Corticosteroids and mental disorder

Abstract

Corticosteroid medication is an essential treatment in almost all medical specialties. Psychiatric side effects of corticosteroids may be both common and severe and include psychosis, mania, depression, delirium and dependence. Only a small evidence base exists about susceptibility to and epidemiology of these conditions. Corticosteroid induced psychiatric disorder typically has an acute onset and is dose related. Manic symptoms predominate acutely however long term use may be associated with depression. Steroid dependence and withdrawal syndromes have been documented. Case reports suggest that a combination of mood stabilizers and antipsychotics may be useful in management severe acute effects. This article will give psychiatrists working in a general hospital a guide to the epidemiology, clinical presentation and management of corticosteroid induced psychiatric disorder.

Introduction

Corticosteroids were first introduced into medical practice in the late 1940s, since when they have been used by almost all medical specialists as effective treatment for autoimmune and inflammatory conditions. Over 5 million prescriptions are written for corticosteroids in the UK each year, at a cost of over £100 million. (NHS Health Care Statistics 2005) About 1% of the general population and as many as 7% of hospitalized patients are receiving oral corticosteroid therapy at any given point in time. (NHS Health Care Statistics 2005) Whilst being renowned for important therapeutic actions they can have many adverse effects which must be considered in long term treatment. Physical effects such as osteoporosis, central obesity and

immunosuppression are frequent in patients receiving corticosteroids. Psychiatric effects include alterations in mood, delirium, dementia and psychosis. As corticosteroids have a critical place in the management of chronic disease, psychiatrists should be equipped with the knowledge to recognize and manage corticosteroid induced mental disorder. This article describes the epidemiology, clinical presentation and management of these conditions.

Indications and Pharmacology

There are several forms of corticosteroid medication licensed in the UK, including: betamethasone, cortisone acetate, deflazacort, hydrocortisone, methylprednisolone (prednisolone) and triamcinolone. Each of these drugs has varying degrees of mineralocorticoid and glucocorticoid activity. All of the above preparations exist in oral or intramuscular form. Inhaled steroid preparations are also will not be discussed as there is little evidence that they can induce mental disorder.

The main indications for these medications are:

Suppression of inflammatory and allergic bowel disease;

chronic or treatment resistant Asthma and COPD;

Immunosuppression in Acute Lymphoblastic Leukemia, Hodgkins and non-Hodgkins disease, and Hormone sensitive breast cancer;

Palliation of symptomatic end-stage malignant disease;

Organ transplant rejection;

Auto-immune (Rheumatic) disease such as Systemic Lupus Erythematosis and Wegners Granulomatosis.

Corticosteroids are rapidly absorbed across the Gastro Intestinal membrane following oral administration. Peak effects can be observed after 2 hours. The circulating drugs bind extensively to the plasma proteins Corticosteroid Binding Globulin (CBG), albumin and transcortin, with only the unbound portion of a dose active. Systemic prednisolone is quickly distributed into the kidneys, intestines, skin, liver and muscle. Corticosteroids also distribute into the breast milk and cross the placenta. Corticosteroids are predominantly metabolized by the liver to active metabolites then further metabolized to inactive compounds. These inactive metabolites, as well as a small portion of unchanged drug, undergo urinary excretion. The plasma elimination half-life is 1 hour whereas the biological half-life of prednisone is 18-36 hours.

Corticosteroids act as glucocorticoid receptor agonists. On binding, the corticoreceptor-ligand complex translocates itself into the cell nucleus, where it binds to Glucocorticoid Response Elements (GRE) in the promoter region of target genes.

Insert Figure 1 about here

The DNA bound receptor then interacts with basic transcription factors, altering gene expression. There are high concentrations of CBG in specific brain areas such as the hippocampus and pre-frontal cortex and these can therefore be thought of as a potential mediator of corticosteroid induced psychiatric disorder.

Chronic disease and corticosteroids

In parallel to the psychiatric side effects of corticosteroid therapy, most chronic medical conditions may be associated with considerable psychiatric morbidity. A primary objective of the psychiatrist is to distinguish between the psychiatric effects of chronic illness and corticosteroids. The 1-year prevalence for ICD-10 depressive episode alone is 3·2% (95% CI 3·0-3·5) and an average of between about 9% and 23% of patients with one or more chronic physical diseases have co-morbid depression. In an international meta-analysis, patients with a variety of chronic physical diseases and co-morbid depression had significantly worse health scores than those with chronic disease alone. (Moussavi et al 2007) There are many potential reasons for this, including physical symptoms such as pain and secondary disability leading to loss of function.

Studies of depression amongst the medically ill almost always fail however to account for possible corticosteroid effects. In patients with severe COPD given 30 mg of prednisolone for 14 days, when lung spirometry and mood state were measured, no changes in spirometry were detected until 7 days of active therapy. However, small but significant reductions in anxiety and depression were measured after 3 days of prednisolone and before any measurable improvement in lung function. This single study is a major part of a small evidence base suggesting that corticosteroids produce a mild sense of wellbeing rather than the wellbeing necessarily being a consequence of physical improvement. (Swinburn et al 1988)

Classification, Epidemiology and Clinical Features

Psychiatric side effects were first described and classified by Rome and Braceland in 1952 shortly after the initial introduction of corticosteroids into the pharmacopoeia. As can be noted in Table 1, the descriptions of symptoms in 1952 have an implicit hierarchy which places psychosis above “ ego” disturbance of a neurotic nature and places these above euphoria. (Rome and Braceland 1952)

Insert Table 1 about here

Epidemiology

The proportion of patients developing psychiatric symptoms during corticosteroid therapy has been reported to range from 3 to 75 percent, with a weighted average of about 28 percent. (Lewis and Smith 1983) Amongst the larger studies, the Boston Collaborative Drug Surveillance Program (Boston Collaborative Drug Surveillance Program 1972) monitored 718 hospitalized medical patients who received prednisolone, of whom just 21 (3%)had acute psychiatric reactions: in 6 of 463 (1%) patients receiving 40mg prednisolone, 8 of 175 (5%) patients receiving 41-80mg and 7 of those receiving above 80mg (18%). The dose-response trend was significant, but the study was conducted in 1972 and deals with relatively small numbers of affected subjects who underwent only a basic psychiatric screening.

In terms of speed of onset, symptoms appear to develop rapidly. In groups of both patients and healthy subjects, psychiatric symptoms occurred between 3 days and one week. (Lewis and Smith 1983, Hall 1979, Naber 1996) Evidence shows that significantly more women than men (P = 0. 009)

develop psychiatric symptoms as a function of corticosteroid treatment. (Nielsen et al 1963)

Prednisolone is the medication most cited to cause psychiatric side effects. In case reports, prednisolone was responsible for 37 cases followed by methylprednisolone, dexamethasone betamethasone, and hydrocortisone. (Lewis and Smith 1983) When dose equivalences were calculated, ranging from 5 to 200mg prednisolone per day, a mean dose of 58. 3mg per day or more was cited as substantially raising the risk of a psychiatric reaction. This does not mean that psychiatric reactions only occur at higher dosages.

While dosage is not related to the risk of developing mental disturbances, dosage nor duration of treatment seems to impact upon the time of onset, duration, severity, or type of mental disturbances and it is unclear whether patients with a history of psychiatric disorder are predisposed to such disturbances. (Ling 1981)

Affective Symptoms

The most common psychiatric reaction during glucocorticoid therapy is mood change, which accounts for almost 90 percent of the psychiatric reactions (Hall 1979, Stiefel 1989) In a review of 56 case studies of psychiatric reactions to steroids, of those reporting mood symptoms (45 cases), mania was observed in 48%, depression in 25%, and a mixed state in 9%. (Flores and Kenna)

Reversible mood change can be seen in healthy control subjects after administration of prednisone and dexamethasone. One study showed that 8/12 healthy controls experienced this, with manic symptoms predominating.

(Brown 1998) A further study which looked at methylprednisone in ophthalmology patients, all of whom were free of psychiatric disorder, found that 36% developed mania or depression during high dose steroid treatment. (Naber 1996) Studies examining the consequences of low dose steroid treatment have found little or no affective symptomatology (Swinburn 1988).

With regard to steroid induced mania, patients typically report sudden euphoric mood, excessive energy, indefatigability and some grandiosity. In addition to the rapid development of mood symptoms, suicidality can be associated with steroid treatment. (Flores and Kenna). In addition to mood symptoms patients have been reported to experience sleep disturbances and weight gain.

Recurrent affective disorder

A further important consideration is whether any such affective disturbance involves one isolated episode or leads on to recurrent disorder. Nine patients whose initial clinical presentation met DSM-IV criteria for a steroid-induced mood disorder were shown in the long term to have a clinical course of bipolar disorder. (Wada 2001) Seven patients initially developed a manic or hypomanic state with sub-acute onset ranging from 1 to 3 months and six patients had manic episodes accompanied by psychotic features. The proportion of manic episodes relative to total mood episodes of the 9 patients was 66%, suggesting manic predominance. Seven patients had future mood episodes that had no direct relationship to corticosteroid therapy and were preceded by various psychosocial stressors. Four of 5 patients who received future steroids rapidly became manic or hypomanic. Recurrent cases of corticosteroid-induced mood disorder therefore appear to

have clinical features such as sub-acute onset, frequent accompanying psychotic features, and similar recurrent episodes in association with psychosocial stressors and corticosteroid use.

Psychotic Symptoms

In a review of 55 case reports of steroid induced psychiatric disorder, 58% of cases demonstrated psychotic symptoms. (Ling 1981) In 72% of the cases with psychotic symptoms, they were combined with an affective disorder. Similarly, in a review of 79 case reports there was a 71% incidence of psychotic symptoms with affective symptoms reported in over 75% of these. Hallucinations occurred in 58% of the cases and delusions in 74% .(Lewis and Smith 1983)

In a more recent review of 56 case reports, psychotic symptoms were reported in 65% of cases. In eight of these, the development of psychotic symptoms was more clearly associated with the withdrawal, rather than with the administration, of steroids. (Flores and Kenna) Interestingly, but perhaps coincidentally, seven of these eight cases occurred in female patients. All eight cases included mood disturbance; 2 with depression, 4 with mania, and 2 with a mixed state.

Cognitive effects

The cognitive effects of corticosteroid therapy have been seen in patients receiving short term or long-term corticosteroids, and relate primarily to declarative or verbal memory. (Flores and Kenna)

In one study, patients on corticosteroids had poorer performance on the Rey Auditory Verbal Learning Test (RAVLT), (a measure of declarative memory),

the Stroop Color Word Test (a measure of working memory) performance, smaller hippocampal volumes and lower levels of N-acetyl aspartate (a putative marker of neuronal viability in the temporal lobe region). (Brown 2001)

Deficits in declarative memory have been observed in subjects receiving as low as 4 to 5 days of dexamethasone or prednisone. (Newcomer 1999) A dose-dependent impairment in declarative memory has been reported with high dose (160 mg/day), but not low dose (40 mg/day) hydrocortisone. It appears that these cognitive impairments may be reversed with the reduction or withdrawal of corticosteroids. Similar results for declarative memory deficits are found in persons with Cushing’s disease. Such findings are consistent with reductions in hippocampal volume which are correlated with cortisol levels. (Starkman 1992)

Steroid Dependence and withdrawal

Several case reports suggest that corticosteroids may be abused for their euphoric effects. (34) Typically this will involve higher doses of oral systemic steroids although there is one report of dependence secondary to a nasal spray. (35)

In a case review, 8 patients out of 11 cases of steroid dependency had a previous psychiatric history (predominantly depressive symptomatology), and 4 had a history of drug or alcohol mis-use or dependence. It has been suggested that patients who may request higher steroid doses or who resist dose reduction despite their improving health should be carefully monitored. (Stoudemire 1994)

In the more recent review of case studies (Flores and Kenna), the development of psychiatric symptoms was also associated with the withdrawal of steroids. Corticosteroid withdrawal symptoms generally include depression and fatigue but mania and delirium have also been reported during dose reduction or discontinuation. Psychiatric symptoms during steroid withdrawal generally improve or resolve when corticosteroids are re introduced.

Cushing's disease and psychiatric disorder

Cushing's syndrome relates to the multi-organ over exposure of iatrogenic or endogenous corticosteroid and is associated with a variety of psychiatric and psychological disturbances. In one study examining 43 patients before and after treatment for Cushing's psychopathology was observed in a considerable number. Only 8 patients of 43 with active Cushing's syndrome (19%) were without psychiatric symptoms. Psychiatric diagnoses included: neurotic depression in 20 (46%), possible neurotic depression in 1 (2%), reactive depression in 6 (14%), and non-specific neurotic symptoms in 8 (19%). Psychoses were suspected in 3 of the patients who were depressed, but none of the 43 patients with active Cushing's syndrome had a definite diagnosis of Schizophrenia, Mania, Obsessive Compulsive Disorder or Generalised Anxiety Disorder.

After treatment in 25 patients, when cortisol levels had been substantially reduced (to within normal limits in 88% of them), the percentage rated as psychiatrically asymptomatic increased from 19% to 68%. Scores for depression and anxiety showed significant improvements after treatment for

Cushing’s syndrome and Eysenck Personality Inventory assessments showed a significant improvement in neuroticism score. (Kelly 1996)

Treatment of Corticosteroid induced psychiatric disorder

There is a very limited literature on the treatment of corticosteroid induced mental disorder, although it can be noted from the forgoing that psychiatric symptoms generally resolve with discontinuation of the medication. In one review of the literature, tapering the dose of steroids alone appears to be effective up to 90% cases. (Flores and Kenna) Case studies also suggest that switching steroids may be of value. (Okishiro et al 2009) The primary objective in managing these conditions is to balance the relative risk of psychiatric disturbance against the medical consequences of withdrawing the steroid.

The management of corticosteroid induced psychiatric disorder can otherwise be largely divided into managing an acute psychotic/manic episode versus managing long term depressive symptoms and dependency. Although little evidence exists either way, it can be assumed that severe behavioral disturbance should be managed as it usually is – symptomatically with appropriate doses of benzodiazepines and antipsychotics.

In terms of managing acute psychotic/manic episodes one study found that of 27 patients treated with lithium carbonate prophylactically none developed severe mood symptoms while receiving corticosteroids. However, six out of 44 patients (14%) not receiving lithium developed mania or depression. (Falk 1979) Antipsychotics, specifically haloperidol, risperidone and olanzapine, are noted from case reports to be useful in mania, mixed

affective states, psychosis and delirium. A further case report suggested the successful use of low-dose olanzapine (2. 5 mg/day) for severe mood swings and suicidal ideation in a patient with asthma on chronic prednisolone therapy.

With regard to depressive symptoms, several case reports have demonstrated some evidence with lithium following the onset of depressive symptoms. Carbemazepine has been reported to be useful in managing both manic and depressive symptoms secondary to corticosteroids. (Wada 2001) There appears to be little benefit from the use of tricyclic antidepressants and in fact, a worsening of neuropsychiatric symptoms has been reported. (Hall 1978) Case reports have been published describing the successful treatment of steroid-induced depression with sertraline, fluvoxamine, and fluoxetine. One such report supports the use of a combination of an antidepressant and antipsychotic in the treatment of steroid-induced psychotic depression (Ismail 2002). Case reports are noted to suggest the effectiveness of benzodiazepines, in the management of specific steroid-induced symptoms as insomnia and anxiety

Conclusions

Above all, it is clear that the literature on the psychiatric adverse effects of corticosteroids is limited and larger studies on medically ill populations need to be carried out. Clinical practice continues to be informed by case reports despite over 50 years of awareness of these problems. There exists a great opportunity for future research to find predictors of steroid response including their genetic and neuroimaging antecedents and it is clear that the literature could be enhanced with prospective studies and clinical trials.

The ICD 10 codes steroid induced psychiatric disorder under F55. 5 “ Abuse of non-dependence-producing substances “ Steroids or Hormones”. No distinction is made about type or chronicity of symptoms. Arguably it may be more useful to classify steroids induced psychiatric disorder under F19.- Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances. Corticosteroid induced psychiatric disorder can pragmatically be classified at present as described in table 2.

Insert Table 2 about here

With regard to the acute corticosteroid syndrome, the clinical presentation can be diverse but the severity of the symptoms appears to be dose dependent and they tend to occur within the first week of steroid administration. Affective symptoms are most common and a hypomanic/manic presentation is most likely. Some patients appear to have sub clinical hypomanic symptoms which they do not report. Symptoms resolve in most cases on discontinuation of the steroid. Cases are best treated with a mixture of a mood stabilizer (possibly prophylactically) and antipsychotic.

With regards to chronic steroid syndrome, the merits of continuation of the steroid must be considered and a small literature suggests that depression in this group can be managed with an SSRI and not a tricyclic antidepressant.

In patients who are on long term steroids, a dependence and withdrawal syndrome may be seen. No evidence exists as to how this should be managed but again negotiation should occur between the clinicians and the

patient on the need for steroids and a gradual tapering of dose should be considered.

Presently it is not known whether individuals have idiosyncratic reaction to steroids or that, given a high enough dose everyone would suffer some mental disturbance. There is a suggestion that those with a previous affective disorder or a family history may be more susceptible to the adverse effects of steroids. If as many as 27% of those on high dose steroids suffer psychiatric symptoms, it is surprising that millions of patients do not present to psychiatric services.

Case vignette: Steroid-induced psychosis

A 40-year-old woman was admitted to a GI ward for corticosteroid treatment as a result of a flare-up of her inflammatory bowel disease (IBD). Her previous psychiatric history included recurrent depression, for which she had been successfully prescribed fluoxetine by her GP for several years. She was treated for 5 days with prednisolone 40mg IV which was then switched to oral prednisolone prior to her discharge home. Over the next week she progressively became increasingly irritable, experiencing hyperacusis, preferring to stay up all night doing housework and decorating, and suffered from marked lability of mood, fluctuating from euphoria to extreme despair and tearfulness, and anxiety. She began to experience command hallucinations of her late father, who had suffered from schizophrenia, telling her to kill herself, as he had in fact done a number of years earlier. She experienced delusions of being unclean and malodorous. She was visibly seen to be responding to unseen stimuli. She was unable to leave her home

for fear that people wished to harm her. On day 5 post-discharge her family sought help from her GP who recommended that she stop her steroids, after noting that 18 years earlier she had experienced a similar episode in response to steroid treatment for her Crohn’s disease. Her GP prescribed Chlorpromazine but unfortunately the patient developed a marked pill-rolling tremor and akathisia. Next day the patient attended a GI outpatient clinic and due to her distress and anxiety a psychiatric opinion was immediately sought. She was informally admitted and commenced on olanzepine and diazepam with a significant diminution of her psychosis and anxiety such that after a few days she was able to be discharged home. Over the next several weeks she was closely followed-up by liaison psychiatry as an outpatient. Her psychotic symptoms had completely resolved with olanzapine treatment. She did, however, continued to experience low mood and anxiety as a result of ongoing stress associated with her IBD and required further treatment with antidepressant medications.