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REVIEW ARTICLE

Chronobiology, Circadian Variations and Chronotherapy of Glaucoma

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Abstract
Advancements in chronopharmaceutics, the traditional goal of pharmaceutics is becoming obsolete. 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, hypercholesterolemia and some neurological disorders during the day. In glaucoma, intraocular pressure, a major risk factor for glaucoma, is known to vary throughout the day, yet glaucoma continues to progress in some patients despite it being well controlled. It is important to understand how other glaucomatous risk factors are affected by circadian variations. It is found that nonphysiologic nocturnal blood pressure dipping and wider circadian fluctuations in ocular perfusion pressure are linked with the development and progression of glaucoma.

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INTRODUCTION

The increasing research interest regarding chronopharmaceutical drug delivery systems may lead to the creation of a new sub-discipline in pharmaceutics known as chronopharmaceutics. 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[1] offers good theoretical reasons for carefully timed drug delivery in the treatment of asthma, arthritis, duodenal ulcer, cancer, diabetes, hypercholesterolaemia and some neurological disorders.

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 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[2]. 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.

Possibility of Chronopharmaceutics Approach

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[3-4]. 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[5].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. In case of glaucoma there is no chronopharmaceutical drug delivery systems tested due to circadian variations. This research will be the next challenge in Chronopharmaceutics.

CIRCADIAN VARIATIONS IN GLAUCOMA

It is well established that circadian rhythms play an important role in maintaining homeostasis in the human body. Various physiologic systems from blood glucose and insulin regulation[6] to cortisol and melatonin production[7] are affected by the circadian clock. The status of certain diseases is also characterized by circadian variations. Cancer growth, for example, is governed by a 24-hour cycle that can be exploited to maximize susceptibility to chemotherapy and improve patient outcomes[8]. It is not surprising then, that similar circadian rhythms influence the eye and ophthalmic diseases, such as glaucoma and non-arteritic anterior ischemic optic neuropathy[9]. It has been known for over four decades that intraocular pressure (IOP) varies throughout the day,[10] but not until more recently has it been shown that other factors affecting the eye such as systemic blood pressure[11], ocular perfusion pressure (OPP)[12] and ocular blood flow (OBF)[13] also follow circadian patterns.

Glaucoma is the second leading cause of blindness globally and is characterized by a multi-factorial optic neuropathy.[14] Elevated IOP is a major risk factor for the disease and is currently its only therapeutic target. However, recent publications indicate IOP fluctuation itself is not an independent risk factor for glaucoma progression, suggesting a possible break from previous research.[15-16] This is supported by the common observation that glaucoma progresses in some patients despite well-controlled IOP.[17-19] Therefore, it is important to understand how circadian variations in other ocular parameters may also influence glaucoma. The purpose of this review is to analyze the literature on circadian variations in blood pressure, OPP, and OBF and to identify consensus findings regarding their potential impact on glaucoma, exploring new avenues of research for clarifying the vascular etiology of glaucoma and its potential treatment strategies.

Circadian Variations in Systemic Blood Pressure and Glaucoma

Blood pressure also follows a distinctive circadian curve characterized by systolic and diastolic declines during sleep, with a trough roughly between 2:00 a.m. and 4:00 a.m. This dip is followed by a transient spike in arterial pressure in the early morning that parallels the peak incidence of cardiovascular events. Literature supports that, nocturnal variations in blood pressure as a potential risk factor in glaucoma. Leske et al observed certain vascular risk factors were predictors of glaucoma progression. Specifically, lower systolic perfusion pressure, lower systolic blood pressure, and cardiovascular disease history emerged as new predictors.[20] Systemic hypertension[21] and hypotension[22-23] have both elsewhere been reported as potential risk factors in glaucoma. It has been suggested that chronic hypertension may cause microvascular damage, whereas hypotension may reduce local perfusion. Both mechanisms may lead to further glaucomatous progression in the face of IOP elevation or poor vascular autoregulation of blood flow.[24] It is also thought that perfusion instability, rather than a steady reduction of ocular blood flow, might contribute to glaucomatous optic neuropathy.[25]

Hayreh et al noted that both glaucoma patients using topical b-blockers[26] and hypertensive patients on oral b-blocker therapy[27] had greater nocturnal dips than other patients. A similar report from Netland et al found timolol to cause significantly lower nocturnal heart rate and bradycardia than carteolol in patients with ocular hypertension and primary open-angle glaucoma. Thessaloniki eye study, treatment with antihypertensive medication was associated with increased cup-to-disk ratio of the optic nerve head.[28]

Circadian Variations in Ocular Perfusion Pressure and Glaucoma

Ocular perfusion pressure is defined as two-thirds of mean arterial pressure minus IOP.[29] It can be further broken down into diastolic perfusion pressure (diastolic blood pressure -- IOP) and systolic perfusion pressure (systolic blood pressure -- IOP). It is not surprising, then, that the nocturnal variations in arterial pressure described in the previous section might also influence ocular perfusion pressure. IOP, the other variable determining OPP, has also been shown to follow a pattern of circadian change. It has been shown in healthy subjects that nocturnal IOP is significantly higher than diurnal IOP, with peak IOP occurring at the end of the night just before awakening.[30-31]Part of the nocturnal increase in IOP has been attributed to a change from sitting to supine position with sleep, but this circadian IOP elevation can be detected even without postural change.[32] The circadian IOP variations observed in healthy subjects have been noted in glaucoma patients too, with peak IOP usually occurring outside of normal clinic

hours.[33] Increased risk for glaucomatous visual field loss has also been associated with wider diurnal fluctuations in IOP rather than elevated peak IOP alone.[34]

Evidence supporting a link between OPP and glaucoma can be found in several large, population- based studies that strongly associate decreased perfusion pressure with an increased prevalence of glaucoma.[35-36] In glaucoma patients, however, it has been observed that OPP is lowest around 7:00 a.m., just before awakening.[29] This finding is in agreement with peak IOP and relative hypotension occurring at the same time, suggesting that regulatory dysfunction in glaucoma patients prevents maintenance of OPP in the face of nocturnal changes in IOP and blood pressure. A more recent study further identified circadian OPP fluctuation as the most consistent clinical risk factor for glaucoma severity.[37] The authors found that both anatomic (retinal nerve fiber layer thickness) and functional (visual field) outcome variables were significantly worse in glaucoma patients with wider circadian OPP fluctuation. They attributed glaucoma progression to daily repetitive ischemic insults followed by reperfusion injury in eyes with defective auto regulatory mechanisms that could not maintain consistent OPP.

Circadian Variations in Ocular Blood Flow and Glaucoma

Circadian variations in OBF were unable to identify a consensus among the currently published literature. Clear evidence was found that dysregulation of OBF occurs in glaucoma, but circadian variations in OBF and their effects on disease state remain to be clarified[38]. Impaired autoregulation of OBF has been implicated because glaucoma patients with the greatest drop in nocturnal blood pressure demonstrate significant alterations in retrobulbar flow parameters.[39] Future studies should encompass larger sample sizes and examine functional outcomes over a longer period of time, and patient sleep disturbance should be minimized while OBF measurements are recorded. Techniques for measuring OBF would also benefit from further characterization of accuracy and reproducibility.

FORSKOLIN AND CHRONOTHERAPY OF GLAUCOMA

There are various advantages of the chronopharmaceutics, which may include decrease first pass metabolism, increase biological tolerance. Also there are various diseases in which chronopharmaceutics are used which include cardiovascular diseases, anti-asthamatic disease, antiulcer disease and very recently antiglaucoma[40]. Glaucoma is a progressively degenerative disease of the optic nerve and is the second-leading cause of blindness in the world affecting 67 million people globally. Sami Labs, Bangalore (India), is the first pharmaceutical company, which derived a product from a plant to be approved in India, which is also the first such eye care product worldwide. The ophthalmic solution of the drug Forskohlin has been accorded approval by the Drug Controller General of India in August 2006. This eye drops formulation will be available in the market under the brand name "Ocufors 2%". Hoechst had identified the efficacy of forskohlin in the treatment of Glaucoma but they could not make an effective formulation and subsequently dropped the studies midway through. According to company's official press release, "Ocufors" is 30 per cent more effective than the most popular drug for glaucoma in the market with no side effects.

Wagh *et al.*, formulated forskolin ophthalmic drug delivery systems to test its efficacy in New Zealand albino rabbits for its antiglaucoma efficacy. Ophthalmic Inserts [41-49] of forskolin extract (OIE) and pure forskolin 98% (OIF) were prepared as matrix controlled delivery with the aim of achieving once a day administration. Ophthalmic Insert Drug Delivery System (OIDDS) for forskolin showed a significant reduction in Intraocular Pressure up to 24 hours and an increased corneal residence time up to 12 hours with sustained therapeutic action which is a desirable feature for an antiglaucoma agent. Gupta S. *et al.* prepared forskolin nanocrystals and stabilized by poloxamer 407. Their investigations proven that the pH and thermoreversible polymeric *in situ* gel forming nanosuspensions with ability of controlled drug release exhibits a greater potential for glaucoma therapy.[50] Wagh V D *et al.*, formulated forskolin ophthalmic chronotherapeutic drug delivery systems to test its efficacy in New Zealand albino rabbits for its antiglaucoma efficacy[51].

CONCLUSION

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. Several risk factors associated with the vascular etiology of glaucoma are influenced by circadian variation. Daily changes in IOP alone cannot fully explain the pathophysiology of glaucoma. Nonphysiologic nocturnal blood pressure dipping and wider circadian fluctuations in OPP have also been clearly linked with the development and progression of glaucoma. The proposed mechanism involves defective autoregulation of OBF with failure to maintain adequate perfusion in the face of changing blood pressure and IOP, resulting in ischemic damage. It is a necessary to see glaucoma disease through the angle of chronotherapy, so that there will be a generation of new medication profile for the better pharmacotherapy of glaucoma patients.

DECLARATION OF INTEREST

It is hereby declared that this paper does not have any conflict of interest.

REFERENCES

1. Youan BBC. Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery? J Control Release. 2004; 98: 337.
2. Moore RY. Circadian rhythms: basic neurobiology and clinical applications. Ann Rev Med. 1997; 48: 253.
3. 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.
4. 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.
5. Vyas SP, Sood A, Venugoplan P, Mysore N. Circadian rhythm and drug delivery design. Pharmazie. 1997; 52: 815.
6. Simon C. Ultradian pulsatility of plasma glucose and insulin secretion rate: circadian and sleep modulation. Horm Res. 1998; 49:185.
7. Selmaoui B, Touitou Y. Reproducibility of the circadian rhythms of serum cortisol and melatonin in healthy subjects: a study of three different 24-h cycles over six weeks. Life Sci. 2003; 73: 3339.
8. Mormont MC, Levi F. Cancer chronotherapy: principles, applications, and perspectives. Cancer. 2003; 97: 155.
9. Hayreh SS, Zimmerman MB, Podhajsky P, Alward WL. Nocturnal arterial hypotension and its role in optic nerve head and ocular ischemic disorders. Am J Ophthalmol. 1994; 117: 603.
10. Drance SM. Diurnal variation of intraocular pressure in treated glaucoma. Arch Ophthalmol. 1963; 70: 302.
11. O'Brien E, Murphy J, Tyndall A, Atkins N, Mee F, McCarthy G, Staessen J, Cox J, O'Malley K. Twenty-four-hour ambulatory blood pressure in men and women aged 17 to 80 years: the Allied Irish Bank Study. J Hypertens. 1991; 9: 355.
12. Liu JHK, Zhang X, Kripke DF, Weinreb RN. Twenty-four-hour intraocular pressure pattern associated with early glaucomatous changes. Invest Ophthalmol Vis Sci. 2003; 44: 1586.
13. Osusky R, Rohr P, Schötzau A, Flammer J. Nocturnal dip in the optic nerve head perfusion. Jpn J Ophthalmol. 2000; 44:128.
14. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, Mariotti SP. Global data on visual impairment in the year 2002. Bull World Health Organ. 2004; 82:844.
15. Bengtsson B, Leske MC, Hyman L, Heijl A. Fluctuation of intraocular pressure and glaucoma progression in the early manifest glaucoma trial. Ophthalmology. 2007; 114 :203.
16. Jonas JB, Budde WM, Stroux A, Oberacher-Velten IM, Jünemann A. Diurnal intraocular pressure profiles and progression of chronic open-angle glaucoma. Eye. 2007; 21: 948.
17. Chauhan BC, Drance SM. The relationship between intraocular pressure and visual field progression in glaucoma. Graefes Arch Clin Exp Ophthalmol. 1992; 230: 521.
18. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol. 2003; 121: 48.
19. Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javitt J, Singh K. Relationship between

intraocular pressure and primary open angle glaucoma among white and black Americans.The Baltimore Eye Survey. Arch Ophthalmol. 1991; 109: 1090.
20. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z. Predictors of long-term progression in the early manifest glaucoma trial. Ophthalmology. 2007; 114: 1965.
21. Wong TY, Wong T, Mitchell P. The eye in hypertension. Lancet. 2007; 369: 425.
22. Graham SL, Drance SM, Wijsman K, Douglas GR, Mikelberg FS. Ambulatory blood pressure monitoring in glaucoma. The nocturnal dip. Ophthalmology. 1995; 102: 61.
23. Hayreh SS. Role of nocturnal arterial hypotension in the development of ocular manifestations of systemic arterial hypertension. Curr Opin Ophthalmol. 1999; 10: 474.
24. Graham SL, Drance SM. Nocturnal hypotension: role in glaucoma progression. Surv Ophthalmol. 1999; 43: S10.
25. Grieshaber MC, Flammer J. Blood flow in glaucoma. Curr Opin Ophthalmol. 2005; 16: 79.
26. Hayreh SS, Podhajsky P, Zimmerman MB. Beta-blocker eyedrops and nocturnal arterial hypotension. Am J Ophthalmol. 1999; 128: 301.
27. Hayreh SS, Podhajsky P, Zimmerman MB. Role of nocturnal arterial hypotension in optic nerve head ischemic disorders. Ophthalmologica. 1999; 213: 76.
28. Topouzis F, Coleman AL, Harris A, Jonescu-Cuypers C, Yu F, Mavroudis L, Anastasopoulos E, Pappas T, Koskosas A, Wilson MR. Association of blood pressure status with the optic disk structure in nonglaucoma subjects: the Thessaloniki eye study. Am J Ophthalmol. 2006; 142: 60.
29. Sehi M, Flanagan JG, Zeng L, Cook RJ, Trope GE. Relative change in diurnal means ocular perfusion pressure: a risk factor for the diagnosis of primary open-angle glaucoma. Invest Ophthalmol Vis Sci. 2005; 46: 561.
30. Liu JH, Kripke DF, Hoffman RE, Twa MD, Loving RT, Rex KM, Gupta N, Weinreb RN. Nocturnal elevation of intraocular pressure in young adults. Invest Ophthalmol Vis Sci. 1998; 39: 2707.
31. Liu OHK, Kripke DF, Twa MD, HoffmanRE, Mansberger SL, Rex KM, Girkin CA, Weinreb RN. Twenty-four-hour pattern of intraocular pressure in the aging population. Invest Ophthalmol Vis Sci. 1999; 40: 2912.
32. Liu JH, Bouligny RP, Kripke DF, Weinreb RN. Nocturnal elevation of intraocular pressure is detectable in the sitting position. Invest Ophthalmol Vis Sci. 2003; 44: 4439.
33. Perlman JI, Delany CM, Sothern RB, Skolnick KA, Murray D, Jacobs RW, Shue JL, Kaplan E, Friedman NC, Nemchausky BA, Ryan MD, Kanabrocki EL. Relationships between 24h observations in intraocular pressure vs blood pressure, heart rate, nitric oxide and age in the medical chronobiology aging project. Clin Ter 2007; 158: 31.
34. Asrani S, Zeimer R, Wilensky J, Gieser D, Vitale S, Lindenmuth K. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. J Glaucoma. 2000; 9: 134.
35. Leske MC, Wu SY, Nemesure B, Hennis A. Incident open-angle glaucoma and blood pressure. Arch Ophthalmol. 2002; 120: 954.
36. Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Hypertension, perfusion pressure, and primary open-angle glaucoma. A populationbased assessment. Arch Ophthalmol. 1995; 113: 216.
37. Choi J, Kim KH, Jeong J, Cho H, Lee CH, Kook MS. Circadian fluctuation of mean ocular perfusion pressure is a consistent risk factor for normal-tension glaucoma. Invest Ophthalmol Vis Sci. 2007; 48: 104.
38. Werne A, Harris A, Moore D, BenZion I, Siesky B. The Circadian Variations in Systemic Blood Pressure, Ocular Perfusion Pressure, and Ocular Blood Flow: Risk Factors for Glaucoma? Survey of Ophthalmology. 2008; 53: 559.
39. Gherghel D, Orgül S, Gugleta K, Flammer J. Retrobulbar blood flow in glaucoma patients with nocturnal over-dipping in systemic blood pressure. Am J Ophthalmol. 2001; 132: 641.
40. Wagh VD, Kalshetti P. Chronopharmaceutics : Dosage form design to rhythms in disease state. J Chronother Drug Deliv. 2011; 2: 23-29.
41. Wagh VD, Inamdar B, Wagh KV, Samanta MK. The effect of Forskolin ophthalmic inserts on intraocular pressure in rabbit eyes. Int J Pharm Pharm Sci. 2009; 1:46-55.
42. Wagh VD. 2007 Development and evaluation of ophthalmic drug delivery systems for natural forskolin and its analogues in the treatment of glaucoma. Ph. D. Dissertation. The Tamilnadu, Dr. M.G.R. Medical University, Chennai, India.
43. Wagh VD, Inamdar B, Samanta MK. Polymers used in ocular dosage form and drug delivery systems.

Asian J Pharm. 2008; 1: 12-17.
44. Wagh VD, Wagh KV, Pati PP, Samanta MK. Formulation and evaluation of ophthalmic insert drug delivery system (OIDDS) of forskolin. Asian J Pharm. 2008; 1: 222-24.
45. Wagh VD, Wagh KV, Samanta MK. Formulation and evaluation of ophthalmic insert drug delivery system of forskolin. J Pharm Res. 2009; 2: 12-25.
46. Wagh VD, Samanta MK. Formulation development and evaluation of HPMC based Ophthalmic Inserts Drug Delivery System (OIDDS) of forskolin. Indian J Pharm. 2010;1: 10-13.
47. Wagh VD, Pathare YS. Herbal medicines and nutritional supplements used in the treatment of glaucoma: A review. Res J Pharm Biol Chem Sci. 2012; 3: 331-39.
48. Tandale YN, Wagh VD. Formulation and evaluation of dorzolamide hydrochloride polymeric film. Int J PharmTech Res. 2011; 3:1817-1824.
49. Wagh VD, Patil PN, Wagh KV, Surana SJ. Forskolin: Upcoming Antiglaucoma molecule. J Postgrad Med. 2012; 58(3): 199-202.
50. Gupta S, Samanta MK, Raichur AM. Dual-Drug delivery system based on in situ gel forming nanosuspensions of forskolin to enhance antiglaucoma efficacy. AAPS PharmSciTech. 2010; 11: 322-35.
51. Wagh VD, Patil PN, Surana SJ. Development and evaluation of chrotherapeutic drug delivery system of forskolin in the treatment of primary open angle glaucoma. Proceedings of National seminar on Current Trends and Recent Advancements on Herbal Formulations, Shirpur, Maharashtra, India.

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