Psychological and Psychiatric Sequelae of Steroid Use in Hematology Treatments: A Review of the Literature.

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ABSTRACT

There is considerable evidence that corticosteroid treatments are frequently associated with severe emotional and even psychiatric disturbances. Since their introduction as therapeutic agents, corticosteroids have been associated with symptoms ranging from mood disturbances to (florid) psychosis. In consideration of the centrality of steroid use in hematology, the expectation is that there should be extensive literature on the psychological and psychiatric interface with steroids in the treatment of these diagnostic groups. To date, however, although the emotional impact of corticosteroid use is reported in a wide range of diagnostic disorders there has been scant attention to this phenomenon in relation to treatment for hematological malignancies. The lack of research insights into this area has left a vacuum for clinical care and psychosocial support. More research needs to be done to address this imbalance, to achieve the optimum outcome for hematology patients and their families. This review provides a starting point by outlining the present literature on the psychological and psychiatric impact of steroid use.

Keywords: *steroids; psychiatry; psychology; psychosocial*

INTRODUCTION

There is considerable evidence that corticosteroid treatments are frequently associated with severe emotional and even psychiatric disturbances (Hong et al., 2006). Indeed, reports of corticosteroid-induced adverse psychiatric effects began to appear in the literature soon after the introduction of these medications in the 1950s (Patten & Neutel, 2000). Since their introduction as therapeutic agents, corticosteroids have been associated with psychiatric symptoms ranging from mood disturbances to (florid) psychosis (Ruiz et al., 2002).

Typical sequelae from the use of corticosteroids can include symptoms such as insomnia, euphoric moods, mood disorders (with depressive, manic and mixed features),

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mania and visual hallucinations (Hong et al., 2006; Naber, Sand & Heigl, 1996; Patten & Neutel, 2000), psychotic disorders and delirium (Patten & Neutel, 2000), severe depression, irritability, violence, (Beshay & Pumariega, 1998), neuropsychological deficits and psychotic states (Naber, Sand & Heigl, 1996). Although documented as uncommon, psychosis is a well-recognised complication of short-term corticosteroid administration (Alisky, 2006; Koh et al., 2002; Hong et al., 2006). For many decades, suicide has been associated with the corticosteroid psychosis (Bräunig, Bleistein & Rao, 1989; Wolkowitz, 1990).

Although generally recorded as an infrequent event, there is some evidence that psychiatric sequelae of corticosteroid therapy are much more frequently encountered than is generally believed (Kostic & Levic, 1989). The strong recommendation in the literature is that high doses of steroids should be used cautiously due to the possibility of psychotic side reactions (Koh et al., 2002).

STEROID USE IN HEMATOLOGY

The term steroid denotes a group of various types of chemical compounds, most commonly hormones. Every steroid possesses a five-ring nucleus to its structure (Williams & Dluhy, 2006). One of the key physiologic features of steroids is their lipid solubility (Guyton & Hall, 2000). As such, they have the ability to enter cells where chemical receptors bind with steroids resulting in the altered, steroid induced, activity of that cell (Hardman & Limbird, 2001).

Steroids are produced and secreted by the adrenal cortex, gonads (ovaries and testes) and the placenta (Guyton & Hall, 2000). The production of a particular type of steroid by the adrenal cortex is of key relevance in hematology oncology. The adrenal cortex produces three groups of steroids: glucocorticoids, mineralcorticoids and androgens (Williams & Dluhy, 2006). Glucocorticoids, like other steroids, interact with cells resulting in altered production of proteins by the affected cell.

Glucocorticoids act to alter metabolic and immune functions of cells (Estrada 2006; Williams & Dluhy, 2006; Hardman & Limbird, 2001). It is these properties that have lead to the use of glucocorticoid medications within haemotologic chemotherapeutic regimes. Lymphoid malignancies, in particular, are susceptible to the actions of glucocorticoids (Hardman & Limbird, 2001). These steroids significantly reduce the number of lymphocytes in the body due to their ability to decrease gene transcription (Hardman & Limbird, 2001) and to induce cell lysis by cell-programmed death in some lymphoid tissue (Estrada 2006; Hardman & Limbird, 2001). The rationale behind the use of glucocorticoids extends further due to their ability to reduce nausea and vomiting, swelling associated with malignancy, inflammation and hypersensitivity to some chemotherapeutic agents (Estrada 2006). Commonly used glucocorticoids in hematology-oncology include dexamethasone and prednisone. Dexamethasone and prednisone both inhibit the recruitment of inflammatory cells and stimulate the production of enzymes that also inhibit inflammation (Estrada 2006). The use of both drugs has been associated with psychiatric side effects, amongst many other multi-system and metabolic consequences (Estrada 2006).

There are numerous regimes for the treatment of the various hematological malignancies in which glucocorticoids are utilised. Frequent combination chemotherapy regimes include CHOP (cyclophosphamide, hydroxydaunomycin (doxorubicin), Oncovin (vincristine), and prednisone) and CVP (cyclophosphamide, vincristine, and prednisone) (Estrada 2006). Cyclophosphamide, doxorubicin and vincristine are cytotoxic medications that, via multiple mechanisms, inhibit cell function, including growth and division, in normal and malignant cells (Estrada 2006). There are, of course, multiple other chemotherapy schedules involving cytotoxic agents, immunomodulators and corticosteroids that can be used as alternatives or as first line treatments. For example, multiple myeloma is commonly treated with regimes M and P (melphalan and prednisone) or VAD (vincristine, Adriamycin (doxorubicin) and dexamethasone) (Rakel and Bope, 2001). Treatment courses for Hodgkin's Lymphoma also differ. Common regimes include MOPP (Mustargen (mechlorethamine), Oncovin (vincristine), procarbazine, and prednisone), ABVD (Adriamycin, bleomycin, vinblastine, dacarbazine) and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone). Regime choice is based on the type of malignancy, patient characteristics, response to treatment and the patient's aims with regard to treatment of the illness.

Variations to treatment courses also include differing doses of the numerous medications, including steroid doses. The high doses of glucocorticoids used to treat lymphoid and myelogenous malignancies have been the subject of multiple clinical queries and studies. It is interesting to note that the very use of corticosteroids in solid cancers, on the other hand, is controversial as there is significant evidence to indicate that glucocorticoids inhibit tumour cell apoptosis and the body's immune response, both of which are essential for the treatment of solid tumours and the prevention of metastases. Within hematological malignancies the situation is the opposite. There is significant evidence that not only do glucocorticoids effectively improve treatment and

outcome, but moreover, high doses have been demonstrated to enhance these results further.

LACK OF LITERATURE ON PSYCHIATRIC ASPECTS OF STEROID USE IN HEMATOLOGY

Liaison psychiatry, the sub-specialty of psychiatry that is involved in the treatment of mental disorders in medical units, has taken the lead role in managing psychiatric complications of steroid use, and reporting on its effects in the scientific literature. In consideration of the centrality of steroid use in hematology, the expectation is that there should be an extensive literature on the psychological and psychiatric interface with steroids in the treatment of these diagnostic groups. To date, however, although the emotional impact of corticosteroid use is reported in a wide range of diagnostic disorders there has been scant attention to this phenomenon in relation to treatment for hematological malignancies. The present literature on the psychological and psychiatric dimensions of corticosteroid use covers a plethora of treatment regimens from a diversity of diagnostic groups such as asthma (Koh et al., 2002), systemic lupus erythematosus (Mok et al., 2006; Chau & Mok 2003), myocardial infarction (Alisky, 2006); orthognathic surgery (Fleming, 2005), autoimmune disorders (Weiss, 2005); severe acute respiratory syndrome (Sheng, 2005), dementia (Sacks & Shulman, 2005), Churg-Strauss syndrome (Ismail & Lyster, 2002), and inflammatory bowel disease (Buchman 2001). In addition, there is increasing evidence of adverse psychiatric effect of the use of steroids in subpopulations such as athletes, bodybuilders, and young people where it is used for gains in strength and muscle mass (Trenton & Currier,2005). Aggression and violence, mania, dependence and less frequently psychosis and suicide are reported as serious psychiatric symptoms associated with steroid abuse in such groups (Trenton & Currier,2005).

In specialties other than hematology, liaison psychiatrists have noted a spectrum of psychiatric complications from steroid use. Acutely, a "steroid psychosis" syndrome has been described ranging from a subclinical euphoria, encompassing psychotic mania, to the triggering of an autonomous bipolar affective disorder (Wada et al, 2000). The treatment of this acute syndrome may encompass steroid dose reduction or cessation, the addition of anti-psychotic medication as well as mood-stabilising medication, usually lithium. Observations on longer-term steroid exposure suggest that this can be associated with a depression (Clark et al, 1953). This is usually treated with steroid dose reduction and antidepressant medication. These treatment strategies are experiential and extrapolated from other fields of psychiatry: the scant evidence base for these treatments in steroid reactions is discussed in greater detail later in this review.

With only one exception of findings from a paediatric leukaemia study (McGrath & Pitcher 2002), there have been no exploratory empirical findings on this important topic available in the literature on hematology. The three articles published over the last two decades on hematological malignancies and the psychological/psychiatric sequelae of steroid use have all been case studies. The first case study is of a patient undergoing allogeneic bone marrow transplantation who demonstrated psychiatric symptoms from steroid use including hallucination, persecution complex, auditory hallucination and sleeplessness (Nakamae et al., 2002). The patient's mental condition was kept stable with antidepressant drugs and tranquilizers, although minor changes in the combination of drugs were required to treat transient exacerbation of psychosis after a short period at home. The authors (Nakamae et al., 2002) concluded that non-myeloablative stem cell transplantation is a useful treatment for patients with hematological malignancy complicated with psychiatric disorders. The second case is of a 15-year-old girl with acute lymphoblastic leukemia who developed a severe steroid-induced depression, which was rapidly responsive to ECT (Sutor, Wells & Rummans, 1996). The third case is of two adolescents with acute lymphoblastic leukemia developed acute psychotic episodes shortly after induction therapy, which included prednisone, was begun. Symptoms included regressive behavior, incontinence, fluctuating levels of activity, and delusions. Both patients regained normal mental status after a number of weeks. Treatment included tapering of steroid dosage, introduction of a highly structured environment, and early use of chlorpromazine. Psychosis persisted beyond discontinuation of steroid therapy, but both patients subsequently received steroids after return of normal mentation, and in neither did psychosis recur (Ducore et al., 1983). The case studies affirm the presence of the distressing psychological and psychiatric sequelae in hematology and begin to posit factors related to cause and response.

Seminal empirical research documenting the psycho-social impact of steroid use in hematology was conducted as part of a five year longitudinal study in paediatric leukaemia (McGrath & Pitcher 2002). The findings focus on the distressing emotional sequelae of the steroid dexamethasone which is used in paediatric acute lymphoblastic leukaemia protocols. The results indicate that it is the emotional rather than the physical side effects of the steroid that are most distressing to both the child patient and their family. The most disturbing psychological problems reported related to aggressive, confused, depressive, dependent, withdrawn and lethargic psychological states. The children's emotional

condition was exacerbated by the fact that the children were up all night eating and did not sleep. All of this was happening at a time when all family members were exhausted from the prolonged treatment process. The strategies used for coping with the impact of the steroid ranged from seeking anti-depressants for the children, engaging in normalizing talk with other parents, or turning to professional counseling support.

Apart from the findings from the paediatric longitudinal study there is a lack of empirical research on the wide range of issues associated with the psychiatric sequelae of steroid use in hematology. The absence of information leaves a wide variety of questions unanswered and creates a vacuum for clinical practice. This situation is of particular concern in view of the fact that steroids use is central to hematology treatments.

MANAGING THE SIDE EFFECTS – INSIGHTS FROM THE NON-HEMATOLOGY LITERATURE

In view of the absence of information from studies in hematology a starting point for beginning to understand how to respond to the clinical challenge has to be from the literature on the topic in relation to other diagnostic groups. However, it is important to note that it is recorded in the literature that only minimal data are available on the treatment of corticosteroid-induced psychiatric symptoms (Brown et al., 2004). The literature concerned with the prevention and management of corticosteroid-induced psychiatric adverse effects is rudimentary, and contains large amounts of clinical anecdotes. Due to the lack of formal and validated studies, these reports currently provide the only available direction to clinicians in managing these problems (Ruiz et al., 2002).

Strategies for managing side effects can range from discontinuation to reduction of corticosteroid administration (Hong et al., 2006; Mok et al., 2006; Weiss, 2005). Indeed, it is noted that in respect to the likelihood of significant side effects, initial high doses should always be tapered to the lowest possible effective dose (Reinhart, 2005).

There are some suggestions of the benefits of psychopharmacologic intervention. Olanzapine, an anti-psychotic agent with mood-stabilising properties, is recorded as well tolerated and appears to be useful for mood disturbances associated with corticosteroid therapy (Brown et al., 2004). Pilot data suggest that lamotrigine, a mood-stabiliser, may be associated with improved mood and performance on cognitive tasks in steroid-treated patients (Brown et al., 2003). However, it is important to note that larger controlled trials are needed to confirm these preliminary findings (Brown et al., 2003). Preliminary finding from one case study indicates a significant improvement with low doses of an antidepressant Venlafaxine; however this is seen as open for further discussion and study (Ismail & Lyster, 2002). Sertraline, another antidepressant, was used to treat depressive as well as psychotic symptoms without the use of anti-psychotics (Beshay & Pumariega, 1998). This successful treatment of steroid-induced mood disorder and psychosis with a serotonin reuptake inhibitor is consistent with the literature describing a decrease in central and peripheral serotonin secretion due to steroids, as well as a possible relationship between mood and psychotic symptoms and low cerebrospinal fluid serotonin levels (Beshay & Pumariega, 1998). Sirois (2003) reports that haloperidol remains a widely used neuroleptic to control most psychotic reactions to steroid therapy because its versatile mode of administration makes it easier to adjust to both acute and subacute clinical situations.

Management, including psychopharmacologic intervention, should be indicated by a consideration of the underlying illnesses and psychosocial stressors (Wada et al., 2000). Education and support also appears to be important, and perhaps neglected (Patten & Neutel, 2000). Some of the psychiatric adverse effects of corticosteroids are mild, and not necessarily clinically significant (Patten & Neutel, 2000).

RISK OR CAUSATIVE FACTORS

While certain clinical groups may be at greater risk of corticosteroid-induced adverse psychiatric effects, corticosteroid-induced psychiatric toxicity is recorded as being remarkably unpredictable (Patten & Neutel, 2000). There is considerable controversy in the literature about causative factors contributing to psychological and psychiatric sequelae of corticosteroid use.

In some studies, factors identified as predictive for anxiety-depression, psychosis or behavioural symptoms include steroid toxicity caused through high dosage of pulse steroid during hospitalization (Lee et al., 2004; Sheng, 2005), with symptoms appearing to be dose dependent and generally begin during the first few weeks of treatment (Brown & Suppes, 1998). The likelihood of psychiatric morbidity seem to correlate with the dosage applied (Kostic & Levic, 1989). Although not usually associated with low dose of corticosteroid (Hong et al., 2006), the long-term use of corticosteroids is recorded as more problematic creating a milieu for the potential for serious and irreversible problems (Buchman 2001). Brown and Suppes (1998) record depressive symptoms associated with long term use and

mania with acute corticosteroid therapy. Receiving tapering steroid dose, also appeared to be a risk factor for attempting suicide (Matsukawa et al., 1994). However, other studies indicate that dosage is unpredictable of such problems (Chau & Mok 2003). Some authors (Wysenbeck et al., 1990; Wolhein1984) have reported that there are not more frequent psychiatric complications with intravenous high dose corticosteroid pulse therapy.

Another controversial area is that of predisposition to morbidity through a family history of psychiatric illness. Some studies indicate higher rates of family history of psychiatric illness (Brown et al., 2002; Lee et al., 2004) or a history of anxiety disorders (Chau & Mok 2003) or posttraumatic stress disorder (Brown et al., 2002). However, there is also considerable contradictory evidence that individuals can experience steroid psychosis without a previous history of psychiatric problems (Lee, Lin & Huang, 2001). Patten (2000) reports that there are no studies providing clear evidence that a previous history of psychiatric disorder increases the risk of psychiatric adverse effects of steroid treatment. Wada and associates' (2000) work on nine patients with recurrent corticosteroid-induced mood disorders demonstrated that none had previous psychiatric episodes, all had their first episode as a result of steroid treatment, and none had a family history of psychiatric disorder.

Psychosocial stressors are also recorded as key factors (Lee et al., 2004). A Korean case study points to family emotional stress as a causative factor exacerbating the psychotic reaction from steroid administration (Koh et al., 2002). Disease and symptom severity, along with social factors (Sheng, 2005) are recorded as possible risk factors.

THE NEED FOR FURTHER RESEARCH

The one area of agreement by authors on this topic is the need for further research. As recently as five years ago is was noted that no study has focused specifically on recurrent corticosteroid-induced mood disorders and considered long-term outcome and treatment strategies (Wada et al., 2000). As Serois (2003) points out, there are very few leads in the literature to identify individuals at risk for steroid psychosis. Although there is consensus in the literature that corticosteroids may induce psychotic disorders, the published evidence documenting the psychiatric sequelae is scant, consisting only of case reports (Ruiz et al., 2002). Risk factors for the development of mood instability or psychosis are not known (Brown & Suppes, 1998). The potential risks of multiple courses of steroid treatment have not been explored (Sirois, 2003). To date, only a few studies have specifically addressed behaviour as well as cognitive functioning in patients under steroid treatment (Naber, Sand & Heigl, 1996). The literature regarding prevention and treatment of corticosteroid-induced adverse psychiatric effects is poorly developed (Patten & Neutel, 2000). Pattan and Neutel (2000) note that the literature remains surprisingly undeveloped from a pharmacoepidemiological perspective, consisting largely of case reports and case series. Few studies have used well-recognized measures of symptoms or clearly defined diagnostic criteria to characterize such mood changes. Early studies relied on informal classification and measurement procedures and tended to utilise nonspecific descriptive terminology (such as 'steroid psychosis') (Patten & Neutel, 2000).

The limited data available suggest that symptoms of hypomania, mania, depression, and psychosis are common during steroid therapy. Early calls in the literature complaining that there is no satisfactory model with which to understand steroid-induced mental disorder have not been heeded (Mullen & Romans-Clarkson, 1993). The lack of research is particularly worrying in relation to hematological malignancies in view of the fact that steroid use is at the core of most treatment protocols.

RECOMMENDATIONS

The lack of research available to inform evidence based hematological clinical practice on this topic is a grave concern. At present there is no consensus on cause, effect or even appropriate therapeutic response to such serious clinical dilemmas as psychosis from the steroids used in hematological treatments. A beginning needs to be made to explore through research the plethora of issues associated with the hematology patient's psychological and psychiatric experience of steroid use. The following list starts the process by providing examples of the type of research questions that need exploring:

- What is the prevalence of psychological and psychiatric morbidity from steroid use in hematology;
- What are the risk and causative factors;
- Does type, dose or duration of administration of steroid impact on morbidity;
- Is a history of psychiatric illness a relevant factor;
- What part do psycho-social stressors play;
- What is the appropriate therapeutic response;
- What are the benefits of psychopharmacologic interventions.

At this early stage of the research cycle open-ended, exploratory, qualitative methodologies are required to begin to tease out the multiplicity of factors involved. As Sirois (2003) points out, clinical trials can only address simple hypothesis-driven questions to be addressed one by one while

what is required at present is 'to document unsettled clinical questions and account for many confounding variable such as previous corticosteroid courses, general clinical status, concurrent administration of other drugs, premorbid information about personality' (Sirois, 2003:32). This is an area where there is much work to be done.

CONCLUSION

For too long, the psychosocial dimension of the use of steroids in hematology has been neglected topic. The lack of research insights in this area creates a vacuum for clinical care and psychosocial support. It is the contention of the authors of this review that this dimension is vital to the success of treatments for hematological malignancies. More research needs to be done to address this imbalance, to achieve the optimum outcome for hematology patients and their families.

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