

Clinical-therapeutic approach to psychiatric side effects consecutive to corticosteroid treatment

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ABSTRACT

Corticosteroids are widely used anti-inflammatory and immunosuppressive pharmacological agents in various pathologies, such as asthma, allergies, rheumatologic or dermatologic conditions, etc. Their incontestable efficiency comes with a price: their multisystemic side effects, such as failure to thrive in children, hypertension, hyperglycaemia, osteoporosis, metabolic disorder, glaucoma, cataract and not least – but often neglected or under-diagnosed – mental disorders. Among the last, it is worth mentioning depression, mania, catatonia, cognitive impairment, behavioural disorders, ideation and suicide attempts. It is fundamental to detect them, considering their potential devastating effects on the patients' functionality and integrity, and in order to find an adequate therapeutic

approach, by decreasing the corticosteroid dosages considering the general state of the individual and by choosing proper psychotropic agents.

KEYWORDS

corticosteroids, hypothalamic-pituitary-adrenal axis, depression, psychosis, mania

INTRODUCTION

Glucocorticoids are a class of hormones released by the adrenal cortex, and their plasmatic concentration is controlled by the hypothalamic-pituitary-adrenal axis and activated by both physical and mental stimuli. Endogenous glucocorticoids influence complex biological processes, such as growth, metabolism and immunity; they also control the hunger centre, the sleep/wakefulness cycle; they affect learning and memorising processes by interacting with specific receptors, localized in the prefrontal cortex, the hippocampus and the amygdale (1, 2, 3). Steroid receptors are expressed in different areas of the brain and their role is related to the regulation of diverse neurotransmitters. More precisely, at the level of central nervous system, glucocorticoids act on the hippocampus – a structure deeply involved in the limbic system – which processes emotional and mnesic information. Numerous studies indicate the correlation between high cortisol levels and hippocampal atrophy, resulting in cognitive dysfunction (1, 2, 10, 16). They are mediators of response to stress, and the drugs derived from them – also called corticosteroids – are widely used pharmacological agents in inflammatory pathologies, such as asthma or immunologic/rheumatologic conditions (1, 6). Glucocorticoids mitigate inflammatory pathology by the pleiotropic effect of glucocorticoid receptors on multiple signalling pathways. Despite their efficiency, they have significant side effects: failure to thrive, immunosuppression, high blood pressure, hyperglycaemia, osteoporosis, metabolic disorders, glaucoma, cataract, as well as psychiatric side effects, such as catatonia, psy-

chomotor agitation, hypoprosexia and hypomnesia, hypnic disorders, behavioural disorders, psychotic manifestations. The last are often under-diagnosed or neglected. Approximately 20 % of the patients under corticosteroid treatment present mental disorders, while 75 % report psychiatric symptoms reversible once the medication is interrupted (1, 2, 17).

Side effects at the level of central nervous system

Studies have found that chronic cortisol administration leads to appetite increase, with consecutive weight gain in 70 % of the patients.

Hypnic disorders manifested by insomnia were found in 73 % of the cases.

A study conducted by Swinburn, in 1988, has found that some of the patients with severe chronic obstructive airways disease given oral prednisolone developed a sense of wellbeing called „steroid euphoria”, characterized by reduction in anxiety and depression, even if there was no improvement in lung function (1, 8, 15).

Literature has also reported cases of psychomotor agitation, accompanied by insomnias correlated with intra-articular administration of methylprednisolone (1, 5).

It has been found recently that long-term increased doses of corticosteroids can be associated with catatonia, expressed by muscular stiffness, insomnia, bizarre behaviour and verbal negativity.

Scientific literature reports that percentages for depression consecutive to therapy with corticosteroids are 40.5 %, for mania – 27.8 %, and for psychotic symptoms – 13.9 %. It is unclear as to the way corticosteroids manage to induce

these symptoms. Administration of prednisone is associated with low levels of corticotropin, norepinephrine and beta-endorphin in the cerebrospinal fluid. Furthermore, corticosteroids induce increased glutamate release, which determines neuronal toxicity by cumulative effect. At the same time, high levels of glucocorticoids are associated with impairment of declarative mnemonic abilities. Considerable scientific evidence suggests that long-term exposure to these pharmacological agents can cause cognitive deficit by cumulative effect and that they can have a long-term influence on hippocampus function and morphology (1, 15, 18).

These psychiatric side effects depend on the dosage, on the duration of treatment and on the susceptibility of each treatment. The onset of steroid-induced psychiatric symptoms is variable; side effects can manifest at the beginning, during or even at the end of treatment. In 39 % of the cases, they manifest from the first dose, in 62 % of the cases, in the first two weeks and in 89 % of the cases, in the first six weeks.

If they are administered chronically, corticosteroids increase the risk of committing suicide (1, 14, 18).

Two extended meta-analyses have found that approximately 6 % of the patient given systemic treatment with corticosteroids presented severe psychiatric reactions, while 28 % of the patients given this pharmacological agent have reported average and mild mental side effects. Though mood swings and cognitive, hypnic, behavioural disorders and even psychotic symptoms are possible, the most common side effect of short-term administration of corticosteroids is euphoria/hypomania. In contrast, long-term administration of corticosteroids usually induces depressive symptoms (18).

The dosage of corticosteroids is directly related to their side effects, but not to their severity or their duration.

Increased daily doses of glucocorticoids and personal neuropsychiatric antecedents are associated with increased risk of such side effects. Women are more prone to depression and less prone to mania, confusion states, disorientation. The risk of corticosteroid-induced mental disorders (depression, mania, delirium, confusion, disorientation) increases with age, while suicidal thoughts and panic attacks decrease with age (11, 12, 14).

Risk factors in the emergence of psychiatric symptomatology in the context of corticosteroid administration

The most important risk factor is the dose of the corticosteroid. *Boston Collaborative Drug Surveillance Program* proved – through an ample study – that, of the patients given less than 40 mg/day of prednisone, only 1.3 % manifested mental disorders as side effects, while, of the patients given more than 41 – 80 mg/day, 4.6 % reported this type of side effect; of those given more than 80 mg/day, 18.4 % had such side effects (11, 12, 13).

Corticosteroid abuse

The literature reports a series of cases that describe the abuse of corticosteroids because they can induce an elation or even euphoric state. Overdoses are usually oral or intravenous. Most cases involved patients with pre-morbid history – either psychiatric or alcohol or substance abuse (1, 4).

Therapeutic approach to corticosteroid-induced mental disorders

Management strategies of mental disorders caused by the administration of corticosteroids are based almost exclusively on case studies and on low-scale statistical analyses. Consequently, several prophylactic strategies were developed in this sense, which pinpointed the efficiency of lithium, chlorpromazine, valproic acid, gabapentin and lamotrigine (1, 2, 3).

Generally, the psychiatric symptomatology associated with the administration of corticosteroids disappears once the treatment ends. However, some of the patients require psychotropic treatment, along with reducing corticosteroid doses or even cutting them off completely. Patients can be treated with the usual medication within psychiatry. Thymoregulators – such as lithium or valproic acid – control the iatrogenically induced symptomatology. Carbamazepine accelerates the metabolism of steroids, thus mitigating its neurotoxic effect (1, 8, 9).

For psychotic symptomatology, it is recommended to use atypical antipsychotics; olanzapine and risperidone were proven effective in this sense (1, 7). Depressive symptomatology is usually treated with selective serotonin reuptake inhibitors, among which fluoxetine has been the most researched. Tricyclic antidepressants lead to significant worsening of symptoms (10).

It is fundamental to assess potential suicidal behaviour, considering that 33 % of the patients with corticosteroid-induced psychosis experience this pathology, which makes it a real psychiatric emergency (Table 1, Table 2) (1, 4).

Though reducing or stopping the corticosteroid medication is the basis of eliminating iatrogenically induced psychiatric, caution is required when it comes to reducing suddenly the dosages of these drugs, mostly in case of patients given maximum dosages *à la longue*. An inadequate reduction can lead to hypothalamic-pituitary-adrenal suppression with secondary adrenaline insufficiency, the recurrence of the disease for which the corticosteroid was prescribed, the withdrawal syndrome manifested by adrenaline insufficiency symptoms. Hence, corticosteroid withdrawal includes lethargy, general malaise, depression, anorexia, nausea, myalgias and arthralgias (15, 16, 17).

1. Assessing the potential suicidal ideation or psychomotor agitation; if present, admission to a hospital is recommended.
2. Reducing the dosage of corticosteroids gradually and in the shortest possible interval, to prevent impairing physiological functions.
3. If the psychiatric pathology persists, psychotropic medication becomes necessary (atypical antipsychotics, considering that mania/hypomania are the most common effects of short-term treatment).

Table I. *Therapeutic algorithm for the patients given short-term treatment with corticosteroids (< 1 month) and reporting psychiatric side effects (1, 4, 7)*

1. Assessing the potential suicidal ideation; if present, admission to a hospital is recommended.
2. Prescribing minimum dosages of corticosteroids or decreasing them gradually until stopping them altogether, if the patient's general state allows it.
3. If symptoms are affective mania psychotic thymoregulators atypical antipsychotics depression – thymoregulators selective serotonin reuptake inhibitors atypical antipsychotics

Table II. *Therapeutic algorithm for the patients given long-term treatment with corticosteroids (< 1 month) and reporting psychiatric side effects (1, 4, 7)*

CONCLUSIONS

Persons given glucocorticoids are twice as prone to develop depression; chances of developing mania, delirium, confusion, disorientation increase four – five times, while suicide attempt or suicide *per se* seven – eight times, compared to the population not exposed to these pharmacological agents. It is fundamental for the patient, the family and the general physician to monitor the neuropsychiatric side effects, for an adequate modulation of corticosteroid dosages, all meant to prevent the onset of side effects.

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