Asthma Severity, Psychiatric Morbidity, and Quality of Life: Correlation with Inhaled Corticosteroid Dose

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ABSTRACT

Objectives. Psychiatric phenomena in asthma has been debated for some time. Inhaled corticosteroids (ICS) are a significant part of treatment. We attempted to quantify the prevalence of psychiatric morbidity relative to asthma severity, quality of life (QOL), and ICS dose. Data Sources. Fifty asthmatic patients (18 ≥ X ≤ 75 years) on ICS, attending an urban clinic had asthma and ICS dose stratified by symptom severity and preparation potency. Peak flow and forced expiratory volume in 1 second (FEV1) were measured. Patients completed general QOL and disease-specific QOL questionnaires, along with psychiatric rating scales. Results. Patients (n = 50) clustered in the 40–59 year range (n = 27, 54%) and were predominantly female (n = 44, 88%) Hispanics (n = 30, 60%), with mild-moderate asthma (n = 18, 36%) and on low-dose ICS (n = 22, 44%). FEV1 ranged from 32 to 123 (mean 76.98, SE 3.01). Peak flow ranged from 210 to 590 (mean 407.83, SE 13.24). Prevalence of anxiety and depressive symptoms were higher than expected (Kendall’s tau-c, n = 50, P < .01). Independently, high ICS dose and asthma severity correlated directly with all measures of psychiatric morbidity (Pearson’s r 0.781, P < .01). High ICS dose correlated inversely with SF-36 Mental Component Scale (Pearson’s r 0.681, P < .01) and directly with FEV1 and peak flow when age/sex adjusted (Spearman’s rho: 0.660, P < .001). Conclusions. Psychiatric morbidity is more prevalent in this population and impacts negatively on QOL.
Use of high-dose ICS benefited pulmonary function and “physical” QOL, yet may have negatively affected patients’ mental well-being. Longitudinal follow-up, extension of sample size, and better study control would allow closer approximation of possible negative associations with ICS.

Key Words: Asthma; Psychiatric morbidity; Quality of life; Inhaled corticosteroids.

INTRODUCTION

Asthma is a chronic, reversible, inflammatory disease of the airways, whose incidence is increasing worldwide (1). It affects 17 million people in the United States (2). Asthmatics have more than 100 million days of restricted activity and 470,000 hospitalizations annually, with 49% of children and 25% of adults reporting missing school or work (3). Asthma can impose restrictions on the physical, emotional, and social life of a patient, leading to impaired coping capacity and an impact on their careers and quality of life (QOL) (4). Forty-eight percent of patients in one survey reported that asthma limits their ability to take part in sports or recreation, 36% reported it limits their normal physical exertion, 25% reported it interferes with their social activities (3) and almost 30% of patients reported being awakened at least once a week (3).

Goals of treatment include: (1) no missed school or work; (2) no sleep disruption; (3) maintenance of normal activity; (4) no (or minimal) need for emergency department visits/hospitalizations; (5) Normal or near normal lung function (3). These goals are for the prevention of mortality, reduction in future morbidity, and improvement in quality of life. Clinical measures of asthma severity and control provide the status of airways, but they reveal little about the functional impairments and impact on psychosocial functioning.

QUALITY OF LIFE IN ASTHMA

QOL includes a large set of physical and psychological characteristics assessing the problem in the social context of life style (6). Health-related QOL (HRQOL) is defined as “the functional effects of an illness and its therapy, as perceived by the patient” (7). Clinical intervention in any chronic illness should result in improvement of QOL. The assessment of HRQOL evaluates its beneficial effect on health status as well as its cost effectiveness (an important component of health care, and, increasingly, an outcome measure in the treatment of chronic illnesses).

Several studies have examined QOL in asthma. Patients with severe asthma tend to have lower general QOL scores than to patients with milder disease (8). There is evidence that correlation between clinical measures and how patients feel and function in daily activities are only weak to moderate (9–12). During a 1-year treatment with budesonide, it was observed by Juniper et al. that improvement in QOL correlated with improvement in clinical indices, but patterns within individuals varied (13). There was poor correlation between change in clinical indices and asthma specific quality of life (AQOL). In another study by Constant et al., significant improvement in lung function with ICS did not improve the QOL of the patient (14).

Because of their beneficial effects on lung function and overall morbidity and mortality, inhaled corticosteroids have become the primary long-term controller medication in asthma. The current standard of care in asthma emphasizes inhaled corticosteroids as the primary controller, supplemen-
inted by long-acting inhaled beta-agonists and leukotriene antagonists. Systemic corticosteroids and short-acting inhaled beta-agonists are used for relief of acute exacerbations.

**CORTICOSTEROIDS IN ASTHMA: SIDE EFFECTS AND PSYCHIATRIC SYMPTOMS**

Corticosteroids have been routinely administered to decrease inflammation in a large number of diseases for the last 50 years (15). Though beneficial, these drugs have several side effects when administered systemically. Their effects on the hypothalamic-pituitary-adrenal (HPA) axis, immunity, glucose metabolism, growth in children, cataract development, and bone mineral density are well-established (16–24). Several studies have also reported oral/parenteral-induced adverse psychiatric effects (25–35). These include mood disturbances, psychosis, confusion, and memory problems. The data published so far suggest that patients on long-term oral/parenteral corticosteroid treatment may have depressive symptoms, whereas acute steroid therapy may, primarily, be associated with mania (15). The risk for developing psychiatric symptoms appears to increase with higher corticosteroid dose (25,29,34). Some studies found no psychiatric symptoms with low doses of oral/systemic corticosteroids, and others found a dose-dependent relation (34,35). Dose of corticosteroids administered is usually adjusted to the severity of asthma, as measured by clinical/pulmonary parameters.

Since their introduction in the 1970s, ICS have become the mainstay of treatment for asthma (36). First administered to patients who were dependent on oral corticosteroid therapy, they were found effective in reducing or eliminating the need for systemic corticosteroids, while maintaining symptom control and lung function with a larger margin of safety for any level of therapeutic efficacy, than systemic corticosteroids (37). Clinical indications for ICS therapy in asthma have broadened considerably over the past 20 years and recommendations extend to mild persistent asthma, as per recent guidelines (38). Meanwhile, the advent of more potent and more concentrated ICS, together with efficient delivery systems, has expanded their therapeutic potential. These changes, and long-term use, have resulted in associated side effects (39).

Concerns over this have been addressed by several published studies on ICS with the discussion of possible systemic side effects (16–24). Cumulative doses of ICS may be an important determinant of effects on the HPA axis (16,17). Wong et al. (23) reported a negative relation between total cumulative dose of ICS and BMD (bone mineral density). In a related study, our results indicated an increased prevalence of BMD loss in postmenopausal women with asthma on ICS, with a linear trend relative to the ICS dose level (24). A large population-based survey found that exposure to ICS increased the prevalence of posterior subcapsular cataract (PSC) about two-fold, and the degree of risk was related to both the current and cumulative life-time dosages (21). On the other hand, in a cross-sectional survey of asthmatic adults and children treated for long periods with ICS, none of the measures of ICS usage correlated significantly with PSC (22).

Van Schoor et al. (18) did not find any humoral immunosupression with high doses of budesonide. In a recent study, it was concluded that children with asthma who have received long-term treatment with budesonide attain normal height, despite contrary anecdotal evidence (20).

Notwithstanding, no study has examined the adverse psychiatric side effects of ICS. Only a few case reports of psychiatric phenomenon with ICS have appeared in the literature (40–44). These rare case reports, compared with ICS widespread use, suggests that severe reactions are uncommon, but do not exclude the possible effects.

**PURPOSE OF THE STUDY**

Interactions between asthma severity, dosage of ICS, the occurrence of mood changes, and their impact on the QOL of asthmatics are complex and largely unclear. In our study, we attempted to quantify the prevalence of certain indicators of psychiatric morbidity and QOL relative to asthma severity and ICS dose in an urban outpatient population.

**METHODS**

Subjects were a consecutive series of 50 patients seen in the outpatient clinic of the Department of Allergy and Immunology of the Long Island College Hospital, New York City, during August and September 1999. Inclusion criteria were: diagnosis of “asthma” by clinical measure (history and physical) and spirometry. Patients were excluded if they were less than 18 years of age or older than 75.
Patients were stratified by asthma symptom severity to one of the following: mild, mild to moderate, moderate, moderate to severe, and severe. Patients were also stratified by ICS potency: none, low, medium, and high (38). (Table 1).

QOL Data

Each patient was administered a semistructured interview by the same interviewer, including self-rated general QOL, and disease-specific QOL questionnaires. The general QOL questionnaire was the Short Form-36 Item (SF-36) (45). The AQOL questionnaire was the disease-specific instrument used (46).

Psychometric Data

Patients also completed self-rated questionnaires for depression (Beck Depression Inventory), anxiety and for observed-compulsive traits traits (Goodman OCD inventory). The patients were administered the physician-rated Hamilton Depression Scale (HAMD), performed by the same interviewer.

Collection of psychometric and quality of life data was incorporated into the routine examination of these patients and the information collected was integrated into their record. No interventions were performed on the patients. The interviewing physician sequentially assigned the patients a unique, randomly generated number, and all identifying data was stripped from the measures. Treatment and examination protocols were not determined by psychometric outcomes; therefore informed consent was not required prior to inclusion in the study. Although psychometric outcomes never determined treatment or exam protocols, algorithms were in place so the interviewing clinician could readily identify a patient during screening and refer for acute psychiatric evaluation and treatment if necessary (never required).

Study Design and Statistical Analysis

A prestudy design proposal using currently accepted population proportions for various psychiatric symptoms was used to establish the necessary number of patients needed for a predetermined power as per standardized methods for ascertaining statistical differences in population proportions (47). Accepted sources have extrapolated the following conservative estimates of lifetime prevalence: mood disorders (in the general population) 5–25%; minor depression 5%; major depression 15%; and major depression in primary care 15% (48). The accepted prevalence for anxiety disorders (in the general population): depression-anxiety 1%; depression-anxiety in primary care 50%; and obsessive-compulsive disorder 3% (48).

To quantify the strength and nature of any relationships between our variables, standard frequency tables and cross-tabulations were created using the data; measures of association were calculated. The ordinal measures of association that we considered were all based on the differences, if any, between the number of concordant pairs and the number of discordant pairs, calculated for all distinct pairs of observations. Because we wanted some of our measures of association to fall within a known range for all tables, we also standardized the differences, so that they fell between −1 and 1, using the standard correction (Kendall’s Tau-c). To calculate correlation coefficients that measured the strength of any linear associations between our variables, the Pearson (using the actual data) and Spearman (a nonparametric alternative using rank values) correlation coefficients were used.

Statview for PowerMacintosh version 5.0.1 (SAS Institute, Inc., Cary, NC) was the statistical software used for the analysis of the data.

RESULTS

The majority of the patients (n = 50) studied clustered in the 40–59 year range (n = 27, 54%) and were

<table>
<thead>
<tr>
<th>Inhaled corticosteroid (mcg)</th>
<th>High dose</th>
<th>Medium dose</th>
<th>Low dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone propionate</td>
<td>&gt; 840</td>
<td>504–840</td>
<td>168–504</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>&gt; 2000</td>
<td>1000–2000</td>
<td>400–1000</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>&gt; 2000</td>
<td>1000–2000</td>
<td>500–1000</td>
</tr>
<tr>
<td>Budesonide</td>
<td>&gt; 600</td>
<td>400–600</td>
<td>200–400</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>&gt; 660</td>
<td>264–660</td>
<td>88–264</td>
</tr>
</tbody>
</table>
predominantly female (n = 44, 88%) Hispanics (n = 30, 60%), with mild-moderate asthma (n = 18, 36%) and on low-dose ICS (n = 22, 44%). FEV\textsubscript{1} ranged from 32 to 123% predicted (mean 76.98, SE 3.01). Peak flow ranged from 210 to 590 L/min (mean 407.83, SE 13.24) (Tables 2 and 3).

The prevalence of anxiety and depressive symptoms in these patients was more than expected (Kendall’s tau-c, n = 50, P < .01) (see Table 3). A population with similar demographics but without asthma was not examined.

Table 2. Race/ethnicity, asthma severity, & ICS doses for 50 patients (6 of whom were male) with asthma.

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black–non-Hispanic</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td>Caucasian–non-Hispanic</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Hispanic</td>
<td>30</td>
<td>60</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Asthma severity</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Mild-moderate</td>
<td>18</td>
<td>36</td>
</tr>
<tr>
<td>Moderate</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Moderate-severe</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Severe</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICS dose</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>Medium dose</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Low dose</td>
<td>22</td>
<td>44</td>
</tr>
<tr>
<td>None</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

Independently, high ICS dose and asthma severity correlated directly with all measures of psychiatric morbidity (Pearson’s r 0.781, P < .01). High ICS dose correlated inversely with SF-36 QOL Mental Component Scale (Pearson’s r 0.681, P < .01). High ICS dose also correlated directly with FEV\textsubscript{1} and peak flow when age/sex adjusted (Spearman’s rho 0.660, P < .001) (see Tables 2 and 3).

Therefore, although high ICS dose was associated with decreased asthma severity, it independently was associated with increased psychiatric morbidity and decreased “mental” QOL. This raises the possibility of a direct negative effect of high ICS dose on these parameters, despite a positive effect on asthma severity.

DISCUSSION

Psychiatric morbidity has previously been associated with asthma. However, its role as cause or effect has not been established. Nor has a direct correlation between psychiatric morbidity and asthma severity been previously observed. We have demonstrated a direct association between these factors in this study. This raises the issue that psychiatric illness may be more a result of negative psychosocial factors that increase based on asthma severity rather than a psychosomatic cause of asthma itself. Further study is necessary to elucidate this relationship.

Adverse psychiatric effects of corticosteroids in various diseases have been the subjects of several
of asthma severity. This raises the issue of a possible negative drug effect and requires further study in well-controlled asthmatics on high-dose ICS.

There are few studies in the literature reporting the effects of ICS on QOL. A 4-year prospective controlled study examined the effects of ICS on QOL of patients with asthma or chronic destructive pulmonary disease (COPD) (14). QOL was assessed by means of the Inventory of Subjective Health and the Nottingham Health Profile. It was reported that beclomethasone dipropionate improved the course of lung function and decreased the severity of symptoms, but did not improve the general well being of asthma or COPD patients. It was suggested that a disease-specific health instrument would have better detected the changes in QOL. However, this lends some support to our findings that high-dose ICS, although positively associated with “physical” QOL in asthma, is negatively associated with “mental” QOL.

In a multicenter randomized controlled study, Juniper et al. (13) studied the long-term effects of budesonide or formoterol on QOL of 470 asthma patients. A disease-specific health instrument, AQOL, was used for assessment. Statistically significant improvement in both QOL and each domain of AQOL was noted during the run-in period when high-dose ICS (budesonide) was used. Mean AQOL scores and the clinical indices had similar pattern, but within individual patients there was poor correlation between change in clinical indices and changes in AQOL scores.

In our study, high-dose ICS correlated directly with clinical indices of asthma control, but an inverse relationship was seen between high-dose ICS and “mental” QOL. This raises the possibility of a drug effect, because, if no negative effects of ICS on “mental” QOL were present, better asthma control should result in improved overall QOL.

There are many limiting factors to the few conclusions we could draw. The most important of which can be the study design itself. The cross-sectional study is one that, at best, demonstrates possible associations that should be investigated by stronger studies. Another very important limitation was our sample size. In our study design protocol, we had calculated from current population prevalence estimates a need for 175 patients to have significant power so as to extrapolate our results to a larger population (47). Because of study design, we were not able to control for any specific variables (i.e., socioeconomic status or prior psychiatric treatment). We were not
able to examine population samples from different clinics of the same hospital system to see if any concordance existed. In future studies we would like to study cumulative ICS treatment, as well as laboratory correlates such as cortisol, ACTH, and corticotropin-releasing factor (CRF) levels in relation to asthma severity, psychiatric morbidity, and QOL.

**CONCLUSIONS**

Despite these limitations, we have established that psychiatric morbidity is more prevalent in this population of predominantly middle-age, asthmatic, Hispanic females, and is impacting negatively on their QOL. Use of high-dose ICS benefited pulmonary function and “physical” QOL, yet may have had negative effects on mental well-being. Longitudinal follow-up, extension of sample size, and better control of variables would allow closer approximation of possible negative effects of ICS on both physical and psychiatric morbidity as well as QOL. In the meantime, as we proposed in our study of BMD in this population (24), all measures should be taken to lower the dose of ICS in any asthma population to that needed for adequate asthma control. This is best accomplished by the addition of other controller medications such as inhaled long-acting beta-agonists and leukotriene antagonists.

Future studies should continue to focus interest on both the root pathophysiological basis of the increasingly more apparent and intricate mind–body connection, and the impact that treatments, despite, efficacy in specific diseases, may have on our patients overall outcomes and the quality of the lives they lead.

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