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Chronobiology and Chronotherapy for rheumatoid arhthritis

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ABSTRACT

Pulsatile drug delivery systems have been a major field of research recently. It is the most interesting time-specific and site-specific system. This system is designed for chronopharmacotherapy which is based on circadian rhythm. This means these systems will deliver drug at the time when disease displays it's most morbid and mortal state within a circadian cycle. The use of these systems has been investigated on diseases like asthma, arthritis, ulcers, cardiovascular diseases, hypercholesterolemia, cancer etc. Various capsular, osmotic, single and multiple unit systems that are modulated by soluble or erodible polymer coatings, rupturable membranes are discussed in the article below.

Keywords: Pulsatile, circardian, delivery, drug.

Introduction

Concept of chronopharmaceutics also referred as chronopharmacotherapy has been emerged nowadays. It consists of two words chronobiology and pharmaceutics. Chronobiology is the science of biological rhythms and its mechanism [1]. Research is devoted to the design and evaluation of chronotherapeutic drug delivery systems that release a therapeutic agent at a rhythm to maintain the adequate drug concentration according to the needs of the physiological states of patient's body and the circadian rhythm. The goal is to distribute the drug in high concentration in accordance with need of time and in less concentration when the requirement is little to reduce side effects.

Concept of circadian rhythm

A Circadian Rhythm is any biological process that displays an endogenous, entrainable oscillation of about 24 h. Biological systems possesses a very prominent temporal structure.

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It was believed that cyclic changes in organisms represented exclusively the simultaneous effects of cyclic changes in environmental factors, such as the alternation of light with darkness and/or of heat with cold over periods of both 24 h and 1 year. Major periodic components of biological rhythms are found around 24 hr and 1year [2]. Circadian rhythms are controlled by an inherited master clock network composed of the paired suprachiasmatic nuclei (SCN) that are situated in the hypothalamus and the pineal gland. The rhythmic activities of specific, so-called, clock genes like per1, per2, per3, bmal, clock, and CRY, among others, and their gene products, plus the cyclic (nocturnal) secretion of melatonin from the pineal gland comprise the central timekeeping mechanism. This master clock network orchestrates the period and phase of the multitude of subservient peripheral circadian clocks located in cells, tissues, and organ-systems. The end-effect is a rather exquisite temporal organization of biological processes and functions. Biological timekeeping is an evolutional adaptation to an environment that is organized in time, displaying discrete and important cyclic phenomenon. Thus, the temporal organization of biological processes and functions during the 24-h period ensures peak functioning of the diurnal human species during

daytime activity and restoration and repair during nocturnal rest [3].

Thus it is found that Circadian rhythm regulates many body functions in humans, viz., metabolism, physiology, behavior, sleep patterns, hormone production, etc.

Rheumatoid arthritis

RA is a chronic disorder in which, the body's own immune system starts to attack body tissues, reasons of which are unknown. This disorder is accompanied with swelling, stiffness and pain In this disorder the attack is not only directed at the joint but to many other parts of the body. In RA, the joint lining and cartilage gets more damaged which eventually results in erosion of two opposing bones. Body parts which get affected in RA are joints in the fingers, knees, wrists, and elbows. Advanced disease stages can lead to substantial loss of functioning and mobility. The triggers for the onset of RA are only speculated, but it is expected that a genetic liability to the disorder, several viruses and bacteria (e.g. EpsteinBarr-Virus and *Mycobacterium tuberculosis;* disruption of the immunological tolerance as well as the psychological condition by further weakening the immune system of people concerned could play a major role . As the causes for RA are still unknown, cures have not been discovered yet as well [4]. All treatments and therapies which are applied so far are intended largely to reduce symptoms and delay the progress of the disease. The onset of RA occurs usually between the age of 30 and 50, but may also occur at any other age. Women are three times more affected by it than men and people who are less educated and with fewer socioeconomic resources experience more problems emerging of RA. In children, the disorder can present with a skin rash, fever, pain, disability, and limitations in daily activities. About 1% of the whole world population is attacked by RA [5]. No one knows why RA occurs and all treatments are focused on easing the symptoms. Pain and fatigue is mainly associated with this disorder and with earlier diagnosis and aggressive treatment, many individuals can lead a decent quality of life.

Rheumatologists have experienced it clinically that patients with RA experience joint pain, morning stiffness, and functional disability in the early morning hours. These diurnal variations display large amplitudes, with the patient's condition being poor in the early morning and disease activity being mild or moderate in the early evening (Figure 1). This was presented by using grip strength as a parameter; grip strength (a nonspecific index, influenced by muscle power and pain) was, on average, 233 mm Hg at 6:00 AM and 297 mm Hg at 6:00 PM, an increase of 27.5% [6], further exemplified by overall pain reported using a 0–10-point visual analog scale, with an average pain score of 6.3 at 8:00 AM and 4.5 at 6:00 PM (decrease of 28.6%) [7].

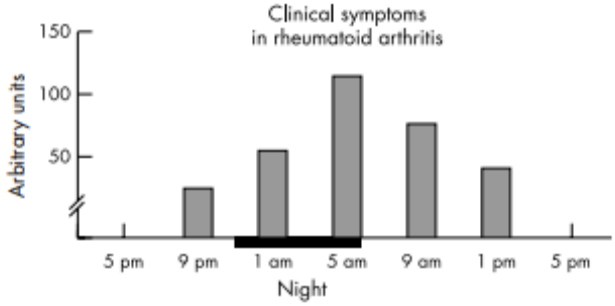

Fig 1: Clinical signs and symptoms of articular inflammation in patients with RA change consistently as a function of the hs of the day: pain and joint stiffness are greater after waking up in the morning than in the afternoon or evening [8]

Therefore it was concluded that clinical signs and symptoms in RA show a rhythm that seems driven by a biological clock and it was observed that daily oscillations in circulating concentrations of disease-mediating cytokines are responsible for such kind of diurnal variations. Two hormones which act as circadian agent are glucocorticoids and melatonin. Both are important in inflammation and regulation of the immune response, and may contribute to the pathogenesis of RA. In Figure 2 it is depicted that joint stiffness and pain are more pronounced in the early morning, and this correlates with the early morning rise in plasma IL-6 levels. The circadian hormone melatonin (which is considered to exacerbate the inflammatory response) is released only during the night, and circulating levels peak in the mid-night. The anti-inflammatory glucocorticoid - cortisol - is also under circadian control, peaking in the early morning. In adult primates,retina receives only visible light (400–700 nm). This photic energy is transduced

and delivered to visual cortex and then to the suprachiasmatic nucleus, the hypothalamic region that directs circadian rhythms. Exposure to visible light modulates the pituitary and pineal glands, leading to neuroendocrine changes. Levels of Norepinephrine, melatonin and acetylcholine decrease with light activation, whereas cortisol, serotonin, γ-aminobutyric acid, and dopamine levels increase[9].

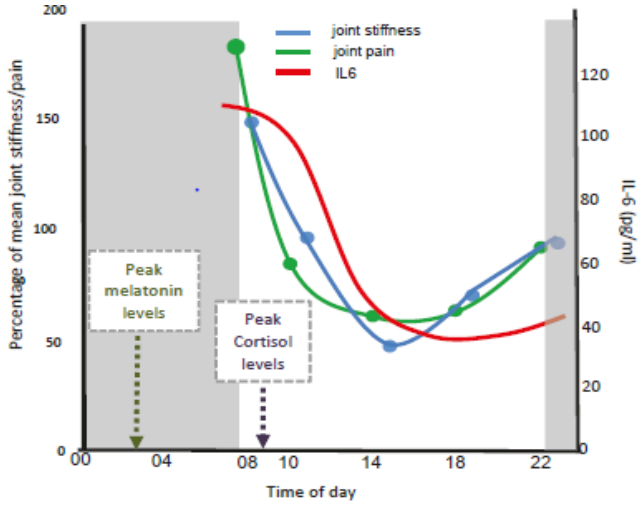

Figure 2: RA shows diurnal variation in disease symptoms and markers[10]

Circadian Rhythm of hormones

Glucocorticoid Tumor necrosis factor (TNF)/interleukin-6 (IL-6) are the inflammatory cytokines which are soluble products of the activated immune system and these stimulate the production of corticotropin- releasing hormone (CRH) in the hypothalamus. This leads to the production of corticotropin, followed by glucocorticoid secretion by the adrenal cortex [11-12]. All these components constitute the hypothalamic – pituitary–adrenocortical (HPA) axis. Increased functioning of HPA axis function resulting in increased cortisol production is a normal response to the stress of inflammation. Cortisol production is associated with the increased production of the Th2 cytokines (e.g.: IL- 10) ,observed in the early morning, following the Th1 cytokine peaking.[13] It was revealed from the studies that in case of patients suffering from RA overall activity of the HPA axis remained inappropriately normal which was found insufficient to inhibit ongoing inflammation [14]. Also, it is reported that there exist a negative correlation betweenof cortisol and IL-6 indicating that, in RA HPA function is insufficient to inhibit ongoing inflammation. In other studies decreased plasma levels of the adrenal androgen (AAs) dehydroepiandrosterone (DHEA) and its sulfate metabolite were found [15]. After correlating all these levels early morning IL-6 peak values were found greater in RA patients than in their healthy controls. [15-16]

Melatonin Level of melatonin increases progressively from 8 pm to the early morning hours inboth patients with RA as well as healthy subjects; however,in case of RA melatonin reaches at peak level at midnight which is at least 2 h earlier compared to controls. It was reported that melatonin concentrations in patients who had RA reached a plateau that lasted for 2 to 3 h; this was not observed in controls. After 2 am, level of melatonin decreases in both patients who had RA and healthy subjects. Thus it was confirmed that nocturnal rhythm of melatonin occurs also in patients who have RA, but with an earlier peak level and a longer duration in the early morning [17]. IFN-g, IL-1, IL-2, IL-6, IL-12, and TNF-a production (Th1 cytokines) reaches peak during the night and early morning, at the same time that MLT serum levels are highest and plasma cortisol is lowest. It was found thatmelatonin was present in high concentration in synovial fluids in patients who had RA and binding sites for MLT were present in synovial macrophages resulting in increased proinflammatory cytokine production [18-19]**.** Similarly, Chikanza et al., 1993 [20] found that serum levels of prolactin during the night were significantly higher in RA patients compared with controls, and this has been confirmed by others [21].

Chronotherapy for RA

As discussed above RA symptoms follow a circadianpattern, therapy based on these rhythms

(chronotherapy) has not yet been developed. In this section chronotherapies that have been observed in basic and clinical studies based on this is discussed.Approach used to treat patients with RA depends upon the timely and judicious use of several types of therapeutic interventions which include early diagnosis, care by an expert in the treatment of rheumatic diseases (rheumatologist) early use of DMARDs with the target of remission or low disease activity and use of anti-inflammatory agents, including non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids. There are various studies that are based on development of chronotherapeutic system that synchronize with the diseased condition.

Glucocorticoids have been used in RA therapy as it posses the anti inflammatory activity against the joint pain and joint stiffness. As discussed earlier Cortisol is an endogenous glucocorticoid, which reaches the peak in the morning in humans. In order to prevent disturbances in the circadian rhythms of endogenous glucocorticoids steroids are generally administered in the morning. Studies were conducted by Silva et al., 1984 [22] and Arvidson et al., 1994 [16] to observe the dependency on dosing time of drug administered in the morning or night according to the 24-h rhythms of endogenous glucocorticoids and RA symptoms. The findings revealed that the duration of morning stiffness and blood IL-6 levels were markedly shorter and lower, respectively, in the night dosing group than in the morning dosing group.

In recent years, chronotherapeutic delivery systems of glucocorticoids have improved the outcomes. Buttgereit et al., 2008 [23] performed a multicentre, randomized, double-blind trial, in which a modified-release formulation of prednisone was developed, which releases the agent -4 h after its ingestion. Patients with RA were randomly given a modified-release tablet at bed-time or an immediate-release prednisone tablet in the morning; relative changes in the duration of joint morning stiffness were significantly higher with the modified-release tablet than with the immediate-release tablet. It was also reported thatchronotherapy with nighttimerelease may improve the efficacy of long-term low-dose glucocorticoid treatment [24-26].Disease-modifying antirheumatic drugs (DMARDs) are commonly characterized by their capacity to reduce or reverse signs and symptoms, disability, impairment of quality of life, and progression of joint damage and thus to interfere with the entire disease process[27]DMARDs form two major classes: synthetic chemical compounds (sDMARDs) and biological agents (bDMARDs). Methotrexate is one of the most commonly used disease-modifying antirheumatic drug. On the basis of clinical trial it was revealed that administering Methotrexate at specific times in accordance with the 24-h rhythm of TNF-α leads to decreased inflammatory responses to RA. Based on animal study and 24-h rhythm of TNF-α in RA patients it was observed that Methotrexate given once-a-day at bedtime improved the disease activity and patient's functional capacity[28-29].

Conclusion

RA exhibit diurnal rhythmicity. Joint pain, stiffness and functional disability is at its most severe in early morning. The treatment of such symptoms can be improved by the administration of the dose at the nighttime, by which the*in vivo* drug availability coordinates with the rhythms of disease, and thus therapeutic outcomes can be optimized.

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