Concept of Chronopharmacology in Ayurveda

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ABSTRACT: Rhythmicity is a ubiquitous phenomenon. Rhythmic temporal patterns are considered and important factor in therapeutics as effective treatments should work in conjunction with body’s clocks. The concept of chronobiology is well evidenced by the cyclic alterations of dosas in the body. The Ayurvedic way of living as well as healing has been developed keeping in mind these biological clocks so as to maintain a balanced state of dosas in the present paper an attempt is made to review the ayurvedic concept of chronobiology and chronotherapy.

CHRONOBIOLOGY

Chronos in greek means time, “Chronobiology being the study of alterations of each organisms temporal structure under various situations”

Circadian implies approximately a day, major periodic components of biological rhythms are found around 24 hrs (Circadian) 30 days (circamensual) and one year (Circannual) Ultradian is rhythm of less than 24 hrs and cycles o more than 1 yr are infradian(1,2)

Circadian rhythms are found in all the organisms, infact the existence of circadian rhythms in living organisms was fist established during a detailed study of leaf movement in plants more than 200 ears ago.

Biological rhythms possess both an internal as well as external component. Rhythmicity has been detected for a number of physiological variables like pulse, temperature, blood pressure, hormonal secretions vi diurnal variation in effects of insulin on blood glucose. (3,4,5) Likewise symptoms of several diseases wax and vane with time.

The concept of chronobiology is inherent in Ayurveda. All the rhythms circadian, circamensual and circannual are recognized in dosas, both qualitatively and quantitatively. Infact circannual rhythms are seen as extension of circadian rhythms, as susruta says-that in a day and night also one should observe n forenoon the features of spring, in mid-day those of summer, in afternoon those of earl rains, in earl night those of rainy season, in mid night those of autumn and at down those of earl winter. (S.Su 6/14).

As shown in Table 1, dosas undergo two cycles of vitiation per day. This diurnal rhythm is attributable to the rotation of earth on its own axis.

As the orbit of earth around the sun is elliptical, the year has been broadly divided
into two-Adana Kala when the earth is nearer to the sun and the period during which the earth is further way from the sun is said to be visarga Kala. The nature of these two semesters are opposite of one another. Northern solstice being hot and dry and southern solstice is colder with predominance of apa mahabhuta. Whole year as been divided into six seasons of two months each (Table 2& 3). Seasonal changes are a form of stress on organisms, frequently as ‘Lack stresses’. Thus is winters organisms are deprived of radiant energy of sun while water is lacking during northern solstice (Table 4). Dosas vary cyclically to keep pace wit seasonal changes. (Table 5) altered chronobiology manifested as vitiated dosas because of change of seasons or altered habits does decrease the performance, that’s why Ayurveda suggests avoidance of sahasa (stress) and observance of regular habits in the form of dinacarya.

Nowadays a major proportion of shift workers face the problem of sleep disturbance symptoms of intolerance are persisting fatigue, emotional irritability, mood alteration and sleep disturbance-poor subjective quality of sleep disturbance – poor subjective quality of sleep. Sleeping pills are wither not effective or effective for short span of time and disturb the normal sleep architecture of REM, NREM sleep. Resynchronization seems to be the better option (6,7)

Vitiation of dosas in different seasons usually does not rise to diseases. However if the body is already weakened due to some other reason or rtucarya is not followed properly, the vitiated dosas may given rise to various diseases phenomenon very similar in concept to chronopathology. This is well illustrated b cyclical convulsions of apasmara (epilepsy). Thus convulsions occur on ever twelth day in vatic, fortnightly in paittic and monthly in kaphaja apasmara. Cricadian rhythms for epileptic seizures have been demonstrated a century back and possible explanations are based on rhythmic variations in concentrations of various neurotransmitters. In Ayurveda, all physiological and pathological phenomenon on delenicate balance of dosas and to precisely regulate dosic biological clocks adjustments are made in the form of dinacarya and rtucarya.

The concept of rtucarya implies dietetics, habits and behavioural adjustments to seasonal changes. Rtucarya aims at health maintenance in all seasons through a balanced state of dosas i.e. dosas samya. A balanced (and well adjusted) diet is the prerequisites for maintaining the optimum state of dosas. Dietary substances are chosen on the basis of complementarity, i.e dietary substance with properties similar to vitiated dosas are avoided while choosing the contrary. (Table 6)

Yasmin yasmin vilhou
Dosah kupyaneye ti Deninam
Thesu Tesu Pradata vija resaste the vijanata

**CHRONOPHARMACOMOGY** (8,9)

Rhythmicity has been observed in the efficiency and orientation of metabolic pathways and in the efficiency and orientation of metabolic pathways and in the sensitivity of target systems to endogenous or exogenous chemical substances. These concepts of biological temporal structure have led to the development of chronopharmacology an its practical significance is well illustrated in the form of chronotheraphy i.e. ‘Prescribing medicines at specified clock hours so as to achieve an optimization of therapeutic administration’ Thus chronopharmacology involves both
investigations of drug effects as a function of biological timing as well as investigation of medicines upon temporal structure, thus making it possible to enhance the desired and reduce the undesired effects of medicines. Following concepts might help to correlate the timed therapeutic intervention with the biological rhythms:

**Chronoptimization (or drug optimization):** This implies rhythmically modulated drug scheduling for a higher degree of benefit and safety in comparison to conventional or non chronobiological schedules. This has been extensively worked out for scheduling the long term synthetic corticosteroid therapy.

**Chronopharmacokinetics;** refers to rhythmic changes in drug bioavailability as well as excretion.

**Chronesthesia:** refers to rhythmic variations detected in the systems. This also includes susceptibility variations detected in parasites, bacteria, tumors etc. Working our chronesthesia of bronchi in man as helped in development of chronesthesia for asthma, a strongly circadian rhythmic disease.

**Chronergy:** of a drug is rhythmic changes in its effects and side effects. This depends on the pharmacokinetics of drug and chronesthesia of various systems.

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**Clinical Chronopharmacology-An Experimental Basis for Chronotherapy**

Subjects synchronization + environmental factors

+ timing in administration of drug or food + circadian changes in metabolic processes

biosystem chronesthesia organismic bioperiodicity

Chronokinetics → Chronergy of drug of food

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However acrophase of chronergy of a drug may not coincide with its peak blood levels. Recognitions of rhythmicity in cellular proliferation and sensitivity has helped in development of scheduled chemotherapy for various carcinomas.\(^{(11)}\)

Chronotherapy for hypertension, asthma, allergic rhinitis and rheumatoid arthritis has been worked out mimicking the natural pattern for cardiovascular diseases, peptic ulcer and carcinomas has helped us to reduces the side effects.\(^{(12,13)}\)

It is also important to recognize the fact that plasma proteins undergo a circadian rhythm. This is significant for drugs binding to plasma proteins.

Antihypertensive drug expressing first dose phenomenon (exaggerated hypotension seen only with first dose) are usually administered at bed time so as to avoid complications due to hypotension.
There is normally a diurnal variation in the concentration of endogenous corticosteroids in the blood being approximately 450nmol/l at 8 a.m and 110nmol/l at 4 p.m. that’s why split daily doses (Two thirds in morning and one third in evening) have been tried.

As rate of cholesterol synthesis is maximum at night, HMG CoA-reductase inhibitors are better administered as single dose with evening meals.

Several studies are being conducted to study circannual and circamensual rhythms, the latter mainly but our exclusively found in women. Further various studies demonstrate higher testicular response (Measured as plasma testosterone levels) to HCG administration was noticed in autumn than spring.

Dysregulations of biological rhythms have been found to be responsible for periodic manifestations of affective disorders. Both desynchronization of circadian rhythms as well as a phase delay in rhythms have been demonstrated for bipolar patients. In so called seasonal affective disorders a special subgroup of patients experience major depressive episodes at specific seasons for the year. The most consistent of these groups are the patients with winter depression where days are significantly shorter. Accordingly antidepressants and lithium have been found to lengthen circadian period. Another way of increasing circadian period is using intense white light (>2000lux) present for a specific period of time. Such patients are benefited by light treatment and are better adjusted near equater (Because day and night cycle are not so extreme there). Ayurveda also stresses the importance of season (Kala) and climate (desa) in treatment.

Desa kala pramia nanam
Satmya Satmys Syachaiva hi
Samyag yoga hyalha hyesam
Pathya maphya-ha tha bhavet
(C.Ci 30/293)
appropriate timing of administration has been stressed in all lexicons, e.g.
Matra kala sraya yuktib,
Sighiryauktou Pratisthita (C.Su 2/16)

Here caraka says that proper drug administration includ34s appropriate dosage and timing; and success of treatment depends on proper administration. Like wise vagbhata while stressing the importance of kala-ausadha sambandha (time –drug relationship) says that time potentiates efficiency of drugs-

Moreover a drug used at inappropriate time is not going to be beneficial.

Nahyapraptati ta kala mousadham
Yougi kam bhavati (A.S. Su 23/12)

Not only drugs, even food substances consumed at different time periods exert different effects, thus sugarcane taken before meals pacifies pitta, after meals vitiates vata, while if included in meals its digestion is difficult and delayed id difficult and delayed.

Similarly a range of effects are seen with milk consumption and to obtain desired effects, intake should be timed accordingly. Milk before 10 am potentiates virya, increase rasa and rakta (highly nutritious) kindles the agni (power of digestion and metabolism) and is Brhana (anabolic effects) Milk in afternoon is balya (Strength promoting), pacifies pitta and kapha and kindles the agni. In the evening milk is beneficial for eyes and pacifies all the three dosas. It also pacifies agni.
Equally important are circumensual and circannual rhythms. As dosas vitiate with cage of season, sodhana is needed to expel vitiated dosas out of body. Caitra, margasirsa and sravana are chosen for expulsion of excessive kapha, pitta and vata respectively (S.Su 6/12). Routine pancakarma is best carried out during sadharana Kala * (C.Vi8/126). For emergencies purificatory treatment is carried out by artificially creating t opposite conditions. Further drugs are made ore suitable by appropriate processing, dosage, mode of use and other procedures.

Appropriate timing of drug administration is a complex process including kalavesksa ie. Observation of specific features of diseases varying with seasonal and diurnal variations, age and meals (C.Ci 30/296)

Accordingly caraka describes following timings for drug administration:

1. **Abhakta:** Drugs are given in the morning because the absorption is maximum and most efficient in the earl hours

2. **Pragbhakta:** Drug is taken just before food. This is advised for diseases of apana vayu, for strengthening and preventing diseases of lower half of the bod and or treating obesity.

3. **Madhyabhakta:** For treating diseases of samana vayu, diseases of kosthas and for paittic diseases, drugs are given in between foods.

*Seasons are basically of three types, cold hot and rainy, between cold & hot and in between rain and cold seasons there are two temporate seasons namely vasanta and sarada respectively. The temporate seasons found between summer and rain season is tat of earl rains (pravrt) (C.Ci B/125).

4. **Pratah Pscadbhakta:** Drugs are given in the morning after food for treating diseases of vyana vayu, for strengthening and treating diseases of upper half of the body, for kaphaj diseases and for treating leanliness.

5. **Sanya Pscadbhakta:** For treating diseases of udana vayu, it is advisable to take drugs in evenings after food.

6. **Muhurmuhuh:** Drugs are repeatedly given for treating swasa (dyspnoea), Kasa (cough), hikka (hiccoughs), chardi (vomiting), visa (poisoning) and pipasa (thirst).

7. **Samudga:** Drug is given before and after light food in hikka, aksepa (convulsions) and in diseases of head and neck.

8. **Sabhakta:** Drugs usually appetizers are given with food, this is preferred in children especially of weak constitution.

9. **Sagrasa:** with morsels of food, drug is given in vitiations of prana vayu, especially for dipana and vajikarana.

10. **Sagrasantara:** In heart diseases and vitiation of prana vayu, drugs are given in between morsels of food.

Vagbhata describes 11 times of drug administration. However he included morning & evening pascadbhaktas in one (Adhobhakta) and introduced antarabhakta, ie. Drug is administered after lunch is digested, and food is taken only after the drug has been absorbed (jirna) and Nisakala (night) (A.S.Su 23/12).
Sarngadhara however described 5 periods of drug administration viz.

1. Suryodaya – (abhakta)

2. Divasa bhojana (with Lunch)

3. Sanya bhojana (with dinner)

4. Muhurmuhuh (frequently)

5. Nisa (In night) [Sa. Sect 1/2/1-12]

Further he says that if time of administration is not mentioned then drugs should be administered in the morning (Sa sect 1/1/47)

CONCLUSION

Thus schedule of drug administration while taking in account cyclic variations of dosas also considers the interference by food in drug absorption, gastric irritability, drug induced vomiting and agni of the patient. As all the timings are mentioned in relation to meals, this highlights psychosocial aspect of treatment to achieve a high level of patient compliance

Table 1

Relation of dosas with body, age, day &night and stage of digestion

|                | VATA                        | PITTA                      | KAPA                        |
|----------------|-----------------------------|----------------------------|-----------------------------|
| 1 Body         | Below umbilicus             | Between umbilicus & heart  | Above heart                 |
| 2 Age (*vaya)  | Old age                    | Young age                  | Child hood                  |
| 3 Day          | 2pm-6pm                     | 10am-2pm                   | 6am-10am                    |
| 4 Night        | 2am-6am                     | 10pm-2am                   | 6pm-10am                    |
| 5 Stage of Digestion | Pakvavastha (end stage of digestion) | Vidagdavastha (midstage of digestion) | Amavastha (Initial stage of digestion) |

Table 2

| Kala           | Rtus    | Mahabhuta | Predominant | Rasas  | Preferred          |
|----------------|---------|-----------|-------------|--------|--------------------|
| Adanakala      | Sisira  | Vayu+Akasa| Tikta       | Amla   | Usna virya         |
|                | Vasanta | Vayu +Prthvi | Kasaya     | Lavana | & guru guna        |
|                | Grisma  | Vayu+Agni | Katu        | madhura| [C.S.Ci6/4, 67]    |
| Visargakala    | Varsa   | Prthvi+Agni| Amla        | Lavana |                    |
|                | Sarada  | Jala+Agni | Kasaya      | madhura|                    |
|                | Hemanta | Prthvi+jala| Katu        |         |                    |

Table 3

Division of seasons

Division of seasons is form two angles

1. According to strength (S.S.Su 6/6)
According to dosa (S.S.Su 6/10)

Table 4

| Kala | Adanakala | Visarga kala | Hina bala (debility) | Madhyabala (Medium Strength) | Srestha bala (Maximum strength) |
|------|-----------|-------------|----------------------|----------------------------|----------------------------------|
|      |           |             | Grisma varsya        | Vasanta                     | Sisira                           |
|      |           |             |                      | Sarada                       | Hemanta                          |

Table -5

Relation of dosas with rtus

| S.No | Dosa | Accumulation | Aggravation | Pacification |
|------|------|--------------|-------------|--------------|
| 1    | Vata | Grisma       | Varsa       | Sarada       |
| 2    | Pitta| Varsa        | Sarada      | Hemanta      |
| 3    | Kapha| Sisira       | Vasanta     | Grisma       |

Table -6

Choice of dravyas in different Rtus

| S. No | Rtus          | Preferred Rasa          | Prefered Guna         |
|-------|---------------|-------------------------|-----------------------|
| 1     | Sisira        | Sweet, sour salt        | Usna (hot)            |
| 2     | Vasanta       | Bitter, pungent, astringent | Ruksa (fat and moisture free) |
| 3     | Grisma        | Sweet                   | Sita (cold)           |
| 4     | Varsa         | Sweet, Sour, salt       | Sita                  |
| 5     | Sarada        | Sweet, bitter astringent | Ruksa                 |
| 6     | Hemanta       | Sweet, sour, salt       | usna                  |

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