Targeting the time of day for glucocorticoid delivery in rheumatoid arthritis

Glucocorticoid treatment for rheumatoid arthritis is generally taken in the mornings, and there is some evidence to support this practice. However, increased understanding of the role of cytokines in the pathogenesis of rheumatoid arthritis, and of their interaction with the hypothalamic–pituitary–adrenal axis, has suggested that glucocorticoids delivered in the early hours of the morning may have additional efficacy. The development of appropriate tablet technology and the conduct of randomized controlled trials and detailed clinical studies have shown that the early morning increase in plasma IL-6 concentrations, and its associated diurnal increase in symptoms such as morning stiffness can both be reduced by nocturnal glucocorticoid treatment. Fears that hypothalamic–pituitary–adrenal axis responses might be further blunted appear to be unfounded.

KEYWORDS: glucocorticoids ■ hypothalamic–pituitary–adrenal axis ■ morning stiffness ■ polymyalgia rheumatica ■ rheumatoid arthritis ■ timed release

John Richard Kirwan

Academic Rheumatology Unit, Bristol Royal Infirmary, Bristol, BS2 8HW, UK
Tel.: +44 117 342 2904
Fax: +44 117 342 3841
John.Kirwan@Bristol.ac.uk

Background: brief historical review

In a 1967 review of the current state of low-dose glucocorticoid therapy in rheumatoid arthritis (RA), Jefferies noted that the administration of a single daily dose of glucocorticoid in the evening, even though an apparently effective anti-inflammatory treatment, may be less physiologic and therefore less safe than morning treatment [1]. The assessment was based on considerations of the negative feedback mechanism of hypothalamic–pituitary–adrenal (HPA) axis control acting through cortisol. Nichols and colleagues had shown [2], in a study of normal subjects given glucocorticoids orally at 8 am, 4 pm or midnight, that dexamethasone administered at 8 am or 4 pm caused only temporary suppression of cortisol secretion, but when given at midnight produced virtually complete suppression of cortisol production for a full 24-h period. Nevertheless, some HPA reserve (i.e. ability to increase cortisol production during a methopyrapone test) was present in all of ten patients who had been taking 5 mg prednisolone at 10 pm each evening for over 2 years [3]. Considerations such as these, together with the recognition of higher incidence of adverse effects when divided daily doses were used [4], had led to initial recommendations to use a single daily dose in the morning [5].

One randomized controlled trial identified some patients who preferred to take 5 mg prednisolone at 10 pm rather than in the morning [6]. Further, an extensive review of HPA function in patients treated with a variety of dosing regimens, including evening treatment, suggested abnormalities were equally likely with all dose regimens [7], and it was recognized that this was due to adrenal cortex suppression [8]. A further study [9] attributed HPA suppression to multiple daily dose regimens. And so routine clinical practice continued to favor morning treatment [4].

A further randomized controlled within-patient trial [10] treated 12 patients with an average dose of 5.6 mg prednisone at 8 am, 1 pm or 11 pm and concluded that a single morning dose was as good as an evening dose and should be used "because adrenopituitary suppression should be minimized". Another randomized controlled within-patient study trial 2 years later found in favor of 10–11 pm dosing as opposed to 6–7 am as it significantly reduced early morning stiffness [11]. Nevertheless, as reported by Arvidson, glucocorticoids "continued to usually be given in the morning in order to minimise the disturbance of the physiological circadian rhythm of endogenous adrenal glucocorticoids" [12]. The case for evening treatment was ambiguous and not clear cut, the possibility of increased HPA axis suppression was suggested but not proven, and there was little further impetus to clarify the situation, so morning treatment continues to be routine clinical practice for the majority of rheumatologists.

The role of IL-6

Arvidson proposed that the circadian variation in symptoms, particularly morning stiffness, might be related to a circadian variation in plasma concentrations of the proinflammatory

future medicine part of fsg

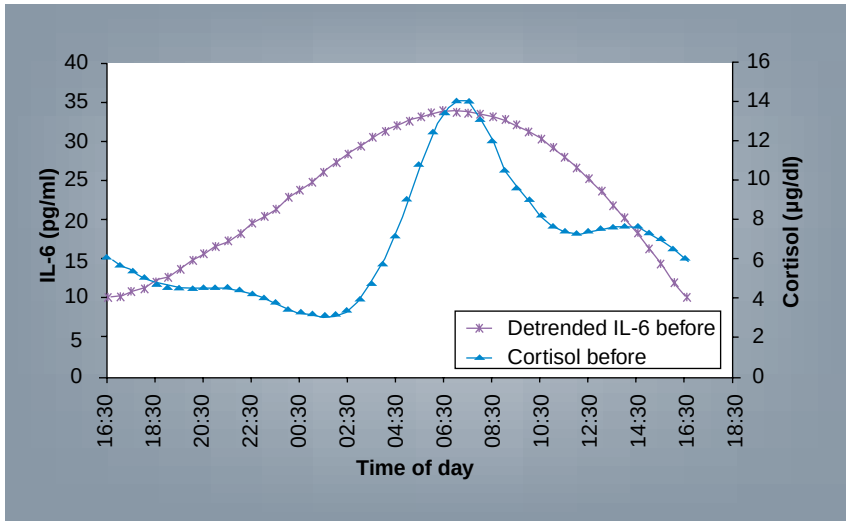

Figure 1. Blood IL-6 and cortisol concentrations in nine patients with rheumatoid arthritis.
Detrended data taken from [23,24].

cytokine IL-6, which were shown to be raised in RA patients and higher in the morning than in the afternoon [13]. Crofford showed that IL-6 changed over 24 h and had peak values at 7 am (when measured every 3 h over 24 h in five newly diagnosed patients) [14].

During this period it became clear that there was an interconnection between IL-6 and HPA axis function. Recombinant IL-6 dramatically stimulates the HPA axis [15] and the potential for a link between the inflammatory cytokines and circadian cortisol control has been increasingly recognized [16–18]. Indeed, the possibility that RA is, in some way, related to a deficiency in glucocorticoid (the hypothesis that stimulated the first treatment of RA patients with cortisone [19]) has re-emerged more clearly as a recognition that there are probably inadequately low serum levels of steroid hormones in relation to IL-6 patients with RA. This may be related to chronic overstimulation by IL-6 and subsequent 'exhaustion' or resetting of HPA responsiveness (for example, see [16]). Glucocorticoids are powerful inhibitors of IL-6 production, and Arvidson, reasoning that the rise in IL-6 might best be counteracted by treatment in the early hours of the morning, compared 2 am prednisone with 7.30 am prednisone and showed it to be superior in the control of symptoms, and to lower morning IL-6 concentrations [12]. We replicated this work in a pilot study [20] but 2 am medication was only possible if the patient woke up, and repeated waking would alter circadian rhythms, so this treatment was not sustainable.

The biologic half-times of effect for different glucocorticoid preparations are from 1.5 to 2.0 times their half-time of disappearance from plasma [21]. Therefore, it may be possible that an immediate release preparation taken at bed time (say 10 pm) will continue to have some effective action spreading into the rising peak of circulating IL-6. However, this will be a very weak effect, and a timed, delayed-release formulation of glucocorticoid would be required for feasible treatment. This would target therapy to the specific time during the circadian cycle when the anti-IL-6 activity might be most useful. Such a formulation has now been developed, probably producing its peak biological effect at approximately 4 am, and has been used in further studies as outlined below.

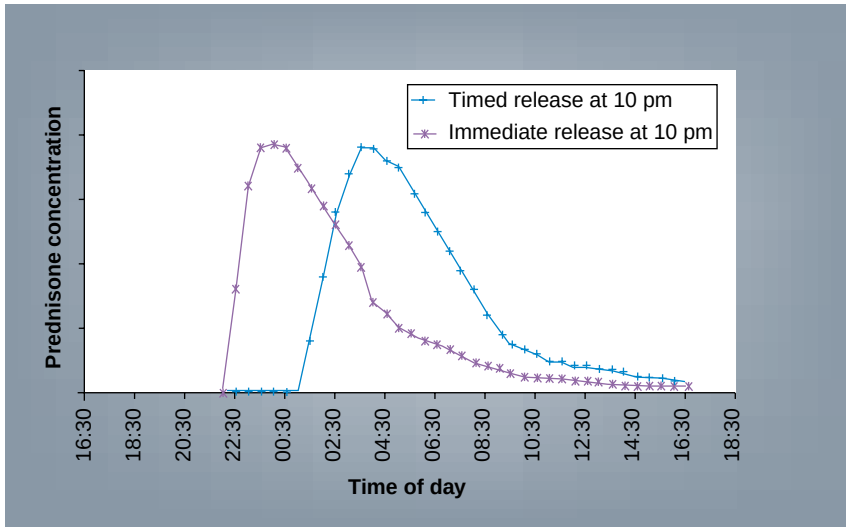

Figure 2. Blood prednisone following standard immediate-release tablets, and the new modified-release medication timed to make the prednisone available for absorption from 2 am.
Originally published in European Musculoskeletal Review © Touch Briefings. Reproduced with permission from [30].

Detailed overnight observations of timed-release prednisone

We have developed a system of frequent blood sampling for cytokine and cortisol measurement in patients with RA, initially in overnight studies and subsequently in 24 h investigations. First, we confirmed with more patients and more detailed analysis that IL-6 concentrations do increase overnight in patients with RA, and reach a peak at around waking time [22]. Furthermore, of the nine cytokines assessed, only IL-6 showed an overnight rise, and this occurred a few hours before the normal nocturnal rise in cortisol. We went on to confirm these initial findings in a new group of patients [23,24], but this time went on to measure IL-6 and cortisol levels before and after 2 weeks of treatment with timed-release prednisone. These results show the circadian pattern

in IL-6 and cortisol more clearly, and also show how they are altered by timed-release prednisone delivered at approximately 2 am.

Figure 1 shows blood IL-6 and cortisol concentrations in nine patients with RA before any glucocorticoid treatment. The values have been taken directly from published data [23,24] but have been detrended. Detrending allows for the steady drift in baseline IL-6 measurements usually found during prolonged measurements using indwelling catheters [22] and makes it easier to concentrate on the pattern of changes. The IL-6 concentrations rise steadily through the night and, from around 3 am onwards, cortisol concentrations increase rapidly, reaching a peak at around the same time as IL-6 at approximately 7 am.

Figure 2 illustrates that the blood profile of prednisone achieved after the modified 'timed'-release tablet is taken at 10 pm is almost identical to that of the standard immediate-release preparation, except for the 4-h delay in delivery. Figure 3 combines the information and includes the likely biological effect times of the circulating prednisone. The biological effect of immediate-release prednisone occurs at the time of lowest endogenous glucocorticoid circulation. It is possible, therefore, that it might have a slightly greater anti-inflammatory effect compared with morning dosing. This may explain the confusing and occasionally supportive results of the clinical studies reported in the historical overview, above. However, the target of interest is the peak in the IL-6 concentration, and this can only be reached with the timed-release preparation.

It has been reported that HPA suppression may be more likely with evening immediate-release glucocorticoid [2] and it might be thought that the delayed-release preparation might make this worse as the exogenous glucocorticoid is delivered at the time of the natural cortisol increase, which might therefore be suppressed by negative feedback. On the other hand, it may be that the suppression of IL-6 by the prednisone might take away some of the effects of the RA on the HPA axis and reduce the relative underactivity. To resolve this question both IL-6 and cortisol were measured in our studies of timed-release treatment, the results of which are shown in Figures 4 & 5.

There is a clear suppression of the IL-6 peak, and this was associated with substantially improved symptoms. This might have been anticipated, but the findings for the cortisol, where there is a statistically significant increase in both peak cortisol and the rate of increase in cortisol during the night, are of particular interest. This finding suggests the possibility of improved, not

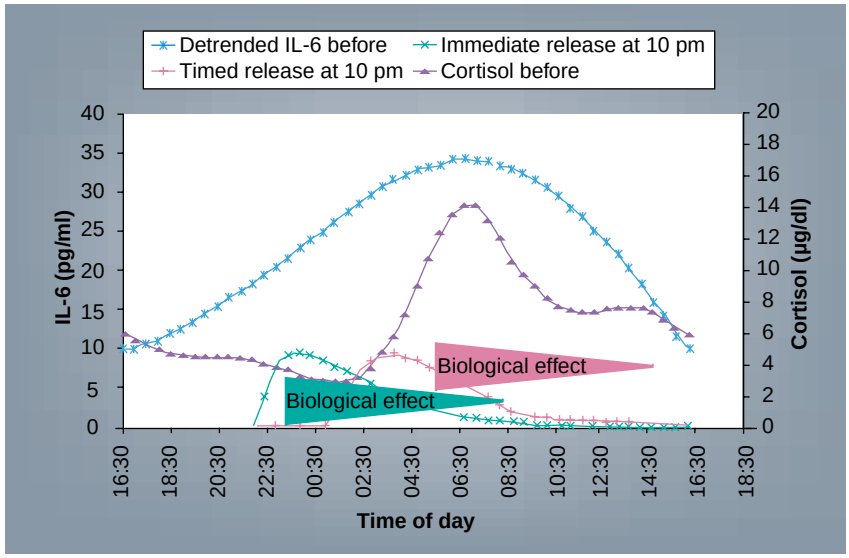

Figure 3. The likely biological effect time for immediate-release and timed-release prednisone.

suppressed, HPA regulation. There was no suggestion of such an improvement in any of the early investigations of HPA axis function in patients treated with evening immediate-release glucocorticoid. This result suggests a specific, regulatory change related to the timing of the glucocorticoid release, not just an anti-inflammatory effect (which would act in the synovitic joints).

An additional finding in this study [23,24] was that, although the group of nine patients taken together showed statistically significant improvements in symptoms, three patients showed little or no improvement. These patients also did not change their circulating IL-6 concentrations, and were the only three patients to have very high

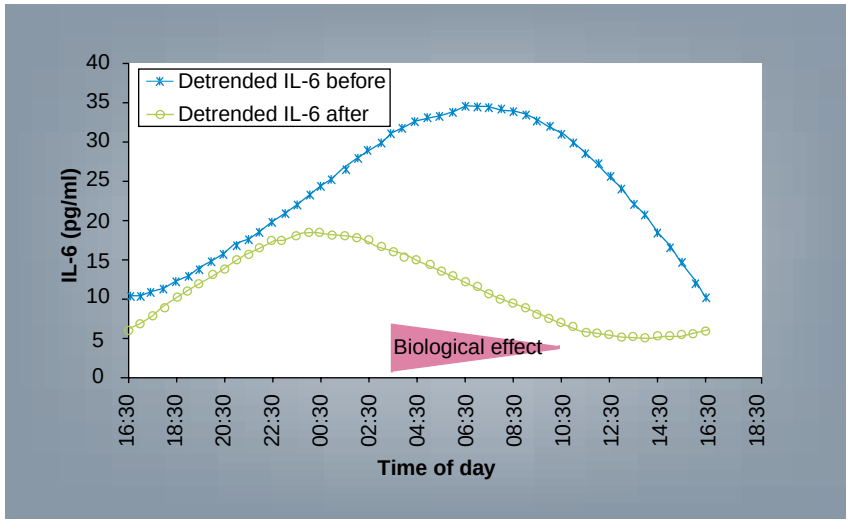

Figure 4. Blood IL-6 concentrations in nine patients before and after 2 weeks of treatment with timed-release prednisone at 10 pm showing the biological effect time of the prednisone.
Detrended data taken from [23,24].

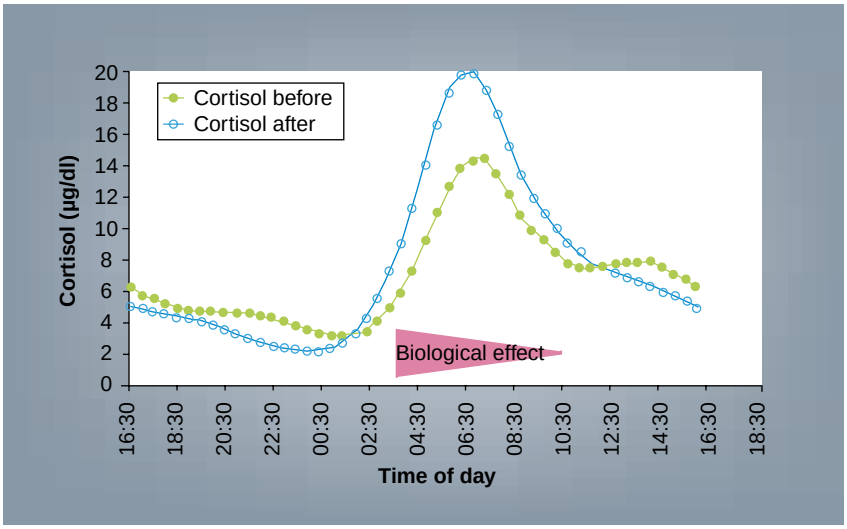

Figure 5. 24-h cortisol in nine patients before and after 2 weeks of treatment with timed-release prednisone at 10 pm showing the biological effect time of the prednisone.
Reproduced with permission from [23,24].

concentrations of IL-4, IL-1ra, IL-1β and TNF, as shown in Figure 6. This raises the possibility of identifying a glucocorticoid-resistant subgroup of RA patients and warrants further investigation.

Clinical outcome studies

This theoretical basis for specific timing of glucocorticoid delivery should produce noticeable clinical improvements when tested in large scale studies. The absolute value of 2 am prednisone treatment has been shown in a placebo controlled trial in 350 patients (CAPRA-2) [25]. Simply changing the timing of the treatment has been tested by switching patients from morning prednisone to timed-release 2 am prednisone in a randomized, controlled, double-blind study in 288 patients (CAPRA-1) [26,27], which demonstrated clear improvements in morning stiffness simply from this change in the timing.

The question of actions on the HPA axis has also been addressed. In a randomized controlled trial that included placebo and prednisolone 7.5 mg daily using traditional immediate-release morning dosing [28], there was a measurable suppression of the response to adrenocorticotropic hormone (ACTH) stimulation as shown in Figure 7 (30 patients in each group).

In the CAPRA-1 study [26], there were 28 patients who had the corticotropin-releasing factor (CRF) test one, two or more occasions during the study, while taking morning immediate-release prednisone or while taking the night time timed-release treatment [29]. The results indicated no deterioration in the HPA axis response by comparing the patient taking night time treatment with those on morning treatment. However, to address the question more directly, I have extracted from this group the 17 patients who had a CRF test when taking their prednisone in the morning, and then again after 3 or 9 months of taking the night time preparation. Taking only these patients allows a direct within-patient comparison and compares 'like with like', the only difference being the timing of the treatment. The results are shown in Table 1, which shows the maximum cortisol

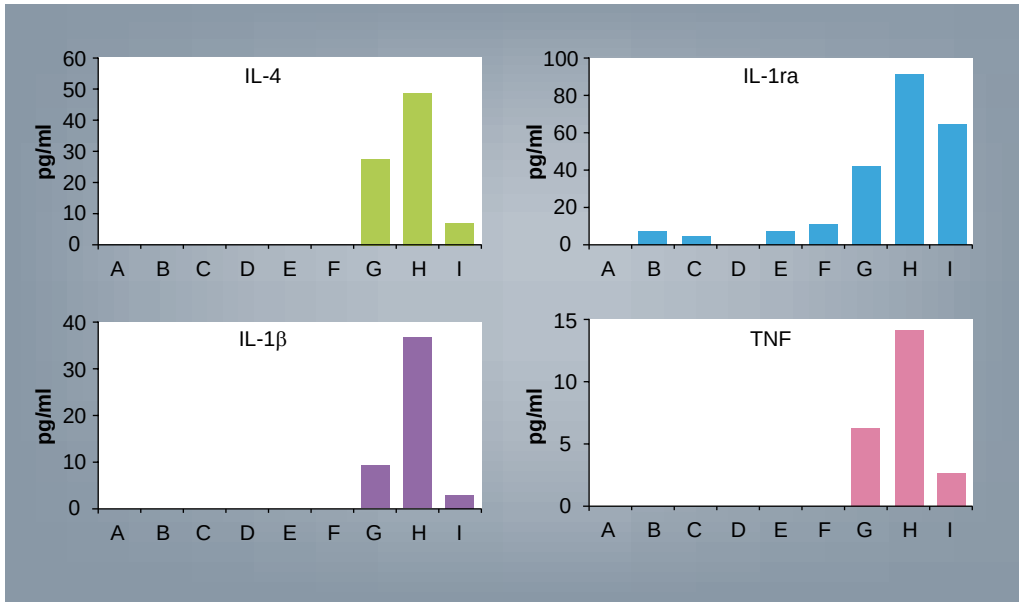

Figure 6. Concentrations of IL-4, IL-1ra, IL-1β and TNF in patients who did (A–F) and did not (G–I) show a clinical response to glucocorticoids.
Data taken from [23,24].

achieved after CRF stimulation, and in FIGURE 8, which shows the mean plasma cortisol during the CRF test. (The pharmaceutical company sponsor provided study data.)

There is a statistically significant increase in the maximum value of cortisol achieved after CRF infusion ($p < 0.05$, paired t-test), showing that in this therapeutic study treatment over several months resulted in improved HPA axis responsiveness.

Commentary

It was not until timed-release tablets were available that it was possible to directly address night time administration of prednisone, targeted specifically at the peak serum IL-6 concentration. There are no pharmacokinetic or biological arguments to support treatment at any other specific time in the diurnal variations of IL-6. There is no evidence of increased HPA axis suppression (even though evening immediate-release tablets may cause greater suppression); indeed, the evidence suggests an improvement in HPA axis function. It is likely that this effect is related to the specific timing of the prednisone within the circadian variations of IL-6 and cortisol, and it is likely that this specific effect is the cause of the improved symptom control compared with morning prednisone.

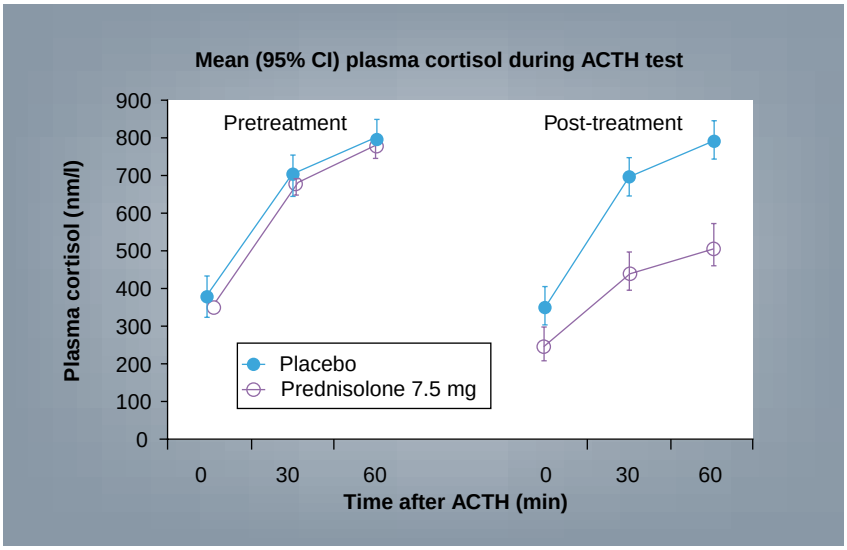

Figure 7. Changes in plasma cortisol levels during the adrenocorticotropic hormone test, before and after 12 weeks of treatment with placebo or prednisolone 7.5 mg in the morning. Values are the mean and 95% CI of 30 patients in each group.
ACTH: Adrenocorticotropic hormone.
Reproduced with permission from [28].

Future perspective

Over the next 5–10 years the role of night time-released prednisone in the routine care of patients with RA will become more clear through the conduct and publication of further

Table 1. Data on 17 within-patient comparisons of the corticotropin-releasing factor test after 3 or 9 months treatment with 7.30 am or 2 am prednisone.

Patient study number	Maximum cortisol on 7.30 am treatment	Maximum cortisol on 2 am treatment	Difference between 7.30 am treatment and 2 am treatment
102	15.01	23.99	8.98
202	20.91	21.02	0.11
204	18.88	17.65	-1.23
206	18.01	21.02	3.01
208	22.29	26.46	4.17
211	18.99	16.02	-2.97
212	11.49	16.02	4.53
215	18.99	17.00	-1.99
216	22.00	17.00	-5.00
221	18.01	18.99	0.98
223	17.00	21.02	4.02
304	23.99	33.02	9.03
310	13.01	18.01	5.00
313	17.00	17.00	0.00
314	17.00	20.01	3.01
226	20.01	18.01	-2.00
309	6.02	12	5.98
Mean	17.57	19.66	2.10†
SD	4.37	4.78	4.07
95% CI	2.08	2.27	1.93

†*p (paired t-test) for mean difference <0.05.*

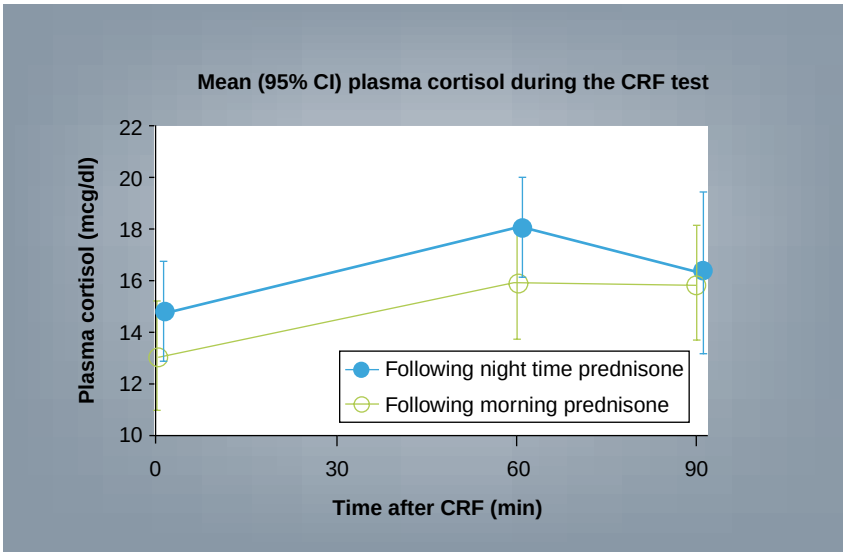

Figure 8. Plasma cortisol response to corticotropin-releasing factor in 17 patients after morning or night time timed-release prednisone.
CRF: Corticotropin-releasing factor.

clinical studies. It is highly likely that night time glucocorticoids will be tested in other diseases. Within rheumatology the condition with the strongest circadian variation in morning symptoms is polymyalgia rheumatica. In this condition doses of glucocorticoids are used that cause frequent adverse effects, and if lower doses of night time prednisone are equally effective this will likely result in a significant improvement in the therapeutic ration. There are other conditions, such as asthma, which may also benefit from circadian treatment, as well as cortisol deficiency diseases. Work is likely to explore the changes in HPA axis function reported here – if they are widely replicated this will result in new understanding about the interaction between RA and cortisol control. Finally, the potential for identifying one source of glucocorticoid resistance will be explored, and may result in findings that will have widespread consequences.

Financial & competing interests disclosure

John R Kirwan has received small honoraria (<$5000) from Horizon Pharma, and holds an unrestricted educational grant awarded 3 years ago by Nitec Pharma (a precursor of Horizon Pharma). Funding for Open Access of this article has been provided by Mundipharma International. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Historical review

- There has been an traditional view, supported by incomplete evidence, that it is preferable to take daily glucocorticoids in the morning.

The role of IL-6

- 15 years ago the first measurements of blood IL-6 concentrations showed them to be raised in rheumatoid arthritis, and to increase during the early hours of the morning.
- There is an interaction between IL-6 (and immune system function in general) and the hypothalamic–pituitary–adrenal (HPA) axis.
- For extraneous glucocorticoids to alter this interaction they would need to be present in the bloodstream at approximately 3 am to 6 am.
- It is not possible to achieve this with existing preparations without waking the patient, which re-sets the variations in the HPA axis and defeats the object of treatment.

Timed release prednisone

- New tablet technology now allows appropriate timed delivery of prednisone after taking medication at 10 pm.
- This medication markedly suppresses the nocturnal rise in IL-6, the purpose for which it was designed.
- Preliminary findings suggest this timing may enhance HPA axis function, rather than suppress it.

Clinical outcome studies

- In small detailed studies and in a large randomized controlled trial, early morning joint stiffness was reduced by using night time-released prednisone rather than standard medication.

Commentary & future perspective

- The theoretical reasons for developing timed glucocorticoid medication have been vindicated by subsequent clinical studies.
- There is potential for this medication to improve the therapeutic ration of glucocorticoid treatment in many diseases.
- Further investigations regarding rheumatoid arthritis and the HPA axis, and about glucocorticoid resistance, will be enhanced by using timed-release glucocorticoids as an investigative tool.

Bibliography

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 Jefferies WM: Low dose glucocorticoid therapy. *Arch. Int. Med.* 119, 265–278 (1967).

2 Nichols T, Nugent CA, Tyler FH: Diurnal variation in suppression of adrenal function by glucocorticoids. *J. Clin. Endo. Metab.* 25(3), 343–349 (1965).

3 de Andrade JR: Pituitary adrenocortical reserve during corticosteroid therapy: a report on the methopyrapone test in ten patients taking long-continued small doses. *J. Clin. Endo. Metab.* 24(3), 261–262 (1964).

4 Klinefelter HF, Winkenwerder WL, Bledsoe T: Single daily dose prednisone therapy. *JAMA* 241, 2721–2723 (1979).

5 DiRaimondo VC, Forsham PH: Pharmacophysiologic principles in the use of corticosteroids and adrenocorticotrophin. *Metabolism* 7, 5–24 (1958).

6 Andrade JR, McCormick JN, Hill AGS: Small doses of prednisolone in the management of rheumatoid arthritis. *Ann. Rheum. Dis.* 23, 158–162 (1964).

7 Diver MJ, Bell AM, Dalakos TG, Buchanan WW: Some clinical observations on the diurnal rhythm of plasma cortisol (11-OHCS) in patients with rheumatoid arthritis treated with oral corticosteroid drugs. *Curr. Med. Res. Opin.* 2, 373–386 (1974).

8 Daly JR, Fletcher MR, Glass D, Chambers DJ, Bitensky L, Chayen J: Comparison of effects of long-term corticotrophin and corticosteroid treatment on responses of plasma growth hormone, ACTH, and corticosteroid to hypoglycaemia. *BMJ* 2, 521–524 (1974).

9 Myles AB, Schiller LFG, Glass D, Daly JR: Single daily dose corticosteroid treatment. *Ann. Rheum. Dis.* 35, 73–76 (1976).

10 Kowanko IC, Pownall R , Knapp MS, Swannell AJ, Mahoney PGC: Time of day of prednisolone administration in rheumatoid arthritis. *Ann. Rheum. Dis.* 41, 447–452 (1982).

11 de Silva M, Binder A, Hazleman BL: The timing of prednisolone dosage and its effect on morning stiffness in rheumatoid arthritis. *Ann. Rheum. Dis.* 43, 790–793 (1984).

12 Arvidson NG, Gudbjornsson B, Larsson A, Hallgren R: The timing of glucocorticoid administration in rheumatoid arthritis. *Ann. Rheum. Dis.* 56(1), 27–31 (1997).

13 Arvidson NG, Gudbjornsson B, Elfman L, Ryden AC, Totterman TH, Hallgren R: Circadian rhythm of serum interleukin-6 in rheumatoid arthritis. *Ann. Rheum. Dis.* 53(8), 521–524 (1994).

14 Crofford LJ, Kalogeras KT, Mastorakos G *et al.*: Circadian relationships between interleukin (IL)-6 and hypothalamic–pituitary–adrenal axis hormones: failure of IL-6 to cause sustained hypercortisolism in patients with early untreated rheumatoid arthritis. *J. Clin. Endocrinol. Metab.* 82(4), 1279–1283 (1997).

▪ **Early paper suggesting the hypothalamic–pituitary–adrenal (HPA) axis is dysfunctional in rheumatoid arthritis.**

15 Mastorakos G, Chrousos GP, Weber JS: Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. *J. Clin. Endocrinol. Metab.* 77, 1690–1694 (1993).

16 Straub RH, Paimela L, Peltomaa R, Scholmerich J, Leirisalo-Repo M: Inadequately low serum levels of steroid hormones in relation to interleukin-6 and tumor necrosis factor in untreated patients with early rheumatoid arthritis and reactive arthritis. *Arthritis Rheum.* 46, 654–662 (2002).

▪▪ **Summary of the evidence then available indicating inadequate HPA function in rheumatoid arthritis.**

17 Cutolo M, Villaggio B, Otsa K, Aakre O, Sulli A, Seriolo B: Altered circadian rhythms in rheumatoid arthritis patients play a role in the disease's symptoms. *Autoimmun. Rev.* 4, 497–502 (2005).

18 Straub RH, Cutolo M: Circadian rhythms in rheumatoid arthritis: implications for pathophysiology and therapeutic management. *Arthritis Rheum.* 56, 399–408 (2007).

19 Hench PS, Kendall EC, Slocumb CH, Polley HF: Effects of a hormone of the adrenal cortex (17-hydroxy-11 deoxycorticosterone: compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis: preliminary report. *Proc. Staff Meetings Mayo Clinic* 24, 181–197 (1949).

▪▪ **Wonderful account of the response of the first patient to ever be treated with glucocorticoids.**

20 Kiwan JR, Roberts C, Harbuz MS, Jessop DS*:* The effects of very low dose prednisolone given at night – a pilot study in rheumatoid arthritis. *Rheumatology* 41(Suppl. 1), 245 (2002).

21 Meikle AW, Tyler FH: Potency and duration of action of glucocorticoids: Effects of hydrocortisone, prednisone and dexamethasone on human pituitary-adrenal function. *Am. J. Med.* 63(2), 200–207 (1977).

22 Perry MG, Kirwan JR, Jessop DS, Hunt LP: Overnight variations in cortisol, interleukin 6, tumour necrosis factor-α and other cytokines in people with rheumatoid arthritis. *Ann. Rheum. Dis.* 68, 63–68 (2009).

▪ **Detailed overnight study showing that, of those cytokines measured, only IL-6 showed substantive overnight variation.**

23 Clarke LL, Jessop DS, Hunt LP, Straub RH, Perry MG, Kirwan JR: Alleviation of morning joint stiffness by low dose prednisone in RA is associated with circadian changes in interleukin-6 and cortisol. *Int. J. Clin. Rheum.* 6(2), 241–249 (2011).

▪▪ **Main report of the detailed effects of timed-release prednisone on the circadian variation in IL-6 and cortisol.**

24 Kirwan JR, Clarke L, Hunt LP, Perry MG, Straub RH, Jessop DS: Effect of novel therapeutic glucocorticoids on circadian rhythms of hormones and cytokines in rheumatoid arthritis. *Ann. NY Acad. Sci.* 1193, 127–133 (2010).

25 Buttgereit F, Mehta DP, Kirwan JR *et al.*: Low-dose glucocorticoid chronotherapy of rheumatoid arthritis: 12 week efficacy and safety of modified-release (MR) prednisone. *Arthritis Rheum.* 62 (Suppl. 10), 392 (2010).

26 Buttgereit F, Doering G, Schaeffler A *et al.*: Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. *Lancet* 371(9608), 205–214 (2008).

▪▪ **Reports the benefits of switching from morning to the same dose of night time-released prednisone.**

27 Buttgereit F, Gisela Doering G *et al.*: Targeting pathophysiological rhythms: prednisone chronotherapy shows sustained efficacy in rheumatoid arthritis. *Ann. Rheum. Dis.* 69, 1275–1280 (2010).

28 Kirwan JR, Hickey SH, Hällgren R *et al.*: The effect of therapeutic glucocorticoids on the adrenal response in a randomised controlled trial in patients with rheumatoid arthritis. *Arthritis Rheum.* 54, 1415–1421 (2006).

▪ **Demonstrates a definite but small reduction in the HPA response in rheumatoid arthritis patients treated with low-dose morning prednisolone.**

29 Alten R, Doring G, Cutolo M *et al.*: Hypothalamus–pituitary–adrenal axis function in patients with rheumatoid arthritis treated with nighttime-release prednisone. *J. Rheumatol.* 37, 2025–2031 (2010).

30 Westhovens R: The Importance of Chronotherapeutics in the Treatment of Rheumatoid Arthritis. *Eur. Musculoskeletal Rev.* 5(1), 9–13 (2010).