



Review Article

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Chronotherapy, Formulation specific Bhashaja sevana kala – A bird's view

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ABSTRACT

Any substance which helps to bring the vitiated doshas back to normalcy and the body to a healthy state is known as Bhashaja. Acharya Vagbhata describes, "Kalobhaishajya yoga krt". A medicine exerts its action properly, only if administered at proper time. Why kaala is mandatory in Aushadha sevana? Kala is Anayathasiddha Nimitta Karana, means for every action in the Universe is bound with the causative association of kala and hence Aushadha employed in a proper Kaala will result in expected kaarya. Time specific administration of medicine results in optimum pharmacological utility of the drug. Bhashaja sevana kala a classical concept is presently studied as chronotherapy in the contemporary science gaining its importance in medical practice. Further here an attempt is made to highlight the formulation specific Bhashaja sevana kala and its rationality, relevance with the present understanding of chronotherapy in certain diseases. The literature review was collected from different Ayurvedic Classics, review and original articles on chronotherapy and Bhashaja sevana kala.

Keywords: Bhashajya yoga sevana kala, Chronotherapy.

INTRODUCTION

Specificity is an art that helps in distinguishing and providing accuracy in any field of science. Treatment comprises mainly Drug specificity: Depending on its habitat, potency, time of collection, properties etc., Prakruti specific i.e., unique to an individual. But formulation and disease specificity with respect to time of administration is a unique concept mentioned in the classics.

Acharya Vagbhata describes, "Kalobhaishajya yoga krt" [1]. In order to provide efficacious treatment it is essential that the medicine is released into the blood stream at a specific time. The variation in doshas occur throughout the life in the form of physiological variations like increase in kapha during the early morning, first stage of digestion and childhood and the pathological condition like exacerbation of diseases like pratishyaya (rhinitis), kasa (cough) and so on. Thus to get the desired effect of the treatment consideration of that particular time for administration of medicine is valuable. Synchronizing the drug therapies with body rhythms will indeed improve the result of treatment and that is studied presently under "chronotherapeutics" [2].

The concept of Bhashajya yoga sevana kala entail the importance of right time of drug administration for accuracy in treatment irrespective of disease status, prakruti etc. Similarly chronotherapy is the time regulated treatment of diseases coordinating with the biological rhythm of the body; therefore the present article provides an insight to highlight formulation specific bhashaja kala and understand the link between the body rhythms and time of drug administration classically.

MATERIALS AND METHODS

The review data was collected from Ayurvedic classics like Bhashajya Ratnavali and Sahasrayogam and also includes review and original articles on chronotherapy and Bhashaja sevana kala.

REVIEW

Knowledge of specific bhashaja kala in various diseases based on dosha is described in Bruhatrayee. Time specific administrations of formulations in specific diseases are categorized below.

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Table 1: Based on diseases ^[3]

| Disease (vyadhi prakarana) | Yoga | Bheshaja kala |
|------------------------------|-----------------------------|------------------------------|
| Jwara | Guduchyadi kwatha | Prataha |
| | Rasnadi kwatha | Muhurdandantara |
| | Kwathapanchaka | Prataha |
| | Deerghapatrakakanaadi yoga | Prataha |
| | Guduchipanchamulikwatha | Prataha-sayam |
| | Kaphaketu (bruhat) | Prataha-sayam |
| | Jwarabhairavo rasa | Prataha |
| | Bhanuchudamani rasa | Prataha |
| | Maharajavati | Prataha |
| | Sarvatobhadrarasa | Prataha |
| | Vishamajwarantakaloha | Prataha |
| | Lakshmilasa rasa | Prataha |
| Jwara-atisara | Mutasanjeevani sura | Muhurmuhu |
| | Kutajavaleha | Prataha |
| Atisara | Putikadikwatha | Sayam |
| | Purnachandrodaya rasa | Prataha |
| Grahani | Bruhat gaganasundara rasa | Prataha |
| | Grahanishardula churna | Prataha |
| | Vartakugutika | Bhojanottara |
| | Dashamula guda | Prataha |
| | Bruhatmethimodaka | Prataha |
| | Madanamodaka | Prataha |
| | Jeerakadimodaka | Prataha |
| | Bruhatjeerakamodaka | Prataha |
| | Agnikumaramodaka | Prataha |
| | Shri nrupativallabha rasa | Prataha |
| | Bruhat nrupativallabha rasa | Prataha |
| | Loha parpati | Prataha |
| | Vijaya parpati | Prataha |
| | Panchamrutamandura | Prataha |
| | Mahashatpalaka ghrita | Bhaktena saha or nirbhakta |
| | Kameshwaro modaka | Bhojanadi or bhojanante |
| | Arshas | Dhaturadi churna |
| Kankayana modaka | | Prataha |
| Guda bhallataka | | Prataha |
| Nalinipatradi prayoga | | Prataha |
| Krishnatilakalka | | Prataha |
| Pranada gutika | | Purva –paschath |
| Agnimandya | Nagarjuna yoga | Bhaktasya upari |
| | Hingwashtaka churna | Pratama kavala bhuktam |
| | Lavangadi vati | Prataha |
| | Agnisandeepano rasa | Sandhyayo (Prataha- sayam) |
| | Bhaktavipakavati | Bhaktottareeya |
| | Pashupato rasa | Bhojanante |
| | Ajeernabalakalanalo rasa | Bhojanante |
| Shankhavati-mahashankhavati* | Prataha | |
| Mahashankhavati ** | Bhojanante | |

| | | |
|-------------|---------------------------------|-----------------------|
| | Kravyada rasa | Bhojanante |
| | Shardulakanji | Bhojanante |
| | Gudashtakam | Prataha |
| Krimiroga | Krimidhulijalaplavo rasa | Prataha |
| | Krimivinashano rasa | Prataha |
| Panduroga | Ayomala prayoga | Bhaktena saha |
| | Triphaladi swarasa | Prataha |
| | Trikatrayadi loha | Bhojanadi-madhya-anta |
| | Panchamruta loha mandoora | Prataha |
| | Trayushnaadi mandoora | Jeerne cha bhojanam |
| | Anandodaya rasa | Sayam |
| | Pandupanchanana rasa | Prataha |
| | Dhatryarishta | Abhakta |
| Rajyakshma | Asrahararishta | Prati yama |
| | Rajatadiloha | Prataha |
| | Shrungarabhra rasa | Prataha |
| | Rasendra gutika | Jeerne cha bhojane |
| | Eladimantha(ghrita) | Prataha |
| | Chagaladya ghrita | Prataha |
| Kasa | Chandramruta rasa | Prataha |
| | Vijayabhairavo rasa | Prataha |
| | Chandramruta loha | Prataha |
| | Bhagottara gutika | Prataha |
| Hikkashwasa | Bhargisharkara | Prataha |
| Murcharoga | Triphala yoga | Prataha |
| Madatyaya | Eladyo modaka | Prataha |
| | Mahakalyana vati | Prataha |
| Unmada | Puranaghrita | Prataha |
| Vatavyadhi | Dashamulyadi kwatha | Sayam |
| | Talakeshwara rasa | Prataha |
| | Ashtadashashatikaprasaranitaila | Bhojanath (with food) |
| | Mashataila | Uttarabhaktikam |
| Vatarakta | Amrutadya ghrita | Bhojyapana |
| Amavata | Shuntyadi kwatha | Prataha |
| | Triphaladiloha | Prataha |
| | Panchananarasa loha | Prataha |
| | Rasona pinda(mahan) | Prataha |
| | Vatari guggulu | Prataha |
| | Vyadhishardula guggulu | Prataha |
| Shularoga | Hingwadi churna | Prataha |
| | Shulaharana yoga | Bhojanante |
| | Vidangadi modaka | Prataha |
| | Shambukadi vati | Prataha-bhojanakaale |
| | Shankarasa | Prataha |
| | Vidyadhara rasa | Prataha |
| | Shularaja loha | Prataha |
| | Dhatri loha*** | Bhaktadi |
| | | Madhya |
| | | Ante |
| | Koladi mandura | Bhaktadi-Madhya-Ante |

| | | |
|-------------------------|--------------------------------|------------------------|
| | Chatuhasama mandura | Bhaktadi-Madhya-Ante |
| | Bheemavataka mandura | Bhaktadi-Madhya-Ante |
| | Taramandura guda | Bhaktadi-Madhya-Ante |
| | Shatavari mandura | Bhaktadi-Madhya-Ante |
| | Guda mandura | Bhaktadi-Madhya-Ante |
| | Puga khanda | Prataha |
| Udaavarta anaha | Naracha churna | Pragbhakta |
| | Pippalyadi kwatha | Prataha |
| | Gudashtaka | Prataha |
| | Rasona prayoga | Prataha |
| Gulmaroga | Hingwadichurna vatika(Tritiya) | Pragbhakta |
| | Gulmakalanalo raso bruhat | Prataha |
| | Vruscheeradyarishta | Jeerne cha bhakta |
| Hrudroga | Kakkubhadi choorna | Prataha |
| Mutrakrucchra | Trinetrakhya rasa | Prataha |
| Mutraghata | Naladitrimamula kwatha | Prataha |
| Ashmari | Shwadamshtadi kwatha | Prataha |
| | Varunadya loha | Prataha |
| Prameha | Sphatika churna | Prataha |
| | Mehakunjakesari rasa | Prataha |
| | Shilajatu prayoga | Jeerne cha bhojane |
| Medoroga | Loharishta | Prataha |
| Udara roga | Samudradya churna | Pratama kavala bhuktam |
| | Punarnavadi kwatha | Prataha |
| Pleehayakrut roga | Shankhadravako rasa | Bhojanante |
| | Shothari churna | Prataha |
| | Shothakalanalo rasa | Prataha |
| | Trikatvadi mandura | Prataha |
| | Rasabhramandoora | Prataha |
| Vridhhiroga | Hareetaki prayoga | Prataha |
| | Triphala kwatha | Prataha |
| Galagandaadi roga | Kanchanara guggulu | Prataha |
| Shleepada | Pippalyadya churna | Abhakta |
| Vidradhi roga | Shobhanjana kwatha | Prataha |
| Upadamsha roga | Rasashekhara | Sayam |
| Kushtaroga | Amrutabhallataka | Prataha |
| | Ekavimshatiko guggulu | Prataha |
| Udarda-sheetapitta-kota | Ardrakakhandam | Prataha |
| Amlapitta | Paneeyabhakta gutika | Prataha |
| | Avipattikara churna | Bhojanadou –madhye |
| | Kshudhavathi gutika | Prataha |
| | Pippali ghrita | Prataha |
| | Drakshadya ghrita | Saha bhojane |
| Mukharoga | Rasendra vati | Prataha |
| Karnaroga | Sarivadi vati | Prataha |
| Netra roga | Triphaladya ghrita mahat | Bhojanadi-madhya-ante |
| Shiroroga | Rasachandrika vati | Prataha |
| Sutika roga | Soubhagya shunti | Prataha |
| | Sutikaari rasa | Prataha |
| Baalaroga | Shivamodakam | Prataha |

| | | |
|----------------------|--|--|
| Rasayana prakarana | Triphala rasayana | Pragbhukte-vibhitake Bhuktwa-(bhojana paschat)-amalaki Jaranante – hareetaki Purvahne-bhuktwagre(pragbhakta)-bhojanasya(bhojanante) |
| | Kimshuka kshara bhavita pippali rasayana | Bhojanadou-pradoshe(sayam) Bhuktwapi bhakshite(pratahakala) |
| | Amrutavartika | |
| | Shivagutika | |
| Vajeekarana | Shatavari modaka (bruhat) | Prataha or bhojanakaale va |
| | Mahakameshwara modaka | Prataha |
| | Vanari vatika | Prataha-sayam |
| Amashayaroga | Pippalyadikwatha | Prataha |
| Gadodwega | Ksheerodadhirasa | Prataha – sayam |
| Snayuroga | Swarnasindhurasa | Prataha-sayam |
| | Maharajatavati | Prataha |
| Somaroga-mutratisara | Himamshurasa | Prataha-madhyahna-nisha |
| Shukrameha | Shilajatwadivati | Prataha |
| Aupasargikameha | Sphatikadichurna | Prataha-sayam |
| Phirangaroga | Saptashali vati | Prataha |
| Mastishka roga | Trivrutaadi modaka | Sayam |
| | Dhatrighrita | Prataha |

*Shankhavati-mahashankhavati: instant agnideeptikara, bhasmarogahara, sarva ajeerna, based on anupana bheda effective in jwara, gulma, panduroga, kushta, shula, prameha, vatarakta, mahashotha, arshas.

**Mahashankhavati: deepana, arshas, grahani

***Dhatri loha – all three bsheshja sevana kala are indicated in different disease conditions.

It is interesting to note that in almost all the vyadhi prakarana the time of administration of medicine is during morning (prataha) and only in the context of shula roga for pain management, the bsheshja is to be administered before, between and after food. Apart from this, formulations like bruhat kapha ketu rasa, vanari gutika, swarnasindhura rasa [3], *Shatavaryadi Kashaya* (in sarvavataroga is to

be administered - morning with eranda taila and saindhava lavana for Koshta shodhanartha and to maintain the agni in the evening with jeeraka and sarkara after meals) [4] etc., are indicated to be taken both in morning and evening suggestive of its utility in treating chronic diseases.

Table 2: Formulations administered in morning and evening [3, 4]

| Formulations | Indications |
|-------------------------|---|
| Bruhat kapha ketu rasa | Kantaroga, shiroroga, peenasa, kaphasanghata |
| Vanari vatika | Dhwajabhanga, vajeekara, sheeghradraavi |
| Swarnasindhura rasa | Snayuroga |
| Sphatikadichurna | Vranameha |
| Kameshwari lehya | Tridoshaja raktapitta, kasa, shwasa, kshaya, pandu, chardi, adhma, gulma, shula, hidhma, hridroga, arshas, grahani, asthisrava, mutraghata, ashmari, mutrakrichra, prameha, sarvaroga hara, bala-pushtikara, shukra vardhaka, ayushya, vajikara and shreshta rasayana |
| Shatavaryadi Kashaya | Sarva vataroga |
| Guduchipanchamulikwatha | Jeernajwara, kaphadhwamsi |
| Amrutavartika | Deepana, kantikara, keshya, chakshushya, pangu, balaprada |
| Ksheerodadhi rasa | Gadodwega, urahakshata, kshaya, raktapitta, prameha, vatapittaja roga, haleemaka, pandu, jeernajwara, arshas |

Another interesting factor here is, various yogas have different action based on the time of administration such as *Dhatri loha*: before food in pitta vataja roga; between food in vishtambha janya roga and prevents vidaha; after food in viruddha anna krita dosha [3].

Nidhidikadi kwatha: administered in evening for urdhwajatu vikara and ratri jwara, in morning for other types of jwara [4].

DISCUSSION

Rationale behind time specificity of drug administration can be incorporated based on the enagement of the three humours – vata, pitta, kapha causing respective diseases.

Based on dosha predominancy [5]

With reference to kala (time), on the basis of aggravated doshas –

With respect to seasons: kaphaja diseases are manifested in spring (vasantha rtu), pittika diseases are manifested in the autumn, and vatika diseases are manifested in (the beginning of) the rainy seasons [5], mainly these time are used for elimination of Dosha for prophylactic purpose and kindling the agni, medicaments are supplemented; for example Chandrakala rasa- greeshma and sharad kala- pitta jwara, amlapitta, pradara, daha (antar-bahya), rasajanya murcha, raktapitta, sarva mutrakruhra, sarva prameha [3].

With respect to Day: During the end of the night and the day, vatika diseases get aggravated, kaphaja diseases get aggravated during the onset of morning and evening, and pittika diseases get aggravated during the midday and midnight

With respect to phases of life: During old age diseases caused by vayu, during middle age diseases caused by pitta and during the adolescence, diseases caused by kapha take a serious turn

With respect to digestion of food: Generally vatika diseases get aggravated after the digestion of food, pittika diseases get aggravated during the digestion of food and kaphaja diseases get aggravated immediately after taking food.

Thus, vata-pitta-kapha respectively exhibits their marked presence in the end, middle and beginning of life, day, night and digestion. Similarly the Bhashaja is administered in accordance with their state of predominancy [6].

For example: talakeshvara rasa is administered during early morning hours when vata is predominant, dashamulyadhi kwatha is to be administered in the evening, oral administration of masha taila is after food (uttarabhaktikam) beneficial in vata vikara [3].

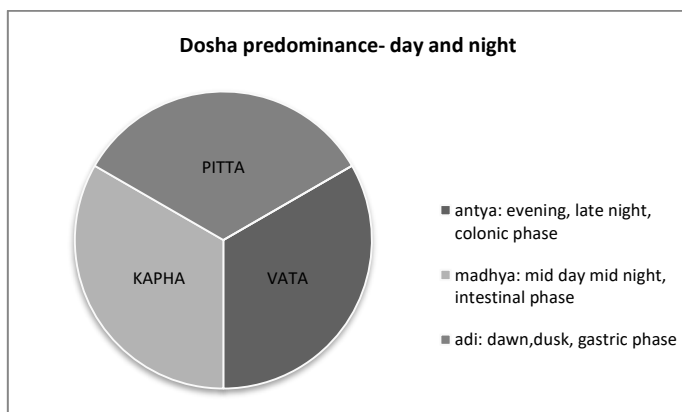


Figure 1: Predominance of dosha in 24 hours

Bhashaja Sevana Kala and Chronotherapy

The novel development in the field of chronotherapy is found to be supportive to substantiate the scientific aspect of Bhashaja Sevana Kala which was well described in Ayurvedic classics years ago. Following are few of the Bhashaja yoga sevana kala with their chrono-therapeutic understanding.

1) Abhakta – Niranna- Pragbhakta: empty stomach

Indication: Apana vata dushti, Mutravaha-Malavaha-Shukravaha Strotas, Pakvashayagata Vyadhi, Arsha, Gudabhransha. pittaja kaphaja vyadhi, for rasayana effect, lekhan karma, when the disease and diseased are strong.

Example: Guda bhallataka, mahakalyanavati, naracha churna, Kanchanara guggulu etc.

Absorption of medicines is the most important factor to provide maximum productiveness. Eventually, on an empty stomach absorption takes place easily. Hence, maximum therapeutic efficacy can be expected. Therefore apana vayu related disorders can be checked as the seat of apana vata is large intestine. Also in chronic diseases to achieve the maximum potential of the drug, empty stomach is preferred.

Gastro intestinal absorption of the drug is influenced not only by the gastro intestinal motility, the intraluminal pH, blood flow to stomach and enzymatic action, but also depends on the circadian rhythms. All the above mentioned factors are also influenced by the time of the day. Drugs that are lipophilic are found to have more rate of absorption in early morning hours rather than any hour of the day [6].

Clinical studies report most of the drugs seem to have a higher rate or extent of bioavailability when they are taken in the morning than when they are taken in the evening particularly in relation to cardiovascular active drugs, non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetics, anticancer drugs, psychotropic drugs, antibiotics and anti-asthmatic drugs [7].

Administration of ACEs inhibitors and antihistamines on an empty stomach increase their effectiveness through increased absorption [8].

Absorption of thyroxine is reported to be more complete on empty stomach but can be variable and incomplete when taken with food [9].

In peptic ulcer patients, high gastric acid secretions; slow gastric motility and emptying at night causes pain, gastric distress and acute exacerbation of the disease which are most likely in the late evening and early morning hours. Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Nocturnal administration of H₂ antagonists or morning administration of proton pump antagonist medications not only reduce acid secretion more effectively but also promote ulcer healing and reduce ulcer recurrence [10].

Further it can be understood that classically more number of formulations are advised to be administered in the early morning hours of the day.

2) Madhya bhakta – in between food:

Indication: Pittaja, Koshtagata – pakvashayagata vyadhi like grahani, gulma, samanavayu vikruti, mandagni, shula.

Example: dhatri loha, avipattikara choorna

Diseases related with the agni can be checked but very few formulations are indicated during this time, mainly shulahara formulations are mentioned.

3) Adhobhakta - After food

This kala is subdivided into pratah-paschatbhakta and sayam-paschatbhakta with different indications as below.

Indication:

- In disorders of Vyana Vata medicine is given at the end of morning food. Vyana vata resides in chest, circulates all-over the body and is responsible for many functions like flexion and extension of limbs, does locomotion etc. imbalance of which causes napunsakata (debility), shopha, jwara, kushta, visarpa, udasinta (depression), body ache, tingling, numbness.

Example: Nagarajuna yoga, masha taila

Salicylates: Irritate the mucous membrane of stomach. Acidic pH of stomach favours the existence of salicylate in the unionized form, which is water insoluble, hence adheres to gastric mucosa producing gastric irritation and there is inhibition of Prostaglandin synthesis. They also reduce motility of stomach and increase gastric emptying time. To avoid gastric irritation, salicylates may be administered after food ^[11].

- b. In disorders of Udana Vata medicine is given after dinner. Udana vata governs memory, speech, enthusiasm, vitality etc, and its imbalance leads to galaroga, chardhi, aruchi, galaganda, sthoulya and urdhvajatrugata vyadhi.

Example: Nidhigdhikadi kwatha, vartaku gutika, Kravyada rasa

Anti-psychotic drugs: Chlorpromazine produces maximum sedative effect when administered at midnight and maximum anti-psychotic effect when administered immediately after awakening ^[12].

Haloperidol shows both sedative and antipsychotic effect when administered in the evening ^[12].

4) Antarabhakta - in between two meals

As per Aharavidhi in Ayurveda, two meals per day are conducive to health. Therefore in the mid-day, that is after digestion of the breakfast and at about mid night, following the digestion of the dinner, coincides with pitta pradhana kala, during this time medicine is administered.

Indication: As per Acharya Sushruta, the bsheshaja given at this kala shows hradya, pathya, deepana, manobalakara effect ^[13], administration of medicines for a long duration, and in disorders of vyanavayu, this time period is favorable. Therefore formulations indicated as jaranante, jeerne cha bhojane can be considered under this kala.

Example: Shilajatu prayoga, Rasendra gutika

Plasma protein binding: Albumin and acid glycoprotein reach their nadir during nocturnal rest and their zenith in the morning. Therefore drugs bound to plasma protein, like valproic acid, carbamazepine, diazepam, lignocaine, prednisolone show increase in free fraction at night ^[14].

5) Sabhakta

Indication: aruchi, sarvanga samshrita vyadhi like kushta, prameha etc.

Example: Amrutadya ghrita, ayomala prayoga, ashtadasha shashtika prasarani taila

Antidiabetic drug glimepiride, a new generation sulfonylurea derivative should be administered with breakfast or the first main meal of the day. It has absolute bioavailability and the absence of food interaction guarantee highly reproducible pharmacokinetics ^[8].

6) Samudgakala

It is also noted that most of the shula hara formulations are to be administered before-between –after food, for sustained release of drug so that pain is under control throughout the day, while samudga kala refers to only before and after food, the combination of samudga and Madhya bhakta can be appreciated.

Indication: Vyana-apana-udanavayu vikruti, hikka, kampa, akshepa, vatata prameha, shukradosha.

Example: pranada gutika

7) Muhurmuhu:

Indication: Pranavaha strotogata Vyadhi- Shvasa, Kasa, Hikka; Udakavaha strotogata Vyadhi – Trishna; Annavaaha strotogata Vyadhi - Chhardi, Visha

Example: Mrutasanjeevani rasa, rasnadi kwatha, asrahararishta

8) Sayam/Nishi

At night– the second highly preferred kala as per formulation specific, where diseases of tridosha are indicated.

(It can also be noted that the formulations under antarabhakta holds good for nishi as well as it coincides with the time after digestion of the evening meal. For example rasendra gutika is indicated in Sarvarupa kshaya, kasa, amlapitta, aruchi, raktapitta and is administered after digestion of food which can be either morning or evening food)/

Indication: Kapha Dosha Vikruti, Urdhvajatrugata Vyadhi, lekhaana, brumhana

Example: trivrutaadi modaka, dhatturadi churna, anandodaya rasa

Allergic rhinitis: The symptoms are reported to be highest during the morning. Administration of long acting antihistamine at night provides better results in controlling this morning discomfort rather than taking the medication in the morning as is frequently recommended ^[7].

Bronchial asthma is characterized by chronic airway inflammation and limitation of airflow in the airways, and attacks begin with paroxysms of coughing, wheezing, and dyspnea. Statistically based on chronopharmacological studies it is observed that the development of asthma symptoms and many types of broncho-spastic attacks is more common from midnight to early morning from 2 A.M. and 6 A.M every day. The main aim of Chronopharmacotherapy for asthma is to obtain maximal effect from bronchodilator medications during the early morning hours. Based on chrono-pharmacology, several drugs for asthma have been developed. One example is the bronchodilator uniphyl, a long-acting theophylline taken once a day in the evening causes theophylline blood levels to reach their peak and improve lung function during the difficult early morning hours ^[6].

Cancer: Chronopharmacotherapy of cancer is based on the chronobiological cycles which differ in the tumour cells and normal cells. Based on study which suggested that the peak of DNA synthesis in the normal human bone marrow cells is around noon while DNA synthesis in lymphoma cells has a peak near midnight, an administration of s-phase active cytotoxic therapy at late nights revealed a decrease in the tumor cell count with a little effect on normal cells ^[6].

Arthritis: The symptoms of rheumatoid arthritis worsen in the morning. Administration of long acting NSAIDs like flubirofen, ketoprofen and indomethacin at bedtime optimizes their therapeutic effect and reduces or averts their side effects ^[6].

Hypercholesterolemia: For the reevaluation of the circadian rhythm of cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors were firstly introduced in the morning doses. The free cholesterol levels have been reported to be lowest at 2 p.m. to 6 p.m. and peak at 6 a.m and morning. It is observed that evening dosing frequency of some marketed preparations like Lescol, Mevacor, Prachol and Zocor is more effective than morning dosing. On the basis of the studies it is recommended that five of the six currently approved HMG-CoA reductase inhibitors can be administered between

the evening meal and bedtime; atorvastatin calcium or Lipitor may be an exception because of its long elimination half-life [15].

In Hypercholesterolemia, mainly lekhana action is indicated and rheumatoid arthritis being a kapha vata dosha vikruti, in all these conditions bhashaja kala indicated is nishi.

CONCLUSION

Most frequently indicated Bhaishajya yoga sevana kala being *Pratah bhakta* is suggestive of its utility in quick and complete absorption of drug.

Muhurmuhu bhashaja kala is advised in emergency conditions like status epilepticus, status asthmaticus, hiccups, poisoning etc. wherein repeated administration of medicine is required for effective control of the life threatening condition. Mrutasanjeevani sura is repeatedly administered in life threatening fevers

Prathama kavala bhukta (first bolus of food) helps kindle the agni, and has anulomana and rochaka effect as specified for Hingwashtaka churna.

Administration of Bhaishajya during *Bhojanadi* serves in sustained release of drug, and reduces irritation of teekshna dravyas.

Bhaktadi-Madhyanta-Ante sevana kala is indicated in conditions which require regular instillation of medicine like Triphaladya ghrita in netra roga, Mandura yogas in shula.

The medicines administered during *Jeerne cha bhojane kala* are most easily receptive to the body during this period and hence useful in agni deepthi and various chronic diseases. Rasendra gutika, Tryushnadi mandura, Vruscheeradyarishta etc., are administered after digestion of previous meal.

Prataha-madhyahna-nishi sevana kala is indicated in mootratisara, as repeated administration helps for sangrahana and to control the symptoms.

Bhashaja sevana kala acts like a guided missile to tackle disease at its most active phase, by precising drug intervention when doshas are at its peak and thus helps prevent irrational, frequent usage of drugs throughout the day thereby reducing the drug intake.

Thus maximum bioavailability of the drug was the prime consideration.

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