

Pharmaceutical Approach For Treatment of Chronic Disease: Hypertension By Chronotherapy

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Abstract

The biological function of the body is controlled by circadian rhythm which is composed by Suprachiasmatic nucleus (SCN) where brain circulates the information to different cells/tissue of the body that make easier for living being to adjust in environment at any time. Hypertension is one of the most common diseases for high rate of morbidity all over the world. The change in blood pressure (BP) and heart rate (HR) is due to 24-hrs circadian rhythm. Chronotherapy plays a vital role in the management of hypertension where patients have to take medication once a day i.e. either in morning or in bedtime. The change in pharmacokinetic and pharmacodynamic of drug had observed due to different time of administration. Administration of antihypertension drugs such as valsartan given during nighttime decreases both diurnal as well as nocturnal BP and reduces excretion of albumin from urine. Various chronopharmaceutical approaches develop to achieve chronotherapy such as pulsatile system, floating system. A biological clock based dosage form is more effective than same dosage form prescribed by its dose. Chronotherapy is also applicable in other diseases like cancer, rheumatoid arthritis, stroke, asthma, obesity, diabetes.

Keywords: Circadian rhythm, Hypertension, Chronotherapy, Chronopharmaceutical approach, Tablet-in-Tablet

Introduction

Chronotherapy is also known as time-based therapy that means the treatment of an ailment according to biological rhythm of the body. The main objective of chronotherapy is to reduce the toxicity or side effects and to increase effectiveness of drug by administering at required time. Chronotherapy has several advantages over conventional therapy due to which it comes in existence (Saini et al., 2014). It is drug free therapy for example patients has to take medication twice or thrice a day but in this case medication is taken during the time of symptoms arises. It is useful for the person who sleeps for several hours. The health condition of an individual may improve because this therapy makes an individual to fall in sleep. Chronotherapy must possess the following characteristic i.e. it should be non-toxic, biodegradable and biocompatible for injectable preparation, cost effective, improve the patient compliance by reducing the dosing frequency, provide specific target to a particular disease and self-regulated system to differentiate the day and night status of disease (Ballesta et al., 2017). Chronotherapy is most widely used for the diseases based on biological rhythm like asthma, rheumatoid arthritis, allergic rhinitis, hypertension, cancer, angina pectoris. Various chronopharmaceutical approaches has been developed like multilayered tablet, compression tablet, sigmoidal release system, time-controlled explosion system, enteric-coated pulsincap, time clock system, osmotic based rupturing system (Kaur et al., 2013). Different effects of corticosteroid agents have been observed by infusion of methyl prednisolone (MP) in day active person at different clock time. When MP was infused between 4-8 pm, suppression of cortisol secretion was moderate but when infused between 12-4 am, the secretion of cortisol suppressed markedly. The suppression of cortisol based on timing of infusion is due to biological rhythm. Cisplatin is better tolerated during 4-8 pm and reduces renal toxicity (Ohdo., 2010). Night time administration of cilnidipine has considerably reduces night BP and administration of valsartan during night time has reduces both diurnal as well as nocturnal blood pressure. Bed time administration of propranolol is recommended because it decreases systolic BP and diastolic BP for 24-hours (Vemula., 2015). Nitrendipine has shown much more reduction in blood pressure if taken at 6:00 am rather than 8:00 am and evening administration reduces night BP. Morning administration of ramipril reduces diurnal BP whereas evening administration reduces nocturnal BP. Morning dosing of spirapril has significantly reduces the day blood pressure

Chronopharmaceutical system

It is amalgamation of Biological rhythm & pharmacology, Time, Dosage form & Formulation

Biological rhythm

It is a cyclic change in the biological functions of an organism at a constant time interval. It can be either endogenous which can be controlled by internal clock like body temperature cycle or exogenous which can be controlled by coordinating internal cycle with external stimuli like sleep/wake cycle and day/night cycle (Reinberg et al., 2003). The fluctuation in number of biological functions is due to circadian pattern. In recent times, a connection among biological pattern and immunological functions has been explained. The survival rate of mouse was very less after administering lipopolysaccharide (LPS) due to increased toxin level, which was determined by biological pattern. During bedtime, the level of TNF- α and IL-6 is higher and a distinct provocative response towards toxin may vary in individual because of different timing of administration of LPS. Thus, the organ disturbance and therapeutic outcome of anti-LPS agents can be controlled by biological pattern. **Yamato et al., 2017**

Circadian rhythm

Circadian rhythm is a type of biological rhythm in which oscillation in the biological, behavioral and physiological function of the body is completed in 24 hours (Kumar et al., 2012). BP changes during morning and evening due to biological rhythm. If BP is more than 120/70 mmHg during night then it is known as nocturnal hypertension, which is mainly occurred due to disturbance of circadian pattern that may result in cardiac diseases and also causes death. Ambulatory blood pressure monitoring (ABPM) is constantly examined to check the fluctuation in BP. Night-time BP can be controlled by chronotherapy where the patients can take drug during bedtime that result in normalization of BP according to the biological rhythm. **(Kristanto et al., 2016; Hermida et al., 2016)**

Chronopharmaceutics

It is a branch of pharmaceuticals, which deals with the design, development, and evaluation of dosage form that releases active ingredient based on the time at which sign and symptoms of

disease occurs. (Kulkarni et al., 2010) Excipient play important role in any drug delivery that indirectly influences on the drug dose and time of release in various diseases. Various dosage form and drug delivery system had impact on the release of drugs and amount of dose with right timing according to biological rhythm. The night-time hypertension chronotherapy is a better chronoprevention against cardiovascular disorder (CVD). The night-time hypertension occurs due to connection of BP with several risks which is greater for ABPM than office blood pressure monitoring (OBPM). Forecast of the cardiovascular disorders can be done by the nocturnal blood pressure rather than awake ABPM or OBPM. If the conventional monotherapy or polytherapy is given during nocturnal time and in diurnal time, it has shown that BP has significantly reduced during bedtime administration than that of diurnal time. Night-time hypertension chronotherapy offers the cheaper chronoprevention against undesirable CVD result in usual and susceptible renal, diabetic, and resistant hypertensive patient. **Smolensky et al., 2017; Prkacin et al., 2015; Mahabala et al., 2013)**

Chronopharmacology:

It is a branch of chronobiology, which deals with the effect of drug over the timing of biological rhythm and endogenous cycle. The main aim of chronopharmacology is to make an individual aware about the changes of circadian rhythm in terms of effectiveness as well as tolerance (Youan., 2010). Administration of antihypertensive drugs during bedtime can reduce nocturnal blood pressure and also the risk of cardiovascular ailment. 79 patients having chronic kidney diseases were taken for the randomized controlled trial where they were treated with antihypertensive drugs either in morning or in the bedtime. The observed result for morning was found 91 % whereas in case of bedtime administration it was found 95 % which implies there is not much difference so, physician or pharmacist can prescribe the medication once a day either in morning or in evening. Smith et al., studied the effect of monotherapy of valsartan and polytherapy of valsartan with hydrochlorothiazide (HCTZ) for the treatment of mild to moderate hypertension as well as central BP. Half of the antihypertensive patients were administered with valsartan alone and other half with amalgamation of valsartan and hydrochlorothiazide. It was observed that both the treatment has shown equal effect in the treatment of mild as well as moderate hypertension. **(Smith et al., 2017; Accetto et al., 2017; Lin et al., 2004; Levi 2001a, 2006b)**

Chronotherapy: The treatment of an illness or ailment by administering the medication during the diurnal time, which is supposed to synchronize with biological rhythm of the body. It is also known as time-based therapy (Saini et al., 2014). Dosing time, number of doses and drugs play a vital role for hypertension therapy. Antihypertensive agents if given at nocturnal time, PQRST pattern is normalized throughout the bedtime and morning and reduce the cardiac arrest or any fluctuation of heart rate, which lead to complication. Chronotherapy had influences the bioavailability and patient compliances. Chronotherapy isn't conducted for all the antihypertensive drugs so, proper result has not obtained. But the medication given for renin-angiotensin-aldosterone system (RAAS) has shown most significant indication. Advance exploration is required to calculate the definitive effect of time-based therapy on cardiovascular outcomes. Stranges et al., 2015; Hasan et al., 2017; Ghareeb et al., 2009; Ghorbani et al., 2018; Giriraj et al., 2014; Equchi et al., 2016; Erdogan et al., 2016; Ahmad et al., 2014)

Pharmaceutical Approach in chronotherapy

Polymeric Nanoparticle

Effect of Nisoldipine loaded Eudragit polymeric nanoparticle when combined with chronotherapy for the management of hypertension. Nisoldipine loaded polymeric nanoparticle coated with eudragit polymer were prepared by nanoprecipitation technique having diameter of 400-600nm size range. In vitro release of Nisoldipine loaded Eudragit nanoparticle has shown delay release with lag time to achieve. (Nepolean et al., 2012; Hu et al., 2017)

Oral pulsatile delivery

Pulsatile delivery is often related to delay release of drug in specific manner, which target the tissue or organ. Oral Pulsatile delivery system is intended to delay the pharmaceutical drug release from dosage form and either lag-time increase in gastric stomach such floating pulsatile formulation or release of the drug in intestine to colon for effective therapy such as enteric coated or trilayer coated formulation, which act as chronotherapeutic formulation based on time. (Thitinan et al., 2012). Losartan potassium pulsatile tablet was prepared with press-coated tablet coated with hydrophilic polymer with lag time of 6hrs with burst release and having chronotherapy effect.

Microsphere drug delivery

Microsphere system based on Chrono-therapeutics, of β -blocker bearing biodegradable polymers (Chitosan) coated with enteric-coated polymers (Eudragit S100) in hypertension. Carvedilol was entrapped in chitosan polymer microsphere formulated by emulsion crosslinking method. To prevent the drug release in acidic environment of stomach and small intestine it was coated with colonic specific pH sensitive polymer Eudragit S100. Therefore, the drug release in colon specific which prevent metabolism of drug and lowers the hypertension with chronotherapeutics theme with delayed release (Patel et al., 2012; Izquierdo-Palomares et al., 2016).

Liposomes based drug delivery

Liposomes are new version of liposomes, which contains Cetyl alcohol and surfactant tween, are highly transported by lymph capillaries to target sites. Liposomes have been aimed at increasing oral bioavailability of lacidipine by increasing its solubility and oral lymph retention. Liposomes are lyophilized and added in enteric-coated capsule, which delay the drug release with chronotherapy based formulation to achieve the therapeutic concentration when it reaches small intestines. Liposomes also prevent the first pass metabolism and enhances the water insoluble drugs bioavailability that was experimented in humans against the commercial product of same drug. (Sivagnanam et al., 2012; Bowles et al., 2018; ElKasabgy et al., 2014; Vernon 2017)

Emulsion

Self-emulsifying drug delivery system (SEDDS) is emulsion, which is oil form, and develop emulsion when it contact with gastric fluids or aqueous phase. SEDDS have been used as chronotherapy dosage form that can delay the drug release and achieve more bioavailability than conventional dosage form. Ansari et al had developed self-micro emulsion drug delivery system containing felodipine as an anti-hypertension drug, which were incorporated in polymer-coated capsules by ethyl cellulose. This polymer-coated capsule containing SEDDS of felodipine has shown lag time 5-7 hrs and release of drug only after lag time, which is time-based dosage form and shown better bioavailability in human patients. SEDDS with polymer coated capsule had chronotherapeutics based formulation to achieve desired concentration on time (Ansari et al., 2014; Ahmad et al., 2014; Smolensky et al., 2015; Hermida et al., 2011; Prkacin et al., 2015)

Conclusion

Chronotherapy is combination of biological clock and modified dosage form with diseases knowledge. In hypertension, timing of dosing at right time with biological rhythm of body which

not only help in bioavailability but decrease the dose and having patient compliance. Various dosage form had developed on the theme of chrono-pharmaceutics to achieve the therapeutic concentration at right timing of cardiac rhythm.

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