

Effect of therapeutic dosages of prednisone on human immunoglobulin G metabolism

Robert C. Griggs, M.D.,* John J. Condemni, M.D., and
John H. Vaughan, M.D.**
Rochester, N. Y.

In order to evaluate factors possibly responsible for the increased incidence of infections in patients treated with corticosteroids, immunoglobulin G (IgG) metabolism was studied in 8 patients before and during the administration of prednisone in a therapeutic range (80 mg. per day). The survival of intravenously administered IgG was determined, and total circulating IgG, fractional catabolic rate, and synthetic rate were calculated. There was no significant decrease in the measured levels of circulating IgG, but all patients had a shortened half-time (5 to 45 per cent) and an increased fractional catabolic rate ($p < 0.01$). Since corticosteroid therapy was the only variable in these paired studies, it appears that corticosteroids can cause a hypercatabolism of IgG in some patients. Therefore, the maintenance of normal levels of IgG must be the result of an increased synthetic rate.

Following the introduction of corticosteroids in pharmacologic doses for the treatment of inflammatory, autosensitivity, allergic, and other disorders, it became apparent that their use was attended by an increased incidence of infection. This predisposition to infection has been related to effects of corticosteroids on phagocytosis, opsonization, and inflammation. In addition, effects on cell-mediated immune mechanisms and on humoral antibodies have been demonstrated.¹

Early investigations in experimental animals suggested that the administration of corticosteroids before or in close proximity to antigenic stimulation could block or diminish synthesis of antibody to the antigen.² Several studies, however, showed no clear effect of corticosteroid administration on antibody activity once antigenic stimulation had been accomplished.³ More recently, however, it has been found during the course of administration of corticosteroids and antimetabolites that humoral as well as lymphocyte-mediated immune mechanisms are markedly suppressed.⁴ Although it might be anticipated that the so-called

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Reprint requests to: Dr. Griggs, Department of Neurology and Medicine, University of Rochester School of Medicine and Dentistry, Rochester, N. Y. 14642.

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TABLE 1. Diagnoses and clinical features of patients

Case No.	Age/sex	Diagnosis	Reason for repeated corticosteroid administration
1	42 F	Scleroderma	Therapeutic trial
2	38 F	Asthma	Exacerbations
3	48 M	Asthma	Exacerbations
4	21 M	Rhinitis	Intermittent steroids for severe symptoms
5	46 M	Asthma	Exacerbations
6	51 F	Severe eczema	Requiring long term intermittent therapy
7	41 F	Sarcoidosis	Deteriorating pulmonary function
8	37 M	Asthma	Exacerbations

lympholytic effect or plasma cell suppression might contribute to the reduction of antibody levels that have been observed, it has been shown in mice more recently that the administration of corticosteroids may shorten immunoglobulin survival,⁶ as had previously been noted for albumin survival in man and experimental animals.^{6, 7}

The present investigation was designed to determine the effect of corticosteroid therapy on IgG survival by doing *control* and *corticosteroid-treated* turnover studies in asymptomatic patients who had required intermittent corticosteroid treatment for their diseases.

MATERIALS AND METHODS

Patients studied

The characteristics of patients studied are summarized in Table 1. All patients but one had required repeated courses of corticosteroid for treatment of their disease entities prior to the study. Case 1 received a therapeutic trial of corticosteroids because of painful and disabling skin edema and inflammation. Informed consent was obtained from all patients. Patients were afebrile at the start of the studies and were afebrile and free from sepsis throughout all studies. None had proteinuria, hypoalbuminemia, or gastrointestinal symptoms. Control studies preceded the corticosteroid-treated studies in all patients except Case 5.

Radioiodinated immunoglobulin G

A single lot of commercially obtained Cohn fraction II (Squibb lot No. 1967) was radioiodinated with ¹²⁵I or ¹³¹I as previously described.⁸ Since some lots of Cohn fraction II contain small amounts of impurities and aggregates, a preparation relatively free from such contaminants was chosen, and the following studies demonstrated its relative purity:

The unlabeled preparation was studied by immunoelectrophoresis against horse antihuman whole serum, and only a single immunoprecipitation line was obtained. On sucrose density gradient ultracentrifugation, the unlabeled protein sedimented as a uniform peak in the 7S range. The purity of the radioiodinated preparation was assessed both by sucrose density gradient ultracentrifugation and by radioimmunoelectrophoresis. Sucrose density gradient ultracentrifugation of the radiolabeled preparation added to whole serum demonstrated that all radioactivity appeared in a single peak in the IgG-containing fractions. Radioimmunoelectrophoresis against horse antihuman whole serum demonstrated only a single labeled

*This preparation has been demonstrated on radioimmunoassay by Dr. John P. Leddy to contain 48 per cent IgG₁, 42 per cent IgG₂, 7 per cent IgG₃, and 3 per cent IgG₄.

Time since last on corticosteroids	Other medication (constant)
No previous administration	None
10 Days	Tedral
10 Days	Tedral, aminophylline
3 Days (2.5 mg. prednisone daily for 1 month previously)	None
10 Days	Tetracycline, Tedral
On 10 mg. prednisone on alternate days	None
30 Days	None
40 Days	Tedral

species. Thus if impurities or aggregates were present in Cohn fraction II, they were either minute in quantity or not detected because of preferential labeling of IgG.

The preparation was sterilized by Millipore filtration and checked for sterility by aerobic and anaerobic cultures.

Study protocol

Paired studies were done in each patient comparing IgG survival during a control period off corticosteroids with an otherwise identical study on corticosteroids.

All patients studied during the control period had been off pharmacologic doses of corticosteroid medication for 10 days or more (Table I). (One patient, Case 5, was on 10 mg. of prednisone on alternate days until 3 days before the control study.) During the corticosteroid period, prednisone therapy was maintained at a dosage of 10 mg. every 8 hours for a minimum of 3 weeks. The radiolabeled preparation was administered after patients were on prednisone for 3 days. Following the study period, steroids were tapered over a 5 day or longer period depending on the patients' clinical status.

Patients were given 5 drops of saturated solution of potassium iodide daily throughout the study to prevent thyroid uptake of the label. Serum IgG levels were determined by radial immunodiffusion⁹ at the start and completion of each study. Following the intravenous injection of a known amount of radioiodinated IgG (10 to 20 μ c), daily serum specimens were obtained for 3 to 4 weeks. Paired studies were done in all patients, with the second study being postponed until no detectable radioactivity persisted from the first study. Urine collections were taken in some but were not feasible in all patients. Stool and skin losses were not assessed. Samples were counted in a well-type automatic gamma ray scintillation counter.

Calculation of data

Plasma die-away curves, fractional catabolic rates, and plasma volumes were calculated as previously described.⁹ As in those studies, fractional catabolic rate was calculated by the method of Matthews¹⁰ from the plasma activity curves and plasma volume determined by dilution of the injected radioactivity at the beginning of the turnover study. Statistical significance of results was assessed by the matched-pair *t* test.¹¹

RESULTS

Control studies: (Table II)

The IgG levels of all patients were within normal range for this laboratory (6.0 to 17.0 mg. per milliliter for white and 7.0 to 20.0 mg. per milliliter for black individuals). Values shown are those at the beginning of the control

TABLE II. Effects of corticosteroids on IgG metabolism

Case No.	Treated and untreated	Serum IgG concentration (mg./ml.)	Survival half-time (days)	Total circulating IgG (mg./Kg.)	Fractional catabolic rate (% plasma pool/day)	Turnover (synthetic) rate (mg./Kg./day)
1	Control prednisone	11.8	14.0		0.122	
		7.4	13.2		0.127	
2	Control prednisone	14.2	19.6	495	0.066	32
		13.7	16.2	480	0.080	39
3	Control prednisone	6.5	24.9	305	0.071	22
		5.9	14.8	275	0.094	26
4	Control prednisone	8.1	18.9	420	0.082	34
		8.1	9.5	420	0.121	51
5	Control prednisone	9.7	24.4	270	0.056	15
		14.6	16.6	394	0.082	25
6	Control prednisone	7.4	15.0	250	0.096	24
		8.8	13.7	306	0.100	30
7	Control prednisone	15.4	13.0	920	0.142	103
		17.1	7.6	1040	0.154	157
8	Control prednisone	8.6	13.2	386	0.126	49
		9.4	10.3	430	0.139	60
	p Value†	0.50	< 0.01	0.50	< 0.01	< 0.01

*Technical mishap precluded calculation of values in this patient.

†Students t matched sample population comparison.

period and end of the prednisone period. The plasma survival half-time for IgG was within the normal range given by others using similar methods (14.9 to 30.9 days [22.9 ± 4.0 days standard deviation]¹⁵) for 5 of the 8 patients and slightly below the normal range for Cases 1, 7, and 8, one of whom had scleroderma and another sarcoidosis. The control fractional catabolic rate was elevated in the same 3 patients but normal in the others (0.0668 ± 0.0152 standard deviation). Although the turnover rate of IgG fell within the normal range (33.7 ± 11.2 standard deviation) in 7 of the 8 patients, in Case 7, with sarcoidosis, the turnover rate had a threefold increase.

Prednisone administration studies: (Table II)

No consistent change in IgG level was observed with prednisone therapy. Differences were small in all patients except Case 1, in whom a 30 per cent reduction in IgG level was observed. Although no consistent change in IgG levels was observed following the administration of corticosteroid, there was a marked shortening of plasma survival half-time during prednisone treatment in all 8 patients. The decrease represented a 5 to 45 per cent reduction of the control half-time value. A similar effect was noted on the fractional catabolic rate which was increased in all patients. The increase was small in 2 patients but significant for the group as a whole ($p < 0.01$). Despite the apparent hypercatabolism of the exogenously administered IgG, the total circulating IgG was not significantly altered. The turnover rate was elevated in all patients.

DISCUSSION

These studies demonstrate that despite the persistence of normal levels of immunoglobulin G during treatment with corticosteroids, the catabolism of administered IgG is substantially accelerated. The calculated synthetic rate was increased and apparently offset the hypercatabolism, normal levels of IgG being maintained during the 3 to 4 weeks of the study. Studies by other workers⁵ using the mouse demonstrated a similar hypercatabolism of immunoglobulin during administration of hydrocortisone, although the levels of immunoglobulin fell as well. However, the doses used (up to 5 mg. of hydrocortisone per mouse and therefore 250 mg. per kilogram) were proportionally much higher than those used in the present study. In fact, at lower doses (0.25 mg. of hydrocortisone mouse, 12.5 mg. per kilogram) no effects on immunoglobulin level or catabolism were observed. There have been no other comparably controlled studies in man, but Andersen¹⁴ studied effects of low-dose prednisone on 3 cirrhotic patients and noted a slight acceleration of catabolism. Recently, Woehner,¹² in studies of immunoglobulin metabolism in connective tissue diseases, incidentally studied IgG survival in 3 patients both on and off corticosteroid therapy. Two of the 3 were found to have a shortened survival of IgG. Woehner¹² also compared survival of IgG in 2 groups of patients with collagen disease, those on and those off corticosteroids, and since there was no difference between the groups, he concluded that corticosteroids had no effect on IgG survival. The variability of survival and catabolic rates between patients, however, makes it preferable to compare the effects of a given factor in the same patient, as was done in the present study.

The derived data in the present study are dependent on the maintenance of a steady state during the study, both in terms of compartment size and in the metabolic processes in each compartment. Since steroid administration was short term, it is possible that cumulative effects of steroid therapy may invalidate the assumption of a steady state. In particular, plasma volume was measured only at the beginning of the study, and changes in compartment size cannot therefore be assessed. For this reason it may be more appropriate to base conclusions on the differences between the plasma survival half-time in paired studies on the same patient rather than using the theoretically more metabolically meaningful determinations of fractional catabolic rate and synthetic rate. The observations of Fischel and associates¹⁵ that antibody titers increased abruptly following the administration of corticosteroids suggest that corticosteroids may well affect the space of distribution or binding of antibody. The recent observations¹⁶ that a significant portion of immunoglobulin is not in rapid equilibrium with what is considered the usual total body pool suggests that corticosteroids could easily effect changes in apparent catabolism by increasing or decreasing the size of this pool. Catabolic rates, such as those determined by the short-term measurements of protein destruction,¹⁷ may well prove a much more accurate measurement of instantaneous catabolism and also provide a better assessment of changes with prolonged administration of corticosteroids. Although other investigators¹⁵ have shown no increase in the catabolism of

antibody nitrogen and have inferred that corticosteroids therefore did not affect the rate of catabolism, the present study shows that at least radiolabeled Cohn fraction II is hypercatabolized, and the lack of change in the serum levels reflects increases in synthesis or change in distribution during corticosteroid administration. It must be pointed out that in 7 of the 8 patients the prednisone study followed the control study. If antibodies were formed to the radiolabeled Cohn fraction II during the first study, a systematic error might have been introduced. However, careful review of the plasma die-away curves during the second study did not support rapid, immune elimination as might have been expected if the apparent hypercatabolism was the result of antiallotype antibodies.

The selection of patients for this study posed a considerable problem. We were unwilling to administer the prolonged dose of corticosteroids necessary for the study to patients who did not require corticosteroids for therapeutic reasons. The report of hypercatabolism of IgG in patients with various collagen diseases¹² and the uncertainty as to how corticosteroids might affect this abnormality led us to choose patients whose disease was less apt to be associated with IgG abnormalities. Accordingly, all but 2 of the patients had asthma, rhinitis, or eczema. Other conditions known to be associated with decreased survival of IgG, such as nephrotic syndrome, myotonic dystrophy, hyperthyroidism, and multiple myeloma,¹³⁻¹⁵ were not present. The pairing of the studies in the same patient provides further assurance that the differences are related to the addition of corticosteroids.

The basis for the shortened survival of IgG with prednisone treatment is not known. The possibility of catabolic enzyme induction has been discussed by others.⁶ Another possible mechanism would be corticosteroid-induced lysis of lymphoid cells which have been shown to have attached immunoglobulins,¹⁶ thereby making a given molecule more vulnerable to attack. However, recent *in vivo* studies¹⁷ of human lymphoid cells have failed to demonstrate any such lysis by hydrocortisone.

The significance of the decreased survival of IgG as an explanation for the increased incidence of infection during corticosteroid administration remains uncertain. It would be of interest and perhaps of more clinical significance to assess the rates of disappearance of labeled antibody species, both those antibodies actively produced by the patient and those administered passively.

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