

Differential effects of inhaled budesonide and oral prednisolone on serum immunoglobulin G and its subclasses in healthy adult volunteers

J. VAN SCHOOR*, J. H. TOOGOOD†, and R. A. PAUWELS*

* Department of Respiratory Diseases, University Hospital, Ghent, Belgium and † Department of Medicine, University of Western Ontario, London, Ontario, Canada

Summary

Background Glucocorticosteroid (GCS) treatment lowers serum IgG and IgG subclass (IgG-SC) levels, but the minimal dose and duration of administration at which this occurs is not known.

Objective The aim of this study was to define the daily dose of a 2-week course of GCS at which IgG(-SC) suppression occurs.

Methods The effects of three GCS treatment schemes on serum IgG(-SC) levels in healthy adults were studied in a double-blind, randomized trial. Group 1 ($n = 10$) was treated with 40 mg oral prednisolone/day, group 2 ($n = 10$) with 10 mg oral prednisolone/day and group 3 ($n = 10$) with 3.2 mg inhaled budesonide/day. Blood sampling was performed at baseline and at the end of the 2-week treatment period.

Results In group 1, IgG1, IgG2 and IgG3 levels were significantly decreased after treatment, while in group 2 this was only so for IgG3. In both groups, the decrease of total IgG tended towards or just reached significance. In group 3, no statistically significant changes were observed.

Conclusion A course of 40 mg oral prednisolone/day for 2 weeks induces significant suppression of serum IgG-SC levels; lower doses cause more subtle changes, indicating that GCS-induced IgG-SC suppression is a dose-dependent phenomenon. Short courses of very high doses of inhaled budesonide appear to be devoid of this side-effect.

Keywords: Immunoglobulin G subclasses, budesonide, prednisolone, glucocorticosteroid systemic effects, asthma, COPD

Clinical and Experimental Allergy, Vol.27, pp. 192–195. Submitted 31 October 1995; revised 26 March 1996; accepted 18 June 1996.

Introduction

Inhaled and systemically administered glucocorticosteroids (GCS) have become increasingly important in the treatment of asthma and, to a lesser degree, chronic obstructive pulmonary disease (COPD) [1,2].

The results of small, open, prospective studies indicate that short courses of systemic GCS induce suppression of serum total IgG in healthy subjects [3] and in asthmatics [4,5]. Cross-sectional studies, performed in patients with asthma [6], aspirin-induced asthma [7] or COPD [8] suggest that systemic GCS lower the serum levels of the IgG

subclasses (IgG-SC) in an aspecific manner. To the best of our knowledge, only two reports have investigated the effects of inhaled GCS on the serum IgG and IgG-SC levels. In an open trial of 10 asthmatics, DeCotiis and Settupane found that inhalation of 400 µg beclomethasone dipropionate/day for 4 weeks was associated with significantly decreased serum total IgG levels [9]. In a double-blind study of 20 healthy adults, we demonstrated that inhalation of 2.4 mg budesonide/day for repeated 4-week periods did not affect serum IgG-SC levels [10].

Deficiencies of serum IgG and IgG-SC have been associated with an increased susceptibility to respiratory infections, both viral and bacterial [11]; these are major triggers of exacerbations of asthma and COPD. Suppression

Correspondence: Jan Van Schoor MD, Department of Respiratory Diseases, University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium.

of serum IgG (-SC) by GCS therapy may therefore be clinically important. In view of these considerations, we compared the effects of different dosage schemes of oral prednisolone and inhaled budesonide on the serum levels of IgG and its subclasses, with the aim of determining more precisely at which dose such suppressive effects become apparent.

Materials and methods

Study design

The serum samples of the present study originate from a trial performed by Hodsman *et al.*, who studied the effects of GCS on serum osteocalcin [12]. The study protocol was approved by the Review Board for Health Sciences Research involving Human Subjects at the University of Western Ontario. In summary, out of the study population of healthy adults (mean age: 33 yr), those 30 subjects (three groups of 10) who were randomly allocated to receive one of the following treatments for 2 weeks were selected for the present study: high-dose oral prednisolone, 40 mg/day (group 1); low-dose oral prednisolone, 10 mg/day (group 2); and high-dose inhaled budesonide, 3.2 mg/day (group 3). In addition, during the second week, half of the subjects in each group was treated with 2.0 µg/day of oral calcitriol (1,25-dihydroxyvitamin D₃), to test the serum osteocalcin response. All study drugs were administered in a double blind fashion. The budesonide was inhaled in a standard fashion from a pressurized metered-dose inhaler, mounted on a 750 ml Nebuhaler[®] spacer [12].

Serum IgG and IgG subclass quantification

Serum samples were obtained at baseline and at the end of the second week of treatment; they were stored at -20°C and batch assayed. Serum IgG and IgG-SC levels were measured using a Behring Nephelometer Analyser (Behringwerke, Marburg, Germany). Total IgG and IgG-SC specific polyclonal antibodies, calibrators and controls were purchased at The Binding Site Ltd, Birmingham, United Kingdom. The lower limit of detection was 0.014 g/l or less for all IgG-SC. The reference ranges for healthy adults (mean ± 2 SD), were as follows: total IgG, 8.000–17.000 g/l; IgG1, 4.560–8.900 g/l; IgG2, 1.990–5.270 g/l; IgG3, 0.168–0.998 g/l; and IgG4, 0.135–0.737 g/l (ranges provided by the manufacturer).

Statistical analysis

The serum total IgG and IgG-SC levels at baseline (t = 0) and at the end of the study period (t = 2 weeks) were compared per group, using the Wilcoxon matched-pairs

Table 1. Changes in total IgG and IgG-SC levels in group 1

	% Change*	P
IgG _{tot}	-13.5 (-54.4 - +18.6)	0.066
IgG1	-14.8 (-51.3 - +17.6)	0.037
IgG2	-12.2 (-49.3 - +26.4)	0.037
IgG3	-24.0 (-48.6 - +3.7)	0.007
IgG4	-4.4 (-57.5 - +42.8)	0.139

* Per cent change from baseline values: median (range).

test. *P* values less than 0.05 were considered to be statistically significant.

Results

In group 1 (high-dose oral prednisolone), levels of IgG1, IgG2 and IgG3 were significantly lower after 2 weeks of therapy, compared to baseline values. The decrease in total IgG reached borderline significance, whereas the changes in IgG4 levels were not significant. Changes were most pronounced in the case of IgG3, displaying a median decrease of about 24% (Table 1). The IgG1 and IgG2 levels showed a decrease in 8 out of 10 subjects and remained virtually unchanged in one. Lowering of IgG3 levels was observed in 9 cases out of 10.

In group 2 (low-dose oral prednisolone), levels of total IgG and IgG3 were significantly decreased after 2 weeks of therapy; the magnitude of their decrease was quite similar to that observed in group 1. The changes in IgG1, IgG2 and IgG4 were not significant, although in the case of IgG2, a trend towards significance was noted (Table 2). The serum total IgG levels decreased in all five cases in which serum was available for analysis; suppression of serum IgG3 occurred in 9 out of 10 cases.

In group 3 (high-dose inhaled budesonide), no significant changes were found in the levels of total IgG and the IgG-SC (data not shown); clear-cut lowering, however, did occur in individual cases (see Figures 1c and 2c).

Table 2. Changes in total IgG and IgG-SC levels in group 2

	% Change*	P
IgG _{tot}	-15.2 (-27.4 - -2.0)	0.043
IgG1	-8.6 (-32.8 - +42.1)	0.203
IgG2	-11.1 (-32.5 - +66.4)	0.074
IgG3	-21.1 (-51.9 - +1.0)	0.008
IgG4	-0.6 (-44.7 - +90.0)	0.878

* Per cent change from baseline values: median (range).

Fig. 1. Changes in the serum levels of total IgG between baseline and the end of the 2-week treatment period ('post') in (a) group 1, (b) group 2, and (c) group 3. The thick line with the closed circles represents the changes in median values.

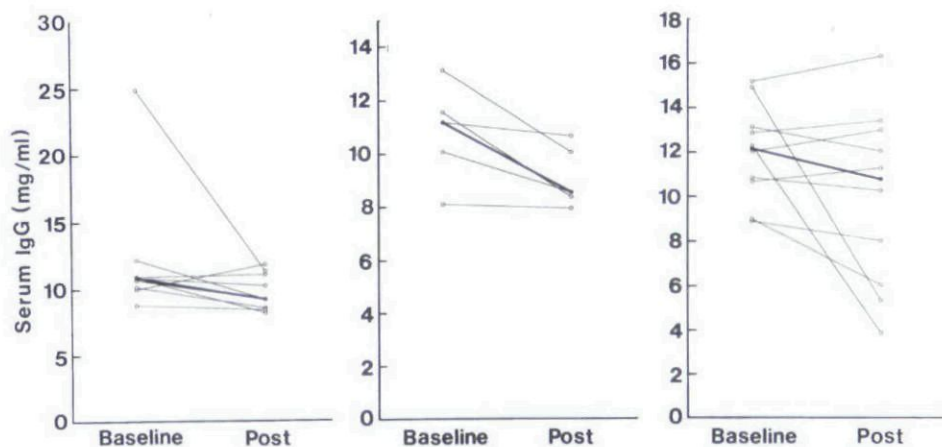
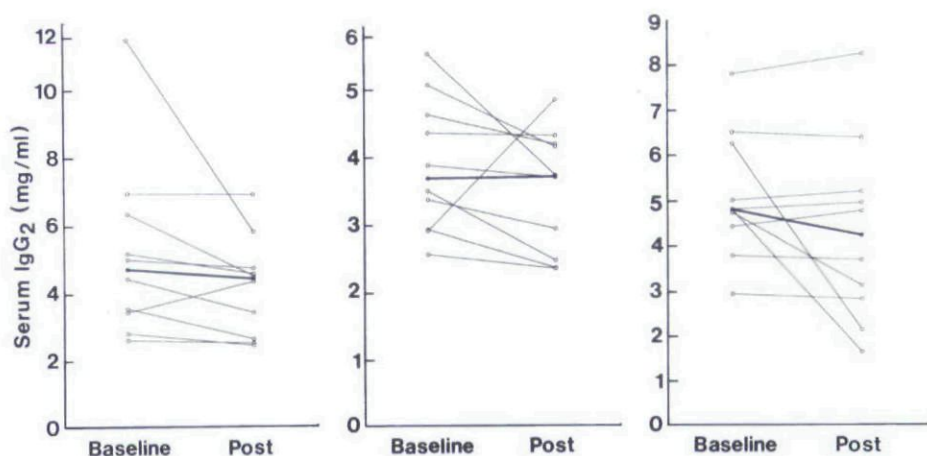


Fig. 2. Changes in the serum levels of IgG2 between baseline and the end of the 2-week treatment period ('post') in (a) group 1, (b) group 2, and (c) group 3. The thick line with the closed circles represents the changes in median values.



The changes in the serum levels of total IgG and IgG2 in each of the three groups are shown in figures 1 and 2, respectively.

Discussion

Suppression of serum total IgG and its subclasses by systemic GCS administration is a known phenomenon [3–8]. Only two prospective studies, however, provided data on the dose, the duration and the type of GCS which induce such changes. Butler and Rossen found that, in healthy volunteers, 96 mg/day of oral methylprednisolone for 3 to 5 days caused an average fall in IgG of about 22%. The IgG nadir occurred during the second and the third week after therapy [3]. Klebl *et al.*, on the other hand, treated 10 healthy adults with 25 mg prednisone/day orally for 7 days and did not find any significant changes in IgG-SC levels during or after the treatment period [13].

Our findings indicate that serum IgG3 is very susceptible to suppression, as a significant decrease was already present at a dose of 10 mg prednisolone/day. This may be related to the shorter serum half-life of IgG3 (about 1 week),

compared to approximately 3 weeks for the other IgG-SC [11]. In addition, the IgG1 and IgG2 levels were lowered (although not significantly), resulting in a significantly decreased total IgG. Following treatment with 40 mg prednisolone/day, statistical significance was also reached in the case of IgG1 and IgG2. It is very likely that even greater decreases would have been detected if sampling had been performed in the weeks following the end of the treatment. Toogood *et al.* found that the asthma control obtained by 2.0 mg of inhaled budesonide/day, equalled that of at least 40 mg of oral prednisone/day [14]. Our data confirm that short courses of inhaled budesonide, at doses having an anti-asthma effect comparable to that of high doses of oral GCS, are safe with respect to serum IgG-SC levels. Calcitriol has an inhibitory effect on IgG production *in vitro* [15]; its administration in the present trial, however, was not considered to be a confounding factor, as all three groups received the same calcitriol treatment.

In summary, systemic GCS treatment is to be added to the list of factors which influence serum IgG and IgG-SC levels, such as age, sex and allotype profile [11]. Suppression of IgG and IgG-SC levels by systemic GCS probably is a

dose-dependent phenomenon. Long-term prospective studies are needed to find out whether these changes induce increased susceptibility to infections. If low serum IgG(-SC) levels really are the cause (or a marker) of a clinically relevant immunodeficiency, substitution with intravenous immunoglobulins might be a valuable therapeutic option in patients with GCS-dependent asthma or COPD, who experience recurrent infectious exacerbations.

References

- 1 Scheffer AL. Global strategy for asthma management and prevention. NHLBI/WHO Workshop Report. National Institutes of Health, Bethesda, Maryland, 1995, Publication No. 95-3659.
- 2 Ferguson GT, Cherniack RM. Management of chronic obstructive pulmonary disease. *N Engl J Med* 1993; 328:1017-22.
- 3 Butler WT, Rossen RD. Effects of corticosteroids on immunity in man. I. Decreased serum IgG concentration caused by 3 or 5 days of high doses of methylprednisolone. *J Clin Invest* 1973; 52:2629-40.
- 4 Posey WC, Nelson HS, Branch B, Pearlman DS. The effects of acute corticosteroid therapy for asthma on serum immunoglobulin levels. *J Allergy Clin Immunol* 1978; 62:340-8.
- 5 Settipane GA, Pudupakkam RK, McGowan JH. Corticosteroid effect on immunoglobulins. *J Allergy Clin Immunol* 1978; 62:162-6.
- 6 Hamilos DL, Young RM, Peter JB et al. Hypogammaglobulinemia in asthmatic patients. *Ann Allergy* 1992; 68:472-81.
- 7 Szczeklik A, Schmitz-Schumann M, Nizankowska E et al. Altered distribution of IgG subclasses in aspirin-induced asthma: high IgG4, low IgG1. *Clin Exp Allergy* 1992; 22:283-7.
- 8 Klaustermeyer WB, Gianos ME, Kurohara ML, Dao HT, Heiner DC. IgG subclass deficiency associated with corticosteroids in obstructive lung disease. *Chest* 1992; 102:1137-42.
- 9 DeCotiis BA, Settipane GA. The effect of inhaled beclomethasone on serum immunoglobulins. *J Allergy Clin Immunol* 1980; 65:218-9.
- 10 Van Schoor J, Toogood JH, Pauwels RA. Short courses of high-dose inhaled budesonide and serum immunoglobulin G subclass levels in healthy volunteers. *J Allergy Clin Immunol* 1996; 97:113-8.
- 11 Jefferis R, Kumararatne DS. Selective IgG subclass deficiency: quantification and clinical relevance. *Clin Exp Immunol* 1990; 81:357-67.
- 12 Hodsman AB, Toogood JH, Jennings B, Fraher LJ, Baskerville JC. Differential effects of inhaled budesonide and oral prednisolone on serum osteocalcin. *J Clin Endocrinol Metab* 1991; 72:530-40.
- 13 Klebl FH, Weber G, Kalden JR, Nüsslein HG. In vitro and in vivo effect of glucocorticoids on IgE and IgG subclass secretion. *Clin Exp Allergy* 1994; 24:1022-9.
- 14 Toogood JH, Baskerville J, Jennings B, Lefcoe NM, Johansson SA. Bioequivalent doses of budesonide and prednisone in moderate and severe asthma. *J Allergy Clin Immunol* 1989; 84:688-700.
- 15 Lemire JM, Adams JS, Sakai R, Jordan SC. 1,25-Dihydroxy-vitamin D₃ suppresses proliferation and immunoglobulin production by normal human peripheral blood mononuclear cells. *J Clin Invest* 1984; 74:657-61.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.