The timing of glucocorticoid administration in rheumatoid arthritis

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Abstract

***Objective*—To test the hypothesis that the timing of prednisolone administration might be critical in determining its effect on the diurnal rheumatoid inflammatory process.**

***Methods*—26 patients with rheumatoid arthritis were randomly divided into two equal groups and allocated to low doses of prednisolone at either 2.00 am or 7.30 am. Because of the diurnal variation in disease activity in rheumatoid arthritis, assessments of the two study groups were performed at 7.30 am both at the start of the study (day 1) and after four doses of prednisolone (day 5). The study protocol differences in the time period from the last dose of prednisolone to assessment were 5.5 hours in the 2.00 am group and 24 hours in the 7.30 am group.**

***Results*—Administration of low doses of prednisolone (5 or 7.5 mg daily) at 2.00 am had favourable effects on the duration of morning stiffness ($P << 0.001$), joint pain ($P < 0.001$), Lansbury index ($P << 0.001$), Ritchie index ($P << 0.001$), and morning serum concentrations of IL-6 ($P < 0.01$). The other study group showed minor but significant effects on morning stiffness ($P < 0.05$) and circulating concentrations of IL-6 ($P < 0.05$). Modest and similar improvements of C reactive protein, serum amyloid protein A, and erythrocyte sedimentation rate were seen in both study groups.**

***Conclusions*—Administration of low doses of glucocorticoids with a rather short biological half life seems to improve acute rheumatoid arthritis symptoms if it precedes the period of circadian flare in inflammatory activity, as defined by enhanced IL-6 synthesis. Further studies are needed to test the relative merits of different timing protocols of glucocorticoid administration in rheumatoid arthritis.**

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Morning stiffness is a characteristic feature of rheumatoid arthritis and is included both in the diagnostic criteria and in the criteria for clinical remission in this disease.[1 2] The circadian rhythm of symptoms in this disease has also been confirmed by objective measurements of joint stiffness and grip strength.[3–5] The circadian rhythm of disease activity has no obvious explanation but may be dependent on a diurnal variation in the inflammatory process or plasma cortisol levels.[5]

Glucocorticoids have been used in the treatment of rheumatoid arthritis since 1948,[6] partly because of their ability to relieve symptoms such as joint stiffness and joint pain. This effect is brought about by their diverse anti-inflammatory and immunosuppressive properties, which include inhibition of the interleukin-6 (IL-6) synthesis.[7–11] The glucocorticoids most widely used today have a biological effect with a rather short half life.[12] They are usually given in the morning in order to minimise the disturbance of the physiological circadian rhythm of endogenous adrenal glucocorticoids.

We have questioned the established regimen of giving glucocorticoids in the morning to patients with rheumatoid arthritis because of our observation that there exists a circadian rhythm in the concentrations of serum IL-6 in rheumatoid arthritis: these peak early in the morning and decline towards normal levels during the afternoon and evening.[11] IL-6 is considered to be the cytokine largely responsible for inducing the synthesis of the acute phase proteins C reactive protein and serum amyloid protein A (SAA),[13–16] and is one of the major cytokines involved in bone resorption.[17–19] Assuming that the rhythm in serum IL-6 mirrors its production and is associated with a flare in inflammatory activity early in the morning, the timing of glucocorticoid administration might be important for its effect on the rheumatoid inflammatory process. In this study, we tested this hypothesis by giving a low dose of prednisolone at 2.00 am to a randomised group of patients with rheumatoid arthritis and compared the effect on clinical and laboratory variables of disease activity in a complementary group of patients with rheumatoid arthritis who received the same dose of prednisolone, but at 7.30 am.

Methods

Twenty six patients, six males with a mean age of 69 (SD 4) years (range 54 to 80 years) and 20 females with a mean age of 62 (4) years (range 23 to 90 years), who fulfilled the criteria of the American College of Rheumatology for rheumatoid arthritis,[1] were included in the study. All patients were referred to the Section of Rheumatology, Uppsala University Hospital, because of active disease and were studied as inpatients after informed consent and approval of the local ethics committee, and according to the Declaration of Helsinki. At the start of the study, the majority of the patients were on long term treatment with non-steroidal anti-inflammatory drugs (NSAID). Two were treated with sulphasalazine and one

Table 1 Clinical and laboratory data in 13 patients with rheumatoid arthritis on admission (day 1) and after four doses of prednisolone given at 2.00 am (day 5). Values are mean (SEM)

	Day 1	*Day 5*	*Δ #*
Age (years)	62 (4)		
Disease duration (years)	10 (3)		
Morning stiffness (min)	242 (38)	53 (27)	−189 (25)¶
Pain at rest (VAS)	4.0 (0.7)	1.5 (0.4)	−2.5 (0.5)‡
Lansbury index	130 (23)	33 (7)	−97 (21)¶
Ritchie index	21 (3)	10 (2)	−11 (2) ¶
IL-6 (pg litre^{-1})	50 (12)	10 (2)	−40 (10)†
CRP (mg litre^{-1})	34 (8)	16 (3)	−18 (5) †
SAA (mg litre^{-1})	562 (184)	223 (63)	−339 (170) NS
ESR (mm/h)	47 (9)	36 (5)	−11 (6) NS
Haptoglobin (g litre^{-1})	2.8 (0.3)	2.7 (0.3)	−0.1 (0.05) NS
Haemoglobin (g litre^{-1})	115 (5)	118 (5)	+3.0 (1.1) †
WBC × 10^9	6.9 (0.4)	7.1 (0.4)	+0.2 (0.3) NS
Polymorphonuclear WBC	4.7 (0.3)	5.3 (0.3)	+0.6 (0.3) NS
Mononuclear WBC	2.2 (0.2)	1.8 (0.1)	−0.4 (0.1)‡
Platelet count × 10^9	308 (19)	336 (24)	+28 (8)*

VAS, visual analogue score; IL-6, interleukin-6; CRP, C reactive protein; SAA, serum amyloid protein A; ESR, erythrocyte sedimentation rate; WBC, white blood cell count
Paired *t* test: ¶P << 0.001; ‡P < 0.001; †P < 0.01; *P < 0.05; # Differences in values between days 1 and 5

with auranofin. None of the patients had been treated with local or systemic glucocorticoids during the three months before inclusion in the study.

The patients were randomly divided into two equal groups and allocated to prednisolone at either 2.00 am (11 female, two male) or 7.30 am (nine female, four male). Four patients in the 2.00 am group and four patients in the 7.30 am group were treated with 7.5 mg daily and the other patients (n = 18) were treated with 5 mg daily. All patients received four doses of prednisolone and were observed for five days. Each patient was evaluated clinically by the same observer (NGA) at 7.30 am before treatment (day 1) and after treatment (day 5) according to the Ritchie index[20] and a simplified Lansbury index.[21] The physician's clinical assessments were made with knowledge of patients' therapy group status. The duration of morning stiffness and joint pain score at rest, using a 10 grade visual analogue scale, was recorded. The assessments were consistently made at 7.30 in the morning, since the symptoms of patients with rheumatoid arthritis are by far the worst in the morning and spontaneously improve towards lunch time. Thus the 2.00 am group was assessed 5.5 hours after the last dose of prednisolone whereas the 7.30 am group was assessed 24 hours after the last dose of prednisolone. A patient self assessment on a five grade scale concerning the global effect of treatment (the overall response and satisfaction throughout the protocol) was recorded on day 5 ("no effect", "poor effect", "fair effect", "good effect", and "excellent effect").

Table 2 Clinical and laboratory data in 13 patients with rheumatoid arthritis on admission (day 1) and after four doses of prednisolone given at 7.30 am (day 5). Values are mean (SEM)

	Day 1	*Day 5*	*Δ #*
Age (years)	64 (5)		
Disease duration (years)	12 (4)		
Morning stiffness (min)	307 (103)	260 (104)	−47 (19)*
Pain at rest (VAS)	3.5 (0.6)	3.4 (0.7)	−0.1 (0.4) NS
Lansbury index	101 (19)	87 (13)	−14 (15) NS
Ritchie index	16 (2)	14 (2)	−2 (1) NS
IL-6 (pg litre^{-1})	45 (13)	28 (8)	−17 (7)*
CRP (mg litre^{-1})	31 (5)	14 (1)	−17 (4)†
SAA (mg litre^{-1})	350 (119)	225 (79)	−125 (85) NS
ESR (mm/h)	40 (5)	31 (4)	−9 (2)‡
Haptoglogin (g litre^{-1})	2.4 (0.3)	2.3 (0.3)	−0.1 (0.1) NS
Haemoglobin (g litre^{-1})	123 (3)	123 (3)	−0.2 (0.8) NS
WBC × 10^9	7.0 (0.6)	7.7 (0.5)	+0.7 (0.2) NS
Polymorphonuclear WBC	4.6 (0.4)	4.6 (0.4)	+0.0 NS
Mononuclear WBC	2.4 (0.2)	3.1 (0.3)	+0.7 (0.1)‡
Platelet count × 10^9	256 (14)	276 (15)	+20 (6)†

For key to abbreviations, see table1
Paired *t* test: ‡P < 0.001; †P < 0.01; *P < 0.05; # Differences in values between days 1 and 5.

Because of the circadian variation in serum IL-6 concentrations in patients with rheumatoid arthritis, with peak values early in the morning, care was taken to draw blood samples at 7.30 am from all patients on day 1 and day 5 after overnight fasting and while the patient was still in bed. The serum samples were collected in glass tubes without anticoagulant and stored for one hour at room temperature, centrifuged at 0°C, and aliquoted in plastic tubes before being stored at −70°C for later analysis of IL-6. The blood samples (normal ranges in parentheses) were analysed for IL-6 (< 3 pg litre^{-1}), C reactive protein (< 3 mg litre^{-1}), SAA (< 3 mg litre^{-1}), ESR (< 15 mm/h), serum haptoglobin (0.29-2.04 g litre^{-1}), haemoglobin (female 113-139; and male 134-166 g litre^{-1}), white blood cell count (WBC; 4-9 × 10^9 litre^{-1}), polymorphonuclear and mononuclear cell counts (3.8-6.8 × 10^9 litre^{-1} and 2.0-5.0 × 10^9 litre^{-1}, respectively), and platelet counts (150-400 × 10^9 litre^{-1}). Plasma cortisol and ACTH were not measured in this study. The IL-6 assay was performed with a Quantikine IL-6 immunoassay kit (R&D Systems, Minneapolis, MN, USA) and the SAA assay were performed with Cytoscreen SAA immunoassay kit (Bio Source International, Camarillo, CA, USA). The assays were performed according to the recommendations of the manufacturers.

STATISTICAL ANALYSIS

Values and differences in values between days 1 and 5 (Δ values) are given as means (SEM). The paired *t* test was used to compare changes due to treatment. A P value of < 0.05 was considered significant.

Results

On admission, the patients with rheumatoid arthritis (n = 26) had symptoms indicating active disease with prominent morning stiffness [275 (SEM 54) min] and high scores for joint indices [Lansbury index 116 (15), Ritchie index 19 (2)]. Laboratory analysis indicated active inflammatory disease with increased serum concentrations of C reactive protein [32 (4) mg litre^{-1}] and SAA protein [465 (109) mg litre^{-1}]. The patients also had increased serum concentrations of IL-6 in the morning [47.3 (8.4) pg litre^{-1}], which correlated with morning stiffness (r = 0.5; P < 0.01) and the acute phase proteins C reactive protein (r = 0.6; P < 0.01) and SAA protein (r = 0.6; P < 0.001).

EFFECT OF GLUCOCORTICOIDS ON CLINICAL SYMPTOMS

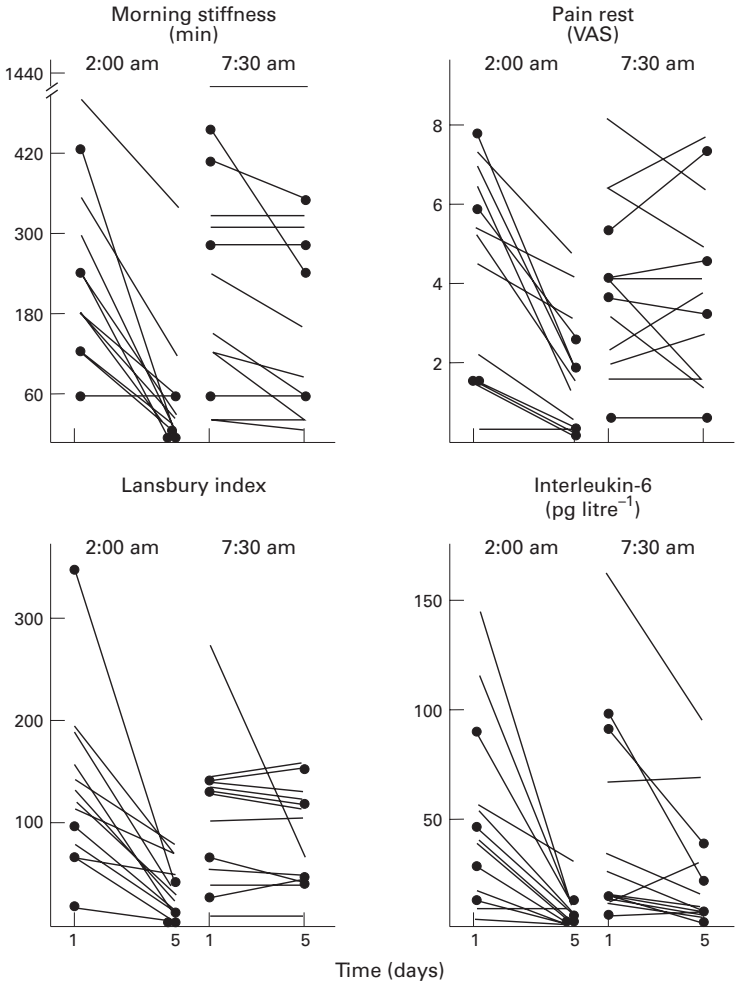
The patients were randomly divided into two groups with prednisolone at either 2.00 am or 7.30 am. On admission (day 1), no differences were seen between the two groups with respect

Table 3 Baseline serum IL-6 and other important baseline data (age, sex, and prednisolone dosage) of the individual patients in each study group

2.00 am dose				*7.30 am dose*			
Age (years)	*Sex (M/F)*	*Dose (mg)*	*IL-6 (pg l^{-1})*	*Age (years)*	*Sex (M/F)*	*Dose (mg)*	*IL-6 (pg l^{-1})*
78	F	7.5	52	77	F	7.5	90
79	M	7.5	87	23	F	7.5	17
52	F	7.5	28	68	F	7.5	12
80	M	7.5	14	85	F	7.5	99
72	F	5.0	114	60	M	5.0	156
69	F	5.0	40	66	F	5.0	35
47	F	5.0	17	54	M	5.0	13
64	F	5.0	56	72	F	5.0	21
51	F	5.0	40	44	F	5.0	27
77	F	5.0	47	71	M	5.0	14
34	F	5.0	4	58	F	5.0	21
43	F	5.0	10	70	M	5.0	7
63	F	5.0	143	90	F	5.0	69

to age, disease duration, or clinical and laboratory indices of disease activity (tables 1 and 2).

In all patients belonging to the 2.00 am group, the administration of prednisolone induced a significant beneficial effect on morning stiffness, joint pain, and joint indices ($P << 0.001$, $P < 0.001$, $P << 0.001$, and $P << 0.001$, respectively). In contrast, no significant improvements in these variables, except for morning stiffness ($P < 0.05$), was observed after prednisolone administration to the patients in the 7.30 am group (tables 1 and 2; figure). The patients' self-assessment concerning the global effect of treatment was scored "good-excellent" (score 3.3) in the 2.00 am group and "poor-fair" (score 1.6) in the 7.30 am group ($p < 0.01$).



The individual values for morning stiffness, pain at rest, Lansbury index, and serum IL-6 in patients with rheumatoid arthritis before (day 1) and after (day 5) treatment with prednisolone at daily doses of 5 mg or 7.5 mg (circles). The patients who received prednisolone at 2.00 am or at 7.30 am are indicated.

EFFECT OF GLUCOCORTICOIDS ON IL-6 AND ACUTE PHASE PROTEINS

The morning serum concentrations of IL-6 decreased in both treatment groups ($P < 0.01$ and $P < 0.05$, respectively; tables 1 and 2). C reactive protein decreased by 52% in the 2.00 am group and by 54% in the 7.30 am group. The relative fall in SAA protein was 60% in the 2.00 am group and 36% in the 7.30 am group.

CHANGES IN IL-6 *v* CHANGES IN ACUTE PHASE PROTEINS AND CLINICAL SYMPTOMS DUE TO TREATMENT WITH GLUCOCORTICOIDS

The 2.00 am group

The change in IL-6 (Δ IL-6) correlated with the change in C reactive protein (Δ C reactive protein), $r = 0.74$; $P < 0.01$, and with the change in SAA (Δ SAA), $r = 0.84$; $P < 0.001$, but not with clinical symptoms of inflammation.

The 7.30 am group

Δ IL-6 correlated with Δ C reactive protein ($r = 0.62$; $P < 0.05$) and with the change in Ritchie index ($r = 0.67$; $P < 0.05$), but not with Δ SAA.

The serum IL-6 concentrations on day 1 correlated with the age of patient for all patients included in the study ($r = 0.38$; $P < 0.05$), table 3. However, Δ IL-6 did not correlate with the age in either the 7.30 am group or the 2.00 am group.

Discussion

In rheumatoid arthritis, a circadian rhythm of disease activity—as measured by repeated estimations of joint pain, morning stiffness, and grip strength—has previously been well documented.[3–5] The mechanism behind this circadian rhythm is not known, but the symptom of morning stiffness has been partly attributed to an increase in the fluid content of joint tissue at night, due to an accumulation of macromolecules such as hyaluronic acid, which is of importance in water homeostasis.[22] Another and possibly related explanation is the presence of a diurnal variation in inflammatory processes linked to the diurnal variation in endogenous cortisol production.[5] Irrespective of the underlying mechanism behind the circadian variation in disease activity in rheumatoid arthritis, the time of the day for making clinical assessments, and in particular when assessments are recorded in clinical trials, must be considered.

We recently reported that the circulating concentrations of IL-6, but not of tumour necrosis factor α, are increased in the morning (at 7.30 am) in patients with rheumatoid arthritis, and decline significantly from early in the afternoon to late in the evening.[11] IL-6

seems to play a key role in the rheumatoid inflammatory process[23–25] and is considered to be the cytokine largely responsible for inducing C reactive protein and SAA protein synthesis.[13–16] The circadian rhythm of IL-6 may possibly influence the clinical features of rheumatoid arthritis but should also be taken into consideration when IL-6 is used as a tool for monitoring disease activity in rheumatoid arthritis. Measurements of IL-6 at different times of the day may explain the previous confusing results which tried to correlate serum IL-6 concentrations to signs of disease activity in rheumatoid arthritis.[26–29] In the present study, we found that serum IL-6 concentrations in the morning correlated with morning stiffness and with the acute phase proteins C reactive protein and SAA.

Assuming that the morning IL-6 peak contributes to the clinical features observed in rheumatoid arthritis, it would be worthwhile to try to minimise the IL-6 influence by the adequate timing of the intake of drugs that inhibit IL-6, such as glucocorticoids.[9] In this study, an effort was made to test the hypothesis that the timing of the administration of steroidal anti-inflammatory drugs might be a significant factor in achieving optimum control of the symptoms. A low dose of prednisolone (5 mg or 7.5 mg daily) given at 2.00 am was found to induce an 80% reduction of IL-6 concentrations and a significant improvement in morning stiffness, pain, and joint index. The other study group received a low dose of prednisolone in the conventional way, that is in the morning. In this group the influence on IL-6 concentrations and symptoms was less obvious. Since the study groups had significantly unequal intervals between their last prednisolone dose and their outcome assessments one cannot properly compare effects of 2.00 am versus 7.30 am dosing. Furthermore, the possible influence of the time of prednisolone intake on the subjectivity in responses was not considered. It could be argued that assessments should not have been performed at a fixed time in the morning but at a fixed time after the administration of the glucocorticoids. However, such a design might have reduced the ability to detect changes, since IL-6 concentrations and symptoms spontaneously decrease in rheumatoid arthritis patients later during the day.[11] In this context, it is worthwhile mentioning that we did not observe any rebound phenomenon with a worsening of symptoms in the afternoon/evening in the 2.00 am prednisolone group. This situation was also reflected by the patients' self assessment of the global effect of treatment.

In rheumatoid arthritis, the most widely used glucocorticoids are prednisone and prednisolone, which are rapidly absorbed after oral administration and peak plasma concentrations are attained after one to three hours, although a wide intersubject variation in plasma concentration has been found after both drugs, suggesting impaired drug absorption in some individuals. The plasma half life of prednisolone is 2.1-3.5 hours[30] and the biological half life of prednisone/prednisolone has been calculated to be six hours.[12] The glucocorticoid effect in rheumatoid arthritis is partly due to acute anti-inflammatory effects on oedema and pain. One therapeutic aim of glucocorticoid treatment in rheumatoid arthritis is to reduce symptoms related to inflammation by using its acute anti-inflammatory effects in the lowest possible dose. An optimal strategy should be based on the pharmacokinetics and biological half life of prednisolone and on the facts that the symptoms in rheumatoid arthritis are more severe in the morning and that the inflammatory flare, defined by the circadian synthesis of IL-6, starts late at night.[11] The small but significant changes in blood leucocyte and platelet counts seen in our patient groups during the study period may not only be due to day to day variations[31] but should also be attributed to glucocorticoid effects on inflammation mediated and naturally occurring variations in circulating blood cells.[32] The significant but opposite effects on mononuclear cell counts seen in the two treatment groups may be of importance in understanding glucocorticoid influences on the diurnal variation of inflammatory activity in rheumatoid arthritis. The glucocorticoid effect on cellular proliferation may have a slower onset of action. In fact, disease modifying effects of prednisolone in rheumatoid arthritis were recently documented by Kirwan *et al*, who reported clinical and radiological efficacy of long term (two years) low dose prednisolone (7.5 mg daily in the morning) in a randomised double blind trial in 128 adults with active rheumatoid arthritis of less than two years' duration.[33]

Glucocorticoids in long term treatment protocols are given in the morning to match the circadian rhythm of endogenous cortisol secretion. Nocturnal administration of glucocorticoids might therefore be controversial. However, this objection to the timing of glucocorticoid administration will be of less importance if the total glucocorticoid intake is reduced. It has also been stated that there is no significant inhibition of the hypothalamic-pituitary-adrenocortical axis if the daily dose of prednisone/prednisolone is kept below 5 mg, and between 5 and 7.5 mg the inhibition is variable.[34] A reduced total glucocorticoid intake as a result of optimal timing of administration should certainly reduce the risk of steroid induced osteoporosis, since glucocorticoids inhibit osteoblast production in a dose dependent manner.[35 36] It has recently been reported that IL-6 is one of the major cytokines involved in bone resorption.[17–19] The results of this study suggest that the morning IL-6 peak in rheumatoid arthritis is reduced by low doses of nocturnal prednisolone to the same extent as previously reported after the administration of 15-20 mg of prednisolone in the morning 24 hours before testing.[11] Analysis of the toxicity of low dose, long term glucocorticoids in the treatment of rheumatoid arthritis has shown that an average dose of prednisolone greater than 10 mg/d correlated most strongly with the

development of adverse events.[37] It is an intriguing possibility that a subtoxic dose of prednisolone at night may reduce the risk of osteoporosis by inducing a prominent inhibition of IL-6 synthesis.

The results of the present study seem to support the concept that the timing of glucocorticoid administration may be important in controlling the acute inflammatory aspects of rheumatoid arthritis. However, further investigations would be needed to better define and document such effects and to determine the optimal administration of low dose glucocorticoids in the long term treatment of rheumatoid arthritis.

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