Glucocorticoid chronotherapy: a mini-review

Abstract

In this mini-review the chronotherapy with glucocorticoids in rheumatoid arthritis (RA) patients is discussed, as an example of the numerous diseases, showing circadian rhythms in disease activity. Underlying pathophysiological mechanisms are reviewed, explaining the usefulness of glucocorticoid chronotherapy in RA patients. The results of the 2 randomized CAPRA trials, leading to the FDA approval of a modified-release prednisone formula, are discussed, as well as the pricing of these drugs. In a chronopharmacology section it is shown, that some modified drug delivery systems, as MR-prednisone and fast acting meal insulins do not require huge R&D investments.

Introduction

This year’s Noble Prize in Physiology or Medicine was awarded to Jeffrey C. Hall, Michael Rosbash and Michael Young, for discovering “key genetic gears” of the body’s 24 hour biological clock. Their work identified genes and proteins, that work together in humans and animals to synchronize activities throughout the day and night, regulating sleep patterns, eating habits, blood pressure and hormones, in circadian rhythms. Another Noble Prize in Physiology and Medicine was awarded in 1950 to Philip S. Hench, for his landmark discovery of the beneficial effects of glucocorticoids in rheumatoid arthritis (RA).

RA is a typical example of a disease with circadian or diurnal variations in symptoms, as e.g. nocturnal asthma. RA symptoms, as morning stiffness, joint pain and functional disability are worse in the early morning. It is now evident, that the morning symptoms in RA, polymyalgia rheumatica (PMR) and ankylosing spondylitis are a result of altered circadian neuroendocrine and inflammatory activities. Cytokines levels, such as tumor necrosis factor-alpha (TNF-alpha) and interleukin 6 (IL-6) are increased in RA patients at night, in the very early morning hours, whereas they are present at very low levels after noon. Neuroendocrine circadian rhythms and “night hormones” as, melatonin and prolactin, as well as the availability of bioenergies at night, are among the triggers of the increased cytokines levels in the early morning hours. The logical next step would be dosing medication for RA patients in the late night.

Cytokines TNF-alpha, IL-1 and IL-6 are secreted from human peripheral blood monocytes in response to melatonin stimulation, and melatonin is detected in RA synovium tissue macrophages and joint fluid. Melatonin levels increase progressively from 8 p.m. to the early morning hours in RA patients, but peak levels are reached 2 hours earlier than in controls, at 2 a.m. The duration of the peak levels, reaching a plateau, was 2-3 hours in patients with RA. This was not observed in controls. Melatonin levels are not correlated with disease activity in RA patients, although early morning melatonin levels are higher in patients with RA of short duration. Studies suggest, that melatonin treatment might aggravate RA, but there are no studies, concerning this subject. Antibodies related to RA, such as the IgA/IgM rheumafactor (RF) and the anti citrullinated protein antibodies (APCA) are also secreted in a circadian manner by B-cells, with a peak in the morning. Constant disruptions of the circadian clock have been linked to cardiovascular diseases, metabolic syndromes, diabetes and cancer. Night shift work showed an increased risk of RA in women.

Glucocorticoids

Acute bacterial infections activate the HPA-axis. This leads for a few days to high levels of ACTH(adrenocorticotropic hormone) and cortisol. In chronic inflammatory diseases, such as in RA, cytokines can harm the HPA-axis at any level, resulting in partial adrenal insufficiency. Cytokines IL-1 beta and TNF-alpha interfere with several steps in steroidogenesis. The circadian rhythm of cortisol is not different in healthy controls and in untreated patients with RA. However IL-6 levels are 10 times higher in RA patients and the cytokine circadian rhythm is quite different from controls. Thus cortisol secretion is inadequate to the stress of persistent active disease. In addition, RA synovial cells have an increased activity of 11-beta-hydroxy -steroid dehydrogenase type 2 (11-beta HSD-2). This results in an increased degradation of the bioactive cortisol to the biologically inactive cortisone and to a decreased reactivation of cortisone to cortisol. The clinical and biochemical improvement
in patients with RA with glucocorticoid (GC) treatment is due to the dampening effect on the pro-inflammatory factors, and the restoration of the steroid milieu. GC therapy, often used as a bridge to DMARD (disease modifying anti-rheumatic drugs) therapy, (that needs a few weeks time to work), can be regarded partly as supplemental therapy in tertiary adrenal insufficiency. The HPA-axis is extended to the kidney and liver by glucocorticoid metabolism in RA patients. Active cortisol is converted to inactive cortisone by beta-HSD1 in the kidney. The liver is the major organ for converting inactive cortisone to active cortisol by 11-beta HSD2. So dysfunction of the HPA-axis in RA patients is in fact dysfunction of the hepato-hypothalamic-pituitary-adrenal-renal axis, by an increased negative feedback loop of active cortisol, and not an adaptation to chronic stress, as supposed before. Factors that determine adrenal insufficiency are; individual sensitivity, GC dose, duration, formulations of GC therapy and timing of application (circadian). The differences in individual sensitivity are not well understood, yet. CRH (corticotrophin releasing hormone) tests one day after dexamethasone administration, showed that a subset of RA patients do not exhibit normal feedback control mechanisms. They had no expected ACTH and cortisol suppression. The frequency of adrenal suppression increases with increasing GC dosages. However, low dose GC treatment with 7.5 mg prednisolone daily of RA patients, resulted in some 50% in blunted ACTH test responses, indicative of adrenal suppression. Abnormal diurnal rhythms of plasma cortisol in patients with RA were found to be related to the total dose of GC given and to the duration of therapy, but not to the mean daily dose or the the daily regimen of therapy. It has been known for a long time, that splitting the daily dose in several divided doses, strongly increases the risk of adrenal suppression. Whereas endogenous cortisol secretion was not altered with a single dose of 8 mg triamcinolone, application of 4 divided 2 mg doses, resulted in marked suppression of cortisol levels. For that reason GC therapy is generally applied as a single daily dose.

**Chronotherapy of GCs**

The time point of application of the single GC dose also plays a role for adrenal suppression. Endogenous cortisol secretion has two peaks; one at 8 a.m and a smaller one at 2 p.m. If exogenous GCs were applied in the evening, this leads to a negative signal on ACTH and endogenous cortisol secretion in the morning. This has been confirmed in several studies. Some RA patients need however dose splitting to control morning stiffness, despite the risk of more HPA-axis suppression. If dose splitting is necessary two third of the dose should be given in the morning (8 a.m.) and one third in the early afternoon (3 p.m.). Several studies have suggested a greater effect of bedtime or night doses (2 a.m.), in comparison of morning doses of conventional prednisone on morning stiffness. HPA-axis suppression was not examined in these studies. Awakening the patient at 2 a.m. was seen as impractical, but conventional prednisone has a pharmacological half-life of only 2 hours. The pharmacokinetics of prednisone have no diurnal rythm. So the search for a slow-release or modified release preparation started, for covering the cytokine and melatonin peak of RA patients in the early morning. Horizon Pharma, a biopharmaceutical company, developed Rayos, synonyme Lodotra, which is essentially prednisone press-coated as a core in a thick coating. The thick coating and the convex form, instead of the flat form, release the prednisone 4 hours later, allowing them to be taken at bedtime, and being active in the early morning hours.

The efficacy of this modified-release (MR) prednisone formula was investigated in two multicenter, randomized, controlled trials named CAPRA (Circadian Administration of Prednisone in Rheumatoid Arthritis). CAPRA-1 aimed to prove the efficacy and safety of MR prednisone compared to immediate release (IR) prednisone, while CAPRA-2 focused on MR prednisone, as an additional GC therapy to an existing medication with DMARDs.

CAPRA-1 included 288 patients, already taking IR-prednisone for RA, who were randomized 1:1 to get MR-prednisone in the evening, or continuing IR-prednisone in the morning. The patients have been treated for 12 weeks in both arms. Thereafter there was an open label extension (OLE) of 9 months. Morning stiffness duration was significantly reduced in the MR-prednisone group, when compared to the IR-prednisone group (22.7% vs 0.4%). This reduction went along with a significant reduction in IL-6 levels, supporting the concept of prednisone chronotherapy. There was no difference in adverse effects (AEs) in both study arms, or in safety profile. The long-term OLE of CAPRA-1 showed similar results with reduced morning stiffness duration, also for the patients switched from IR to MR-prednisone. The influence of long term, low dose chronotherapy with MR-prednisone on the HPA-axis was investigated in a subset of 28 patients in the CAPRA-1 study by CRH-tests. There were no measurable differences in mean cortisol changes after CRH injection, between baseline and the end of the study. 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 pre-existing insufficiency. Fifty percent of patients showed a normal response, 37% showed a suppressed response, and 13% showed no response, equally divided about both treatment arms. Clarke et al. showed an increase in endogenous cortisol secretion after 2 weeks MR-prednisone therapy in patients with active RA, who had received no GCs in the preceding 3 months. Because IL-6 rise in the morning was suppressed, this might be consistent with a changing relationship between the HPA-axis and the immune system during treatment with MR-prednisone. Further studies are required to test this hypothesis.

CAPRA-2 included 350 RA patients with an existing DMARD therapy and no IR-prednisone medication, 6 weeks prior to the screening. All patients had at least a morning stiffness of 45 minutes. They were randomly assigned to either receive 5 mg MR-prednisone or placebo in the evening. The primary endpoint was a 20% improvement in RA signs and symptoms (ACR20 response, Table 1), at the end of the 12-week study. After 12 weeks the MR-prednisone group did not only showed significant improvement in ACR20 response (48% vs 29%; p=0.001), but also to ACR50 response (22% vs 10%; p=0.006). The reduction in morning stiffness was (-55% vs -35%; p=0.001). Studies correlating improved symptom control with the frequency of longterm RA complications are not available.

**Table 1 ACR 20 Response**

| A decrease of at least 20% in both the number of tender and swollen joints along with 20% reduction in at least three of the following |
|--------------------------------------------------------------------------------------------------------------------------|
| Patient assessment of disease status                                                                                 |
| Patients assessment of pain                                                                                           |
| Physicians’s assessment of pain                                                                                       |
| C-reactive protein level                                                                                            |

MR-prednisone is not a new medicine, but at most a new drug design. In Europe Lodotra costs $1 per tablet, which is still 20 times more than one tablet IR-prednisone. However in the U.S., Rayos is sold for over $1600 for 30 tablets ($50 per pill), 350 times more than one single IR-prednisone tablet. This raises the question, whether the use of MR-prednisone is justified and if some patients should set their alarm-clock at 2 a.m. and use IR-prednisone at that time.
Chronic inflammation can alter cell or core clock genes. Melatonin endocrine system mediates the dissemination of timing signals. The supra chiasmatic nucleus (SCN) and the immune system. The hormones as melatonin and cortisol play by their interaction with metabolic genomes.

Conclusion

RA patients, without prior GC medication. The price of MR-prednisone is unacceptable high, however. Therefore it should be reserved for those RA patients, in whom morning stiffness can not be controlled. As a lot of diseases, such as diabetes, RA, asthma, hypertension, myocardial infarction, stroke show circadian rhythms, chronopharmacology should have a bright future.

Aknowledgement

None.

Conflic of interest

None.

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Citation: Naafs MAB. Glucocorticoid chronotherapy: a mini-review. Endocrinol Metab Int J. 2018;6(2):118–122. DOI: 10.15406/emij.2018.06.00164
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Citation: Naafs MAB. Glucocorticoid chronotherapy: a mini-review. *Endocrinol Metab Int J.* 2018;6(2):118–122. DOI: 10.15406/emij.2018.06.00164
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