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Chronopharmacology In Cancer: A Review

Dr. Preeti Kulkarni*[1], Malesh Prajapati[1] , Dr. Bhaskar Vaidhun[1], Saba Khan[1], Harshada Khandge[1], Shweta Chaurasia[1], Rucha Bhangale[1]
[1]*Gahlot Institute of Pharmacy, Navi-Mumbai, Maharashtra.*
Corresponding author: Dr. Preeti Kulkarni

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ABSTRACT: Chronopharmacology is the science of exploiting in pharmacological terms what the clock has set in motion, as it is tied to the cyclical nature of biological phenomena. This serves as rationale for pacing the delivery of drugs to optimize patients benefit. This system of pharmacology factors into circadian rhythm of body which is endogenous and is controlled by external factors like light and temperature. In this review with the help of case studies, we discuss the role of chronopharmocology palys in decreasing toxicities from anticancer drugs like cisplastin where wild type mice were administred in evening times, there was an enhanced rate of removal of cisplastin-DNA adduct and less toxicity than morning treated mice. Also in comparing extent of toxicities between doxorubicin and eirubicin in relation to cicardian rhythm in treated mice, it was reported that the circadian timing of doxorubicin affects bone marrow and gut toxicity in mice to a greater extent than when compared to epirubicin. The enzyme dihydropyrimidine dehydrogenease (Dpi) which catalyzes catabolism of 5-FU is showed to have varying activity according to the time of the day. Therefore, there is huge scope of utilizing chromotherapy in decreasing toxicity and enhancing efficacy of anticancer drugs, since anticancer drugs have potentials for serious adverse reaction which further leads to decreased patients compliance and loss in quality of life of patients receiving anticancer drugs.

KEYWORDS: Chronopharmacology; Anti-cancer; Chronobiology; Circadian rhythm

I. INTRODUCTION:

Chronopharmacology is a branch of science that deals with variation in pharmacological action of various drugs over biological timing and endogenous periodicals. Circadian rhythm is a natural internal process that regulates the sleep-wake cycle which repeats roughly every 24 hours. The study of biological temporal rhythms, such as daily, tidal, weekly, seasonal and annual rhythms is called chronobiology. Circadian rhythms are endogenous and are formed by external factors like light, temperature and redox cycles. This cycle also refers to oscillations in biological, physiological and behavioral functions of an organism with a periodicity of 24 hours. Moreover, it also coordinates with digestion, temperature and hormones[1] Circadian pacemaker which is also known as biological clock is a suprachiasmatic nuclei (SCN) located in the hypothalamus. When light falls on the eye, the light signals are transmitted by afferent nerves from the retina which enter by the retinohypothalamic tract into paired suprachiasmatic nuclei in the hypothalamus. Then SCN passes the information to the pineal gland and releases melatonin. SCN impulses connection with ANS set the sensitivity of endocrine glands (thyroid, adrenal, ovary, etc.)[2] Coordination of circadian clocks is by endogenous physiological rhythms so that they tick in synchrony in most tissues that can be damaged by anticancer agents. So circadian cycle can modify by 2-10 fold the tolerability of anticancer medications in experimental models and cancer patients. Some of improved efficacy is also seen when drugs are given near their respective times of best tolerability, due to poor circadian entrainment of tumor and persistent circadian entrainment of healthy tissues. Host clocks are disrupted with anticancer drugs when administered at their most toxic time. Moreover, circadian disruption accelerates experimental and clinical cancer processes. [3,4]

IMPACT OF CHRONOPHARMACOLOGY ON EFFECT OF DRUG

The effect is due to our body's rate of activity vary during day & night time. Some of them are i) gastric motility is double in the daytime than at night. ii) Plasma protein concentration is higher in the day than at night. iii) Hepatic flow is greatest at 8 am. iv) Lipophilic drugs are better absorbed in the morning because of faster gastric

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emptying time and higher GI perfusion in the morning.[2]

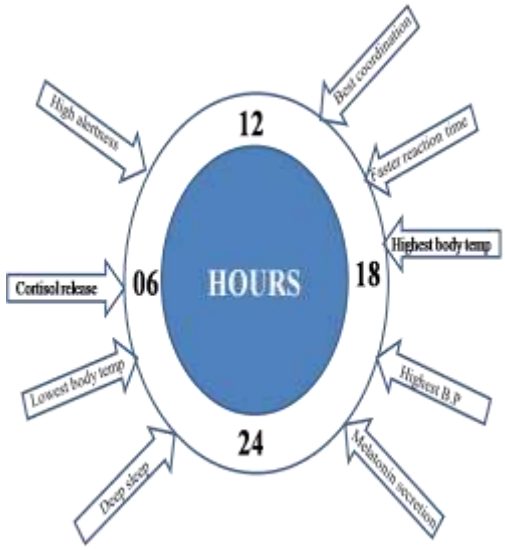

Fig 1: Time dependent body's response

ROLE OF CHRONOPHARMACOLOGY IN CANCER

The normal cell (host cell) and tumor cell (cancer cell) differ in their chronobiological cycles. This fact is the basis of chronopharmacotherapy of cancer. Based on the study, DNA synthesis in normal human bone marrow cells has a peak around noon while the peak of DNA synthesis in lymphoma cells is near midnight. The S-phase active cytotoxic therapy at late night is generally administered and it was found that there is a decrease in tumor cells with a little effect on normal cells and this is what we want in the treatment of cancer.[2]

There are many drugs used to treat cancer according to the rate of proliferation of cells concerning time and also cell cycle. The activity of dehydropyrimidine dehydrogenase in human mononuclear cells increases by 40% around midnight. There are different biological rhythms for normal and tumor cells. Tumors grow fast at 2 pm and slow at 10 pm. Cancer drugs are prescribed according to the duration of the phase of the cell cycle and cell proliferation. Cancer drug (S-phase-specific) is administered more in the night time because cancer cells divide more in night time and host cell in the morning. But in the case of drugs like 6-mercaptopurine and methotrexate evening doses are given to patients.

In colorectal cancer, oxaliplatin is given during daytime but fluorouracil at night time. In breast cancer, surgery done during the later half (luteal phase) of the menstrual cycle, gives more clearance rate in the early half. As progesterone rise during ovulation, it inhibits the enzyme responsible for the spread of cancer cells.[2] Several strategies are aimed at increasing the selectivity of anticancer agents against cancer cells. They are based on tumor cell biology like new drug development, resistance, etc. Others are target at host cells development of analogs with fewer toxicities, scheduling or supportive care to increase chemotherapy tolerability, etc. A dose efficacy relationship has been repeatedly established for Cancer chemotherapy.

Circadian dosing time influences the extent of toxicity of ~30% anticancer drug, including cytostatic and cytokines. For all drugs, the survival rate varies by 50% or more according to circadian dosing time of a potentially lethal dose. Large differences are observed irrespective of injection route, intravenous or intraperitoneal, or number of injections that may be single or repeated.

CASE STUDIES

According to a study, pirarubicin an anthracycline compound mostly exerts a myelosuppressive effect, which is lowest following dosing in the second half of the diurnal rest span. Another anthracycline-related compound, mitoxantrone display the lowest hematological toxicity in 8 hr. later. Other drugs like platinum complex analog cisplatin, carboplatin and oxaliplatin are best tolerated, despite the differing target tissues of toxicity of these compounds. Cisplatin is mostly toxic to both kidney and bone marrow. Carboplatin is toxic to bone marrow and colon mucosa and oxaliplatin to jejunal mucosa and bone marrow.[5]

1. Chronotherapy with 5-fluorouracil, oxaliplatin and folinic acid in colorectal cancer[7,8,9,10]

In this experiment, 12 hr. infusion of oxaliplatin followed by a similar 12 hr. infusion of 5-FU and folinic acid was given to a group of patients with a variable rate. A control group of patients with a constant rate of infusion of all 3 drugs for 24 hrs as also maintained. Various observations were recorded by 12 and 24 hrs combination therapy. Based on this experiment it can be interpreted that a 12hr infusion system has advantages over a 24 hr. continuous infusion

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regimen. This experiment cannot point out the specific role of chronotherapy upto an extent.

2. Circadian expression of Dihydropyrimidine Dehydrogenase, Thymidylate Synthase, c- myc and p53 mRNA in mouse liver tissue[11]

The inhibition of Thymidylate Synthase (TS) is the mediatory aspect of 5–FU while dihydropyrimidine dehydrogenase (DPD) is the rate-limiting and initial catabolic enzyme of 5-FU. This study explores mouse liver DPD, p53 and c-myc. 24 male mice were exposed to alteration of 12hr of light and 12hr of darkness for 4 weeks for synchronization. With an intra-peritoneal sensor, the body temperatures and rest-activity were monitored. At 3,7,11,19,23 HALO (hours after light onset) all the mice were sacrificed respectively and the liver samples were obtained and immersed in liquid nitrogen. From those samples, total RNA was extracted and one step real-time quantitive RT-PCR was performed using Light Cycler-RNA Amplification SYBR Green I system. At about 16 HALO DPD showed a circadian expression in m-RNA level with a peak value while TS showed a trend for circadian rhythm with a peak during light.

3. The circadian clock regulates cisplatin-induced toxicity and tumor regression in melanoma mouse and human[12]

Studies using murine models and human models have shown that the time of day of cisplatin treatment influences renal and blood toxicities. The hypothesis of the mechanism responsible for the outcomes is by circadian clock. The experiments were conducted using wild-type and circadian disrupted per half % of mice treated with cisplatin at selected morning and evening times. When wild-type mice were treated in evening times there was an enhanced rate of removal of cisplatin-DNA adduct and less toxicity than morning treated mice. Time of day effect is linked to circadian clock has been suggested since the temporal variation in toxicity was less in per half % clock. More robust immune responses and slow tumor growth rate was observed in half % of mice indicating the circadian clock also influences immune response to melanoma tumors. The study indicates that cisplatin chronopharmacology induces circadian clock control of DNA repair as well as immune responses and thus affects both cisplatin toxicity and tumor growth. It suggests that influencing the circadian clock (eg- through bright light treatment) may be used as a tool to improve patient outcomes.

4. Experiment performed to compare toxicities of doxorubicin & epirubicin.[13]

In this experiment, timing & administration of equitoxic epirubicin doses affected toxicological response in female mice as that of doxorubicin is tested. It was observed that, compared to doxorubicin equimolar epirubicin toxicity is reduced by about 50% by epimerization of hydrogen and the hydroxyl group at the fourth position of the anthracycline sugar moiety. Also, the circadian timing of doxorubicin affects bone marrow & gut toxicity in mice & clinical toxicity. Besides, there is a seasonal effect was found with fewer deaths occurring after epirubicin was given in summer as compared to winter most safe circadian timing for epirubicin is earlier in the day than for doxorubicin while their seasonal patterns are quite similar.

5. Experiment on circadian variation of dihydropyrimidine dehydrogenase mRNA in leukocytes and serum cholesterol level in patients with healthy control compared to patients with advanced gastrointestinal carcinomas.[14]

In the human body, the rate-limiting enzyme in fluorouracil (5-FU) that is DPD has varying activity according to the time of the day. Based on this data the 5FU infusion has been investigated in the treatment of advanced colorectal cancer. This study had been conducted on 10 patients with advanced gastrointestinal carcinoma and 5 healthy control. The observation done for circadian changes in mRNA expression of DPD in leukocytes and simultaneously serum cortisol level (SCL) was measured to evaluate the endogenous circadian hormone rhythm. In both patients and control the SCL showed a consistent circadian rhythm with the mean peak value at 8 a.m. and mean trough value at 11 p.m. however, compare to control the mean minimum-maximum serum cortisol difference of SCL was found to significantly lower inpatient. In controls, a trend towards a circadian rhythm of DPD mRNA expression was observed with the peak at 5 a.m. and trough at 2 p.m. while in contrast to this DPD mRNA expression in patients with advanced gastrointestinal carcinomas did not demonstrate any consistent circadian rhythm.

6. Pronounced-between subject and circadian variability in thymidylate synthase and dihydropyrimidine dehydrogenase enzyme activity in human volunteers.[15]

For tolerability of efficacy of fluoropyrimidine drugs the enzymatic activity of

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dihydropyrimidine dehydrogenase (DPD) and thymidylate synthase (TS) are important. This experiment studies a comparison between-subject variability and cardiac rhythmicity in DPD and TS activity in human volunteers. In DPD activity (n=20) in peripheral blood mononuclear cells (PBMC) and in plasma measured using dihydrouracil (DHU) and uracil (U) the ratio of DHU:U was (n=40) and TS activity in PBMC (n=19) was examined. To examine the circadian rhythmicity in DPD and TS Activity in PBMCs samples were collected every 4hrs throughout 1 day (n=12) in PBMCs and DHU:U plasma ratio (n=23). The activity of DPD and TS activity was explored by effects of genetic polymorphism and gene expression. Population mean DPD activity in PBMCs and DHU:U ratio was 9.2 n mol mg and 10.6 respectively. Rhythmicity was demonstrated for all phenotype markers between 0.03h and 02:00h DPD activity in PBMC peaked while the DHU:U plasma ratio and TS activity in PBMC showed trough activity. Peak-to-trough for PBMCs was 1.692 and 1.62 for DPD and TS activity respectively. For DHU:U peak-to-trough ratio was 1.43. DPD circadian rhythmicity might be tissue-dependent. Phenotype-guided fluoropyrimidine suggested an influence in circadian rhythms and high dose fluoropyrimidine administration during the night suggested implications for chronotherapy.

II. CONCLUSION

More treatment options to match a patient's circadian or, daily rhythms are preferred by 75% of doctors surveyed. According to a survey in 1996 by the American medical association found that half of the doctors or physicians in the US were not familiar with chronotherapy. This chronotherapy can provide quality drug delivery devices for ambulatory disease monitoring systems and can be more effective. Initiation is needed for the development of some more technologies for the large-scale production of this therapeutic system. Adverse effects are major problems of anti-cancer drugs which can be reduced by working on chronopharmacological aspects. It also helps in optimizing the therapeutic effects.

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