Behavioral Side Effects of Corticosteroid Therapy

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Behavioral side effects of corticosteroids and corticotropin have been recognized since the introduction of these drugs into routine medical usage. Despite over 40 years of clinical experience, however, and the obvious importance of such data to clinical management, definitive conclusions regarding predicted incidence and character of psychiatric symptoms and associated risk factors must be tempered by the recognition that the majority of studies reviewed are either anecdotal or retrospective in character. Furthermore, the few prospective studies that exist pay insufficient attention to the use of trained clinicians, operational criteria, and objective instruments in the evaluation of behavioral symptomatology, and do not control for possible confounding variables.

INCIDENCE AND CHARACTERISTICS OF NEUROPSYCHIATRIC SYMPTOMS

The reported incidence of behavioral change varies widely among studies, depending in part on the criteria set for severity and the sensitivity of the assessment methods chosen. Mild euphoria is commonplace upon initiation of corticosteroid treatment, affecting the majority of patients. With time, and particularly when higher doses of corticosteroids are employed, depression may become more paramount, although, as noted by Rome and Brunel in their classic review and by others since, there is no definitive or pathognomonic presentation.

A prominent disturbance in mood was noted in approximately 3/4 of patients showing behavioral change in one well-documented series. Anxiety, obsessive-compulsive behavior, and disturbances in consciousness consistent with the diagnosis of delirium also occur, as can insomnia, irritability, and subtle changes in sensory perception, attention, concentration, and memory. Hall and colleagues emphasize emotional lability and "sensory flooding" as particularly distinctive. Severe reactions, such as disturbances of body image, delusions, negativistic mutism, auditory or visual hallucinations, and frank dementia, are more rarely observed, with an estimated incidence of 5% derived from a weighted average of studies on record.

The largest survey to date, the Boston Collaborative Drug Surveillance Program, found a 3% incidence for psychosis and formal mania, although this may be an underestimate, as it was based only on acute reactions in patients who had had no prior psychiatric symptomatology. Subtle behavioral effects,
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which may not be observable but are subjectively distressing, have also been noted.\textsuperscript{7,22} Some investigators have suggested that suicidal ideation may be particularly apparent in corticosteroid-induced psychosis, perhaps through alteration of serotoninergic metabolism,\textsuperscript{23,24} but specific evidence in support of this hypothesis is minimal.\textsuperscript{25} When psychosis occurs, classic bipolar features are frequently present, including grandiosity, pressured speech, irritability, paranoia, and a preoccupation with religious, sardonically self-referential, and persecutory themes.

A clear delineation between functional and organic diagnoses is often difficult to achieve on phenomenologic grounds alone, but the delusional material is generally not well systematized.

**DOSE, DURATION OF TREATMENT, AND ASSOCIATED RISK FACTORS**

The incidence of steroid-induced behavioral reactions is clearly dependent on the underlying condition being treated; the potency of the specific corticosteroid agent employed; and the dosage and, possibly, duration of treatment. A particularly high incidence of psychiatric side effects has been found in individuals with systemic lupus erythematosus, but drawing conclusions from this study is complicated by the very high doses employed (500 mg per day) and the fact that the disorder itself frequently causes changes in mental status.\textsuperscript{9} In general, however, there is no strong evidence that either the underlying medical condition or a past history of psychiatric disturbance predisposes patients to an increased risk for psychiatric side effects when administered steroids. A past experience of steroid-induced behavioral change does not clearly predict a recurrence on reexposure to the drug, but neither does the absence of same in the past ensure future protection.\textsuperscript{11}

The majority of cases reported are in patients between the ages of 21 and 60, a finding that may be dependent in whole or part on the age prevalence of diseases for which corticosteroids are indicated. The finding that significantly more women than men appear in the case reports published may be due to similar factors, i.e., the marked female predominance in autoimmune disturbances and connective tissue diseases.

Variance in the incidence of psychiatric side effects among studies, as well as a perceived decrement in incidence from the earliest reports to present day, may be partly ascribable to differences in total equivalent doses of the steroids prescribed, as well as changes in the pattern of their administration. In the Boston study, a significant relationship between behavioral pathology and dosage was noted, with the incidence of psychosis increasing from 3% to 4.6% in patients receiving 41 mg to 80 mg per day, to 18.6% in those who were prescribed greater than 80 mg per day.\textsuperscript{21} This correlation has been confirmed by other studies, but there is as yet little evidence that duration of steroid treatment contributes to altering incidence in the same degree.

Behavioral sequelae to single doses of steroids have been reported, while many individuals may be maintained on high doses for extended periods of time without significant alteration in mentation or mood.\textsuperscript{26} It has been suggested that alternate-day dosing may decrease the incidence and severity of side effects, including behavioral change, but Sharfstein and colleagues\textsuperscript{27} described three patients who developed apparent rapid mood cycling on a regimen of 50 mg to 80 mg of prednisone every other day. These subjects exhibited agitation, impulsivity, irritability, and psychomotor agitation on the day in which the medication was given, and lassitude, memory impairment, social withdrawal, and depression on the subsequent day of no therapy. In each case, as the prednisone dose was tapered, the affective symptomatology remitted.

The use of more focal, parenteral means of steroid administration, as in nasal sprays, would seemingly decrease the risk of behavioral pathology, but isolated case reports are suggestive of possible risk.\textsuperscript{28} Newer steroid compounds, such as deflazacort, which does not cross the blood-brain barrier as readily, would similarly seem to be less likely to produce a change in mental status, but controlled studies documenting this are yet to be conducted.

The elapsed time on steroid treatment before psychiatric symptoms are precipitated varies widely, from an almost immediate presentation to as long as several months. One integrated review of the literature indicates a median onset of approximately 11 days, with over 60% of cases noted in the first two weeks
of treatment. Earlier investigations for the most part emphasized an even earlier onset of from three to six days. TREATMENT-RELATED ISSUES

Even when psychiatric symptoms develop, they are usually largely reversible with a reduction in dosage or discontinuation of the specific steroid. Several early reports commented on a “steroid withdrawal syndrome” that develops in a minority of patients and that may be more likely following abrupt steroid withdrawal. The syndrome typically lasts two to eight weeks and resolves spontaneously, but is occasionally more persistent and may require somatic treatment. Symptoms that have been reported include depression, lassitude, anhedonia, a sense of emptiness and depersonalization, “haziness,” “fuzziness,” fatigue, loss of energy, anorexia, confusion, disorientation, impaired memory, and difficulty maintaining sequential thinking. The risk of suicide may also be increased following steroid withdrawal.

In general, there are no long-term adverse sequelae to brief courses of steroid treatment, although one of the patients described by Sharfstein continued to exhibit an incapacitating, disabling dementia even after his prednisone taper, while in another reported case a woman developed persistent bipolar illness after only a single course of corticosteroid treatment. Too rapid a tapering of dose is undesirable, as it may result in an increase in anxiety and depression, in addition to a recrudescence of the underlying disease process.

Even when no objective evidence of significant adrenal suppression is evident, physical as well as psychological dependence on corticosteroids may exist and impede medical management. In a number of the published cases, patients have steadily increased their self-administration of the prescribed drug in an attempt to overcome tolerance to the initial euphoria, sometimes to the point of inducing a frank Cushingoid status. The behavioral changes noted are similar to those already described, although because of the high dosages and long durations sometimes achieved, quite dramatic courses can occur. In one remarkable report involving five years of self-medication with prednisone, an individual developed a severe rapid cycling mood disturbance that transformed over time into a fugue-like state, with adoption of a second identity and commission of an apparently irrational crime.

If the steroid taper cannot be achieved expeditiously enough, or if the behavioral pathology is too severe, adjunctive psychopharmacologic intervention may be necessary. In the management of psychosis, treatment with neuroleptics, either traditional phenothiazines or haloperidol, has been associated with prompt therapeutic benefit. Electroconvulsive therapy has also been used occasionally in severe cases of mania or depression.

Interestingly, although depressive symptoms are often paramount, tricyclic antidepressants may exacerbate symptomatology, inducing visual and auditory hallucinations. Whether the mechanism involved is similar to the deterioration sometimes noted when antidepressants are given to patients with a bipolar mixed diagnosis, or whether it simply reflects steroid alteration of tricyclic blood level, is unknown.

In the rare case when a “pure” depression is present (i.e., not in the context of delirium, a “mixed” state, or psychosis), antidepressants may possibly be efficacious. A few investigators have suggested that lithium carbonate possesses specifically unique benefits in the treatment and prophylaxis of steroid-induced psychosis. In one study involving multiple sclerosis patients, Falk et al found that patients who had been pretreated with lithium showed no adverse behavioral side effects to steroid medication, while 14% of those given placebo developed psychotic symptoms when treated with steroids. Additional clinical case reports and one animal study have followed. Lithium has been shown to inhibit endogenous pituitary-adrenal metabolism, and it is possible that it modulates the physiologic effects of pharmacologically administered corticosteroids in a similar fashion.

POSSIBLE BASIC MECHANISMS

Over the past 20 years it has become clear that steroid compounds not only regulate traditional endocrine activities, but also are integrally involved in the function of the central nervous system, possessing organizational as well as activational effects that are mediated both genomically and nongenomically. In the former case, corticosteroids enhance transcription through direct binding to cytoplasmic and cell nuclei receptors and induce a confor-
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...ational change that alters DNA binding. Corticosteroids also affect the excitability of neuronal networks, particularly in the hippocampus, where the highest density of glucocorticoid receptor sites has been observed. There is increasing evidence that extended exposure to corticosteroids may have a neurotoxic effect on hippocampal neurons, possibly through an inhibition of glucose uptake and that dysregulation of corticosteroid metabolism serves as the final common pathway through which the effects of aging, stress, and hypoxic insult result in neuronal loss in this region of brain.

Animal studies have shown independently that glucocorticoids can have a pharmacologic action across myriad neurotransmitter and neuropeptide systems. Glucocorticoid administration, for example, may alter central dopamine, noradrenergic, serotonergic, cholinergic, and gabergic activity, as well as second messenger pathways. Corticosteroids also have significant effects on electrolyte function, in the direction of inducing a hypokalemic alkalosis, and are significant modulators of immune system response as well.

On a more organismic level, pharmacologic administration of corticosteroids can alter animal performance in a variety of paradigms thought to be analogous to human anxiety and depression; in humans, specific alterations in attention and memory, sleep, and EEG have been reported, in addition to mood change. Which, if any, of these cellular or physiologic actions of corticosteroids is directly integral to the expression of behavior remains unanswered, as does the central question of whether the effects are direct or indirect. Even corticosteroid suppression of immune system response may be of relevance, given recent data indicating that disturbance in cytokine regulation may itself be associated with mood change.

Over the past 10 years, we have conducted several prospective studies aimed at elucidating the mechanisms by which exogenously administered corticosteroids may alter behavior. In our first studies, intact rats were chronically administered corticosterone, and behavioral and biochemical changes were jointly assessed. These animals demonstrated significant increases in locomotor activity and in caudate homovanillic acid (HVA) level and a near-significant increase in caudate 5-HIAA level, suggesting increased release of dopamine and serotonin.

Rothschild et al. observed that dexamethasone significantly increased dopamine levels in rat brain. These biochemical findings may relate to the clinical observations that neuroleptics are often effective in treating steroid psychosis, whereas tricyclic antidepressants, which increase intrasynaptic levels of norepinephrine and serotonin, may rapidly aggravate such conditions. In a recent replication study, we noted that pretreatment of rats with lithium carbonate (which may prevent the development of steroid psychosis in humans) significantly attenuated both the behavioral and biochemical changes seen with corticosterone alone.

Consistent with a dopamine-stimulating effect of corticosteroids, we and others have also reported that dexamethasone, acutely administered to normal volunteers, significantly increased plasma levels of dopamine or HVA. Such findings may relate to vulnerability to experiencing psychotic reactions with corticosteroid treatment and to reported amphetamine-like reactions to acutely administered dexamethasone in certain patients.

In an effort to more closely model clinical conditions in which steroid psychosis may develop, we administered prednisone, 80 mg per day for five days, in a double-blind manner to 12 medically healthy volunteers. In accord with the literature reviewed above, no consistent behavioral changes were observed. Seventy-five percent of the volunteers, however, exhibited mild affective (e.g., depression or elation of mood, irritability), cognitive, or somatic (e.g., decreased sleep, restlessness) symptoms. In addition, decreases in levels of several behaviorally active central neurotransmitter and neuropeptide substances were noted, i.e., norepinephrine, ACTH, β-endorphin, and somatostatin. Further, significant slowing of brain electroencephalographic activity (similar to that reported by Hoefer and Glaser with ACTH and by Hall et al. with corticosteroids) was observed in the volunteers. More research will be needed to determine if such neurochemical and electrophysiological changes are directly related to the behavioral findings.

One aspect of behavioral change that may be particularly problematic for patients receiving corticosteroid treatment is cognitive difficulty, manifest as diminished concentration and memory, and, in extreme cases, as a dementia-like syndrome. In our acute dexamethasone and subchronic prednisone
studies in healthy volunteers, we noted significant, albeit mild, deterioration in verbal free recall and recognition memory. An increased susceptibility to intrusion, or commission, errors was particularly evident. In the case of the subchronic prednisone study, memory performance returned to baseline levels after prednisone was discontinued. Interestingly, these cognitive changes were phenomenologically similar to those observed in hypercortisolemic depressed patients. The biological underpinnings of such changes are the subject of further study.

REFERENCES