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CHRONOPHARMACEUTICS AS A NOVEL APPROACH FOR DRUG DELIVERY.

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ABSTRACT.

All functions in man are highly organized in time as biological rhythms of diverse periods, both in health and in disease. This represents a challenge for those involved in the development of drug-delivery systems to make possible the treatment of illness according to these physiological biological rhythms as a means of improving therapeutic outcomes. Pharmaceutical companies are experiencing obstacles in discovering new medications that represent significant advances in the treatment of disease.

Keywords: Circadian rhythm, Chronopharmaceutics, Drug-delivery system, Chronotherapy.

Introduction

Chronopharmaceutics has been described as a branch of pharmaceutics devoted to the design and evaluation of drug delivery system that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy. Youan [1] Chronotherapeutics takes into account predictable administration-time-dependent variation in the pharmacokinetics of drugs as well as the susceptibility of target tissues due to temporal organization of physiochemical processes and functions of the body as circadian and other rhythms. Rani Shobha [2] One approach to increase the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and best tolerated. The chronotherapy of a medication may be accomplished by the appropriate timing of conventionally formulated tablets and capsules, and a special drug delivery system to synchronize drug concentrations to rhythms in disease activity. The concept of chronotherapeutics is not new, the roots of clinical chronobiology date back to 1814, when Joseph Virey empirically recommended that opium should be dosed late in the evening, rather than in the morning. In the last few years recognition of the importance of the circadian rhythm to the health sciences has increased significantly.

In fact the human circadian time structure presents peaks of actions directly related to the daily routine of most human beings. As human physiology and biochemistry predictably vary during a 24 hour period it is easy to understand that some medical conditions present prevalence at certain periods of the day. The peak in serum cortisol, aldosterone, testosterone, platelet adhesiveness, blood viscosity and NK-cell activity is observed during the initial hours of daytime. Hematocrit is greatest and airway caliber (FEV1) best around the middle and afternoon hours, respectively. Insulin, cholesterol, triglycerides, platelet numbers, and uric acid peak later during the day and evening. The rhythms of basal gastric acid secretion, white blood cells (WBC), lymphocytes, prolactin, melatonin, eosinophils, adrenal corticotrophic hormone (ACTH), follicle-stimulating hormone

(FSH), and luteinizing hormone (LH) shows a peak at specific times during the nighttime. 24 hour rhythms in the processes that make up the pathophysiology of diseases cause prominent day-night patterns in the manifestation and severity of many medical conditions. The onset of migraine headache is most frequent in the morning around the time of awakening from nighttime. The sneezing and runny nose in allergic and infectious rhinitis are worst in the morning upon arising from nighttime. The symptoms of rheumatoid arthritis are worst when awaking from nighttime, while those of osteoarthritis are worst later in the day. The morbid and mortal events of myocardial infarction are greatest during the initial hours of daytime. The incidence of thrombotic and hemorrhagic stroke is greatest in the morning around the time of commencing diurnal activity. Ischemic events, chest pain, and ST-segment depression of angina are strongest during the initial three to four hours of daytime. Pain and gastric distress at the onset and acute exacerbation of peptic ulcer disease are most likely in the late evening and early morning. Epilepsy seizures are common around sleep, onset at night and offset in the morning. The symptoms of congestive heart failure are worse nocturnally. The manifestation of ST-segment elevation in Prinzmetal's angina is most frequent during the middle to latter half of the nighttime. The risk of asthma attack is greatest during nighttime. Sustained Release systems have been consistently developed academics and the pharmaceutical industry during the last decades. The principal advantages to be gained from controlling the variables of drug release in sustained release formulations are as follows: (i) a more uniform plasma drug profile with fewer occasions when super or subtherapeutic concentrations of the drug, or its active metabolite(s), occur; and (ii) a smoother therapeutic response over the dosage interval (provided the time course of drug effects reflects the plasma concentration-time profile).

One of the goals of these systems is to provide zero order, constant rate, delivery of bioactive agents, however it is now well known that living organisms do not require constant rate delivery or provide “zero order” response to drugs. The circadian rhythm also affects the organism-drugs interactions. Consequently the fact that kinetics and dynamics of drugs are directly affected by biologic rhythms and the time of drug administration is very important to the pharmacological effect. As an example, one can quote the decrease of ranitidine effect during overnight hours, probably related to partial blockade of the H_2 receptor. For some diseases enough scientific evidence has been collected in order to recommend the use of chronotherapeutics instead of a conventional drug administration. The role of chronotherapeutics in hypertension management is based on the recognition that blood pressure does not remain constant during the day, tending to be higher in the early morning and lower in the evening. This seems to be related to the arousal propensity in the morning and the sleep requirement after an awake period. Wake propensity is mediated through factors as increase in body temperature, respiration, cortisol and adrenaline levels, which has obvious effects on heart rate and blood pressure. This documented rise in blood pressure near the time of awakening is responsible in significant part for the increase of cardiovascular risk in the morning. Prisant [3] The circadian period of blood pressure is a challenge for sustained delivery systems, as blood pressure may be lowered excessively during certain times due to the zero order drug delivery provided by the system. Chronopharmaceutics

address this limitation by delivering drug in concentration that vary according to the body's circadian rhythms. In this way it is possible to reduce blood pressure at the times where patients are at highest risk for cardiovascular events without excessive reduction during low periods.

Circadian changes can also be observed in lung function and affect disease like asthma. It has been demonstrated that airway resistance increase progressively at night in asthmatic patients. Martin [4] Since bronchoconstriction and excacerbation of symptoms vary during the day, asthma is well suited for chronotherapy, namely with beta 2- agonists and oral corticosteroids. Also glucose and insulin levels' circadian variation have been studied and their clinical importance acknowledged. A. N. Rigas [5] Since the goal of insulin therapy is to mimic the normal physiologic patter of endogenous insulin in healthy individuals, chronotherapeutics seems an obvious path for insulin substitution therapies. Chemotherapy has also been reported as being more effective and less toxic when drugs are administered at selected times that take advantage of tumour cell cycles. Haus.& Halberg [6] The blood flow to tumours and tumour cell cycles. The blood flow to tumours and tumour growth rate are much higher during day activity phase than during the daily rest phase. Clinical studies that determine the times at which effects are higher with lower undesirable side effects are of great importance to establish new drug regimens. Chronopharmaceutics also plays a major role at pain control therapies. Many scientists are convinced that pain intensity is rarely constant over a 24 hours period. The daily pain profile must be used to determine the best time to administer an analgesic drug to a patient. The time dependent rhythms in pain intensity depend on the medical conditions present. Morning pain is found in patients with angina pectoris, myocardial infarction, migraine, tooth ache and arthritis rheumatoid whereas nighttime's pain is more common in arthritic pain, gastro-oesophageal reflux and renal colic. Bruguerolle & Labrecque [7] In many other solutions as hypercholesterolemia, in some neurological diseases (mainly those related to nor adrenaline levels), in duodenal ulcers and gastrointestinal tract diseases chronotherapy can be used as a great tool to optimize the drug regimen, thus increasing the efficiency of treatment.

Marketed Systems

Various systems have been developed taking chronopharmaceutics in consideration. Systems like CONTIN®, OROS®, CODAS®, CEFORM®, DIFFUCAPS®, and TIMERx® have been proposed. The use of hydrophilic matrixes is also very promising as release can be tailored to achieve the desired release programs without the need of specific industrial machines; the GEOMATRIX® is good example. More complex strategies can include the use of microchips in controlled release systems in order to obtain a determined release program. Santini, [8] Hydrogels, namely stimuli-sensitive – hydrogels and temperature sensitive hydrogels have been reviewed as interesting drug delivery technology for chronopharmaceutics. Smolesnky [9] Chronopharmaceutics certainly seems to hold the potential to improve patient outcomes and optimize disease management in the future. The selection of appropriate technology will have to take in consideration factor as the application range, ease of manufacture, cost-effectiveness and flexibility of the desired pharmacokinetic profile.

Recognition of the importance of rhythms, especially circadian (~24-hour) rhythms, to physiology, pharmacology, molecular biology, and the health sciences has increased rapidly
over the past few years. It is now well established that all living creatures are endowed with biological clocks that orchestrate, during the 24 h and other time periods, all of life's processes and functions at every level of organization.

Conclusion

One goal of this article is to educate biologists, clinicians, and pharmaceutical scientists of the importance of biological clocks and chronobiology to health and disease. A second goal is to stimulate further experimental and clinical research in the field of chronopharmacology. However, the most important goal of the issue is to motivate the development and applications of chronotherapeutics as a practical means of improving the outcomes and safety of medical treatment. In time where pharmaceutical companies strive to offer better solutions to the market the use of these intelligent systems could not only offer better therapeutic results but also increase patient's compliance.

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