

Perioperative Drug Reactions in Cystic Fibrosis Lung Transplant Recipients

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ABSTRACT

Cystic fibrosis (CF) is one of the leading indications for bilateral sequential lung transplantation at the end stage of the disease. The association between cystic fibrosis and an increased predilection to atopic drug reactions is poorly understood. Little current information exists on the potential risk of atopic CF patients in the perioperative transplantation period compared with nonatopic CF patients. This study reviewed whether CF patients with a history of allergic disease who undergo lung transplantation may be at any increased risk for adverse reactions to drugs and blood products given intraoperatively and postoperatively. Our review of the 37 CF patients who underwent lung transplantation between January 1988 to mid 1997, at Stanford University Medical Center indicates for the first time that a history of allergic bronchopulmonary aspergillosis (ABPA) may be a risk factor for adverse drug reactions in the perioperative period, whereas atopy with allergen avoidance does not place the CF patient at any increased risk for a drug reaction. (*Pediatr Asthma Allergy Immunol* 1998;12[2]:147–150.)

INTRODUCTION

CYSTIC FIBROSIS (CF) PATIENTS in the end stage of their disease are often referred for lung transplantation, and this patient population accounts for approximately one third of all bilateral sequential lung transplantations nationwide.⁽¹⁾ CF patients often have a history of atopy, particularly to aeroallergens and antibiotics. This predilection to atopy and an elevation of serum IgE levels is well recognized among this population.⁽²⁾ Another associated allergic disease that is prevalent among approximately 12% of CF patients is allergic bronchopulmonary aspergillosis (ABPA), which is a specific allergic response to *Aspergillus* fungus leading to serum IgE levels >1000 IU/mL.⁽³⁾

The use of antibiotics, especially those used to treat *Pseudomonas* infections, is a potential risk factor for intraoperative and postoperative anaphylactoid reactions. The pathogenesis of anaphylaxis is based on a systemic response resulting from IgE-mediated mast and basophil degranulation. The most common clinical manifestations include urticaria and angioedema.⁽⁴⁾ Non-IgE-related pathways also exist for anaphylactoid reactions that include antigen-antibody formation and activation of the complement system. Many agents can activate the complement system directly, leading to release of mediators that play an important role in the development of an anaphylactoid reaction.⁽⁵⁾ This study evaluated whether CF patients with a

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TABLE 1. PRE-OPERATIVE ATOPY AND POSTOPERATIVE REACTIONS

<i>Postoperative</i>	<i>Preoperative history of atopy</i>
Adverse reaction	3/37
No reaction	10/37

history of allergic disease who undergo lung transplantation may be at increased risk for adverse reactions to drugs, colloid, and blood products given intraoperatively and during the postoperative period.

METHODS

Charts of the 37 CF patients who had undergone bilateral sequential lung or heart-lung transplantation at the Stanford University Medical Center between January 1988 and April 1997 were retrospectively reviewed. Of the 37 patients studied, 17 were men and 20 were women. The mean age at the time of transplantation was 27 years (range 7 to 43 years). Fifteen patients had bilateral sequential lung transplants, whereas 22 patients underwent heart-lung transplantation. All transplant recipients received standard triple immunosuppressive therapy (CSA [cyclosporin], azathioprine, and prednisone) and rat antithymocyte globulin (RATG) during induction.⁽⁶⁾ Antibiotics, typically tobramycin and piperacillin or another selected antipseudomonal regimen, are started on the first day. Of the 37 CF patients who had lung transplantation, 16 had IgE levels measured within 6 months of the transplantation (range 1 to 6 months). The results were expressed as international unit per milliliter (IU/mL), and a value of 100 IU/mL was defined as positive. The histories of all patients (n = 37) were assessed by extensive retrospective chart review. Specifically, the parameters assessed were 1) a history of atopy, as defined by a history of atopic disease, specific preoperative drug reaction, positive radioallergen sorbent (RAST) testing, or hypersensitivity skin test responses to commercial extracts of common aeroallergens; 2) an established history and treatment for ABPA; and 3) a positive respiratory fungal culture on the day of surgery. These preoperative findings were then correlated with the occurrence of any adverse drug, colloid, or blood product atopic or anaphylactic reactions either intraoperatively or in the first 14 days following transplantation. Statistical analysis was by Kendall's correlation and Fisher's exact test was completed. A *p*-value of <0.05 was considered statistically significant.

RESULTS

Our findings indicate that 13 of the 37 CF patients studied had a defined pre-existing history of atopy to drugs, but only 3 had an established history of ABPA. None had fungal colonization or active ABPA at the time of surgery. All three patients with ABPA had a drug reaction in the perioperative period. When the intraoperative and postoperative incidence of drug reactions was compared between the 13 CF patients with

TABLE 2. RISK FACTORS FOR POSTOPERATIVE DRUG REACTIONS

<i>Patient characteristics</i>	<i>p-value</i>
ABPA vs. perioperative drug reactions	0.016
ABPA vs. IgE	0.02
Atopy vs. perioperative drug reaction	ns
IgE vs. RATG reaction	0.04

ABPA, allergic bronchopulmonary aspergillosis; RATG, rat antithymocyte globulin; ns, not significant.

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a history of atopy and those 24 patients with no such history, no significant difference was found (Table 1). Seven patients had a postoperative adverse reaction within the first 14 days following transplantation. The drug reactions were all in response to doses of intravenous antibiotics, and the specific adverse reactions included mild hypotension, facial edema and erythema, rash, pruritis, and chest tightness. There were no reactions to blood or colloidal products.

Specific atopic reactions in temporal relation to the administration of RATG were observed in 4 of the 37 patients. Manifestations included hypotension, rash, or associated respiratory distress. The RATG reaction was mildly associated with an elevated preoperative IgE ($p = 0.04$, $r = 0.53$), but not with a history of ABPA. Two of the seven patients with adverse drug reactions had a RATG reaction as well.

The mean preoperative IgE level for the group studied was 173 ± 76 ($n = 16$). Our study shows that among the CF patients studied who had received transplants, those with a history of ABPA were more likely to have an elevated preoperative IgE level ($p = 0.02$) and a postoperative drug reaction ($p = 0.016$). However, a history of atopy alone or elevation of IgE alone did not significantly increase the risk for a drug reaction during or in the early postoperative period, in the absence of ABPA. The mean IgE levels of those with and without postoperative reactions were not significantly different (184 versus 73 IU/mL, $n = 16$).

DISCUSSION

Anaphylaxis is a serious potential occurrence in the perioperative period. The use of colloidal and blood products, antibiotics, and RATG in the perioperative period is associated with allergic and anaphylactic reactions following heart-lung or lung transplantation. In patients with cystic fibrosis, we hypothesized that the CF-related predilection to atopy or ABPA may result in an increased risk of a postoperative drug reaction. Our findings indicate for the first time that CF patients with a history of ABPA may be at increased risk for a perioperative drug reaction. These patients had a higher pre-operative IgE and because anaphylaxis is mediated via IgE receptors on mast or basal cells, this may explain their identifiable perioperative risk for an adverse drug reaction. Our study further indicates that in the absence of ABPA, a history of atopy or elevated preoperative IgE alone, does not increase the risk of an anaphylactoid reaction.⁽⁷⁾

Although the association between atopy and cystic fibrosis is common, it is not well understood. Reports have noted the association of repeated exposure to antibiotics to the increased incidence of atopy in this patient population.⁽⁸⁾ In one study, atopic CF patients did not have a different long-term prognosis or baseline lung function compared with the nonatopic group.⁽⁹⁾ Other studies have shown the prevalence of allergic diseases, such as allergic rhinitis, to be twice that of the normal population, which suggests a pathogenic role of allergic mediators in the disease.⁽¹⁰⁾ Yet other studies have demonstrated an almost equivalent incidence of allergic rhinitis and urticarial reactions to the general population.⁽¹¹⁾ Many investigators have found that CF patients have a higher serum IgE level than that found in the general population, and a higher incidence of immediate hypersensitivity reactions than in the general population.⁽¹²⁻¹⁴⁾

Treatment of the atopic CF patient during the perioperative period should involve the avoidance of known or related allergens. If the preoperative history reveals a significant number of past adverse reactions to allergens, a referral should be made to an allergist for a complete assessment. Desensitization protocols are available if treatment necessitates the use of a drug to which the patient is allergic.

Our study indicates that a history of ABPA may be a risk factor for adverse drug reactions in the perioperative transplantation period, whereas atopy with allergen avoidance does not place the CF patient at any increased risk for a drug reaction. RATG reactions may be mediated as well through non-IgE pathways, and the correlation reported with preoperative IgE was marginally significant. Further large multicenter studies should be conducted to examine the perioperative risk factors for anaphylaxis among this patient population.

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