corticosteroids alone although there is some increased risk when using them with NSAIDs.[2] A later cohort study[3] found a modest increase in risk of gastrointestinal bleeding with current use of corticosteroids, which increased when NSAIDs were also used. It has been suggested that it might be prudent to avoid such combination therapy whenever possible.[4]

Doubt has therefore been cast on the prophylactic value of anti-ulcer therapy given with corticosteroids.[1,5] If an ulcer does develop and there is good reason to continue treatment then corticosteroids may be continued along with some form of ulcer therapy.[1]

There have been several reports of corticosteroids being associated with gastrointestinal perforation.[6-9] There is a risk that the anti-inflammatory properties of corticosteroids may mask the signs of perforation and delay diagnosis with potentially fatal results.

1. Spiro HM. Is the steroid ulcer a myth? *N Engl J Med* 1983; **309:** 45–7.
2. Piper JM, *et al.* Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. *Ann Intern Med* 1991; **114:** 735–40.
3. Nielsen GL, *et al.* Risk of hospitalization resulting from upper gastrointestinal bleeding among patients taking corticosteroids: a register-based cohort study. *Am J Med* 2001; **111:** 541–5.
4. Guslandi M, Tittobello A. Steroid ulcers: a myth revisited. *BMJ* 1992; **304:** 655–6.
5. Marcus P, McCauley DL. Steroid therapy and H -receptor antagonists: pharmacoeconomic implications. *Clin Pharmacol Ther* 1997; **61:** 503–8.
6. Arsura EL. Corticosteroid-associated perforation of colonic diverticula. *Arch Intern Med* 1990; **150:** 1337–8.
7. Ng PC, *et al.* Gastroduodenal perforation in preterm babies treated with dexamethasone for bronchopulmonary dysplasia. *Arch Dis Child* 1991; **66:** 1164–6.
8. O'Neil EA, *et al.* Dexamethasone treatment during ventilator dependency: possible life threatening gastrointestinal complications. *Arch Dis Child* 1992; **67:** 10–11.
9. Epstein A, *et al.* Perforation of colon diverticula during corticosteroid therapy for pemphigus vulgaris. *Ann Pharmacother* 1993; **27:** 979–80.

Effects on growth. Corticosteroids impair normal growth in children when given systemically,[1-3] and although alternate-day therapy may reduce the effect on growth it does not abolish it. There has been some concern about possible effects of inhaled corticosteroids on growth.[1,4] Some studies have not found an effect of inhaled corticosteroids on growth if doses are modest, even when treatment is prolonged.[1,5,6] Others have found that inhaled corticosteroids, particularly in high doses, do have some effect on growth parameters,[5,7-10] but it is unclear whether this has long-term effects on the child's ultimate height, and the alternative in children requiring such high-dose therapy is likely to be an oral corticosteroid, with its consequent effects. Some studies,[11,12] in children with mild to moderate asthma, have suggested that a small reduction in growth velocity may occur in the first year of treatment, but that it then normalises and adult height is not adversely affected. Nonetheless, in the light of the increasing number of studies suggesting some effects of inhaled or intranasal corticosteroids on growth the FDA has required the inclusion of a warning in US labelling that such products may slow growth rates. For a suggestion that inhalation of a single dose of budesonide in the morning had less effect on growth than twice daily dosage, see Administration, p.1521.

1. Allen DB, *et al.* A meta-analysis of the effect of oral and inhaled corticosteroids on growth. *J Allergy Clin Immunol* 1994; **93:** 967–76.
2. Lai H-C, *et al.* Risk of persistent growth impairment after alternate-day prednisone treatment in children with cystic fibrosis. *N Engl J Med* 2000; **342:** 851–9.
3. Mushtaq T, Ahmed SF. The impact of corticosteroids on growth and bone health. *Arch Dis Child* 2002; **87:** 93–6.
4. Hanania NA, *et al.* Adverse effects of inhaled corticosteroids. *Am J Med* 1995; **98:** 196–208.
5. Wolthers OD, Pedersen S. Controlled study of linear growth in asthmatic children during treatment with inhaled glucocorticosteroids. *Pediatrics* 1992; **89:** 839–42.
6. Volovitz B, *et al.* Growth and pituitary-adrenal function in children with severe asthma treated with inhaled budesonide. *N Engl J Med* 1993; **329:** 1703–8.
7. Wolthers OD, Pedersen S. Short term growth during treatment with inhaled fluticasone propionate and beclomethasone dipropionate. *Arch Dis Child* 1993; **68:** 673–6.
8. Todd G, *et al.* Growth and adrenal suppression in asthmatic children treated with high-dose fluticasone propionate. *Lancet* 1996; **348:** 27–9.
9. McCowan C, *et al.* Effect of asthma and its treatment on growth: four year follow up of cohort of children from general practices in Tayside, Scotland. *BMJ* 1998; **316:** 668–72.
10. Sharek PJ, Bergman DA. The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. Abstract: *Pediatrics* 2000; **106:** 129. Full version: http://pediatrics.aappublications.org/cgi/content/full/106/1/e8 (accessed 27/04/04)
11. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000; **343:** 1054–63.
12. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med* 2000; **343:** 1064–9.

Effects on immune response. Owing to their immunosuppressant effect, giving corticosteroids in doses greater than those required for physiological replacement therapy is associated with increased susceptibility to infection, aggravation of existing infection, and activation of latent infection. An additional problem is that the anti-inflammatory effect of corticosteroids may mask symptoms until the infection has progressed to an advanced stage; the altered response of the body may also permit the bizarre spread of infections, frequently in aberrant forms, such as disseminated parasitic infections. The risk is greater in patients receiving high doses, or associated therapy with other immunosuppressants such as cytotoxic drugs, and in those who are already debilitated. Children receiving high doses of corticosteroids are at special risk from childhood diseases, such as chickenpox, but vaccination with living organisms is contra-indicated since infection may be induced (killed vaccines or toxoids can be given but the response may be reduced).

This increased susceptibility to infection and masking of symptoms may also be caused by topical or local corticosteroid therapy. Thus, topical application to the skin has led to unusual changes such as atypical ringworm infection. Fungal infections (particularly candidiasis), generally restricted to the mouth and throat, are associated with corticosteroid inhalations. Severe damage to the eye has followed the ocular use of corticosteroids in herpetic infections, and a generalised spread of herpes infection may follow application to the mouth in the presence of herpes infection.

Conversely, the effect of corticosteroids on the symptoms and course of some infections may be life-saving (see Infections, under Uses and Administration, below). Before embarking on a long-term course of corticosteroid therapy general measures for the reduction of risk of infection include a diligent search for active or quiescent infection and, where appropriate, prevention or eradication of the infection before starting, or giving chemoprophylaxis during corticosteroid treatment.

Effects on lipid metabolism. Glucocorticoids have potent effects on lipid metabolism, facilitating the effects of growth hormone and endogenous stimulants of lipolysis. As a result they increase both high- and low-density lipoprotein cholesterol concentrations in the blood.

On prolonged use glucocorticoids also have a dramatic effect on body fat distribution, resulting in the characteristic Cushingoid appearance of moon face, and increased fat at the back of the neck and supraclavicular area.

Effects on mental state. Mental disturbances caused by corticosteroids include depression, mania, euphoria, and delirium.[1] Psychotic symptoms, insomnia, and hyperactivity have also been reported in children and adolescents treated with inhaled,[2,3] oral, and intravenous corticosteroids.[2] The risk of adverse effects appears to be dose-related, but there are reports of cases associated with very low dosages. Reversible impairment of memory has been associated with intravenous methylprednisolone.[4,5]

1. Patten SB, Neutel CI. Corticosteroid-induced adverse psychiatric effects: incidence, diagnosis and management. *Drug Safety* 2000; **22:** 111–22.
2. Stuart FA, *et al.* Adverse psychological effects of corticosteroids in children and adolescents. *Arch Dis Child* 2005; **90:** 500–506.
3. de Vries TW, *et al.* Reported adverse drug reactions during the use of inhaled steroids in children with asthma in the Netherlands. *Eur J Clin Pharmacol* 2006; **62:** 343–6.
4. Oliveri RL, *et al.* Pulsed methylprednisolone induces a reversible impairment of memory in patients with relapsing-remitting multiple sclerosis. *Acta Neurol Scand* 1998; **97:** 366–9.
5. Brunner R, *et al.* Effect of corticosteroids on short-term and long-term memory. *Neurology* 2005; **64:** 335–7.

Effects on the neonate. Various adverse effects have been reported in premature neonates given corticosteroids, see under Dexamethasone, p.1526.

Effects on the nervous system. Paraesthesia, usually localised to the perineum, has been associated with intravenous use of dexamethasone sodium phosphate[1-4] and hydrocortisone sodium phosphate,[5] but not with hydrocortisone sodium succinate.[5] Descriptions of this reaction include itching, burning, tingling, and severe pain. It can begin within seconds of giving the injection, and clear within minutes of stopping. This reaction appears to be caused by the corticosteroid phosphate ester itself, and clears in the time it takes for the drug to be hydrolysed. It has been suggested that the reaction can be abolished or avoided by giving the drug as a dilute solution, over at least 5 to 15 minutes.[2-4]

Epidural lipomatosis (fat deposition around the spinal cord) is a rare complication of systemic corticosteroids.[6] It has been associated with both high daily doses (more than 30 mg prednisone daily) and lower doses given over several years. The onset of symptoms is usually gradual, ranging from 6 months to more than 20 years after beginning corticosteroid use. Spinal cord compression causes back pain radiating to the lower limbs, and severe neurological complications can develop. The lipomatosis may regress or disappear after the corticosteroid is withdrawn or the dose is lowered, but patients with myelopathy or rapidly progressive neurological deficit may need emergency surgery.

1. Czerwinski AW, *et al.* Effects of a single, large, intravenous injection of dexamethasone. *Clin Pharmacol Ther* 1972; **13:** 638–42.
2. Allan SG, Leonard RCF. Dexamethasone antiemesis and side-effects. *Lancet* 1986; **i:** 1035.
3. Neff SPW, *et al.* Excruciating perineal pain after intravenous dexamethasone. *Anaesth Intensive Care* 2002; **30:** 370–1.
4. Perron G, *et al.* Perineal pruritus after iv dexamethasone administration. *Can J Anesth* 2003; **50:** 749–50.
5. Novak E, *et al.* Anorectal pruritus after intravenous hydrocortisone sodium succinate and sodium phosphate. *Clin Pharmacol Ther* 1976; **20:** 109–12.
6. Hierholzer J, *et al.* Epidural lipomatosis: case report and literature review. *Neuroradiology* 1996; **38:** 343–8.

Effects on the pancreas. Acute pancreatitis has been associated with corticosteroid use,[1-3] although evidence supporting the association has been challenged on a number of grounds, both clinical and experimental.[2]

1. Nakashima Y, Howard JM. Drug-induced acute pancreatitis. *Surg Gynecol Obstet* 1977; **145:** 105–9.
2. Banerjee AK, *et al.* Drug-induced acute pancreatitis: a critical review. *Med Toxicol Adverse Drug Exp* 1989; **4:** 186–98.
3. Felig DM, Topazian M. Corticosteroid-induced pancreatitis. *Ann Intern Med* 1996; **124:** 1016.

Effects on the skin. Topical corticosteroids are associated with a number of local adverse effects on the skin, principally due to their antiproliferative effects on keratinocytes and fibroblasts (leading to skin thinning and atrophy), and to possible interference with the skin flora (leading to increased risk of superinfection or opportunistic infection).[1] Skin thinning is more likely if corticosteroids are applied under occlusion (this is especially true of halogenated corticosteroids, which are more resistant to inactivation by enzymes in the epidermis). Striae, which occur usually in intertriginous areas such as axillae and groin where skin is thin, moist, and occluded, are the most readily appreciable manifestation of skin atrophy, and are irreversible, unlike more minor degrees of atrophy. Other local adverse effects include telangiectasias and purpura.[1] Acneform pustules at the site of application have occurred.

The balance between benefit and the likelihood of local or systemic adverse effects on topical application of corticosteroids will depend on the chemical structure of the drug (i.e. its lipophilicity and resistance to enzymic degradation), the formulation of the vehicle, the way in which it is applied, and the nature of the skin to be treated.[1]

Skin thinning, bruising, and purpura have also been reported in patients receiving inhaled corticosteroids.[2-4] There have been a few case reports of eczematous and erythematous lesions of the face and body, and urticaria, following inhalation or intranasal use.[5]

The adverse skin effects arising from systemic corticosteroids also include striae and skin thinning as well as acneform eruptions. Somewhat counter-intuitively a case-control study has suggested an increased risk of Stevens-Johnson syndrome or toxic epidermal necrolysis in patients receiving corticosteroids, particularly in the period shortly after beginning therapy.[6]

1. Mori M, *et al.* Topical corticosteroids and unwanted local effects: improving the benefit/risk ratio. *Drug Safety* 1994; **10:** 406–12.
2. Shuttleworth D, *et al.* Inhaled corticosteroids and skin thinning. *Br J Dermatol* 1990; **122:** 268.
3. Capewell S, *et al.* Purpura and dermal thinning associated with high dose inhaled corticosteroids. *BMJ* 1990; **300:** 1548–51.
4. Tashkin DP, *et al.* Skin manifestations of inhaled corticosteroids in COPD patients: results from Lung Health Study II. *Chest* 2004; **126:** 1123–33.
5. Isaksson M. Skin reactions to inhaled corticosteroids: incidence, avoidance and management. *Drug Safety* 2001; **24:** 369–73.
6. Roujeau J-C, *et al.* Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333:** 1600–7.

Effects on the voice. Dysphonia is associated with inhaled corticosteroids.[1] Although oropharyngeal candidiasis and dysphonia may occur at the same time, many patients with dysphonia do not have candidiasis, and the two conditions do not appear to be directly related. The cause of this dysphonia has not been fully explained, but clinical investigations have found changes including bowing of the vocal cords due to bilateral adductor myopathy, mucosal changes, and supraglottic hyperfunction.

1. Lavy JA, *et al.* Dysphonia associated with inhaled steroids. *J Voice* 2000; **14:** 581–8.

Hypersensitivity and anaphylaxis. There have been occasional reports of hypersensitivity reactions, and sometimes