DOI: 10.5567/sciintl.2013.22.28

Chronopharmacology for Anthelmintic: Immune and Modified Release of Drugs Prospectus

Adenilda Cristina Honorio-França, Patrícia Kelly Dias Lanes, Elton Brito Ribeiro and Eduardo Luzia França
Institute of Health and Biological Science, Federal University of MatoGrosso, Barra doGarças, MatoGrosso, Brazil

ABSTRACT

The chronopharmacology aims to improve therapeutic outcomes, minimize side effects and decrease resistance to drugs, specifically for anthelmintic, studies still accurately be investigated and should take into account the changes chronobiological and immune responses to the parasite. With the advancement in the field of chronobiology, modern approaches for drug delivery have widespread chronopharmacology a new concept, this is, the ability to modify the release of the therapeutic agent to the patient depending on the time and site specific. However, the main drawback is the painstaking development of systems that match the circadian rhythm, which should take into account varieties intra/inter biological. This review gives cronopharmaceutical emphasis on anthelmintics and immunological potential that can be harnessed as an alternative target for delivery of drugs.

Key words: Chronopharmacology, anthelmintic, immunology, parasitology and drug delivery

Science International, 1 (2): 22-28, 2013

INTRODUCTION

Chronobiology is the science that studies the biological processes that follow chronological rhythms, concentrating the analysis of biological rhythms and temporal characteristics of the organisms. Applied pharmacology and coupled with the advances of technology systems for drug delivery, proves to be extremely interesting in understanding and adjustments scheduled time for administration of drugs[1].

Humans, as well as any living organism, present themselves physiologically organized in function of time and are composed of a variety of biological processes, whose activity is not constant, showing rhythmic variations and for the foreseeable period. The biological rhythms have an impact not only on the basis of physiology, but also in the pathophysiology, which can directly influence the pharmacological treatment to be deployed[2].

The chronopharmacology is the science that investigates and elucidates the dependencies of biological rhythms front to drugs, trying to understand their effectiveness and toxicity. Understanding the circadian rhythm of the disease shows the dependencies of knowledge pharmacokinetic and pharmacodynamic drug, these effects and safety constitute the rationale for drug/chronotherapy[2]. Studies have shown that the time of drug administration, especially with reference to circadian rhythms, may affect the kinetics and dynamics of several classes of drugs, including drugs of the gastrointestinal system as anthelmintics[3].

The gastrointestinal motility, intraluminal pH, blood flow to the stomach and enzymatic action are not the only factors that influence the gastrointestinal absorption of the drug. It still depends on circadian rhythms and all these factors are also influenced by time of day[4].

What actually occurs is that the above mentioned factors are not rigorously checked before starting the treatment, moreover, for some of the most common helminth infections there is only one drug available for human use, therefore, understand more about chronopharmacology these drugs may prevent the spread of resistance and enhance helminth therapy. In this context, this study aims to review and discuss the current landscape of chronopharmacology anthelmintic trends indicating immune system and modifies drug release.

CHRONOPHARMACOLOGY

The chronopharmacology is a specialty pharmaceutical company that studies the rhythmic variations of drugs in the body, depending on the time of day and the biological variations. The art is based on the facts that the present chronobiological aspects individual variables as a function of time as different physiological functions, metabolic and behavioral. Thus, we seek to

Corresponding Author: Eduardo Luzia França, Instituto de Ciências Biológicas e da Saúde, Universidade Federal de Mato Grosso, Barra do Garças-MT, Rodovia BR 070, Km 05 s/n°, CEP 78 600-000. Barra do Garças – MT, Brazil Tel: 55 66 34012112 Fax: 55 66 34021117

demonstrate that administration of the drug may play different intensities of responses and symptoms[2].

The first work demonstrate that the effects of the drugs vary depending on the time of administration, the differentiating characteristics of biological rhythms[5]. They identify three important dimensions of chronopharmacology: chronopharmacokinetics, cronopharmacodynamics and cronotoxicology[6].

Chronopharmacokinetics studied the effects which the body makes the drug, considering the differences in absorption, distribution, metabolism and elimination as the time of drug administration. Circadian rhythms in terms of gastrointestinal pH may affect drug dissolution and gastric emptying in terms of mobility and blood flow may affect the rate of drug absorption. You can also alter the flow and hepatic enzyme activity that may affect the biotransformation and glomerular filtration and tubular function that can affect the elimination of the drug. Therefore, the circadian rhythm can directly affect the pharmacokinetic parameters of various drugs[3,7].

Cronopharmacodynamics refers to dosage time, is dependent rhythm and causes differences in the effectiveness of drugs. Such administration is variable due to variations in the fraction of drug, the number and conformation specific receptors and the steps of the metabolic pathway. Both beneficial effects as the unwanted/adverse drug can vary significantly depending on your time of administration[3,7].

Cronotoxicology is an aspect of cronopharmacodynamics, refers essentially to the manifestation of adverse effects and many patients with intolerance to the drug, taking into account the time of day. There are classes of drugs that have high effects and adverse relatively narrow therapeutic window, presenting probably some significant differences in time of administration security[3,7].

ANTHELMINTICS

A drug traditionally considered to be anthelmintic, must be capable of penetrating the superficie of the parasite or have access to the alimentary tract helminth. Briefly the anthelmintic may interfere with the metabolism of the parasite or produce paralysis/injury cuticular resulting in partial digestion or degradation of the parasite by immunological mechanisms. Furthermore, many anthelmintic agents modulate the activity of neuromuscular parasites by increasing the inhibitory signaling, the excitatory antagonism of signaling (blocking non-depolarizing) or tonic stimulation of excitatory signaling (blocking depolarizing)[8].

The wide use and incorrect dosage of anthelmintics in conjunction with other factors are resulting in serious problems of drug resistance, causing a serious threat to effective control of helminth infections. Anthelmintic resistance in both humans and animals are not genetically susceptible individuals choosing to current treatments, which leads to increased populations and genes that confer resistance to drugs[9].

The works have punctuated relevant investigations about the biochemical mechanisms of drug resistance with respect to action sites. Mechanism of resistance to anthelmintics has been described for antimicrotubule agents, nicotinic agonists, macrocyclic lactone antiparasitic and oxamniquine, while the biochemical basis of resistance to other drugs, including praziquantel, triclabendazole and anthelmintic salicylanilide, are still unknown[9].

Therefore, changes dosage bioavailability or factors involving raise questions relevant to resistance problems of expansion and control of nematode infections in humans. These facts are reinforced by evidence that acceptable goals of efficacy have not been clearly established, moreover, parasite burden and consequences to public health have been inadequately documented by Geary[10].

The mechanisms of action and resistance showed that anthelmintic drugs can be influenced directly interfering in their pharmacological targets. For most modern anthelmintics the action mechanism is at least partially understood, while the target site for some other not yet been clarified. Evidence molecular, biochemical and physiological suggest that the mechanisms of action and resistance are complex, non-uniform and can vary between different helminth species and due to the characteristics of the host chronobiological.

IMMUNE RESPONSE ANTHELMINTIC

The immune response plays a key role in the defense against infectious agents and is the main impediment to the spread of infection. In contrast, immune deficiencies, be of innate immunity (phagocyte deficiencies and complement) and adaptive immunity (antibodies or functional deficiency of T cells), are associated with increased susceptibility to infections[11].

The ability of the helminths to modulate the host immune system has aroused interest in understanding the molecular basis of helminth immunomodulation. Examples of immunopathological that helminths may lead to a dysregulated response are checked to schistosome infections (e.g., *Schistosomamansoni*) and filarial (e.g., *Brugiamalayi*) resulting in lack of response specific for the antigen on T cell populations from the peripheral blood of patients with severe infection. Thus, it is important to know the mechanisms by which the host immune system have to fight helminth infections[12].

Although the complement factors and other natural immune response may contribute to the defense against

helminth infection, specific immune response with production of antibodies and cytokines are important. Generally, the immune response to helminth occurs when T CD4+ ou TCD8+ cells type producing cytokines such as IL-4, IL-5 e IL-13 that, among other functions, induce the production of IgE for B cells and activation of eosinophils, basophils and mast cells, respectively, key components in the defense against helminths. Class antibodies IgE bind to circulating basophils and tissue mast cells, inducing the release of histamine and other mediators of immediate hypersensitivity reaction, which leads to the destruction of helminths[11,13,14].

The works have emphasize the importance for clinical diagnosis played by eosinophils during intestinal infections. The blood and tissue eosinophilia in helminth infections are common and often eosinophils accumulate in tissues soon after parasite invasion for carrying out various functions. This happens also in immunocompetent hosts without prior exposure to the parasite invader, indicating that eosinophils play a role in innate defense against this type of pathogen. This rapid and non-specific eosinophilic response may be a mechanism for limiting barrier against the invasion of many tissue helminths. Most helminth infections stimulate Th2, T cell responses, as well as the synthesis of IgE polyclonal[15].

It has been shown that eosinophils can function as antigen presenting cells (APCs) and they can process and present microbial antigens, including several parasite antigens. In addition, eosinophils secrete a variety of cytokines can promote T cell proliferation and polarization Th1/Th2[15].

Although eosinophils present clinically important indicator of intestinal infection, the immune response mechanisms in multiple helminth infections are due to the size and metabolic diversity of parasites and offer escape mechanisms are no longer foreign to the immune system[13]. These different pathogens induce immune responses in comparison with bacteria, fungi, viruses or protozoa. Cells of the innate and adaptive immune system are important in the initiation of immune type 2, characterizing the response to helminth infection and allergic reactions. Importantly, Th2 lymphocytes trigger resistance to helminths, despite this, the immune system works perfectly when the immune cascade occurs chronologically[16].

The works have confirmed the complexity and multiplicity of immunological defense against helminths, in particular the integral role of cells of innate immunity both as inducers and effectors at different stages of infection. Cells of the innate immune system have been recognized as major contributors of cytokines (IL-4, IL-5 e IL-13) leading the response anthelmintic type 2. Adaptive immunity encompasses Th2 effector cell populations and regulatory T which minimizes disease, but can block the expulsion of parasites. Important role is checked to B lymphocytes, which can act both as to discourage stimulate immune cells, this behavior can also be observed in dendritic cells and macrophages. Induction immunosuppressive these populations may explain the ability of helminth infections to reduce allergies and other imunopathologies[17].

Immunomodulation must be controlled and efficient to protect the host from excessive pro-inflammatory responses which can lead to organ damage, but can lead to an ineffective response which, in a way, can protect the eradication of helminths. These and other factors are associated with only the host immune response may not be sufficient in all cases requiring pharmacological treatment[12].

CHRONOPHARMACOLOGY FOR ANTHELMINTICS

The gastrointestinal tract is undoubtedly the most popular route of administration of anthelmintic drugs because of ease of administration, patient compliance and large surface area for systemic absorption. However, the pathway is complex and versatile approaches are required for delivery of drugs and therefore the treatment efficiency[8].

The chronopharmacology to anthelmintics has influenced on the exact site of absorption, because usually the mechanism of action of anthelmintic occurs directly in the parasite and its absorption must occur in the same stratum corneum, unlike most drugs that should undergo systemic absorption. Depending on the time of day, local blood flow and flow can occurgrastistestinal local pH changes and diffusion difficulty with this, the drug may be more systemically absorbed, which hamper its action on parasite[3].

The works argue that an important factor related to the host is significant variation in the pharmacokinetics of anthelmintics and their greater understanding can contribute significantly to improved parasite control[18]. Others works also indicates the lack of pharmacokinetic and pharmacodynamic data of anthelmintics in humans[10].

The spectrum anthelmintic activity of compounds depends on the presence benzodiazolics prolonged effective concentrations of drug at the site where the parasite in the host is[18]. It is confirm that in humans the increased concentration of drug in the site and prolong the period of exposure to the parasite drug results in greater efficiency[19].

These data are directly linked with chronotherapy therefore directly influences the time the medically should be administered to avoid more serious problems of bioavailability. It is discloses that studies with humans

for the fivefold increase in absorption of albendazole is administered with a fatty meal, thereby the drug does not remain in the active site in a concentration and time effective to prevent successful treatment[18].

Without a comprehensive understanding of the drug-parasite interactions, optimization of formulation and dosing regimens become compromised. Variations such as intestinal transit time and diet can change the speed of transit, thereby reducing the duration of exposure to the parasite anthelmintic, reducing the effectiveness[19].

These changes in bioavailability site-specific addition of therapy inefficiency generate another important problem, that is the development of resistance by helminths. The low dosage selection generates helminth with biochemical mechanisms of escape to the active principle, generating individuals increasingly resistant[9]. The Keiser[20] has report that benzimidazole such as albendazole and mebendazole control human infections such as *Ascarislumbricóides*e *Trichuristrichiura*, in a single-dose regimen of albendazole (400 mg) or mebendazole (500 mg), although in some cases, Individual doses are less effective against hookworms e *T. Trichiura*[20]. The microemulsion systems discussed release repeated capable of solving problems as inadequate kinetics with individual doses, which can be adapted perfectly to drugs anthelmintics[21].

The work has developed delivery systems based on pH-sensitive cationic hydrogels searching for specific release in stomach eradication of infectious processes sites. By means of such formulation can circumvent the changes cronofisiológicas that may occur, besides allowing a site-specific release in all auger gastrointestinal main targets of most helminths[22].

This discussion of bioavailability can often lead to an understanding that is the intraluminal concentration of the drug that is primarily responsible for exposing the parasite to the drug. However, many of these drugs are absorbed and metabolized in a variable manner and metabolites may or may not be active against the parasite. Additionally, the parasite may be exposed to the drug while the blood supply feedback occurs via the enterohepatic recirculation[18].

Chronobiological changes related to age, changes in the distribution of drugs, drug interactions, due to concomitant therapy (anti-inflammatory drugs or antibiotics) and co-morbidities (gastrointestinal diseases, malnutrition and immunodeficiency) may also affect the efficacy anthelmintic. Moreover, some food and drugs such as cimetidine and antacid, have an effect on the cytochrome P450-mediated drug thus modifying the pharmacokinetics[23].

Importantly, many drugs require a competent immune system to reach full effectiveness. It discusses how helminth infections can impact the function of the immune system. Studies suggest that the absence of helminth infections may be associated with increased allergic diseases and autoimmune diseases, whereas the continuing presence of such infections by helminths may have a detrimental effect on the immune response to infectious diseases such as malaria[24].

These changes may also occur in chronobiologicalhelminth parasites causing these can make use of biochemical and physiological mechanisms to promote re-infection and immune suppression avoiding selective Th2 responses of the host. Extrinsic inhibition of regulatory T cells is a key element of suppression Th2. Furthermore, Th2 cells in chronic infections become functionally impaired, indicating intrinsic regulation, which compromises mechanism Th2 memory[14]. The development of the Th2 CD4+ phenotype has important implications for the treatment of infections and the development of memory, unlike the effector cells remain functionally deficient and unable to kill the parasite[25].

Certain substances have been identified for supplying a potential as immunomodulators, which allows controlling the immunosuppression promoted by helminths. One of these, tetrahydro-6-phenylimidazo thiazole (levamisole), which was initially used only as an anthelmintic. Since 1971, levamisole has been recognized as an immunomodulatory drug, being employed to support and anticarinigênicas drugs to treat immunosuppressive diseases in animals[26]. The works reported several studies that demonstrate the immunostimulatory potential of levamisole with control capability of various infections, including parasitemias[26,27].

Another example of inadequate treatments that can trigger mechanisms of resistance by helminths has been described. It reported that helminths may secrete molecules to interfere with specific inflammatory responses mediated by eosinophils during helminth infection. For example, the larvae of *Toxocaracanis* secrete proteins that compromise the strength of eosinophils in mice[28].

The factors that contribute to the development of resistance to anthelmintics can be summarized four: (1) initial resistance allele, is a phase in which there is almost no information on the basis of parasites in humans; (2) frequency treatment, is an important determinant of the speed of selection of anthelmintic resistance because the higher the frequency of treatment doses and, faster selection of resistant strains; (3) refuges, which is the proportion of the population that is not exposed parasites to drugs, one important factor that is often overlooked; and (4) underdosing, specific dosage regimens may select resistance in different ways[18].

Therefore, chronopharmacology can be a tool that can benefit the development of therapeutic strategies for

helminth infections and various diseases as well as provide insight cronotherapeutics as a way to optimize current therapies.

DRUGS DELIVERY SYSTEMS IN CHRONOPHARMACOLOGY

As discussed chronopharmacology is the science that investigates and elucidates the dependencies of drugs across the biological rhythm, so the efficacy and toxicity of many drugs vary with time and dose rates associated with biochemical, physiological and behavioral processes under the control of circadian cycle. Since many drugs show efficacy and/or toxicity associated with the rhythm of the biochemical, physiological and behavioral intra-individual variability and inter-individual variability must be considered in order to further improvement of rational drug therapy[2].

From the viewpoint of pharmaceutical application of the biological rhythm to pharmacotherapy can be achieved by adjusting the dosage of conventionally formulated tablets and capsules. However, in many cases this type of formulation is not suitable for chronotherapy, with it, new drug delivery systems have been developed seeking a special release kinetics synchronize drug concentrations to biological rhythms and/or disease activity[1].

The chronological development of systems for drug delivery must devote to design and evaluate the kinetics of drug release at a pace that matches the requirement ideal biological therapy for a particular disease. Generally, such systems should incorporate the drug and promote distribution control the time and location-specific drug release. This type of administration has the advantage of being more secure, efficient and reliable trigger therapeutic effect, because they take into account the processes chrono bio/pharmacological[29].

Modified release formulations could be divided in differentsgroups, controlled release, delayed release and pulsatile release, according to the type of components formulations. The goal here is not to understand the differences of each, but we must understand that formulations modified release should make the control of release time and site specific dosage. As constant plasma levels of the drug must be avoided, which is the target of chronotherapy, the modified release formulations are preferred, particularly in treating the symptoms at specific times of day. In chronotherapy after drug administration the peak concentration in plasma should be obtained within the optimum time which allows the number of daily doses to be reduced. Saturable first-pass metabolism and development of tolerance can also be prevented with this type of formulation[30].

A delivery system efficient and widely used in chronopharmacology are coated microspheres for controlled release. The microspheres obtained are uniform and nearly perfectly spherical and have high capacity to incorporate drug. The microspheres may be used in a wide variety of dosage forms, including tablets, capsules, suspensions and effervescent tablets. The microspheres can be coated for controlled release with an enteric coating enabling the release and intestinal depending on the constituents enables one to control the absorption and/or stay site[31,32,33,34].

Alternatively the delayed release systems may further benefits cronotherapeutics. This type of system consists of a waterproof housing with two plugs latency, surrounding the core with the drug. After the time of the specific erosion inert layers the drug is released, determining the delay time. Thus, the release time can be adapted to the rhythm pathophysiologic[35,36,37,38].

Another delivery system that can be tailored to solve major problems anthelmintic drug delivery system is pulsatile. The works reports that this is a system in which the drug is released after a well defined time, according to circadian rhythms and the pathological condition. This delivery system is suitable in cases in which the drugs undergo metabolic degradation and should act on that specific site. This method is effective for drugs with first-pass metabolism and those directed to specific locations in the gastrointestinal tract. In such a system the possibility of drug resistance are less frequent because the desired concentration of the drug is available at a given time[31].

Another interesting release system in chronopharmacology to anthelminticsare systems for drug delivery sensitive to pH. This type of delivery system contains two components, one is the type of immediate release and the other is pulsed release that releases the drug in response to changes in pH. In the case of pH-dependent system are the advantages that exist in the environment of the gastrointestinal tract different pHs, enabling different degrees of diffusion and absorption, which should be determined during development to obtain release in time and location desired[39].

Therefore, systems, modified release of drugs certainly have the potential to improve treatment outcomes and improve the management of disease, however, the selection of appropriate technology must take into account factors such as the range of application, ease of manufacture, cost-effectiveness and flexibility pharmacokinetic profile.

CONCLUDING REMARKS

Current research increasingly comprehensive and multidisciplinary, primarily focused on health, must be increasingly consonant with the changes and pharmacotherapeutic changes in biological rhythms.

Chronopharmacological factors must be rigorously checked before starting the treatment of several diseases and helminthic infections can't be ignored. As we see, for some helminth infections there is only one drug available for human use, so we understand more about the chronopharmacology these drugs may prevent the spread of resistance and enhance helminth therapy.

Evidence molecular, biochemical and physiological suggest that the mechanisms of action and resistance are complex, non-uniform and can vary between different species of helminths and chronobiological characteristics of the host. Furthermore, drugs that beyond the conventional mechanism can trigger the immunomodulation should be better understood and chronopharmacology can be an important way not only to chronopharmacology anthelmintic but for all types of pathology.

The chronobiology can certainly improve the results and improve the management of the disease in the future. Research chronopharmacology demonstrate the importance of biological rhythms on drug therapies, which led to a new approach to the development of drug delivery systems. Excellent clinical results may not be desired if plasma concentrations of the drug are contained, furthermore, if symptoms of a disease show circadian variation, the drug release should also vary over time. Different technologies have been applied to develop modified release systems since the time of drug administration has significant impact on the treatment success, so chronotherapy is a promising area for continuing research.

ACKNOWLEDGMENTS

Thisreviewreceivedgrantsfrom Fundação de Amparo à Pesquisa de Mato Grosso (FAPEMAT) and Conselho Nacional de Pesquisa (CNPq). The authors declare no conflict of interest and nonfinancial competing interests.

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