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THE EFFECT OF THERAPEUTIC GLUCOCORTICOIDS ON THE ADRENAL RESPONSE IN A RANDOMISED CONTROLLED TRIAL IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract

Objective To measure the effect of low dose systemic glucocorticoid treatment on the adrenal response to ACTH in patients with rheumatoid arthritis (RA).
Methods Patients with RA who took part in a double blind randomized placebo controlled trial of budesonide (3mg daily and 9 mg daily) and prednisolone (7.5 mg daily) had a short (60 minute) synacthen test at baseline and the day after completing the three months treatment programme. Plasma cortisol measurements were compared from baseline to three months within and between the treatment groups. Individual patients were classified as normal or abnormal responders to ACTH if changes were more than 2 standard deviations below the values found in all the patients taken together before treatment.
Results Short synacthen tests were carried out on 139 patients before they commenced study medication and on 134 after cessation. There were no changes in the placebo group. Mean plasma cortisol following treatment was reduced in all treatment groups. In addition, mean values were significantly reduced for the 30-minute and 60-minute responses to synacthen. The maximum reduction (35%) occurred in the prednisolone group at 60 minutes. Following treatment, 34% of patients taking budesonide 9 mg and 46% taking prednisolone 7.5 mg fail to reach the normal maximum cortisol response to ACTH. Four patients failed to achieve the normal percentage increase in cortisol, but only one patient failed to attain both criteria.
Conclusion Low doses of a glucocorticoid result in depression of baseline and synacthen stimulated cortisone levels after 12 weeks of therapy. Although, the responsiveness of the HPA axis in individual patients generally remains within the normal range, these changes should be investigated further.

Glucocorticoids have been used to treat rheumatoid arthritis (RA) ever since they first became available for use in humans in 1948 (1). Clinical experience suggests that it often is difficult to withdraw glucocorticoids (2). A number of other reports deal with suppression of the of hypothalamic-pituitary-adrenal (HPA) axis in RA patients taking glucocorticoids. In 1961 Shuster and Williams (3) showed that RA patients taking low doses of cortisone (25mg daily) had normal adrenal response to a pyrogen and to corticotrophin, but a small proportion of those taking 37.5 to 50 mg cortisone daily had a reduced response. Treadwell and colleagues (4) surveyed HPA function in 41 patients (38 with RA) taking long-term prednisolone, and found normal responses in those taking 7.5 mg daily or less, who had also been on therapy for less than 30 months. In contrast, many patients on higher doses, who had also been on treatment for longer, showed a reduced response to metyrapone. After the short synacthen test was developed (5) it was applied in RA patients and shown to work satisfactorily (6). One third of patients taking long term glucocorticoids had a reduced HPA response, but no details of doses were provided. In a study of 19 patients taking a wide range of glucocorticoid doses for differing lengths of time, Jasani (7) found that 6 had a subnormal response to synacthen compared to RA patients who had never taken glucocorticoids. A further study by Hicklin and Wills (8) identified deficiencies in HPA response in some patients who had been taking a variety of doses of glucocorticoid for at least 12 months.

These studies have some common characteristics: they compared patients who had been treated with glucocorticoids to those who had not; most of the patients had received more than low dose treatment (prednisolone 7.5mg or less (9)); and there was a proportion of patients amongst those with higher dose and longer duration treatment who showed deficiencies in their HPA axis response. Thus while the results taken together raise the suspicion that some HPA suppression may occur in some patients with low dose treatment, they cannot provide definitive evidence for the severity or frequency of such deficiencies. In 1976 Chamberlain

and Keenan (10) performed a 30 min synacthen test on 41 patients who had taken placebo, prednisolone 3mg daily or prednisolone 5mg daily for 2 years. They reported as mild supression in the HPA axis. It is remarkable that in the intervening years, no further investigations seem to have addressed an issue, which is of considerable importance in weighing the benefits of glucocorticoid treatment against the risks. Therefore, as part of a multi-centre, double-blind, randomized, placebo-controlled, 12-week trial of two types of glucocorticoid in RA (11), we investigated HPA axis function by conducting short synacthen tests before and immediately after treatment.

Patients and Methods

Patients and treatment: Following research ethics committee approval, patients with rheumatoid arthritis, as defined by the ACR criteria (12) and with onset of disease over 16 years of age, were recruited to the study (11) from 16 centres in the United Kingdom, Belgium and Sweden. All had active disease as shown by early morning stiffness equal to or greater than 45 minutes and at least 6 tender joints, of which at least 3 had associated soft tissue swelling. Patients were either on no treatment or stable doses of non-steroidal anti-inflammatory and/or disease-modifying anti-rheumatic drugs. No glucocorticoids had been given by any route for at least 30 days.

The primary purpose of the trial was to test the efficacy of budesonide, a glucocorticoid that is 90% metabolized during first pass through the liver (13,14), and is generally used in a controlled release capsule to treat inflammatory bowel disease (15). A 9mg oral dose is considered equivalent to a systemic glucocorticoid dose equivalent to approximately 7.5 mg prednisolone. Subjects were randomized to receive budesonide CIR 3mg, budesonide CIR 9mg, prednisolone 7.5mg or placebo once daily. Treatment was continued for 12 weeks.

Adherence to the dosing instructions was checked at 2, 4, 8 and 12 weeks by patient interview and counting returned packs of medication. Patients taking <=80% of the treatment, or missing study medication for >= 3 consecutive days were considered non-adherent. Further details of inclusion and exclusion criteria, together with data relating to treatment efficacy, have been reported elsewhere (11).

Measurement of adrenal function: Measurement of adrenal function was performed at baseline and after 12 weeks using the short ACTH (synacthen) stimulation test. Venous samples were taken for serum cortisol estimation before, 30 and 60 minutes after an intra-muscular injection of 250mcg synacthen. Cortisol concentrations were measured by a gas chromatography mass spectrometry method to avoid cross-reactivity with the exogenous steroid (16). Post-treatment samples were taken 24 hours after the last treatment dose and all samples were taken at 9am.

Statistical analysis: The mean values and 95% confidence intervals (CI) concentrations of serum cortisol and the mean and 95% CI change in response to ACTH were calculated for each group before and after treatment, and were compared using the paired t-test within groups and the unpaired t-test between groups. Log(10) transformation was used for the change scores to allow for a nonparametric distribution.

Individual patients were classified as normal or abnormal responders to ACTH according to their initial, final and change values of serum cortisol following ACTH administration. Abnormal levels were defined as those more than 2 standard deviations below the values found in all the patients taken together before treatment.

RESULTS

143 patients were randomized to the four treatment groups. One did not receive study medication and was excluded from the analysis. Patient demographics are shown in Table 1. Short synacthen tests were carried out on 139 patients before they commenced study medication and on 134 after cessation.

Mean plasma cortisol concentrations in the synacthen tests before and after treatment are shown in Table 2 and illustrated in Figure 1. There were no significant differences between groups before treatment for baseline, 30-minute and 60-minute measurements. In the placebo group plasma cortisol did not change following 12 weeks treatment with the trial medication, nor were the 30-minute and 60-minute concentrations in response to synacthen significantly changed. However the mean plasma cortisol concentration following treatment was reduced in all treatment groups. In addition, mean values were significantly reduced for the 30-minute and 60-minute responses to synacthen. For budesonide 3mg the reductions at baseline, 30mins and 60 mins were 14%, 16% and 13%; for budesonide 9mg reductions were 26%, 33% and 34%; for prednisolone 7.5mg reductions were 28%,34% and 35%; and for placebo reductions were 5%, 1% and 0 ($P<0.05$ for all values except placebo group)..

Table 3 shows the results when patients were individually classified as being abnormal if they had a plasma cortisol concentration more than 2 standard deviations below the pre-treatment values for all the patients taken together. At each of the time points of the ACTH test there was a proportion of patients in the budesonide 9 mg and prednisolone 7.5 mg treatment groups which had lower plasma cortisol.

Because some patients attained maximum plasma cortisol concentration before 60 minutes, the maximum of the 30-minute and 60-minute plasma cortisol concentrations was taken as the maximum response to ACTH. The mean value for pre-treatment patients was 787 nmol/L with a standard deviation of 161. Patients were individually classified as being abnormal for maximum plasma cortisol if they had a concentration more than 2 standard deviations below the pre-treatment maximum values for all the patients taken together (i.e. less than 465 nmol/L). The maximum response to ACTH was also used to calculate the percentage increase in plasma cortisol for each patient. The results had a skewed distribution, which was corrected by log(10) transformation. The mean and standard deviation of the transformed values were 2.04 and 0.25, the lower limit of normal was taken as the mean minus 2 standard deviations, and the resultant value transformed back to give an increase of 35% as the minimum acceptable normal value.

The numbers of patients falling below the lower limit of normal for: baseline plasma cortisol; maximum plasma cortisol after ACTH injection; the normal percentage increase, and below various combinations of all three measures are shown in Table 4. Following treatment, a substantial proportion of patients taking budesonide 9 mg (34%) or prednisolone 7.5 mg (46%) fail to reach the normal maximum cortisol concentration after stimulation by ACTH. A few patients fail to achieve the normal percentage increase in cortisol, but only one patient (taking budesonide 9 mg) fails to attain both criteria. Thus, all patients with low baseline cortisol following the study treatment were able to mount a satisfactory relative increase in response to ACTH so that they attained a maximum cortisol concentration or a percentage increase in plasma cortisol that was within the normal range (last column of Table 4).

DISCUSSION

This randomized, placebo-controlled trial of budesonide (3mg and 9mg daily) and prednisolone (7.5mg daily) showed a dose-dependent reduction in the HPA response to the synacthen test in patients with moderately active rheumatoid arthritis. For prednisolone 7.5mg daily the mean reduction in maximum production of cortisol in response to ACTH was 35%. However, almost all patients who, following glucocorticoid therapy, failed to achieve a normal percentage increase in cortisol in response to ACTH did achieve maximum plasma cortisol levels within the normal range. Thus it is clear that even low doses of a glucocorticoid result in measurable depression of baseline and synacthen stimulated cortisone levels after 12 weeks of therapy. However, all patients were able to respond to ACTH by increasing their plasma concentrations of cortisol, and those who achieved a lower than normal percentage response still achieved an absolute value within the normal range. For comparison with normal subjects the median (5th-95th percentile values) in 100 healthy volunteers were: baseline, 349(164-870); 30 min, 811 (626-1431); 60 min, 972 (766-1655); 0-30min, 488 (289-776); 0-60 min, 645 (433-1063) (17).

There is some evidence from clinical studies that in patients with RA there is a blunting of the diurnal rhythm of hormonal secretion compared to patients with chronic osteomyelitis (18). Patients with rheumatoid arthritis also have a blunted cortisol response to the stress of surgery (19) and impaired cortisol secretion in the presence of intact ACTH secretion consistent with relative adrenal glucocorticoid insufficiency has also been reported (20). However, patients with new onset RA have morning levels of ACTH and cortisol that are similar to normal age- and sex-matched controls (21,22). A review of the literature concluded that most studies have not revealed major differences in HPA axis activity in patients with RA compared with that in control individuals (23). However, subtle differences may exist that influence the time course or severity of inflammation. Crofford and

colleagues (22) have suggested that the normal serum ACTH and cortisol they measured in RA patients was inappropriately low, considering the levels of joint inflammation and raised plasma IL-6. Another study employed the dexamethasone-CRF test to explore HPA control mechanisms in RA (24). Dexamethasone taken 18 hours before an intravenous injection of CRF completely suppresses the ACTH and cortisol response in normal controls, but three of seven patients with active RA were able to escape from this feedback control mechanism. This suggests that there may be a subpopulation of patients with RA who have impaired glucocorticoid feedback.

The synacthen test has been used as an estimate of the HPA response to stress since it was first developed. However, other stressors, such as insulin hypoglycaemia (10, 25) or the administration of pyrogen (3), have been found to produce a normal response in patients taking glucocorticoids (for a variety of reasons) who had a reduced response to ACTH (25). Thus it is not clear that the reduction in response to ACTH following low dose prednisolone revealed in the present study is of physiological significance. Another question is whether the reduced response to ACTH is recovered quickly. In 14 patients who had been taking high doses of prednisone (up to 100mg/m^2/day) for up to 29 days there was a clear suppression of adrenal function, but in the large majority of these patients the HPA axis response was restored in less than 7 days (26). A further study of 75 patients who received at least 25 mg prednisone daily for up to 30 days found that half had a reduced response to CRF on the day after stopping treatment. All but 2 of these patients recovered ACTH function within 2 weeks. (27). It seems likely that recovery from the less marked suppression induced by low dose glucocorticoids would be at least equally rapid, but further measurements will be required to confirm this. An entry requirement for this study was no glucocorticoids in the preceding 30 days. It is possible that some patients received glucocorticoids before then (we did not record that information) but it seems unlikely that this would have affected our results.

Low dose oral prednisolone therapy has attracted added interest in recent years following the recognition that this therapy can prevent the joint destruction of RA (28). The present data show that low doses of a glucocorticoid result in depression of baseline and synacthen stimulated cortisone levels after 12 weeks of therapy. Although the responsiveness of the HPA axis in individual patients generally remains within the normal range, these changes should be investigated further.

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Table 1. Patient characteristics (mean values or proportions).

		Treatment Groups				
		Budesonide 3mg	Budesonide 9mg	Prednisolone 7.5mg	Placebo	Combined
N		37	35	39	31	142
Age (years)		54.2	57.8	53.4	54.7	55.0
Proportion Female (%)		70	77	62	77	71
Weight (Kg)		73.5	74.6	73.9	71.4	73.4
Height (cm)		166	165	168	166	166
Disease Duration (years)		13.1	8.5	7.0	7.2	9.0
Proportion with erosions (%)		84	66	54	87	72
Number taking NSAIDs		30	27	30	26	113
Number taking DMARDs		28	25	26	20	99
Disability (HAQ) Score	Baseline	1.61	1.57	1.51	1.52	1.55
Disability (HAQ) Score	12 weeks	1.57	1.41	1.11	1.48	
Tender joint count	Baseline	14.2	11.8	12.3	12.6	12.7
Tender joint count	12 weeks	11.0	7.7	6.6	11.7	
Swollen joint count	Baseline	12.9	9.8	11.6	11.8	11.5
Swollen joint count	12 weeks	10.2	6.2	7.2	11.5	
Patient's assessment of pain (mm)	Baseline	54.1	65.5	49.2	56.9	56.22
Patient's assessment of pain (mm)	12 weeks	47.9	47.6	28.8	54.8	
Patient's global*	Baseline	50.6	59.0	54.4	54.4	54.54
Patient's global*	12 weeks	48.1	42.4	31.8	55.8	
Clinician’s global**	Baseline	3.1	3.2	3.0	3.1	3.1
Clinician’s global**	12 weeks	2.8	2.7	2.3	3.0	
Early morning stiffness (minutes)	Baseline	111	98	93	105	102
Early morning stiffness (minutes)	12 weeks	54	73	73	94	
CRP (mg/L)	Baseline	22.5	32.9	30.2	39.9	28.8
CRP (mg/L)	12 weeks	21.0	33.3	10.8	34.2	

*Patient's global assessment of disease activity ** Clinician’s global assessment of disease activity

Table 2. Mean (96% CI) plasma cortisol concentrations (nmol/L) during the ACTH test for patients before and after treatment.

			Time after ACTH injection								
			Baseline			30 mins			60 mins		
Occasion	Medication	N	Mean	95% CI		Mean	95% CI		Mean	95% CI	
Before Treatment	Budesonide 3 mg	37	397	(341, 453)		672	(619, 726)		743	(679, 807)	
	Budesonide 9 mg	34	387	(344, 429)		711	(664, 758)		821	(767, 875)	
	Prednisolone 7.5 mg	38	348	(318, 378)		674	(634, 714)		786	(737, 835)	
	Placebo	30	366	(311, 422)		695	(642, 749)		790	(738, 842)	
After Treatment	Budesonide 3 mg	36	341	(297, 393)	**b	565	(514, 616)	***bc	646	(594, 698)	*a, ***bc
	Budesonide 9 mg	32	286	(228, 344)		479	(401, 557)	***d	545	(467, 622)	***d
	Prednisolone 7.5 mg	37	251	(208, 295)	**e	443	(394, 491)	***e	511	(456, 565)	***e
	Placebo	29	349	(296, 402)		690	(639, 740)		788	(736, 840)	

*P<0.05, **P<0.01, ***P<0.001; [a] Budesonide 3 mg vs. Budesonide 9 mg; [b] Budesonide 3 mg vs. Prednisolone 7.5 mg; [c] Budesonide 3 mg vs. Placebo; [d] Budesonide 9 mg vs. Placebo; [e] Prednisolone 7.5 mg vs. Placebo

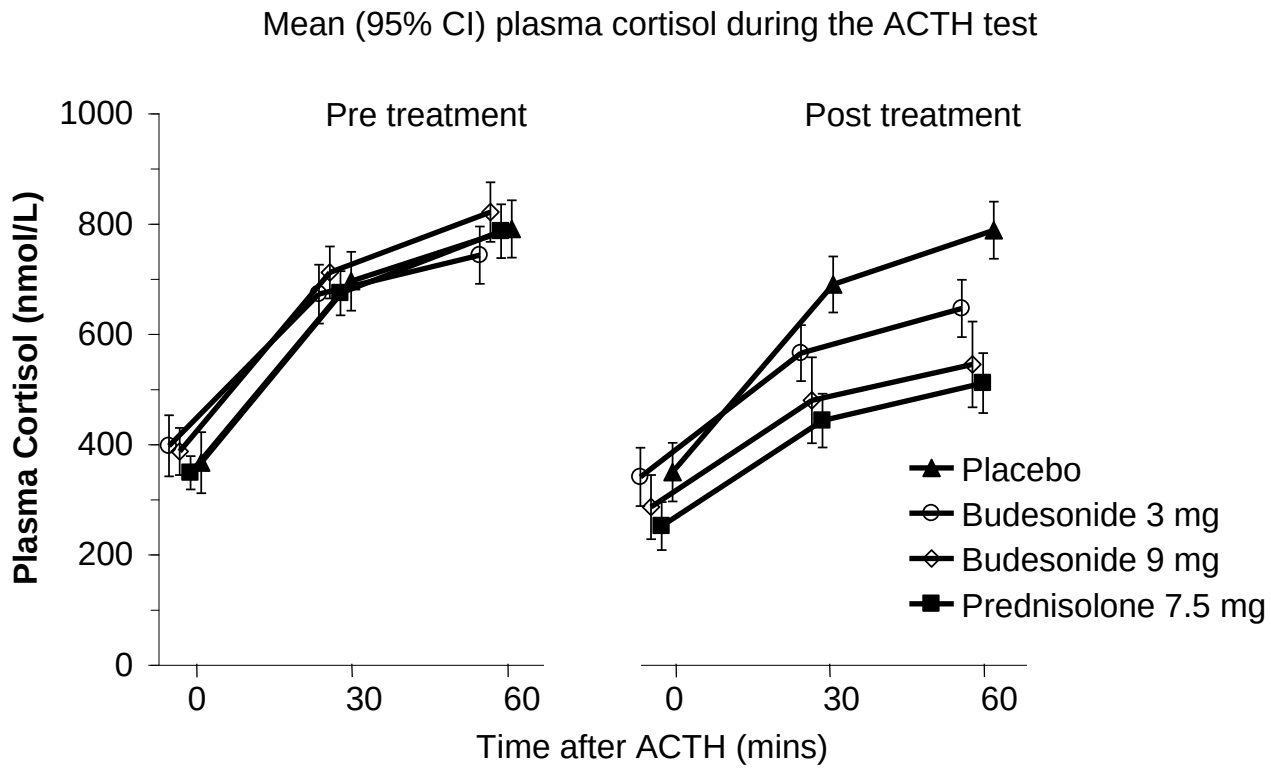
Table 3. Number (percent) of patients with plasma cortisol more than 2 standard deviations below pre-treatment values

	Time after ACTH injection					
	Before Treatment			After Treatment		
Treatment Group	Baseline	30 mins	60 mins	Baseline	30 mins	60 mins
Budesonide 3 mg	0 (0)	1 (3)	2 (5)	1 (3)	4 (11)	3 (8)
Budesonide 9 mg	0 (0)	0 (0)	0 (0)	7 (21)	11 (34)	11 (34)
Prednisolone 7.5 mg	0 (0)	1 (3)	1 (3)	5 (14)	14 (38)	14 (38)
Placebo	1 (3)	1 (3)	1 (3)	0 (0)	0 (0)	0 (0)

Table 4. Number (%) of patients failing to meet 'normal' criteria for change in plasma cortisol following ACTH injection.

Occasion	Medication	Baseline	Maximum	Increase	Baseline *and* Maximum	Baseline *and* Increase	Maximum *and* Increase	Maximum *or* Increase	Baseline *and* Maximum *and* Increase
Before Treatment	Budesonide 3 mg	0 (0)	1 (3)	4 (11)	0 (0)	0 (0)	0 (0)	5 (14)	0 (0)
	Budesonide 9 mg	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)
	Prednisolone 7.5 mg	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)
	Placebo	1 (3)	1 (3)	1 (3)	1 (3)	0 (0)	0 (0)	2 (7)	0 (0)
After Treatment	Budesonide 3 mg	1 (3)	3 (8)	0 (0)	0 (0)	0 (0)	0 (0)	3 (8)	0 (0)
	Budesonide 9 mg	7 (21)	11 (34)	3 (9)	6 (19)	0 (0)	1 (3)	14 (44)	0 (0)
	Prednisolone 7.5 mg	5 (14)	17 (46)	1 (3)	4 (11)	0 (0)	0 (0)	17 (47)	0 (0)
	Placebo	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Figure 1. Changes (mean and 95% confidence intervals) in plasma cortisol during the ACTH test before and after treatment with placebo, budesonide 3mg, budesonide 9mg and prednisolone 7.5mg. [Time points slightly displaced for clarity.]


Mean (95% CI) plasma cortisol during the ACTH test
Pre treatment
Post treatment
Plasma Cortisol (nmol/L)
1000
800
600
400
200
0
0
30
60
0
30
60
Time after ACTH (mins)
Placebo
Budesonide 3 mg
Budesonide 9 mg
Prednisolone 7.5 mg