

## CHRONOTHERAPY IN RHEUMATOID ARTHRITIS APPRAISAL FOR RATIONALITY

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### ABSTRACT

Arthritis is a disease state with pathological symptoms like joint stiffness, swelling and restricted movements. All these symptoms are at their prime in the morning hours. In diseased individuals higher concentration of pro-inflammatory mediators like Interlukin-6, nocturnal hormones like melatonin and lower concentration of glucocorticoids have been reported, thus pathological states of rheumatoid arthritis can be regulated by working on interactions between above listed mediators. Conventional treatment approaches use large dose of drugs and thus are not safe to the patients; moreover, their administration time leads to non-compliance of the patients. Novel approaches making use of chronotherapy have shown good results, as they not only reduce the risk of overdose but also improve the patient compliance.

### KEY WORDS

Chronotherapy, Rheumatoid Arthritis, Chronotherapeutics, Circadian rhythm, Chronopharmacokinetics & Chronopharmaceutics.

### INTRODUCTION

Many functions of the human body vary considerably in a day. These variations cause changes both in disease state and in plasma drug concentrations. Human circadian rhythm is based on sleep-activity cycle, is influenced by our genetic makeup and hence, affects the body's functions day and night (24-hour period) [1]. The dependence of bodily functions in certain disease states on circadian rhythm is well known. A number of hormones are released by the brain in the morning, while others are released during sleep. Blood pressure and heart rate are highest during the hours of 6.00 a.m. to 12.00 noon [2]. Diseases, such as hypertension, asthma, peptic ulcer, arthritis, etc, follow the body's circadian rhythm [3]. For example, osteoarthritis worsens during the day and is most bothersome in the evenings but for people with rheumatoid arthritis, the pain usually peaks in the morning and decreases as the day progresses. Cardiovascular diseases such as hypertension and angina, and chest pain, also follow a definite circadian rhythm. Epidemiologic studies have

documented the heightened morning-time risk of angina, myocardial infarction, and stroke [4].

The goal in drug delivery research is to develop formulations to meet therapeutic needs relating to particular pathological conditions. Research in the chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy, and this has brought a new approach to the development of drug delivery systems. Optimal clinical outcomes cannot be achieved if drug plasma concentrations are constant. If symptoms of a disease display circadian variation, drug release should also vary with time. Utilization of different technologies in the development of time-controlled, pulsed, triggered and programmed drug delivery devices has intensified in recent years. Another issue that has emerged from circadian variation of physiological function is that drug pharmacokinetics can be time-dependent (i.e., chronopharmacokinetics) [5]. Therefore, variation in disease state and drug plasma concentration need to be taken into consideration in the development of drug delivery systems intended for the treatment of diseases with adequate dose at the appropriate time.

The term, 'Chronopharmaceutic drug delivery system', is used to describe a kind of drug formulation which can cause circadian variation in drug plasma levels [6-8].

### CHRONOTHERAPEUTICS

The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Researchers have concluded that all living organisms are composites of rhythms with varying frequencies that may range from seconds to seasons. Perhaps the best known and studied chronobiologic frequency is the circadian rhythm which approximates the earth's 24-hour rotation around the sun [9]. Researchers have recently concluded that both disease states and drug therapy are affected by a multitude of rhythmic changes that occur within the human body [3].

Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. It is based on the observation that there is an interdependent relationship between the peak-to-trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs [10]. As more continues to be learned about chronobiology and chronotherapeutics, it is becoming increasingly more evident that the specific time that patients take their medication may be even more significant than was recognized in the past. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-hour period, may be changing as researchers' report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms[1].

#### Diseases and chronotherapeutics

Up to now, design of drug delivery systems has been governed by the homeostatic theory [11]. This theory is based on the assumption of biological functions that display constancy over time. However, chronobiological studies have established circadian rhythm for almost all body functions, e.g., heart rate,

blood pressure, body temperature, plasma concentration of various hormones, gastric pH and renal function [12]. It has become apparent that rhythmic processes are indispensable for the treatment of human diseases. Just as physiological functions vary over time, pathological states of disease have circadian rhythms [13].

The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, and peptic ulcer disease[3]. Patients with allergic rhinitis often report that they suffer their worst symptoms when they wake up in the morning. Patients may obtain better results in controlling this morning discomfort if they were to take a long-acting antihistamine at night rather than taking the medication in the morning as is frequently recommended [1].

#### CHRONOPHARMACOKINETICS

Chronopharmacokinetics entails the study of temporal changes in drug absorption, distribution, metabolism and excretion [15]. Pharmacokinetic parameters, which are conventionally considered to be constant in time, are influenced by various physiological functions displaying circadian rhythm. Circadian changes in gastric acid secretion, gastrointestinal motility, gastrointestinal blood flow, drug protein binding, liver enzyme activity, renal blood flow and urinary pH may play a role in time-dependent variation of drug plasma concentration [15-17]. Numerous chronopharmacokinetic studies have been conducted over the last 20 years [15,18]. The results of these studies demonstrate that time of administration affects drug kinetics.

Studies in man have been reported, particularly in relation to cardiovascular active drugs, non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetics, anticancer drugs, psychotropic drugs, antibiotics and anti-asthmatic drugs [16]. Most of the drugs seem to have a higher rate or extent of bioavailability when they are taken in the morning than when they are taken in the evening.

### Arthritis [14-19]

Arthritis (derived from Greek word arthro: joint, itis: inflammation), is a condition involving damage to joints of the body. Arthritis may broadly be classified as under:

- a. Rheumatoid arthritis (RA)
- b. Septic arthritis
- c. Juvenile arthritis
- d. Ankylosing spondylitis

RA is a disease in which body's own immune system starts to attack body's tissue. Immune complex composed of Ig-M (Ig: immunoglobulin) activate

complement and release cytokines which are chemotactic for neutrophils. These inflammatory cells secrete lysosomal enzymes which damage cartilage and bones, while prostaglandins produced in the process cause vasodilatation and pain. Attack is directed not only to joints but also on different body parts. In RA damage mostly occurs to the joint lining and cartilage resulting in erosion of two opposing bones. Common symptoms includes varied level of pain, swelling, joint stiffness and sometimes a constant ache around the joints.



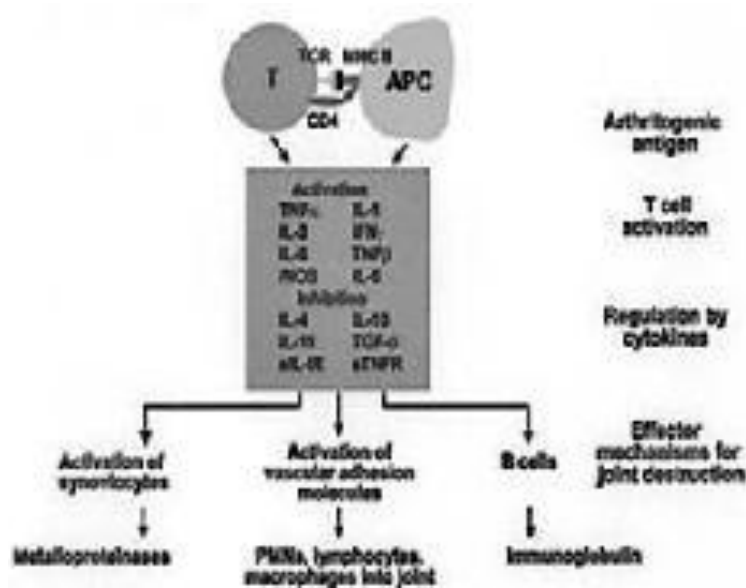
### Theories regarding pathogenesis of RA

- a) T-cell on interaction with unidentified antigen is responsible for initiating an inflammatory response. Origin of this theory lays in the thought that there is association of RA with class 2 Major Histocompatibility antigens (Fig: 2).
- b) According to another theory T-cells may be important in initiating the disease, but chronic inflammation is self perpetuated by macrophages and fibroblasts. Absence of

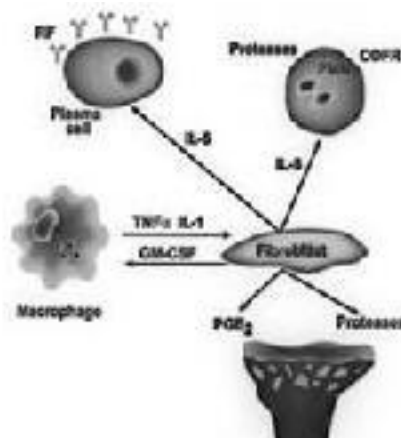
activated T- phenotypes in chronic RA and presence of activated macrophage and fibroblast phenotypes lays substance to this theory. At site of inflammation fibroblast of affected cartilage secretes:

- i. Cytokines: IL-6, IL-8 (IL: Interleukin)
- ii. Prostaglandins
- iii. Protease enzyme

Protease and prostaglandins act directly to erode and destroy bones and cartilage thus producing inflammation and other symptoms of arthritis



T-cell model for synovitis in rheumatoid arthritis



Macrophage model for synovitis in rheumatoid arthritis

**Conventional treatment approaches for arthritis**

From past few decades scientists have been attempting to develop drugs (except corticosteroids), which can suppress the rheumatoid process and bring about a remission, but do not have nonspecific anti-inflammatory or analgesic action. Commonly used treatment approaches for RA includes use of:

Non Steroidal Anti-inflammatory Drugs (NSAID's) [4]: NSAID's blocks the cyclo-oxygenase thus inhibits the synthesis of prostaglandins which is a common inflammatory mediator, thus are used commonly to treat RA, e.g., Indomethacin, Ibuprofen, Diclofenac sodium.

Glucocorticoids [20, 22 & 24]: Glucocorticoids are amongst the most prominent class of drugs used for treatment of RA glucocorticoids are immunosuppressant and have the anti-inflammatory potential; this proves glucocorticoids to be an important contender for RA therapy, e.g., Prednisolone.

Disease modifying anti-rheumatic drugs (DMARD) [7, 8, 24 & 25]: They are also known as slow acting anti-rheumatic drugs (SAARD). They possess the potential to reduce or prevent joint damage. These drugs are used in cases where inflammatory disease does not respond to cyclo-oxygenase inhibitors. Commonly

used DMARD are Methotrexate, Leflunomide, Chloroquine, Penicillamine, Gold salts etc.

Anti-cytokine therapy [16, 18 & 19]: It has been reported that interleukins and tumor necrosis factor- $\alpha$  are prominent cytokines in pathogenesis of RA. When secreted by synovial macrophages, IL-1b and tumor necrosis factor - $\alpha$  (TNF- $\alpha$ ) stimulate synovial cell to proliferate and synthesize collagenase, thereby degrading cartilage, stimulating bone resorption and inhibiting proteoglycan synthesis. Thus drug which are antagonist to these cytokines have the potential to prove effective in treating rheumatoid arthritis. Etanercept, Infliximab, Adalimumab, Anikara are the commonly used cytokine inhibitors.

Chronobiology and Chronotherapy of Arthritic Diseases Rheumatoid Arthritis

Rheumatoid arthritis is a chronic inflammatory autoimmune disorder. The cardinal signs of rheumatoid arthritis are stiffness, swelling and pain of one or more joints of the body characteristically most severe in the morning. Rheumatoid arthritis shows a marked circadian variation in its symptoms. A group of British volunteers self-assessed the pain and stiffness of affected finger joints every 2 to 3 hours daily for several consecutive days. They also measured the circumference of the arthritic joints to gauge the amount of their swelling, and they performed grip strength tests to determine the effect of the arthritic condition on the hands [1, 2]. Ratings of the severity of joint pain swelling and stiffness were about 3 times higher between 08:00 and 11:00 than at bedtime. In contrast, hand strength was lower by as much as 30% in the morning than at night. This is typical of rheumatoid arthritis sufferers [3-5].

### **Osteoarthritis**

The circadian rhythm of pain and stiffness in osteoarthritis differs from that of rheumatoid arthritis. Osteoarthritis is a degenerative disease of the joints and is the commonest of all joint diseases, affecting nearly everyone at least to some degree by age 70. The weight bearing joints of the hip, knee, back, toes and fingers are mostly affected.

The pain of osteoarthritis sufferers is typically less intense in the morning than in the afternoon or evening. This is illustrated by the findings of a Canadian study of 20 persons troubled with

osteoarthritis of the knee [6]. Participants did pain self-ratings 10 times daily for 7 consecutive days. For the group as a whole, pain intensity was rated about 40 percent higher on average between 20:00 and midnight than between 06:00 and 10:00. However, the exact nature of the 24-hour pattern of pain differed from person to person. In 40 percent, pain was greatest between 14:00 and 20:00, and in 25 percent, it was highest between 20:00 and midnight. In 15 percent, it peaked at 2 different times of the day, and in 20 percent, the level of pain exhibited no day-night variation whatsoever. Interestingly, 40 percent of the people exhibited weekly rhythms in pain intensity, although the exact day of the week it was worse varied. In some, it was more intense at the end of the week and in others the beginning.

A French study on 57 osteoarthritis sufferers also found great individual variation in the temporal patterns in pain [7]. In 33 percent, pain was most intense between 14:00 and 20:00. In 14 percent, it was worse between midnight and 08:00, and in 5 percent, it was worse between 08:00 and 14:00. A large proportion, 40 percent, had two peaks of pain daily, while 7 percent showed no temporal pattern. In summary, the day-night cycle of pain in osteoarthritis varies from one individual to another. Some experience worse pain in the morning and others at night. Some experience 2 peaks, in the morning and evening, while still others experience pain of equal intensity through out the 24 hours. The successful treatment of osteoarthritis requires that medications be taken at the right time relative to the day-night pattern of pain in each person.

### **Ankylosing Spondylitis**

Ankylosing spondylitis is characterized by swelling and discomfort of the joints of the back. In its occurrence it is an inherited disorder that is more common in men than women. One investigator used questionnaires to study daily cycles in the back symptoms of 39 people suffering from this disease [8]. Overall, back stiffness and pain were a problem throughout the 24 hours, but pain intensity was rated 2 to 3 times higher and stiffness about 8 times greater between 06:00 and 09:00 than between noon and 15:00 when each was least bothersome.



The symptoms also exhibited a second less prominent peak between 19:00 and 21:00. The findings of a French study of 26 people suffering from this medical condition were identical [9]. Ratings of the intensity of back stiffness and pain were higher in the morning and evening than in the afternoon. Marked seasonal variation in ankylosing spondylitis was also prominent. The onset of backache and stiffness was 12 times more frequent in winter than summer. Moreover, reoccurrence of back problems occurs 2 to 3 times more often in winter than summer [8].

### **Chronotherapy Arthritic Problems**

The treatment of arthritic conditions relies on medicines that fight joint swelling, stiffness, and pain. Several European investigators have studied how rhythms affect arthritic medications known as non-steroidal anti-inflammatory drugs, or NSAIDs for short. NSAIDs reduce the swelling, stiffness, and pain of arthritis, but they also cause disturbing side effects such as indigestion, stomach ulcers, headache, anxiety and dizziness. The side effects of NSAIDs can be so bothersome that some people must stop taking them.

A number of studies clearly show that the time when NSAIDs and other anti-arthritic medicines are taken is critical. Taking the medicines at the wrong time of day compromises their effectiveness and increases the risk of side effects [10]. Chronotherapy provides ways of increasing the effectiveness and safety of arthritis medications.

### **Chronotherapy of rheumatoid Arthritis with NSAIDs**

The chronotherapy of arthritic disease involves determining the best time to take NSAIDs or other types of medicines to enhance their desired effects and avoid or minimize unwanted ones. Already in 1976, Huskisson discovered that an evening once-a-day treatment schedule of the NSAID, indomethacin, was much more effective in controlling the prominent morning symptoms of rheumatoid arthritis than a morning one [5]. Moreover, he found people much better tolerated the medicine and with less complaint of side effects when administered as a single daily dose in the evening than morning.

Another study examined the role of treatment schedule on the therapeutic effect of the NSAID,

flurbiprofen [1]. 17 rheumatoid sufferers self-assessed the severity of their symptoms 6 times daily for 3 or 4 days while being treated by different medication schedules. One schedule consisted of 4 small equal flurbiprofen doses taken at equal intervals during the activity period. Three other schedules consisted of 2 large doses that were taken at different clock times during different weeks of study. For one week, the medicine was taken in the morning and midday, for another in the morning and at bedtime and for another at midday and bedtime. The twice-a-day schedules, consisting of a large bedtime dose, best controlled the bothersome morning symptoms of rheumatoid arthritis. The other treatment schedules failed to control the morning symptoms. The findings of a second study on flurbiprofen were exactly the same [11]. To control the morning symptoms of rheumatoid arthritis -- swelling, stiffness, and pain, a large daily NSAID dose must be taken in the evening or at bedtime.

### **Chronotherapy of Osteoarthritis with NSAIDs**

Medical interest in the chronotherapy of osteoarthritis with NSAIDs commenced in Europe almost 20 years ago. One French investigation evaluated the effect of a long-acting ketoprofen product when taken at different times of day [12]. On one occasion 118 people took 200 milligrams of the medicine at 08:00 and a look-alike inactive sugar-filled placebo pill at 20:00. On another, they took the placebo in the morning and the active medicine at night. Both treatment schedules were equally effective in controlling the symptoms of osteoarthritis. However, taking the medicine in the morning rather than evening caused twice as many people to experience bothersome side effects, mainly stomach pain, nausea and diarrhea.

The largest study of the chronotherapy of osteoarthritis with NSAIDs was conducted in France during the 1980s [7]. It involved 240 persons suffering from osteoarthritis of the hip, 240 suffering from osteoarthritis of the knee and 37 suffering from osteoarthritis of some other joint. The object of the study was to determine the best time to take the long-acting, once-a-day formulation of indomethacin. Each participant did self-assessments of their pain intensity every 2 hours during day and evening for a

couple of days before and after treatment. During different study weeks, people took the medicine at a single time of day, either at 08:00, noon or 20:00.

The risk of experiencing bothersome side effects of the indomethacin was strongly dependent on the time of day it was taken. Taking indomethacin at 08:00 as opposed to 20:00 resulted in a quadrupling of the number of complaints of dizzy spells, headaches, anxiety, nausea, stomach pain and indigestion [7, 13-16]. Overall, 44 persons withdrew from the study because of intolerable side effects of the medication. Remarkably, 66 percent of the withdrawals took place while taking indomethacin in the morning.

### **Chronotherapy of Arthritis with Corticosteroids**

Severe forms of arthritis often require treatment with corticosteroids such as prednisone, prednisolone, methylprednisolone and triamcinolone to control both pain and stiffness. Unfortunately, when these are taken for a long period of time, they can cause dangerous side effects, such as suppression of the endogenous corticosteroids, stomach ulcers, bone weakening, cataract formation, and mood alterations. The time of day these medicines are taken determines the risk of suffering suppression of normal cortisone production and other drug-induced side effects. Treatment schedules that involve an evening or nighttime ingestion time result in greatest cortisone suppression [17-19]. Morning or early afternoon once-a-day schedules are least detrimental [20]. Thus, the best way to minimize or avoid the side effects of these medications, especially when large doses are involved, is to take them in the morning.

Morning is the safest time to take cortisone-like medicines, but is this the right time to take them to best control the symptoms of arthritic diseases? During the past 30 years, several research studies have assessed the safety and effectiveness of various types of twice-a-day and once-a-day morning, afternoon and evening treatment schedules for rheumatoid arthritis. Some arthritis specialists recommend low dose cortisone-like medications at bedtime over twice-a-day or morning once-a-day schedules, since they feel it better controls the extreme pain and stiffness in the morning [21, 22]. Others argue that taking even low doses of these

medications at bedtime can lead to harmful side effects [17-20 & 23]. Three studies compared the safety and efficiency of dosing schedules that involved multiple daily doses to once-day morning ones [24-26]. The results of all the studies were the same. The 2 treatment schedules were equivalent in controlling the prominent morning symptoms of rheumatoid arthritis; however, morning dosing best avoided the development of drug-induced side effects.

### **SUMMARY**

The symptoms of rheumatoid arthritis are always worse in the morning. Taking long-acting NSAIDs like flubiprofen, ketoprofen and indomethacin at bedtime optimizes their therapeutic effect and minimizes or averts their side effects. 12-hour sustained-release NSAIDs that are taken twice a day must include a night or bedtime ingestion time to ensure adequate control of the prominent morning symptoms of rheumatoid arthritis.

The temporal pattern of pain and stiffness in osteoarthritis sufferers differs between persons. Thus, an individualized chronotherapy of NSAIDs is necessary. The chronotherapy of osteoarthritis involves the administration of once-a-day forms of ketoprofen, indomethacin and other such medicines in relation to the time of day pain is worse. If pain is worse at night or early in afternoon, an evening once-a day NSAID schedule is recommended. If pain is worse in the afternoon or night, a once-a-day morning or noontime treatment schedule is best, providing the amount of side effects produced by the morning one, in particular, is minimal.

If the arthritic condition is severe, synthetic corticosteroids are often of benefit. Morning once-a-day dosing of these medicines is least likely to cause side effects especially if they are taken for a long period of time. Splitting the daily dose of medicine into several small ones for ingestion with meals and at bedtime or taking the entire daily dose at night is not recommended unless absolutely necessary. The risk of severe side effects from these medications increases when they are taken more than 8 to 9 hours after the customary time of awakening, after 15:00 for most people. The later in the day these medications are taken, the greater the risk of side

effects. If the relief from the morning symptoms of rheumatoid arthritis sufferers is not attained by a once-day morning schedule, an increase in the morning dose is recommended.

The results of one study suggest an early afternoon once-a-day treatment schedule might be beneficial for those people who fail to get significant relief from the morning pain and stiffness of rheumatoid arthritis when taking medicine in the morning.

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