Review article

A LAISSEZ-FAIRE APPROACH TO SHORT BURSTS OF CORTICOSTEROIDS MAY LEAD TO OVER-EXPOSURE IN THE FETUS AND THE YOUNG CHILD

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ABSTRACT
Corticosteroids, in whichever form they occur, are potent drugs with serious short- and long-term side effects. Their indications for use encompass many diseases and all age groups, even extending to the fetus. In view of the potency and dangers of corticosteroids though, those who prescribe them must do so only for evidence-based indications and with informed consent. Documenting all exposures reflects corticosteroid stewardship and an awareness of a cumulative end point which determines toxicity rather than the dose and duration of therapy.

Keywords: corticosteroid short-bursts, overexposure, fetus, young child

INTRODUCTION

A laissez-faire professional approach to the short-term use (≤ 14 days) of oral corticosteroids (OCSs), in particular, is the order of the day in paediatric and adult medicine.[1–5] The prescription of so-called harmless oral short bursts for non-indicated conditions in otherwise healthy, non-asthmatic young children is both common and unsupported by scientific evidence. In fact, denial of the risks related to the severe adverse effects (SAEs) resulting from systemic cumulative exposure continues to prevail. Short bursts of OCSs in adults are associated with a cumulative burden irrespective of the dose and duration and lead to long-term SAEs such as osteoporosis, cardiac disease and diabetes mellitus.[6,7] This information is starting to emerge in non-asthmatic children exposed to short bursts of OCSs in addition to the risk of fracture after four short bursts of OCSs.[1,8]

The fetus and the young child nevertheless continue to bear the brunt of short-burst OCSs, for three main reasons. First, because the fetus' affliction is potentially life-threatening (pulmonary immaturity) and the young child's affliction is common (acute respiratory tract infections). Secondly, because the fetus and the young child may experience lifelong permanent SAEs. And, thirdly, because the fetus and the young child are vulnerable and voiceless, which implies that the responsibility for ethical behaviour lies within the prescriber's domain.

This laissez-faire professional approach is perpetuated by an erroneous professional belief of harmlessness because the duration of the therapy is 'short' (≤ 14 days), informed consent is waived (even though it may be an off-label medication), the absence of documentation on a patient-retained record (Road to Health Card) and also that the fate of redundant medication in the household is ignored. Needless to mention, this professional approach has a negative collateral effect on the primary caregivers of vulnerable infants, who are led to believe that corticosteroid therapy, in whichever form and duration it is administered, is harmless.

Moreover, the exposure of undocumented OCSs in the form of short bursts may lead to undiagnosed over-exposure and to SAEs not linked to a 'subtle' therapeutic intervention, with long-term consequences. This 'modern' scenario is reminiscent of the unregulated use of untrialled cortisone almost a century ago and as described in the historical vignette below.

The objectives of this narrative review are to revisit, first, historical events which exposed the dangers of exogenous corticosteroids followed by mitigatory efforts and, secondly, the evidence-based indications for short-burst oral and intramuscular corticosteroid therapy in the young non-asthmatic child and the pregnant woman after 24 weeks of gestation respectively.

HISTORICAL BACKGROUND OF CORTICOSTEROID THERAPY

'THE QUEST FOR CORTISONE'[9]

The history of cortisone therapy dates back to the late 1940s, when it was first administered in the Mayo Clinic as a new, untrialled drug to Mrs G, a 28-year-old, married lady with debilitating rheumatoid arthritis (RA). She was desperate for relief and vowed not to leave the hospital in pain. Her doctors had planned to initiate a study to determine the feasibility of a new drug called Compound E in patients with RA, but her desperation moved them to administer it untrialled. The dose of 50 mg twice a day by way of the intramuscular route effected a miracle clinical response within three days and as a result cortisone became a wonder drug overnight. When her limb pain recurred, though, the dose was increased. This symptom turned

out to be an SAE and it was soon followed by other SAEs. The dosages were manipulated to facilitate reasonable control of the clinical symptoms but the SAEs were not eliminated. The treatment was administered until her discharge, which occurred five months later. Mrs G died after two years from an SAE related to therapy with adrenocorticotropic hormone (ACTH) and contemporaneously with her doctor's nomination for the 1950 Nobel Prize in Physiology or Medicine.[10]

This historical vignette highlights, inter alia, the reality that, as a clinical response, systemic exposure should be titrated to the minimum in order to decrease the risk of SAEs, but that prevention will remain unlikely – and this remains to be the case to this very day.[11]

Asthma in adults became an additional indication of parenteral cortisone therapy in 1950 and that was subsequently followed by the addition of countless conditions being linked to this therapy.[12]

TOWARDS NON-SYSTEMIC THERAPY IN ADULT ASTHMA

In 1956, the results of a randomised placebo-controlled trial showed that oral therapy with cortisone acetate was as effective as parenteral cortisone but that it did not prevent SAEs.[13] Inhaled therapy in the form of beclomethasone dipropionate (BDP) became available only in the early 1970s and replaced systemic therapy.[14,15] By 1974, placebo-controlled studies showed that the clinical effect of BDP was indeed paralleled by the mitigation of SAEs.[16]

The next step was to combine an inhaled corticosteroid (ICS) in a low or medium dose with a long-acting beta$_2$-agonist (LABA) as the standard steroid-saving therapy with which to control and relieve asthma. This combination was effective in the majority of patients.[17]

Additional improvement could, however, not be achieved with a high dose of an ICS and was also not achieved by the simultaneous use of oral and nasal steroidal preparations because these defeated the steroid-sparing effect of inhalers.[18]

For childhood asthma, many decisions are currently based on data obtained from adult studies such as inhalers containing ICS and LABAs, which have also become standard of care in children.[19] Greater representation of children in research trials is needed so that they can also benefit from new concepts.[20]

SHORT-BURST SYSTEMIC CORTICOSTEROID THERAPY: INFANTS AND YOUNG NON-ASTHMATIC CHILDREN

INDICATION

Croup

Systemic corticosteroid therapy in the form of dexamethasone administered intramuscularly (IM) is indicated at diagnosis and not repeated during the same episode.[21]

CONTRA-INDICATION

Preschool wheezing

Mild and infrequent wheezing is treated with a short-acting beta$_2$-agonist (SABA).[20] If it recurs more than three times per year or if a severe episode occurs which necessitates admission to a special care unit in the presence of eosinophilia (> 0.3 × 10^9/L) with or without aeroallergen sensitisation, a trial of low-dose ICS for 6–12 weeks is indicated followed by withdrawal and reassessment.[20] If the symptoms improve on ICS and then recur, the low-dose ICS should be restarted.[20] If the symptoms do not improve or if the attacks are severe, the inhaler technique should be checked and an alternative diagnosis considered in consultation with a paediatric pulmonologist, if possible.[20]

Upper respiratory tract infections, bronchiolitis and community-acquired bronchopneumonia of moderate severity

Short bursts of OCSs are contra-indicated in these conditions.[22,23,24] Their repetitive nature will lead to over-exposure of OCSs should the latter be administered in short bursts and in a non-indicated and non-evidence-based manner.

SHORT-BURST SYSTEMIC CORTICOSTEROID THERAPY: FETUS (BY ANTENATAL ADMINISTRATION)

Antenatal administration of systemic corticosteroids to a pregnant woman.

INDICATIONS

Imminent premature delivery at a gestation of 24–34 weeks

Pulmonary maturity in the fetus is reached during the term period (40 0/7 – 41 6/7 weeks of gestation) and is heralded by the spontaneous initiation of labour. Pulmonary maturity was shown in a randomised controlled trial (RCT) to be accelerated by betamethasone (12 mg IM q24h × 2) administered to a woman in spontaneous imminent premature labour in a gestational window of 24–34 weeks.[25] The results of this RCT showed a decrease in respiratory distress syndrome (RDS) and neonatal death and were reported in 1972.[25] Subsequently, a decrease in intraventricular haemorrhage (IVH) and necrotising enterocolitis (NEC) was also demonstrated.[26]

By the mid-1990s and supported by about 20 RCTs, antenatal corticosteroids (ANCs) became the standard of care for similar indications and using betamethasone in the same dosage as in the original study.[25] Dexamethasone was subsequently adopted (6 mg q12h × 4), with similar results. For an optimal effect, delivery should not occur within two hours or after seven days of administration.

The majority of women in spontaneous premature labour within 24–34 weeks of gestation, will, however, not deliver and the pregnancy may proceed to any gestation beyond 34 weeks, in which case corticosteroids must not be administered again during the remainder of the pregnancy. Those women whose initial premature labour terminates can experience premature labour again and later in the same pregnancy and, should the gestation still be < 34 weeks (and more than seven days after the first course of ACS), a second course of corticosteroids can be administered, followed by no more courses.

Indicated premature delivery (by Caesarean section) at a gestation of 24–34 weeks and in periviable pregnancies < 24 weeks

ACSs are increasingly being used for extended indications (and in the absence of labour), which include indicated premature deliveries between 24 and 34 weeks of gestation by Caesarean section and periviable pregnancies < 24 weeks.[27]

CONTRAINDICATIONS

Women with a gestation > 34 weeks

The late preterm (34 0/7 to 36 6/7 weeks), early term (37 0/7 to 39 6/7 weeks) and term (40 6/7 – 41 0/7 weeks) periods have not been subjected to adequate scientific scrutiny for the efficacy and safety of ACSs to be indicated and therefore these are not indications for both ACSs and spontaneous deliveries during these periods.[27,28]

Exposure of the fetus to exogenous potent corticosteroids beyond 34 weeks decreases the benefits of accelerated pulmonary and organ maturity while increasing the risks.[27,28] Of concern are the long-term risks which may manifest during adulthood and not be associated with the exposure of increasingly larger population groups to ACSs.[29]

This scenario also has a collateral effect on women: one course of ACSs is associated with an increased risk of sepsis, heart failure and gastrointestinal haemorrhage.[5]

CONCLUSIONS

Exogenous corticosteroids have powerful therapeutic effects when administered for indicated conditions. At the same time, they also have powerful side effects which are difficult to eliminate or mitigate. In order to inflict the least harm, a precautionary practice would be to focus on the risks. Should the risk : benefit ratio be unfavourable, the drug is contra-indicated. Giving a powerful drug in small doses to the smallest and most vulnerable human beings for a short period of time will not remove the wolf which is hidden by sheep's clothing and the effects of the balance between risks and benefits will prevail.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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REFERENCES

1. Yao T-C, Wang J-Y, Chang S-M, et al. Association of oral corticosteroid bursts with severe adverse events in children. JAMA Pediatr. 2021;175:723–729. https://doi.org/10.1001/jamapediatrics.2021.0433.
2. Waljee AK, Rogers MA, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States:Population cohort study. Br Med J. 2017;357:1415. https://doi.org/10.1136/bmj.j1415.
3. Dvorin EL, Lamb MC, Monlezun DJ, et al. High frequency of systemic corticosteroid use for acute respiratory tract illnesses in ambulatory settings. JAMA Intern Med. 2018;178:852–854. https://doi.org/10.1001/jamainternmed.2018.0103.
4. Bloechliger M, Reinau D, Spoendlin J, et al. Adverse events profileof oral corticosteroids among asthma patients in the UK: Cohort study with a nested case-control analysis. Respir Res. 2018;19:75. https://doi.org/10.1186/s12931-018-0742-y.
5. Yao T-C, Huang Y, Chang S, et al. Association between oral corticosteroid bursts and severe adverse events. A nationwide population-based cohort study. Ann Intern Med. 2020;173:325–330. https://doi.org/10.7326/M20-0432.
6. Sullivan PW, Ghushchyan VH, Glove G, Schatz M. Oral corticosteroid exposure and adverse effects in asthmatic patients. J Allergy Clin Immunol. 2018;141:110–6.e7. https://doi.org/10.1016/j.jaci.2017.04.009.
7. Chung LP, Upham JW, Bardin PG, Hew M. Rational oral corticoid use in adult severe asthma: A narrative review. Respirology. 2020;25:161–172. https://doi.org/10.1111/resp.13730.
8. Van Staa TP, Cooper C, Leufkens HGM, Bishop N. Children and the risk of fractures caused by oral corticosteroids. J Bone Joint Miner Res 2003;18:913–918. https://doi.org/10.1359/jbmr.2003.18.5.913.
9. Rooke T. The quest for cortisone. East Lansing (MI): Michigan State University Press. 2012.
10. The Nobel Prize in physiology or medicine 1950. Nobelprize.org. Nobel Media AB; 2014. Available at: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1950/.
11. Burns CM. The history of cortisone discovery and development. Rheum Dis Clin N Am. 2016;42:1–14. https://doi.org/10.1016/j.rdc.2015.08.001.
12. Carryer HM. The effect of cortisone on bronchial asthma and hay fever occurring in subjects insensitive to ragweed pollen. J Allergy.1950;21:282. https://doi.org/10.1016/0021-8707(50)90059-1.
13. Report to the Medical Research Council by the Subcommittee on Clinical Trials in Asthma. Control ed trial of the effects of cortisone acetate in chronic asthma. Lancet. 1956;1:798. https://doi.org/10.1016/S0140-6736(56)92240-1.
14. Brown HM, Storey G, George WNS. Beclomethasone dipropionate: A new steroid aerosol for the treatment of allergic asthma. Br Med J. 1972;1:585. https://doi.org/10.1136/bmj.1.5800.585.
15. Cameron SJ, Cooper J, Crompton GK, Hoare MV, Grant IWB. Substitution of beclomethasone aerosol for oral prednisolone in the treatment of chronic asthma. Br Med J. 1973;4:205. https://doi.org/10.1136/bmj.4.5886.205.
16. Hodson ME, Batten JC, Clarke SW, Gregg I. Beclomethasone dipropionate aerosol in asthma. Transfer of steroid-dependent asthmatic patients from oral prednisolone to beclomethasone dipropionate aerosol. Am Rev Respir Dis. 1974;110:403.
17. Sears MR, Taylor DR, Print CG, et al. Regular inhaled beta2-agonist treatment in bronchial asthma. Lancet. 1990;336:1391. https://doi.org/10.1016/0140-6736(90)93098-A.
18. Gidaris D, Stabouli S, Bush A. Beware the inhaled steroids or corticophobia? Swiss Med Wkly. 2021;151:w20450. https://doi.org/10.4414/smw.2021.20450.
19. De Benedictis FM, Bush A. Corticosteroids in respiratory diseases in children. Am J Respir Crit Care Med. 2012;185:12–23. https://doi.org/10.1164/rccm.201107-1174CI.
20. Scotney E, Fleming L, Sagiani S, Sonnappa S, Bush A. Advances in the pathogenesis and personalised treatment of paediatric asthma. BMJ MED 2023;2. https://doi.org/10.1136/bmjmed-2022-000367.
21. Aregbesola A, Tam CM, Kothari A, et al. Glucocorticoids for croup in children. Cochrane Database Syst Rev. 2023;1(1):CD001955. https://doi.org/10.1002/14651858.CD001955.pub5.
22. Connolly R, Aye P, Reeves T, et al., On behalf of the Guideline Committee. Otits media with effusion under 12s: summary of updated NICE guidance. BMJ. 2023;383:2314. https://doi.org/10.1136/bmj.p2314.
23. Dalziel SR, Haskell L, O'Brien S, et al. Bronchiolitis. Lancet 2022;400(10349):392–406. https://doi.org/10.1016/S0140-6736(22)01016-9.
24. Stern A, Skalsky K, Avni T, et al. Corticosteroids for pneumonia. Cochrane Database Syst Rev. 2017;12:CD007720. https://doi.org/10.1002/14651858.CD007720.pub3.
25. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of RDS in premature infants. Pediatrics. 1972;50:515–525. https://doi.org/10.1542/peds.50.4.515.
26. Crowley P. Prophylactic corticosteroids for preterm birth. The Cochrane Database of Systematic Reviews.1996;1:CD000065. https://doi.org/10.1002/14651858.CD000065.
27. Jobe AH, Goldenberg RI. Antenatal corticosteroids an assessment of anticipated benefits and potential risks. Am J Obstet Gynecol. 2018;21:62–74. https://doi.org/10.1016/j.ajog.2018.04.007.
28. Kemp MW, Schmidt AF, Jobe AH. Optimizing antenatal corticosteroid therapy. Semin Fetal Neon Med. 2019;24:176–181. https://doi.org/10.1016/j.siny.2019.05.003.
29. Jobe AH. Commentary: Antenatal corticosteroids – a concern for lifelong outcomes. J Pediatr. 2020;217:184–188. https://doi.org/10.1016/j.jpeds.2019.09.015.