CHRONOPHARMACOLOGY AND OPTIMISATION OF DOSAGE SCHEDULE*

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Zoologists and botanists in India have been quite active in the field of chronobiology. Their main objective is to uncover the factors influencing biological rhythms. Biological rhythms have also been demonstrated in human beings. Best known among these are 0.8 sec cycle of heartbeat, 4 sec cycle of respiration, even hormones like insulin and costicosteroids have definite circadian periodicity with increasing levels in the early hours of morning.

These rhythmic variations in physiological processes are of great significance to physicians as they might influence disease process and therapeutic results. Pharmacologists are more concerned with applications of this knowledge to optimisation of dosage schedule. But unfortunately physicians in general and particularly in India have not paid attention to this fact. It is only recently that we have started taking note of biological rhythms and its relation to drug effects. It is only when we have enough knowledge of biological periodicity in physiological process that studies on optimisation of dosage schedule can be undertaken to get better control of drug effect.

The data which is presented in the Symposium on Circadian Rhythms had been collected by me and my collegues in last 5 years, which clearly demonstrate that biological rhythms may influence pharmacokinetic parameters by changing absorption, metabolism and elimination of drugs. It may affect pharmacodynamic response by changing receptor sensitivity or susceptibility of host in relation to time.

Change in absorption :

Fig. 1 depicts the concentration of phenoxy methyl penicillin after 30 min of oral administration at 2 a.m, 6 a.m., 10 a.m., 2 p.m., 6 p.m. and 10 p.m. With same dose of phenoxy methyl penicillin given orally to healthy medical students who were diurnally active, serum concentration at 30 min was found to be twice as high after 10 a.m. administration as compared to the levels at 10 p.m. or 2 a.m. However, serum levels at 2 hours were not significantly different.

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A similar 30 min absorption difference has been shown to be present in iodine tracer studies.

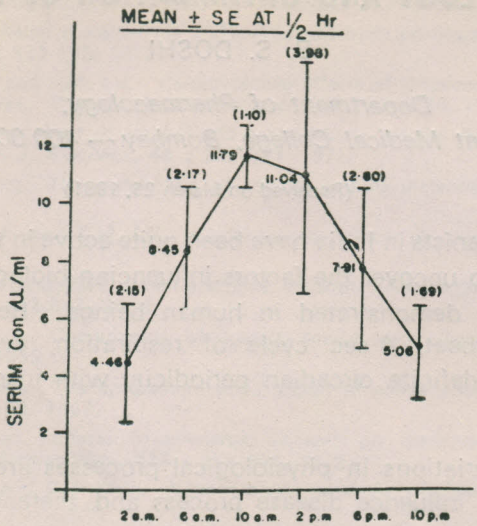

Fig. 1 : The concentration of phenoxy methyl penicillin after 30 min of oral administration.

Fig. 2 shows uptake of radio active iodine by thyroid gland given at 2 a.m., 6 a.m., 10 a.m., 2 p.m., 6 p.m. and 10 p.m., The uptake at 10 a.m. is three times more as compared to the thyroidal iodine concentration at 2 a.m. The thyroidal iodine uptake is directly related to iodine levels of radio active iodine in blood which also showed maximum concentration after 10 a.m. oral dose.

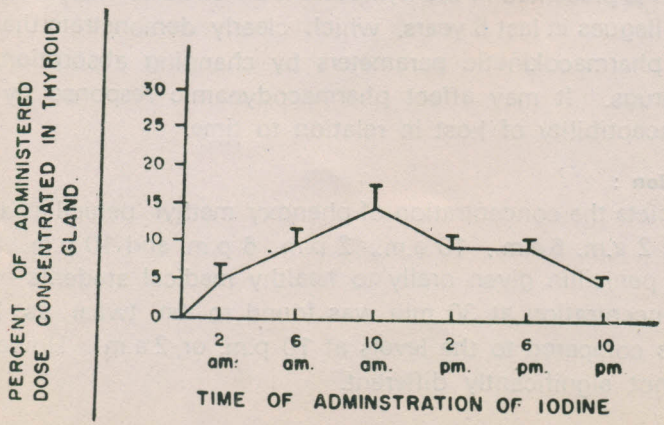

Fig. 2 : Uptake of radio active iodine by thyroid gland.

However, we did not find any change in the blood levels of tetracycline given at 8 p.m. or 8 a.m.

It appears for that drugs like tetracycline which are rather slowly absorbed, their rates of absorption do not seem to be affected by time. However, absorption rates of drugs like penicillin and iodine which are rapidly absorbed get affected with the time. The peak concentration is also variable with time of administration. If peak concentration of drug has any relevance to therapeutic efficacy then the drug dosage should be increased at the time when absorption is poor, or if peak concentration is related to the side effects, then the increased dose at the time, when absorption is poor, is likely to be better tolerated. We can determine approximate dose and time of administration to derive maximum benefits with minimum adverse reaction.

Change in metabolism :

Fig. 3 shows levels of total and free sulfonamides at 30 min after oral administration of sulfomoxole at 4 p.m., 8 p.m., 12 midnight, 4 a.m., 8 a.m. and 12 noon.

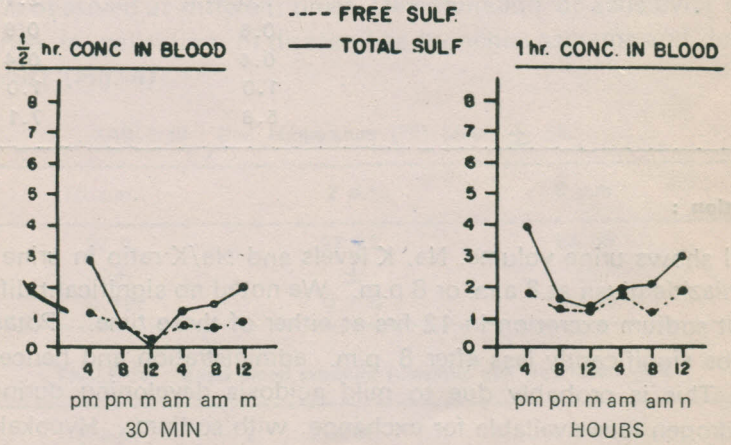

Fig. 3 : Levels of total and free sulfonamide at 30 min after oral administration of sulfomoxol.

Total sulfonamide levels were higher after 4 p.m. administration as compared to the dose at midnight, indicating again variability in the rate of absorption. But rate of absorption of sulfa has different time sequence as compared to iodine and penicillin. The acetylated sulfa as shown by the difference in the total and free sulfonamide levels also showed circadian variation. The acetylation at 30 min was maximum after 4 p.m. administration and negligible at 8 p.m., 12 midnight and 4 a.m. Not only absorption of

sulfa but acetylation is also time dependent which emphasizes that even metabolism of drug may be influenced by time.

Recently study was done to determine phenotypes of oxidative metabolism using debrisoquine. We could not find any change in oxidative metabolism of debrisoquine when drug was given at 8 a.m. or 11 p.m. Though this does not exclude the possibility of circadian variation in oxidative metabolism as the study was done only at two times. It is quite possible that metabolic rates may be variable as absorption rates. Collecting urine samples every 30 min would definitely bring out these differences (Table I).

TABLE I : Metabolic ratio of unchanged debrisoquine and 4-hydroxy debrisoquine.

Vol. No.	*Drug at 8 a.m.*	*Drug at 11 p.m.*
1	1.0	0.8
2	2.0	3.0
3	1.0	2.1
4	0.6	0.9
5	0.4	0.4
6	1.0	1.0
7	5.6	7.1

Change in excretion :

Table II shows urine volume, Na, K levels and Na/K ratio in urine with 12.5 *mgm* of hydrochlorthiazide given at 8 a.m. or 8 p.m. We noted no significant difference in urine volume and net sodium excretion in 12 hrs at either of these time. Potassium excretion was found to be significantly less after 8 p.m. administration and hence Na/K ratio was also variable. This is probably due to mild acidosis developing during sleep, which make more hydrogen ions available for exchange with sodium. Hypokalemia is a known side effect with chronic administration of hydrochlorthiozide. This difference in the excretion of kious can be useful in reducing this possibility of hypokalemia, but this advantage is ofset by the inconvenience caused to the patients who have to get up frequently at night and for this reason therapy is better given in the morning with potassium supplement.

Change in receptor sensitivity :

We have developed a simple method of studying β-1 and β-2 receptor sensitivity to adrenaline. The study was done in normal volunteers following design Latin Squre

in standard fasting and resting status at each of these study times. We have already demonstrated distinct temperature rhythm (Table III). Basal B.P. also shows steady increase from

TABLE II : Showing the effect of 12.5 *mgm* of hydrochlorthiazide given at 8 a.m. or at 8 p.m. Measured over following 12 hours.

Time of administration	*Urine volume ml*	*Sodium excretion meq*	*Potassium excretion meq*	*Na/k ratio*
8 AM	967	269.65	34.77	9.93
	±78	±19.78	±2.25	±1.17
8 PM	1063	274.32	20.47	1826
	±79	±17.68	±1.49	±2.08
	NS	NS	P<.01	P<.01

early morning to night (Table IV). With constant adrenaline infusion of 2.4 *µg/min,* the fall in diastolic B.P. is maximum in the evening at 6 p.m. and minimum at 10 a.m. This change in the response parallels the temperature rhythm. However, percent rise in pulse-rate in response to adrenaline shows maximum response in the morning. Variability in β-1 and β-2 receptor is observed at different times. Determination of sensitivity of β-2 receptor may have relevance to causation of disease like bronchial asthama and determination of dosage of B agonist (Fig. 4).

TABLE III : Oral temperature (°F) Mean ± SE.

6 a.m.	*10 a.m.*	*2 p.m.*	*6 p.m.*	*10 p.m.*
96.46	97.8	97.72	98.08	97.8
±	±	±	±	±
0.437	0.182	0.102	0.049	0.0

TABLE IV : Basal blood pressure (diastolic mm Hg) Mean ± SE.

6 a.m.	*10 a.m.*	*2 p.m.*	*6 p.m.*	*10 p.m.*
59.5	66	70	70	77.2
±	±	±	±	±
9.56	6.40	1.67	5.70	6.60

Changes in susceptibility of host :

As we know, nocturnal and early morning wheezing is very common in asthamatics. Many sudden deaths from asthma occurs in early morning. Figure 5 is taken from N.E.J.M. April 1980. Five young asthmatics showed definite circadian variation in expiratory peak flow. Plasma levels of epinephrine and histamine also showed distinct

rhythm, measurement times were 8 a.m., 12 noon, 4 p.m., 8 p.m., 12 midnight and 4 a.m. All asthmatics had circadian peak flow with highest values recorded at 4 p.m and lowest at 4 a.m. which paralleled plasma epinephrine levels. Plasma histamine showed inverse pattern to that of epinephrine (Fig. 5).

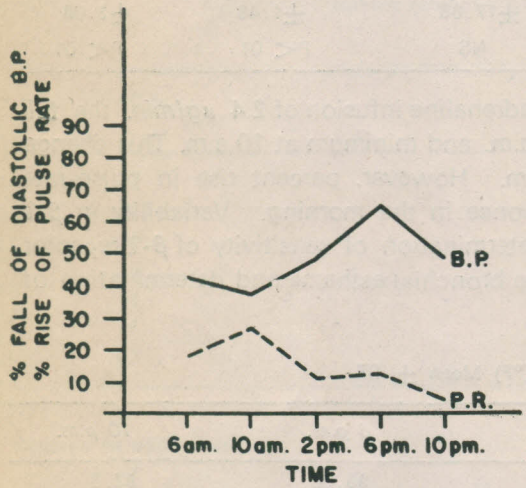

Fig. 4 : Percentage fall of diastolic B.P. and percentage rise of pulse rate.

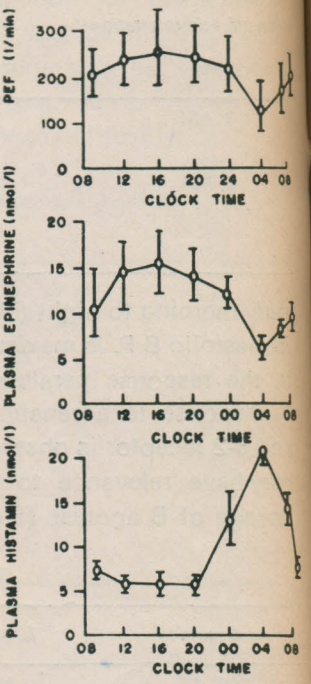

Fig. 5 : Plasma histamine showing inverse pattern to epinephrine.

The highly significant correlation in plasma expiratory peak flow suggest that reduce circulating levels of epinephrine in early hours could contribute in nocturnal wheezing. Second factor being less sensitivity of β-2 receptors in the morning as shown in previous figure. Similar change in plasma epinephrine level is also observed in normal subject but there is no significant rise in histamine levels. The implication is that it may be possible to prevent nocturnal wheezing by stimulating β-2 receptor using adrenergic agonist.

In case of cancer chemotherapeutic agents like adriamycin and cytarabine, chrono-schedules have definite edge over regular schedule in reducing toxicity and increasing efficacy.

It is obvious that biological rhythms have great significance in medicine. Using more standardised procedures for longer period in human subjects would give us better knowledge of chronopharmacology. It is for physiologists and pharmacologists to generate more such data and it is for physicians to apply it for enhancing the beneficial effects and reducing the side effects.