

Use of corticosteroids for the treatment of respiratory and other disorders: Estimating benefit to risk relationship

Viktor I Goudochnikov*

Council of International Society for DOHaD, Santa Maria – RS, Brazil

Abstract

The main principles for managing corticosteroid therapy are described. Adverse side effects of systemic and inhaled corticosteroids are considered. It is suggested to pay more attention on the possibilities of pharmacotoxicologic programming / imprinting and embedding caused by corticosteroids.

Introduction

A history of corticosteroids

In 1855 a syndrome of adrenal insufficiency was described by Thomas Addison in England, attracting more attention to the vital importance of adrenal glands. Almost a century later, from 1945 to 1947 Edward Kendall in USA and Tadeus Reichstein in Switzerland were able to obtain cortisone, hydrocortisone and corticosterone by means of chemical synthesis, and in 1949 Philip Hench in Mayo Clinics was the first to use cortisone for the treatment of rheumatoid arthritis. In 1950 Kendall, Hench and Reichstein have received Nobel Prize of Medicine for the discovery of corticosteroids [1].

Already during the decade of fifties in 20th century approximately 50 million prescriptions were filled for corticosteroids. This situation was maintained till the end of the last century [2] and up to the present moment. The use of corticosteroids in modern health care is widespread, including pulmonology and respiratory medicine. In the present mini-review we aimed at estimating the benefit to risk relationship for corticosteroids, focusing mainly on inhaled preparations.

The main classes of corticosteroids

Although cortisol and hydrocortisone designate the same compound as a principal corticosteroid in humans, the endogenous hormone is usually named as cortisol, leaving the name of hydrocortisone to exogenously applied, pharmaceutical preparation [3]. Together with cortisone and corticosterone, cortisol / hydrocortisone constitutes the class of natural corticosteroids. However, in order to be active, cortisone should be transformed to cortisol in the liver, and corticosterone is a principal corticosteroid in some animal species like rats and mice, but not in humans. The main feature of natural corticosteroids is a combination of glucocorticoid and mineralocorticoid activities, what greatly limits their use as anti-inflammatory and immunosuppressive agents. Instead of them, synthetic corticosteroids with additional double bond in ring A are used, first of all prednisone, prednisolone and methylprednisolone that have greatly diminished mineralocorticoid activity. Moreover, in another class of fluorinated corticosteroids such synthetic drugs as dexamethasone, betamethasone and triamcinolone are virtually devoid of mineralocorticoid activity and therefore, should be called glucocorticoids [4].

For treatment of respiratory disorders, the last two classes of synthetic corticosteroids are used mainly as pharmaceutical systemic preparations, whereas the most important corticosteroids for inhaled application include budesonide, beclomethasone and fluticasone [5]. It is necessary to mention here that many synthetic corticosteroids are used not as free alcohols but in esterified forms, in order either to facilitate their water solubility for intravenous administration or on the contrary, to obtain long-acting, depot forms [6].

The benefit to risk relationship

Shortly after introduction of corticosteroids to clinical practice, the reports of their adverse side effects began to appear. Today it is affirmed that although in general, corticosteroids are extraordinary hormones [7], being frequently life-saving and therefore, absolutely necessary drugs [8], nevertheless their use should be managed by skillful health professionals (first of all, physicians and specialists in pharmacy and nursing), since in certain situations these drugs may be life-threatening and sometimes creating literally catastrophic and devastating consequences [9-12]. Moreover, in such cases the tragic events usually cannot be previewed with certainty and beforehand, because for many corticosteroid preparations, principally in systemic usage, the adverse side effects are slowly accumulating and depend on drug potency, dose level, treatment duration and even on age category or may be, pharmacogenetics of the patients.

Here we shall not be able to discuss in detail all the adverse side effects of corticosteroids, addressing the interested readers to the literature references cited. In contrast, our principal aim is only to describe shortly the principal concepts that will help the practitioners to make adequate decisions, when managing corticosteroid therapy.

We shall begin with corticosteroids for oral, systemic administration that are used in pulmonary and respiratory medicine, for example, in

*Correspondence to: Viktor I Goudochnikov, Council of International Society for DOHaD, Santa Maria – RS, Rua Matoso Camara 73, CEP 97050-500, Santa Maria-RS, Brazil, E-mail: victorig40@hotmail.com

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the treatment of severe asthma and sometimes, even in infants not accepting facial mask for inhalation. The main principles of such usage are the following:

1. Try to use the lowest dosage during the shortest time period possible;
2. Do not allow to stop the treatment abruptly, almost always try to use a tapering regimen for corticosteroid withdrawal;
3. As a rule, make an attempt to administer the corticosteroid as unique dose in the morning or at least, with much lower dose in the afternoon; if possible, try to use alternate day regimen [13].

Although these principles are well-known and easy to remember, the history of adverse events associated with corticosteroid use is plentiful mainly because of not following such principles, partly due to failures of communication between practitioners and their patients or among various categories of health professionals. Therefore, the education of patients should be the main task of every practitioner managing the use of corticosteroids [14]. Obviously, this task is not so simple, because of the reality of steroid phobia, but in compensation, the results of systemic corticosteroid pharmacotherapy in optimized version may be much more successful and safer. One of important tools is the use of identification cards informing long-term use by patients of systemic or inhaled corticosteroids. These cards diminish the aforementioned failures of communication between the patients and health professionals.

Let's explain now in brief the reasons of such principles of systemic corticosteroid treatment. At present it is clear that unfortunately, adverse side effects of corticosteroids are proportional to their therapeutic actions. Therefore, it is important to use the lowest dose that at the same time, is efficacious in the treatment of disease [3]. And since adverse effects of corticosteroids are cumulative, it is essential to use these drugs for the shortest time period possible.

The principal danger of abrupt interruption of corticosteroid treatment is acute adrenal insufficiency, possibly leading to cardiovascular collapse in the cases of sudden and intense stress like trauma or surgery [14,15]. The necessity of administering the main part of daily corticosteroid dosage in the morning is dictated by circadian rhythm of cortisol, considering also the possibility of more severe atrophy of the adrenals, when corticosteroid administration is performed in the evening. In regimen of alternate day administration of corticosteroids, the extent of such atrophy is also much lower [16].

Adverse side effects of inhaled corticosteroids

The corticosteroids for inhaled use mentioned earlier, have two principal features:

- a) They are extremely potent locally, with affinity to glucocorticoid receptor approximately 10-fold higher, as compared to dexamethasone;
- b) Their metabolism to inactive forms is almost complete during the first pass through the liver, so in theory, systemic side effects should be negligible [17].

In addition, corticosteroids help diminishes down-regulation of adrenergic receptors that occurs in the case of chronic use of beta2-agonists [18].

As a matter of fact, the inhaled corticosteroids are already considered to be quite potent and safe [17], but unfortunately, it does not mean that they are completely devoid of adverse effects. What practitioners

working in the field of pulmonology and respiratory medicine ought to consider in this respect? First of all, at least high doses of inhaled corticosteroids, when used chronically can result in some degree of adrenal atrophy [2,3], so the low-dose, systemic maintenance therapy should be prolonged for many months and even years, trying to perform the withdrawal of corticosteroid in slow mode, by means of tapering regimen. It is important not to forget that the price of even small degree of adrenal atrophy will be payed by the patients in emergency room, because of stress due to trauma or surgery.

Secondly, the chronic use of even moderate doses of inhaled corticosteroids may provoke systemic catabolic consequences, primarily the decrease of bone mineral density leading to osteoporosis and finally, to higher risk of bone (especially, vertebrate) fractures, as well as skin thinning and decrease in muscle strength, including that of inspiratory muscles [2,3,15]. In addition, inhaled corticosteroids are not completely devoid of some potentially dangerous properties of systemic preparations in enhancing the risk of serious infections including pneumonia and tuberculosis, or in provoking hypertension and insulin resistance, cataract and glaucoma, depressive and psychotic symptoms [2,3,15,19,20].

Particularly essential is the necessity of greatly enhanced attention to special groups of patients, including pregnant and lactating women. In this regard, the interested readers are addressed to our recent mini-review on the use of corticosteroids in the cases of prematurity, as referred to possible programming / imprinting phenomena, with life-long consequences [21].

The safety of inhaled corticosteroids is diminished in early postnatal ontogeny, because of immaturity of cytochrome P-450 enzymes, responsible for the first-pass metabolism of inhaled corticosteroids in the liver [3]. Moreover, in some cases the safety of inhaled corticosteroids may be decreased also due to drug interactions, for example, in patients with AIDS, treated with protease inhibitors like ritonavir that interfere with hepatic corticosteroid metabolism [22].

At last, as already was suggested in our previous publication [23], long-term treatment even with inhaled corticosteroids can provoke the phenomenon of pharmacotoxicologic embedding, not only because of systemic, slowly accumulating consequences, but also due to local effects, including for example, the tendency to higher number of neutrophils in the airways, probably as a result of apoptosis inhibition in these cells by highly potent inhaled corticosteroids [24].

Conclusion

Although there occurred recently some progress in elaboration of new, so called dissociated corticosteroids with largely reduced adverse side effects [2], the conventional corticosteroids, mostly developed in the second half of the last century, continue to dominate the pharmaceutical market and health care. So it is extremely pertinent to learn, how to use these conventional corticosteroids in a maximally safe and efficacious mode. On our opinion, it is highly unwise to ignore the obvious adverse side effects of corticosteroids, including inhaled forms. On the contrary, it is essential to find out the ways for diminishing such unfavorable effects, for example, by means of adjunct antioxidant usage [25,26] or employing some antistress compounds like melatonin [27-30]. This is especially important for the treatment of pregnant and lactating women, children and elderly patients, for which the benefit to risk relationship should be constantly evaluated in the short and long term, paying more attention to the possibilities of pharmacotoxicologic programming / imprinting and embedding.

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