Prednisone chronotherapy

C.M. Spies1, M. Cutolo2, R.H. Straub3, G.-R. Burmester1, F. Buttgereit1

1Department of Rheumatology and Clinical Immunology, Charité – Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany; 2Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy; 3Laboratory of Experimental Rheumatology and Neuroendocrinology, Department of Internal Medicine I, University Hospital Regensburg, Regensburg, Germany.

Cornelia M. Spies, MD
Maurizio Cutolo, Professor, MD
Rainer H. Straub, Professor, MD
Gerd-Rüdiger Burmester, Professor, MD
Frank Buttgereit, Professor, MD

Please address correspondence to:
Dr Cornelia M. Spies,
Department of Rheumatology and Clinical Immunology, Charité-Universitätsmedizin Berlin, Campus Mitte, Charitéplatz 1, 10117 Berlin, Germany.
E-mail: cornelia.spies@charite.de
Received and accepted on August 27, 2011.
© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2011.

Key words: chronotherapy, chronotherapeutics, modified release prednisone, MR prednisone, prednisone chronotherapy, timing, glucocorticoid, therapy, rheumatoid arthritis, morning stiffness

Competing interests: M. Cutolo has served as a speaker for Nitec, Mundipharma and Horizon; G.-R. Burmester receives honoraria for lectures for Merck Serono and Mundipharma, Germany; F. Buttgereit receives consultancy fees, honoraria and travel expenses from Merck Serono, Horizon Pharma (formerly Nitec Pharma), Mundipharma Int. Ltd., and grant support from Merck Serono and Horizon Pharma; the other co-authors declare no competing interests.

ABSTRACT
Glucocorticoids (GCs) are widely used in clinical medicine because of their anti-inflammatory and immunosuppressive effects. However, these agents have a considerable potential for adverse effects, especially if used in high doses. The currently most advanced approach to improve the risk-benefit ratio of GCs is low-dose prednisone chronotherapy with modified release (MR) prednisone timing drug release to chronobiological rhythms. In RA, the circadian rhythms of pain, stiffness and functional disability show maximum symptoms in the early morning hours, which is preceded by elevated levels of pro-inflammatory cytokines, in particular interleukin 6. It was hypothesised that preventing the nocturnal rise of pro-inflammatory cytokines by GC therapy is more effective than treating established symptoms in the morning. As waking in the night for tablet intake is impracticable, modified release (MR) prednisone was developed, which releases prednisone approximately four hours after ingestion (i.e. at approximately 2 am if taken at 10 pm bedtime). Data from two large-scale trials in rheumatoid arthritis (RA) (CAPRA-1 and 2) document that MR prednisone has greater efficacy for long-term, low-dose glucocorticoid treatment in patients with RA, with a significant reduction in morning joint stiffness, in addition to all known therapeutic effects with conventional prednisone and a similar safety profile without additional suppression of hypothalamic-pituitary-adrenal (HPA) axis. For patients with RA on low to medium doses of prednisone, especially those who continue to experience a long duration of morning stiffness, MR prednisone appears a valuable additional treatment option.

Introduction
Since the discovery of the anti-inflammatory and immunosuppressive effects of cortisone, glucocorticoids (GCs) have been widely used in the treatment of many diseases, including rheumatic diseases such as rheumatoid arthritis (RA), polymyalgia rheumatica and vasculitides, as well as allergic airway conditions, inflammatory bowel diseases, dermatological and other diseases. The overall prevalence of GC use over the past 20 years has been more or less stable (1, 2). As soon as mineralocorticoid-related and numerous other adverse effects (AEs) of GCs became apparent, such as osteoporosis, myopathy, skin atrophy, oedema and glaucoma, new drugs were synthesised with less mineralocorticoid activity but significant higher glucocorticoid potency (3).

In recent years our clinical view of GCs has changed considerably (3). First, low-dose GCs are no longer seen as providing “only” fast relief of inflammation, but also having the capacity to slow radiographic joint damage in early RA (4). Second, the toxicity profile of low-dose GCs was shown to be modest, in contrast to high-dose therapy in RA (5). Guidelines for safe use of GCs and monitoring of AEs have been developed (6, 7). Nevertheless, dose-related AEs of GCs and the risk-benefit ratio remain issues and driving forces for further research (8, 9).

The currently most advanced approach to improve the benefit of GCs is to use low-dose, taking advantage of knowing the chronotherapeutic strategy (3), in addition to possible selective glucocorticoid receptor agonists, nitroso-GCs, liposomal GCs and others. In prednisone chronotherapy, a new modified-release (MR) prednisone delivery system adapts the release of the administered GC to the circadian rhythms of the disease in order to improve efficacy (10). This review briefly summarises the development of chronotherapy with low-dose prednisone in RA and the current evidence for the efficacy and safety of MR prednisone.

Chronotherapy and the “single morning dose” in GC therapy
The roots of clinical chronobiology date back to the 5th century when
the nocturnal occurrence of asthma was described (11, 12). The concept of chronotherapeutics – i.e. timing medication to biological need to optimise beneficial outcomes or to reduce or eliminate adverse effects (11, 13, 14) – was used by Thomas Sydenham [1624–1689], who recommended that opium (laudanum) be dosed late in the evening, rather than in the morning, for optimum narcotic effect (11, 12). Currently, emerging concepts are being explored to design chronotherapeutics for major chronotherapeutically relevant diseases such as asthma, allergic rhinitis, cardiovascular disorders, rheumatoid arthritis and cancer, and many other conditions (15).

According to Smolensky et al. the first “chronotherapy” to be widely applied in clinical practice was the alternate-day morning schedule of glucocorticoids introduced in the 1960s (13, 16). At that time, the timing of GC administration was focused primarily on chronotoxicological aspects (i.e. rhythm-dependent differences in the manifestation and severity of adverse effects (17)) – rather than on chronoeffectiveness (i.e. rhythm-dependent differences in the magnitude of the desired therapeutic effects (17)).

Administration-time differences in adrenocortical suppression of GC medications have been described since 1956 (13, 18). A series of studies indicated that once-daily ingestion of small to moderate doses of GCs in the morning caused little or no adrenocortical suppression; however, when a part or all of a moderate daily dose of GC was administered later in the day, especially in the evening between dinner and bedtime, the risk of adrenocortical suppression was heightened (18-22). These findings significantly impacted the manner in which GC therapy was prescribed as single-daily or alternate-day morning doses in the following years (13, 16, 18).

“The nightly dose” – effect on morning stiffness

Despite the practice of the single morning dose, some RA patients required a nocturnal glucocorticoid dose to control morning stiffness (23). Some studies, as early as in 1964, specifically found a nightly prednisolone dose more effective regarding morning stiffness than an equivalent morning dose (24-26). However, other studies described no differences in effectiveness between administration of prednisolone at three different times of day (27).

Chronobiology of inflammation in RA

In RA, the circadian rhythms of pain, stiffness and functional disability as well as the underlying cyclic variations in hormone levels and cytokine concentrations are well-known phenomena (28). It was demonstrated that the major signs and symptoms in RA, such as pain, inflammation and stiffness, vary with the time of the day, usually with maximum severity in the early morning hours (29-34). Furthermore, it was shown that these clinical symptoms are preceded by elevated levels of pro-inflammatory cytokines, especially of interleukin 6 (IL-6) (28, 35-37), and a causal beyond a temporal relationship was suggested (3, 10, 38).

A hypothesis was generated, based on these considerations, that improved timing of GC administration may help to optimise RA therapy (3, 10), to target IL-6 and other humoral factors as well as cellular reactions involved in RA pathophysiology (39). The rationale for this hypothesis was provided by the following points (3, 10): (i) pain, fatigue, morning stiffness and immobility are important symptoms of RA which significantly affect the patient’s quality of life and the ability to remain gainfully employed (40); (ii) the nightly increase of IL-6 and other pro-inflammatory cytokines is thought to trigger a cascade of events promoting these symptoms (28, 41); (iii) preventing the nocturnal rise of pro-inflammatory cytokines should be more effective than treating established symptoms (28, 42, 43). From this point of view, administration of GCs between 6 am and 8 am was suggested to be suboptimal.

MR prednisone – formulation

In 1997, Arvidson and co-workers demonstrated that low doses of prednisolone taken at 2 am had significantly better therapeutic effects on duration of morning stiffness, joint pain and morning serum concentrations of IL-6 than equivalent doses taken at 7:30 am after only 5 days of treatment (44). However, a regimen which requires regular waking of the patient at 2 am was considered to be impractical for the therapeutic routine, whereas evening treatment may not be optimal due to the short, 2 hour, half-life of prednisolone (28).

These considerations and observations led to the development of a new modified-release (MR) prednisone formulation, which allows timed release of glucocorticoids 4 hours after oral administration at 2 am (10). The MR prednisone tablet is a “tablet-in-tablet dosage form”, which consists of an immediate-release prednisone core tablet surrounded by an inactive outer tablet shell (10). MR prednisone releases prednisone approximately four hours after ingestion, (i.e. at approximately 2 am if taken at 10 pm bedtime). Prednisone release is triggered by penetration of gastrointestinal fluid into the tablet shell. The pharmacokinetic profile and total drug exposure (maximum concentration and area under the curve) of 5 mg MR prednisone have been shown to be very similar to those of 5 mg conventional immediate-release prednisone – of course apart from the 4-hour delay (10).

Efficacy and safety of MR prednisone – the CAPRA-1 study

The efficacy and safety of MR prednisone was investigated in a 3-month, double-blind, double-dummy, controlled clinical study (Circadian Administration of Prednisone in Rheumatoid Arthritis (CAPRA-I)) (10). Altogether, 288 patients with active RA were randomised to receive their current prednisone dose (2.5–10 mg prednisone per day) either as MR prednisone administered at approximately 10 pm or as conventional immediate-release (IR) prednisone administered in the morning. MR prednisone was shown to be clinically superior to the conventional IR preparation with respect to reducing morning joint stiffness, the primary endpoint of this study. This beneficial effect was noted in addition to clinical
control of disease resulting from treatment with conventional prednisone. IL-6 serum concentrations were also significantly decreased by MR prednisone after 3 months of treatment but remained unchanged by IR prednisone. The safety profile did not differ between the two regimens (10).

The CAPRA-1 study was followed by a 9-month, open-label extension, during which all patients were treated with MR prednisone (45). Reduction in morning stiffness duration and IL-6 serum levels was sustained during 12 months of treatment with MR-prednisone, with a reduction from baseline by approximately 50% (45). Similar improvements were observed in patients who switched to MR prednisone in the open-label phase. Furthermore, 37% of all patients were improved according to ACR20 criteria (45). Adverse events did not differ from the known profile of low-dose prednisone.

Effect of MR prednisone on HPA axis

The hypothalamic-pituitary-adrenal (HPA) axis plays an important role in regulating and controlling immune responses, and dysfunction of the axis has been implicated in the pathogenesis of RA and other rheumatic diseases. The influence of prednisone therapy on the HPA axis function remains a matter of concern, particularly for longer treatment duration, as knowledge is rather limited.

In order to investigate the influence of long-term, low-dose chronotherapy with MR prednisone on the HPA axis, corticotrophin releasing-hormone (CRH) tests were performed in a subgroup of 28 patients of the CAPRA-1 study (48). The CRH tests were performed (i) at baseline, (ii) at the end of the double-blind phase, and (iii) at the end of the 9-month open-label extension. There was no indication that changing treatments from IR prednisone to MR prednisone increased the risk of HPA axis insufficiency, or resulted in deterioration of preexisting suppression. In addition, no adverse events that could be attributed to HPA axis insufficiency were observed during the treatment with low-dose MR prednisone for the entire treatment period of 12 months (48).

MR prednisone vs. placebo – the CAPRA-2 study

A second, large-scale, double-blind, placebo-controlled multicentre study (CAPRA-2) was conducted in order to quantify the net effect of low-dose MR prednisone in patients with RA poorly controlled by disease-modifying antirheumatic drugs (DMARDs). In this 12-week study, 350 RA patients were randomised to 5 mg MR prednisone or placebo once daily in addition to their pre-existing DMARD treatment. The ACR20 response rate at 12 weeks was 48% for patients randomised to MR prednisone versus 29% for patients randomised to placebo (p<0.001). Significant improvements were evident within two weeks of therapy initiation. Improvements in health-related quality of life, in particular physical functioning and fatigue, were also noted, while the safety profile of low-dose prednisone chronotherapy was comparable to that of placebo (unpublished observations). These initial results were presented at the European League against Rheumatism (EULAR) meeting 2010.

Prednisone chronotherapy in other diseases?

Indications of circadian rhythms are reported in some other rheumatic diseases such as polymyalgia rheumatica and ankylolyzing spondylitis (41). In asthma, several drugs have been developed based on chronopharmacology, primarily administered once at night, including systemic and local GC preparations (17, 49, 50). Some data for chronotherapeutical applications of GC in other diseases are reported, e.g., multiple sclerosis (51). Modified-release hydrocortisone (MR-HC) is currently being tested in substitution treatment of congenital adrenal hyperplasia (CAH) (52). However, available data are scarce and studies such as in RA are needed in other diseases.

The concept of chronotherapy for RA might also be extended to other drugs. For example, it has recently been reported that switching RA patients from a standard methotrexate (MTX) application three times/week to once-a-day at bedtime improves disease activity and functional capacity (53-55).

Conclusions

GCs remain important anti-inflammatory and immunosuppressive drugs; however, the potential of these agents to produce adverse effects is notable. The currently most advanced approach to improve the risk–benefit ratio is chronotherapy with low-dose prednisone, in which the programmed delivery of MR prednisone is coordinated with chronobiological rhythms of RA to optimise treatment outcome. Two large-scale trials (CAPRA-1 and 2) in RA support the view that MR prednisone is superior to conventional prednisone for significant long-term reduction of morning stiffness in addition to the conventional GC effects. Furthermore, adverse effects of MR prednisone appear to be unchanged from conventional GCs and without additional suppression of HPA axis. Thus, MR-prednisone can improve the risk–benefit ratio of long-term low-dose GC treatment in patients with RA and provides an additional treatment option, in particular in RA patients with long-standing and disabling morning stiffness.

References


7. VAN DER GOES MC, JACOBS JW, BOERS M et al.: Monitoring adverse events of low-dose glucocorticoid therapy. EULAR recommen-


