ISSN 0976 – 3333

Available Online at www.ijpba.info.

International Journal of Pharmaceutical & Biological Archives 2011; 2(2): 630-638

REVIEW ARTICLE

Chronopharmaceuticals In Nocturnal Asthma- A Review

Panwar.A.S[1]*, Agrawal.A[2], Nagori.V[1], Darwhekar G.N[1]., Jain D.K[1].

[1] *College of pharmacy I.P.S. Academy Indore. (M.P.)*
[2] *Mandsaur Institute of Pharmacy, Mandsaur. (M.P.)*

Received 28 Feb 2011; Revised 30 Mar 2011; Accepted 09 Apr 2011

ABSTRACT

Due to advances in chronopharmaceuticals, the traditional goal of pharmaceutics (like drug delivery systems with a constant drug release rate) is becoming obsolete. The major bottleneck in the development of drug delivery systems that match the circadian rhythm may be the availability of appropriate technology. Until now, the emphasis has been on formulations that maintain constant drug levels throughout the day. But we now need to develop more biologically appropriate formulations that take account of variations in bodily functions, such as blood pressure, asthma, arthritis, duodenal ulcer, cancer, diabetes, hypercholesterolaemia and some neurological disorders during the day. In asthma, a drug that could address the progressive increase in airway resistance during the night could offer better symptom control in the early morning hours. In chronopharmacotherapy drug administration is synchronized with circadian rhythms. If the peak of symptoms occurs at daytime a conventional dosage form can be administrated just before the symptoms are worsening. If symptoms of the disease became worse during the night or in the early morning the timing of drug administration and nature of the drug delivery system need careful consideration.

Key Words: Nocturnal Asthma, Circadian, Forced expiratory volume, Chronopharmaceuticals.

INTRODUCTION

Asthma is a common respiratory disease among both adults and children whose prevalence is increasing worldwide; affecting 15-20 million Indians [A]. Asthma leads to significant degrees of morbidity and mortality. It is characterized pathologically by a lymphocytic and eosinophilic infiltration of the bronchial tree with associated airway narrowing and thus it is a disease of the lung airways (bronchi). It is syndrome characterized by symptoms (dyspnea, wheeze, chest tightness, and cough), airway dysfunction and airway inflammation with eosinophils and met achromatic cells [1]. Causes of asthma include allergies, cold air, air pollutants, drugs, cigarette smoke, molds, exercise, and infections. Asthma attacks (rapid worsening of symptoms) typically occur in episodes. Intervals between attacks can be days, weeks or years. Scientists now believe that asthma attacks vary according to the time of day.

The occurrence of asthma attacks is not random during the day. Asthma symptoms are frequently worse at night (nocturnal) for a majority of asthma sufferers. A group of active asthma patients recorded the occurrence of acute asthma attacks, manifested by dyspnea (difficulty breathing) and wheezing, during a medication trial. The incidence of asthma attacks was more than 100 times greater during nighttime sleep, especially around 4 a.m., than it was during the middle of the day [2].

Circadian regulation: Nocturnal asthma is a variable exacerbation of the underlying asthma condition associated with increase in symptoms, need for medication, airway responsiveness, and/or worsening of lung function. These changes are related to sleep and/or circadian events. Simple definitions that in the medical literature are diurnal meaning daytime; nocturnal meaning nighttime and circadian meaning the 24-hour cycle.

The function of circadian regulation is to impose a temporal organization on physiologic processes and behavior. In addition to the sleep- wake cycle, other examples of circadian regulation occur in body temperature, multiple hormones, and the

***Corresponding Author:** Panwar.A.S, **Email:** aakash_ips@yahoo.com.sg

autonomic nervous system. Disorders of circadian regulation are typically expressed as sleep disorders. However, diseases may be promoted or exaggerated by normal circadian control, and alternatively, disturbances of circadian regulation secondary to disease processes may exaggerate manifestations of the disease. Circadian rhythms have two principal features: they run freely in the absence of temporal cues, particularly the light-dark cycle; and under normal environmental circumstances they are entrained to the light dark cycle [3].

These features indicate that a neural system that expresses and regulates circadian function must have the following features: circadian pacemaker(s); photoreceptors and visual pathways that transduce photic information into neural information and transmit it to the pacemakers; and pacemaker output to the effector systems that express circadian function [3, 4]. These effector systems then express physiologic control mechanisms. However, there is a paucity of information about the effect of this interaction on lung function and immunology. In asthma, the resistance increases progressively across the night, whether subjects sleep or not, although the increase is much greater during sleep [5]. The findings of these as well as other studies suggest that the frequency, severity, and duration of late asthmatic reactions to allergen challenge are increased at night and result in further enhancement of bronchial responsiveness. This nocturnal increase in bronchial responsiveness can contribute significantly to the nocturnal worsening of asthma symptoms. Allergic rhinitis, for example, can intensify airway responsiveness and even provoke asthma symptoms. Active sinusitis can also cause an increase in the asthma process. Another study demonstrated that patients with nocturnal asthma had an increased proportion of low-density eosinophils at 4:00 A.M. as compared with 4:00 P.M., and also as compared with that of asthmatic subjects without nocturnal asthma or of normal subjects [6]. Chronotherapeutics is the synchronization of medication levels in time with reference to need, taking into account biologic rhythms in the path physiology of medical conditions, and/or rhythm-dependencies in patient tolerance for given chemical interventions. Chronotherapeutics can sometimes be achieved by the judicious timing of conventional sustained-release (SR) formulations, although reliance on special drug-delivery systems seems to constitute a more dependable means of matching drug level to biologic need and tolerance[7, 8].

Chronobiology is the study of the biologic rhythms of physiologic and pathologic processes. Circadian cycles have approximately a 24-hour period, diurnal and nocturnal are part of the circadian cycle refer to the day and night periods. A mammalian circadian pacemaker located in the suprachiasmal nucleus of the brain controls many physiologic functions such as core temperature which itself is used to monitor the phase of the circadian rhythm. In man, the circadian cycle is about 24 hours in length.

Circadian changes in pulmonary function: Normal and asthmatic subjects show circadian variation in pulmonary function as assessed by Spiro metric parameters such as forced expiratory volume in one second (FEV1) and peak expiratory flow rate (PEFR), which are maximal around 4 PM and lowest around 4 AM [9]. Circulating hormones vary in a circadian fashion in everyone and may contribute to overnight fall in lung function [10]. There are dynamic changes in airway resistance overnight. In one study, Lower airway resistance to airflow rose progressively from 12 midnight to 6 AM in asleep asthmatic subjects. This pattern of change was also seen, albeit to a milder degree, during a subsequent night when sleep was withheld [11, 12].

CHRONO THERAPY FOR NOCTURNAL ASTHMA

The increasing research interest surrounding chronopharmaceutical drug delivery systems may lead to the creation of a new sub-discipline in pharmaceutics known as chronopharmaceutics [13]. Matching drug release to the body's circadian rhythms has been the elusive goal of many drug delivery companies for at least two decades. But the hazards of the gastrointestinal tract have meant that only a handful of truly chronopharmaceutical products have reached the market, and few are in development. The idea of targeting release to the specific time of day when there is maximal clinical manifestation of a disease has obvious advantages, and there is no shortage of ingenuity in designing formulations for time-delayed drug release. But the difficulty lies in designing products that are resistant to breakdown by the fluids in the GI tract. As well as in hypertension and other cardiovascular disease, Dr Youan offers good theoretical reasons for carefully timed drug delivery in the treatment of asthma, arthritis, duodenal ulcer, cancer, diabetes, hypercholesterolaemia and some neurological

disorders. In asthma, a drug that could address the progressive increase in airway resistance during the night could offer better symptom control in the early morning hours. A number of systems have been developed for timed release of commonly used medicines. Most established is probably the OROS technology marketed by Alza. OROS uses osmosis to release the drug contained within a semi-permeable membrane. As water from the GI tract enters the tablet, a layer of osmotically active agents expands and pushes on the drug core, so that the drug is released through laser-drilled holes in the outer membrane. An additional layer between the active drug core and the semi-permeable membrane enables release to be delayed. An alternative approach, used by Elan in its chronotherapeutic oral drug absorption system (CODAS), relies on a combination of water soluble and water insoluble polymers, coated on to drug-loaded beads to delay release by four to five hours after ingestion. The polymer coat is gradually dissolved by water from the GI tract, and the drug diffuses through the resulting pores in the coating. In contrast, US-based drug delivery company, Penwest, uses a gum matrix for its TIMERx controlled release technology. On exposure to GI fluids, the combination of xanthan and locus bean gels becomes hydrated and the drug core is gradually released. The TIMERx system is being adapted for chronopharmaceutical applications, with lag time controlled by variations in the gum matrix [14].

Research in chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy optimal clinical outcome cannot be achieved if drug plasma concentrations are constant. If symptoms of disease display circadian variations drug release should also vary over time. Formulations should be justified by biopharmaceutical and pharmacokinetic study in order to choose the best hour for administration. Another point raised by circadian variation of physiological function is that drug pharmacokinetics can be time-dependent. Variations in physiological and pathophysiological functions in time, also need for variations of drug plasma concentration has brought a new approach to the development of drug delivery systems, Chronopharmaceutical drug delivery. Chronobiological studies have established circadian rhythm for almost all body functions. They are in synchrony with sleep activity cycle of the individual. The rhythms tend to fall into one of two groups. In the first are those that peak during the daytime and are associated with the activity phase of the individual: body temperature, mental, physical and gastrointestinal activities, blood pressure, heart rate, secretion of adrenaline etc. The second group, where rhythms show a peak during nocturnal sleep, includes secretion of several hormones, among which are growth hormone, cortisol and melatonin. Most asthma attacks occur at 04:00 to 06:00 hours. Nocturnal asthma is a complex interaction of several coincident circadian rhythms (figure 1) e.g. secretion of hydrocortisone and adrenalin.

In chronopharmacotherapy drug administration is syncronised with circadian rhythms. If the peak of symptoms occurs at daytime a conventional dosage form can be administrated just before the symptoms are worsening. If symptoms of the disease became worse during the night or in the early morning the timing of drug administration and nature of the drug delivery system need careful consideration. In this case modified-release dosage forms must be used. The influence on chronokinetic of the route of administration must also be considered. For example, there are studies showing that chronopharmacokinetic variation is not found when drug is administrated rectally [15, 16]. It is not possible to support the idea that oral administration of conventional (immediate- release) formulations at different times of day leads to constant plasma level. Modified-release formulations have many advantages over immediate-release formulations. With these formulations a less frequent drug administration is possible, lower peak concentrations can be obtained to avoid adverse effects and patient compliance can be improved. The modified-release dosage forms can be divided into subgroups of rate-controlled-release, delayed-release and pulsed-release formulations. Delayed-release formulations include time-controlled release and site-specific dosage forms. Time-delayed delivery systems (time-controlled release formulations and pulsed release formulations) are the best approach to deliver drugs in accordance with circadian rhythms of the disease. The mentioned approach serves a purpose especially in the treatment of early morning symptoms. By timing the drug administration, plasma peak is obtained at an optimal time. Number of doses per day can be reduced. When there are no symptoms there is no need for drugs. Saturable first pass metabolism and tolerance development can also be avoided [17].Enteric-coated formulations are used mainly in connection with site-specific

delivery, but they can be used also in time-controlled delivery systems when the lag time is needed. Bogin and Ballard (1992) have used successfully the salbutamol formulations for the treatment of nocturnal asthma. In this case the polymers dissolving in the intestinal pH level above 6 were used [18]. Several attempts have recently been made to develop chronotherapy for nocturnal asthma, using theophylline, inhaled corticosteroid, inhaled anticolinergic agent and beta 2-agonist. Pharmacological chronotherapy is the administration of medication according to biological rhythm to maximize pharmacological effects and minimize side effects. The circadian rhythm of biological rhythms is particularly important in understanding the declined changes in lung function of asthmatics at night [19]. The circadian rhythm in peak expiratory flow (PEF) was altered according to the severity of the asthma. In patients with symptoms present between midnight and early morning, an evening dose of theophylline chronotherapy can be prophylactically used for nocturnal asthma attacks. Consideration of the circadian rhythm and bathyphase of PEF is useful in selecting appropriate chronotherapy for nocturnal asthma [20]. Theophylline is a non-selective inhibitor of phosphodiesterase the enzyme that degrade cyclic-3, 5-adenosine monophosphate, of which there are seven isoenzymes. These results in increased levels of intracellular c-AMP and therefore broncho dilation, it is the inhibition of phophodiesterase-3- and –4 isoenzymes in particular which is belived to result in airway smooth muscle relaxation [21, 22]. Since diurnal variations of PEF obtained from asthmatics, include circadian rhythms at a high rate, it is thought that PEF may be suitable for evaluating the effect of chronotherapy. Chronotherapy of a once-daily evening dose of a new controlled-release theophylline preparation that achieves to peak blood concentrations at 10-12 hours after dosage effectively improved the values of PEF and symptoms of nocturnal asthmatics [23]. When nocturnal symptoms were present, the bathyphase (trough time) of the PEF rhythm narrowed to around 04:00; during this time of unstable asthma, the amplitude of the PEF pattern increased 3.9-fold compared to the symptom-free period. No significant group circadian rhythm was detected during theophylline chronotherapy. Evening theophylline chronotherapy proved to be prophylactic for persons whose symptoms before treatment had occurred between midnight and early morning [24]. Many patients with asthma experience a worsening of symptoms at night and in the early morning, resulting in sleep disruption and possibly altered daily performance. A bronchodilator agent that exerts its maximal effect overnight to control nocturnal symptoms, without a worsening of the disease during the daytime, should improve the treatment of asthma. This investigation examined the efficacy and kinetics of a new chronotherapeutically optimized, sustained-release theophylline formulation administered once daily (OD) in the evening at 8:00 P.M. in comparison with a conventional sustained-release theophylline administered twice daily (TD) at 8:00 A.M. and at 8:00 P.M. in the same dose However, between 2:00 and 6:00 A.M., PEF and FEV1 were significantly greater with OD than with TD. The improvement in PEF and FEV1 at this time, because of OD, was correlated with the serum theophylline level. This was not the case for TD. The improvement in airflow over baseline values between 2:00 and 6:00 P.M. [25].

Asthma and COPD worsen at night and in the early morning, due to various circadian influences. So uninterrupted sleep, stable lung function over 24 h, and reduced and stable airways responsiveness is primary therapeutic goals in asthma and COPD. Once-daily evening theophylline chronotherapy meets these goals, providing rising blood levels at night and in the early morning, when most needed. This regimen is now indicated for morning and evening dosing for reversible airway obstruction, in the United States and Canada, and marks the first available treatment for these diseases to include dosing time in the therapeutic strategy. It reflects increasing recognition by the medical community of the need to consider the individual patient's timing of symptoms in relation to the kinetics of the drug [26]. The theophylline levels remained practically constant for 24 hours under conventional theophylline treatment with twice-daily administration. In contrast, the variations of the theophylline serum levels and the night levels were higher after once-daily dosage of Euphylong, and the daytime levels and especially at the end of the dosage interval were lower [27].

As many as 80 percent of asthmatics experience nighttime or early-morning episodes, which are difficult to treat and potentially fatal. The greater-than-normal amplitude of circadian airflow variation in many asthmatics contributes heavily to the genesis of the early 'morning dip'. Beta-agonists and corticosteroid are of limited

usefulness in nocturnal asthma, and slow-release theophylline drugs, while potentially effective, vary in 24-hr blood profile and hence their influence on nocturnal episodes. Traditional 12-hr 'symmetric' theophylline regimens, instead of meeting increased nocturnal demands, may actually produce lower night- than daytime blood levels. On the other hand, appropriately timed administration of a once-daily theophylline drug might provide maximum blood levels when needed and help stabilize 24-hr airflow. Chronotherapeutic potential of single-daily evening doses of a controlled-release theophylline preparation (Uniphyl 400-mg tablets) in nocturnal and early morning asthma. Nighttime blood concentrations with this regimen were higher than were those with Theo-Dur tablets, B.I.D., in the same total daily doses, or with once-daily morning Uniphyl administration.

In fed and fasted subjects, evening administration of Uniphyl 400-mg tablets was well tolerated and did not lead to 'dose dumping'[28]. Coordinating biological rhythms (Chronobiology) with medical treatment is called chronotherapy. It considers a person's biological rhythms in determining the timing--and sometimes the amount--of medication to optimize a drug's desired effects and minimize the undesired ones. According to Smolensky, patients are more likely to follow schedules for taking their medications when those medications are formulated as chronotherapies because of better medical results and fewer adverse side effects. "With better compliance, the disease can be better contained, which means fewer doctor visits and potential trips to the hospital because of acute flare-ups". The area in which chronotherapy is most advanced drug therapy does not involve new medicines but using old ones differently. Revising the dosing schedule, reformulating a drug so its release into the bloodstream is delayed, or using programmable pumps that deliver medicine at precise intervals are some of the simple changes that may reap enormous benefits. Normal lung function undergoes circadian changes and reaches a low point in the early morning hours. This dip is particularly pronounced in people with asthma. Chronotherapy for asthma is aimed at getting maximal effect from bronchodilator medications during the early morning hours. One example is the bronchodilator Uniphyl, a long-acting theophylline preparation manufactured by Purdue Frederick Co. of Norwalk, Conn., and approved by FDA in 1989. Uniphyl causes theophylline blood levels to reach their peak and improve lung function during the difficult early morning hours [29].

TREATMENTS

Certain SR formulations of theophylline can be administered so that a rising blood level of the drug occurs when airway obstruction is increasing, while adverse effects are reduced. For this purpose, SR theophylline is administered once daily, in the evening, for the management of nocturnal asthma [30]. Another aspect of theophylline therapy is how it can work in conjunction with inhaled corticosteroids as part of a chronotherapeutic regimen. This interaction is important, since inhaled corticosteroid therapy used in patients with moderate to severe asthma failed to control a significant percentage of nocturnal asthmatic symptoms [31]. Various tablet formulations for the sustained-release of β-agonists have been used in a chronotherapeutic fashion for the management of asthma [32]. As with theophylline, very little information exists about comparing the effects of or adding a long-acting β 2-agonist oral preparation to an inhaled corticosteroid using chronotherapeutic techniques.

Class	Name	Action
β-agonists	salmeterol and formoterol [33, 34]	**have a lower adverse-effect profile than do long-acting oral agents[35, 36]** Salmeterol has been shown to control symptoms of nocturnal asthma to a substantial degree, and to improve sleep quality and daytime cognitive performance in patients with chronic asthma [37, 38]
cholinergic antagonists	ipratropium bromide	Reduced the morning decline in airflow in asthmatic individuals [42, 43].
	oxitroprium bromide	
Oral Corticosteroids inhaled corticosteroids[46]	Prednisone[45]	Long-term oral administration at 8:00 A.M. and 3:00 P.M. was more effective in controlling nocturnal asthma than the same doses given at 3:00 P.M. and 8:00 P.M.[44].
Leukotriene modifiers	Zileuton[47], zafirlukast[48] and montelukast	Alleviate the symptoms and the decrement in lung function seen in nocturnal asthma.

Table 1: Treatment of Nocturnal Astma

It is important to note that any advances in β2-agonist therapy will need to take into account the down regulation of the β2 receptors that occurs at night in nocturnal asthma[39], and which is related to glycine 16 polymorphism [40]. Drugs that antagonize the vagal nervous system should be useful in the management of nocturnal asthma as a means of counteracting the enhanced nocturnal parasympathetic tone that occurs in the disease [41]. Other studies have shown that a single 3:00 P.M. dose of prednisone improved lung function and reduced airway inflammation more effectively than the same single dose given at 8:00 A.M. and 8:00 P.M.[45]. Although the leukotriene-active drugs, including zileuton, zafirlukast and montelukast, are new in the treatment of asthma, they have been shown to alleviate the symptoms and the decrement in lung function seen in nocturnal asthma. It has been shown that zileuton in particular decreased nighttime increases in leukotriene B4 (LTB4) and (LTE4) while improving lung function [47]. Zafirlukast has also been shown to decrease nighttime awakenings and improve morning PEF rates [48]. Although these agents have only been studied at set doses and times regardless of the presence or absence of nocturnal asthma, the improvements observed were significant, and it is likely that these agents will prove very useful in the treatment of nocturnal asthma when used chronotherapeutically[49].

Three leukotriene modifiers are currently available for the treatment of asthma as monotherapy in patients with symptoms less frequently than once a day and as add-on treatment in patients with more severe asthma who is currently receiving inhaled corticosteroids. They may provide added protection against triggers such as exercise in patients who are already receiving inhaled corticosteroids. Little differences in clinical efficacy are apparent between zileuton (Zyflo®), zafirlukast (Accolate®) and montelukast (Singulair®) but significant differences exist in the pharmacokinetics, drug interactions, and adverse effects. Montelukast (Singulair®) offers once daily administration, has no currently known drug interactions, has few adverse effects, and is available in a chewable tablet formulation for children. For these reasons, it is the preferred leukotriene modifier in the treatment of asthma. Chronotherapy studies with inhaled corticosteroids have shown optimal therapeutic benefit when steroids are administered four times per day (QID) or once daily at 3 PM [50]. An individually adjusted dose of once-daily theophylline administered in the evening is at least as effective as conventional therapy with controlled-release terbutaline in preventing nocturnal and early morning asthma, when both drugs are added to regular medication with inhaled sympathomimetics and steroids [51]. AMIAID TBL TAPE [53] is designed to act according to the circadian rhythm of the respiratory function to deliver the drug in the quantity needed at the time needed. In other words, as illustrated in (**Fig. 1**), it represents a further advance on conventional sustained-release preparations, which sustain a constant level of effect; applying a concept known as chronotherapy, it not only maintains effect constantly, but also varies the level of effect so that it is highest when respiratory function is at its weakest effect. The tape preparation consists of a backing layer, an adhesive layer and a release liner. The active ingredient tulobuterol, a bronchodilator, is uniformly dispersed through the adhesive layer in a crystal state. Drug concentration rises rapidly after application and is sustained over time, with maximum (C max) reached 10-14 hours after application.

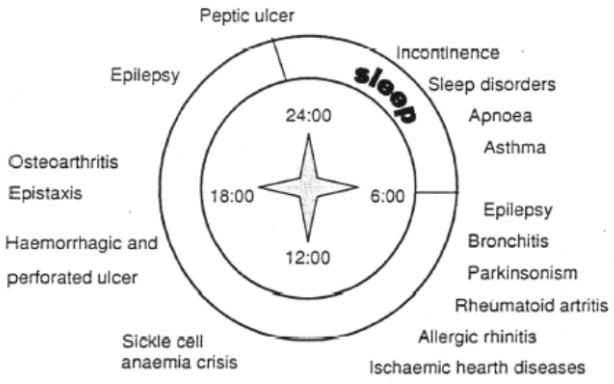

Fig 1: Diseases displaying Circadian rhythm

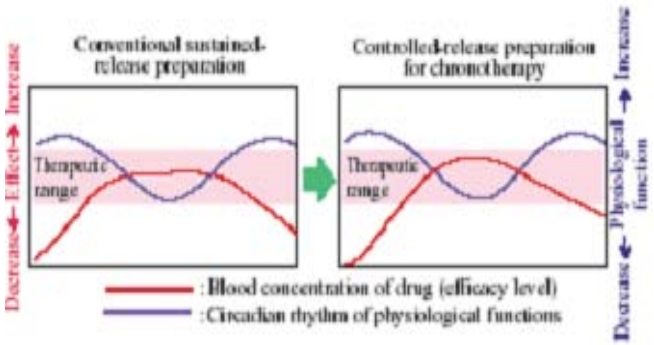

Fig. 2 Outline of chronotherapy

CONCLUSION

It is concluded that the treatment of asthma with the Chrono-optimized preparation over night is more effective than treatment with a conventional preparation in twice-daily dosage. In addition, lung function showed greater stability, throughout the day, with once-daily evening therapy than with traditional 12 hr dosing. It is well known that human body temperature, blood pressure, and pulse rate reach high values during the day and fall at night. Similarly, all other physiological functions and activities are subject to a daily cyclical variation known as their circadian rhythm. The respiratory function is no exception and is known to experience a trough in activity from late night until early morning.

In other words, as shown in the diagrammatic illustration in application once daily at bedtime could be expected to prevent asthma attacks for practically the entire 24-hour period and, as maximum blood concentration is reached in the early morning, would be particularly effective against attacks caused by morning dip[54].

REFERENCES

1. Gokhle AB, Saraf MN, Recent Development in asthma therapy, **Indian Drugs** 39(3) MARCH **2002**, P-121
2. http://www.medicinenet.com/asthma/page 3.htm
3. Moore, R. Y., Circadian rhythms: basic neurobiology and clinical applications. **Ann. Rev. Med. 1997** 48: 253-266.
4. Moore, R. Y., Entrainment pathways and the functional organization of the circadian system. **Brain Res. 1996**111: 103-119.
5. Montplaisir, J., Walsh, j., and J. L. Malo. 1982. Nocturnal asthma: features of attacks, sleep and breathing patterns. **Am. Rev. Respir. Dis.** 125: 18-22
6. Calhoun, W. J., M. E. Bates, L. Schrader, J. B. Sedgwick, and W. W. Busse.. Characteristics of peripheral blood eosinophils in patients with nocturnal asthma. **Am. Rev. Respir. Dis. 1992** 145: 577-581
7. Pappenheimber, J. R., G. Koski, V. Fencyl, M. L. Karnovsky, and J. M. Krueger.. Extractions of sleep-promoting factors from cerebrospinal fluid and from brains of sleep-deprived animals. **J. Neurophysiol. 1975** 38: 1299-1311.
8. Richard J. Martin and Susan Banks-Schlegeld. Chronobiology of Asthma**. Am. J. Respir. Crit. Care Med.,** Volume 158, Number 3, September 1998, 1002-1007.
9. Hetzel MR, Clark TJ., Comparison of normal and asthmatic circadian rhythms in peak expiratory flow rate. **Thorax 1980**; 35:732–738.
10. Kraft M, Pak J, Martin RJ. Serum cortisol in asthma: marker of nocturnal worsening of symptoms and lung function? **Chronobiol Int 1998**; 15:85–92.
11. Ballard RD, Saathoff MC, Patel DK, et al. Effect of sleep on nocturnal bronchoconstriction and ventilatory patterns in asthmatics. **J Appl Physiol 1989**; 67(1): 243–249.
12. Philip E Silkoff, and Richard J Martin., Pathophysiology of nocturnal asthma ,**ANNALS OF ALLERGY, ASTHMA, & IMMUNOLOGY,** VOLUME 81, NOVEMBER, **1998**, 378–387.
13. Youan, BBC. Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery? **, Journal of Controlled Release** Vol. 98, No. 3, pages 337(2004) DOI:10.1016/j.jconrel.2004.05.015 ISSN: 0168-3659 Publisher : Elsevier
14. **The Pharmaceutical Journal** Vol: 274 No.: 7333 p90-91 January 2005
15. Nakano S., Watanabe H., Ohdo S., Ogava N., Circadian-stage dependent changes in diazepam and valproate kinetics in man: a single and repetitive administration study. **Annu. Rev. Chronopharmacol**. **1986**, 3, 421-424.
16. Yoshiyama Y., Nakato S., Ogawa N.,. Chronopharmacokinetic study of valproic acid in man: comparison of oral and rectal administration. **J. Clin. Pharmacol. 1989**, 29, 1048-1052.
17. Vyas S.P., Sood A., Venugoplan P., Mysore N.,. Circadian rhythm and drug delivery design. **Pharmazie**, **1997** 52, 815-820.
18. Bogin R.M., Ballard R.D.,. Treatment of nocturnal asthma with pulsed-release albuterol. **Chest 1992**,102, 362-366
19. Burioka N, Sasaki T. Chronopharmacology and chronotherapy for asthma by using PEF PMID: 8950937 [PubMed - indexed for

MEDLINE] Chronobiol Int. 2000 Jul;17(4):513-9.
20. Burioka N, Sako T, Tomita K, Miyata M, Suyama H, Igishi T, Shimizu E. Theophylline chronotherapy of nocturnal asthma using bathyphase of circadian rhythm in peak expiratory flow rate. Third Department of Internal Medicine, Faculty of Medicine, Tottori University, Yonago, Japan.URL burioka@grape.med.tottori-u.ac.jp
21. Lipworth BJ.Modern drug treatment of chronic asthma. **BMJ 1999**; 318:380-4
22. Mahinaz H, Alexandra T, William OF, and Debbie C. Current Drug treatment of Asthma, **Hospital Pharmacist, October 2001** Vol-8,, Page 242.
23. BuriokaN, SasakiT., Chronopharmacology and chronotherapy for asthma by using PEF, **Chronobiol Int. 2000** Jul;17(4):513-9.
24. Burioka N, Suyama H, Sako T, Shimizu E., Circadian rhythm in peak expiratory flow: alteration with nocturnal asthma and theophylline chronotherapy.,**Biomed Pharmacother. 2001**; 55 Suppl 1:142s-146s. PMID: 10908127 [PubMed - indexed for MEDLINE]
25. D'Alonzo GE, Smolensky MH, Feldman S, Gianotti LA, Emerson MB, Staudinger H, Steinijans VW et al. Twenty-four hour lung function in adult patients with asthma. Chronoptimized theophylline therapy once-daily dosing in the evening versus conventional twice-daily dosing.,. , Pulmonary Division, University of Texas Health Science Center, Houston.
26. Goldenheim PD, Schein LK. Purdue Frederick Company ,Chronotherapy of reversible airways disease with once-daily evening doses of a controlled-release theophylline preparation, , Norwalk, Connecticut 06856.
27. D'Alonzo GE, Smolensky MH, Feldman S et al. University of Texas, Health Science Center,24-hour lung function in asthmatic patients: chrono-optimal theophylline therapy as once-daily Euphylong administration vs conventional twice-daily administration, (UTHSCH), School of Medicine, Department of Internal Medicine, Houston.
28. Goldenheim PD, Conrad EA, and Schein LK. Medical Department, Purdue Frederick Company, Norwalk, Treatment of asthma by a controlled-release theophylline tablet formulation: a review of the North American experience with nocturnal dosing. CT 06856.
29. Isadora Stehlin .,A Time to Heal:Chronotherapy Tunes In to Body's Rhythms, **FDA Consumer magazine** (**April 1997***)*
3. D'Alonzo, G. E., M. H. Smolensky, S. Feldman, L. A. Gianotti, M. B. Emerson, H. Staudinger, et al. Twenty-four-hour lung function in adult patients with asthma. **Am. Rev. Respir. Dis. 1990**142: 84-90.
30. Langdon, C. G., and L. J. Lapsey. Fluticasone propionate and budesonide in adult asthmatics: a comparison using dry powder inhaler devices. **Br. J. Clin. Res. 1994** 5: 85-99.
31. D'Alonzo, G. E., M. H. Smolensky, S. Feldman, Y. Gnosspelius, and K. Karlsson. Bambuterol in the treatment of asthma. **Chest 1995** 107: 406-412.
32. Fitzpatrick, M. F., T. Mackay, H. Driver, and N. J. Douglas.. Salmeterol in nocturnal asthma: a double blind, placebo-controlled trial of a long acting inhaled β2 agonist. **Br. Med. J. 1990** 301: 1365-1368 [Medline].
33. Rabe, K. F., R. Jorres, D. Nowak, N. Behr, and H. Magnussen. Comparison of the effects of salmeterol and formoterol on airway tone and responsiveness over 24 hours in bronchial asthma. **Am. Rev. Respir. Dis. 1993** 147: 1436-1441.
34. Brambilla, C., C. Chastang, D. Georges, L. Bertin, and the French Multicentre Study Group.. Salmeterol compared with slow-release terbutaline in nocturnal asthma. **Allergy 1994**, 49: 421-426 [Medline].
35. Muir, J. F., L. Bertin, D. Georges, and French Multicentre Study Group. Salmeterol versus slow-release theophylline combined with ketotifen in nocturnal asthma: a multicentre trial. **Eur. Respir. J. 1992**, 5: 1197-1200.
36. Selby, C., H. M. Engleman, M. F. Fitzpatrick, P. M. Simem, T. W. MacKay, and N. J. Douglas. Inhaled salmeterol or oral theophylline in nocturnal asthma? **Am. J. Respir. Crit. Care Med. 1997**, 155: 104-108 [Abstract].

37. Szefler, S. J., R. Ando, L. C. Cicutto, W. Surs, M. R. Hill, and R. J. Martin.. Plasma histamine, ephinephrine, cortisol, and leukocyte β-adrenergic receptors in nocturnal asthma. **Clin. Pharmacol. Ther. 1991**, 49: 59-68.
38. Turki, J., J. Pak, S. A. Green, R. J. Martin, and S. B. Liggett.. Genetic polymorphisms of the B2-adrenergic receptor in nocturnal and non-nocturnal asthma: evidence that Gly16 correlates with the nocturnal phenotype. **J. Clin. Invest. 1995** , 95: 1635-1641.
39. Morrison, J. F. J., and S. B. Pearson.. The effect of the circadian rhythm of vagal activity on bronchomotor tone in asthma. Br. **J. Clin. Pharmacol**. **1989**, 28: 545-549 [Medline].
40. Coe, C. I., and P. J. Barnes. Reduction of nocturnal asthma by an inhaled anticholinergic drug. **Chest 1986.** 90: 485-488
41. Wolstenholme, R. J., and S. P. Shettar. Comparison of fenoterol with ipratropium bromide (Duovent) and salbutamol in young adults with nocturnal asthma. **Respiration 1989**. 55: 152-157.
42. Reinberg, A., P. Gervais, M. Chaussade, G. Fraboulet, and B. Duburque. Circadian changes in effectiveness of corticosteroids in eight patients with allergic asthma. **J. Allergy Clin. Immunol. 1983.** 71: 425-433 [Medline].
43. Beam, W. R., D. E. Weiner, and R. J. Martin. Timing of prednisone and alterations of airways inflammation in nocturnal asthma. **Am. Rev. Respir. Dis. 1992.**146: 1524-1530 [Medline].
44. Pincus, D. J., S. J. Szefler, L. M. Ackerson, and R. J. Martin. Chronotherapy of asthma with inhaled steroids: the effect of dosage timing on drug efficacy. **J. Allergy Clin. Immunol. 1995.** 95: 1172-1178.
45. Wenzel, S. E., J. B. Trudeau, D. A. Kaminsky, J. Cohn, R. J. Martin, and J. Y. Westcott. Effect of 5-lipoxygenase inhibition on bronchoconstriction and airway inflammation in nocturnal asthma. **Am. J. Respir. Crit. Care Med. 1995**. 152: 897-905 [Abstract].
46. Spector, S. L., L. J. Smith, M. Glass, and the Accolate Asthma Trialists Group. Effects of 6 weeks of therapy with oral doses of ICI 204,219, a leukotriene D4 receptor antagonist, in subjects with bronchial asthma. **Am. J. Respir. Crit. Care Med. 1994.** 150: 618-623 [Abstract].
47. Richard J. Martin and Susan Banks-Schlegel, Chronobiology of Asthma. **Am. J. Respir. Crit. Care Med.,** Volume 158, Number 3, September 1998, 1002-1007,
48. Pincus DJ, Humeston TR, Martin RJ. Further studies on the chronotherapy of asthma with inhaled steroids: the effect of dosage timing on drug efficacy. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9438485&dopt=Abstract Feb 28 2005
49. Vilkka V, Brander P, Hakulinen A, Laitinen J, Sahlstrom K, Aalto E, Silvasti M, Karttunen P. Once-daily theophylline in the treatment of nocturnal asthma. Department of Pulmonary Diseases, Etela-Saimaa Central Hospital, Tiuruniemi, Finland
50. Kathryn Blake, Pharm.D. New Pharmaceutical Agents In The Management of Asthma, **Jacksonville Medicine** / November, 1999
51. T. Uematsu, M. Nakano, K.Kosuge, M. Kanamaru, and M. Nakashima, **Eur. J. Clin. Pharmacol, 1993 .** 44, 361
52. Nakano Y. Transdermal Patch for Asthma Therapy, **NITTO TECHNICAL REPORT**, VOL,38, No- 2, DECEMBER 2000.