Dexamethasone Treatment Has No Effect on the Formation of Pneumococcal Antibodies during Community-Acquired Pneumonia

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In this study, the effect of dexamethasone on the formation of pneumococcal antibodies during community-acquired pneumonia (CAP) was investigated. No differences between CAP patients receiving dexamethasone as additional therapy and patients receiving a placebo were found with respect to immune response rates and mean baseline and convalescent-phase antibody concentrations.

Community-acquired pneumonia (CAP) is a very common disease causing considerable morbidity and mortality worldwide (4). *Streptococcus pneumoniae* is the most frequently identified causative agent of CAP (15). Natural defense against *S. pneumoniae* is mediated by serotype-specific anticapsular IgG (9). Recently, a study was conducted in which the addition of dexamethasone, a glucocorticosteroid, to antibiotic therapy in patients with CAP reduced the median length of hospitalization by 1 day (8). Beneficial effects of glucocorticosteroids in CAP are due primarily to damping of the systemic inflammatory response (10). Although these agents suppress mainly cell-mediated immunity, they can also affect humoral immunity (1, 3, 6, 7). In this study, we investigated the potential negative effect of dexamethasone on the formation of pneumococcal antibodies during CAP.

Patients participated in a double-blind, placebo-controlled trial investigating the effect of dexamethasone therapy on the length of hospitalization for CAP (8). All patients were above 18 years of age and nonimmunocompromised. Patients were randomized to receive 5 mg dexamethasone or a placebo once a day for the first 4 days after hospital admission. In the present study, only patients in whom *S. pneumoniae* was diagnosed as the causative agent were included. These patients were with a positive blood or sputum culture with *S. pneumoniae* or with a positive urine antigen test (BinaxNOW). Pneumococcal strains were serotyped by the Quellung reaction. Serum samples for antibody measurements were obtained from day 0 to day 3 (baseline samples) and from day 11 to day 100 (convalescent-phase samples) after hospital admission. Excluded were patients with a duration of symptoms of more than 10 days before admission, because in these cases, a possible immune response at the onset of disease would remain undetected. The concentrations of IgG against 14 pneumococcal serotypes were measured using the Luminex XMAP Pneumococcal Immunity Panel (Luminex Corporation, Austin, TX). The serotypes included in this panel are 1, 3, 4, 6B, 7F, 8, 9N, 9V, 12F, 14, 18C, 19A, 19F, and 23F (Danish nomenclature). A positive immune response was defined as at least a 2-fold antibody concentration increase between the baseline and convalescent-phase serum samples with an end concentration of at least 0.35 μg/ml (16). If the increase in antibody against a certain serotype was at least 2-fold higher than the increase in antibody against any other serotype, it was determined to be the infecting serotype (16). Statistical significance of the difference between the immune response rates of the dexamethasone- and placebo-treated groups was determined by using the χ² test. In patients in whom the infecting serotype could be determined, the mean concentrations of antibody against the infecting serotype in both the baseline and convalescent-phase samples were compared between the treatment groups by the Student t test. A P value of <0.05 was considered to represent a statistically significant difference.

In the original trial, 304 patients were enrolled, of which 151 were randomized to receive dexamethasone and 153 were randomized to receive a placebo (Fig. 1). The baseline characteristics of the patients in the two treatment groups were comparable. *S. pneumoniae* was identified as the causative agent of CAP in 64 patients, 35 in the dexamethasone group and 29 in the placebo group. Three and two patients in both groups, respectively, were excluded due to a duration of symptoms of more than 10 days before admission. Representative baseline and convalescent-phase serum samples for antibody measurements were available for 48 patients, 25 patients in the dexamethasone group and 23 patients in the placebo group, the total number of patients included in this study. Pneumococcal strains isolated from 22 of the 48 pneumococcal pneumonia patients were serotyped; in 18 cases, the etiological diagnosis was based solely on a positive urine antigen test, which made serotyping impossible, and in 8 cases, the isolate was not available for serotyping. The most frequently identified serotype was serotype 1 (n = 6), followed by 7F (n = 3), 4, 8, 14, and 9V (all n = 2). A pneumococcal immune response was elicited in a total of 31 patients (2-fold increase in antibody concentrations in time and an end concentration of >0.35 μg/ml), 18 (72%) of 25 patients in the dexamethasone group compared to 13 (57%) of 23 patients in the placebo group (difference nonsignificant [NS]). In 19 of these patients (11 in the dexamethasone group and 8 in the placebo group), the infecting pneumococcal serotype could be determined because the increase in the concentrations of antibody against this serotype was at least 2-fold higher than the increase in the concentrations of antibody against any other serotype. All but one serotype-specific antibody responses corre-
sponded to the type of the isolated strain identified with the Quellung reaction; in one patient infected with *S. pneumoniae* serotype 6A, serotype 6B was determined to be the infecting serotype by a positive immune response. The mean baseline concentration of antibody against the infecting serotype was 0.45 (range, 0.03 to 1.90; standard error [SE], 0.16) μg/ml in the dexamethasone group compared to 0.39 (range, 0.01 to 0.87; SE, 0.12) μg/ml in the placebo group (NS) (Fig. 2). The end concentrations were 6.00 (range, 0.74 to 23.30; SE, 2.34) μg/ml and 6.50 (range, 0.39 to 17.00; SE, 2.30) μg/ml, respectively (NS).

In a recently published trial, the addition of dexamethasone to antibiotic therapy for patients with CAP reduced the median length of hospitalization by 1 day. Many of the possible effects of this therapy on natural immunity remain uncertain. In this study, it was shown that dexamethasone does not negatively affect the formation of serotype-specific antibodies in pneumococcal CAP patients. The immune response rate in the dexamethasone-treated group was even nonsignificantly higher than in the placebo treated group. In earlier studies, the relationship between the long-term use of corticosteroids and suppression of the humoral immune system was established (3, 6, 12). Several in vitro and in vivo studies provided evidence that even short-term use of corticosteroids can negatively affect IgG subclass concentrations (1, 7). Until now, no negative effect of corticosteroid use on the antibody response to pneumococcal vaccination has been described (2, 13). This study is the first to provide evidence that short-term corticosteroid use does not affect pneumococcal antibody formation during natural infection. The cutoff value of a positive immune response in this study was set at 0.35 μg/ml. This is the protective concentration of pneumococcal antibodies in children designated by the WHO (11). The protective concentration of pneumococcal

FIG 1 Flow chart of the inclusion criteria and number of patients included in this study. Three hundred four CAP patients were randomized to receive either dexamethasone or placebo therapy. A diagnosis of *S. pneumoniae* as the causative agent was based on either a positive sputum or blood culture or a positive urine antigen test. A baseline serum sample drawn from day 0 to day 3 and a convalescent-phase sample drawn from day 11 to day 100 of hospitalization had to be available.

FIG 2 Concentrations of IgG against the infecting pneumococcal serotype in CAP patients receiving dexamethasone (A, n = 11) or a placebo (B, n = 8). The baseline serum sample was obtained from day 0 to day 3 after hospital admission, and the convalescent-phase serum sample was obtained from day 11 to day 100 after hospital admission. The open circles are mean antibody levels ± SE.
antibodies for CAP in adults is not known, and therefore, it is not possible to interpret the immune responses observed in our patients in terms of function. It is, however, reasonable to assume that dexamethasone does not negatively influence the functionality of antibodies irrespective of their concentration. Patients participated in a double-blind, placebo-controlled trial which allows for an unbiased comparison between therapy groups (8). There were, however, differences between the two groups in the serotype distribution of the infecting strains, which may have had an impact on immunogenicity (5). An immune response against serotype 6B was elicited in one patient infected with S. pneumoniae serotype 6A. This type of cross-reactivity has been described after pneumococcal vaccination (14). Potential negative effects of corticosteroids on the immune system might limit the general applicability of dexamethasone in CAP. Our data indicate that dexamethasone therapy does not affect the formation of pneumococcal antibodies during CAP. No drawback to the incorporation of dexamethasone in the standard therapy scheme for CAP was found with respect to the pneumococcal immune response.

REFERENCES