[*Current Medical Practice* (1980): (24), 8, 305]

Biological Rhythms and Medicine*

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(* Guest lecture by Dr. R.D. Kulkarni at the V Annual Conference of Pharmacologists of Maharashtra, Miraj, September 1979.)

Most biological processes show rhythmic variations. The best known among these are the 0.8 sec. cycle of the heart beat, 4 second cycle of respiration, diurnal variation in urine secretion and sleep rhythm. These rhythmic variations in physiological functions are of great significance to the physician because they might influence disease processes, diagnostic tests and therapeutic results. Hence the study of biological rhythms and their influence on disease and drugs should be of paramount importance in every speciality of medicine. For example, a demonstration of acrophase of natural deaths in hospitalised patients should prompt hospital administrators to give maximum medical attention at that hour. The impact of time on glucose tolerance curve should caution the pathologist in reporting on border line impairment.

One could cite innumerable such instances of physiological rhythmicity influencing the outcome of disease with or without treatment. But being basically a pharmacologist, I shall restrict myself to those areas where drug effects are significantly affected because of biological rhythms. In these areas also, I would illustrate these influences as shown by several of my colleagues.

The biological rhythms may influence drug action by any of the following five mechanisms: 1. change in absorption, 2. change in elimination, 3. change in metabolism, 4. change in receptor affinity or efficacy and 5. change in the susceptibility.

CIRCADIAN VARIATION IN THE ABSORPTION OF DRUGS:

Some years back, Dr. Worlikar and others in our Department showed a marked variation in 30-minute serum concentration of phenoxy-methyl Penicillin in healthy human volunteers who were diurnally active and nocturnally resting by habit (Fig. 1). It is seen that for the same dose given on an empty stomach, blood concentration at 30-minutes is twice as high at 10 a.m. as compared to 10 p.m. However, the differences at subsequent time intervals i.e. 1 hour and 2 hours, are not significant and the area under the serum concentration time curve is not significantly different.

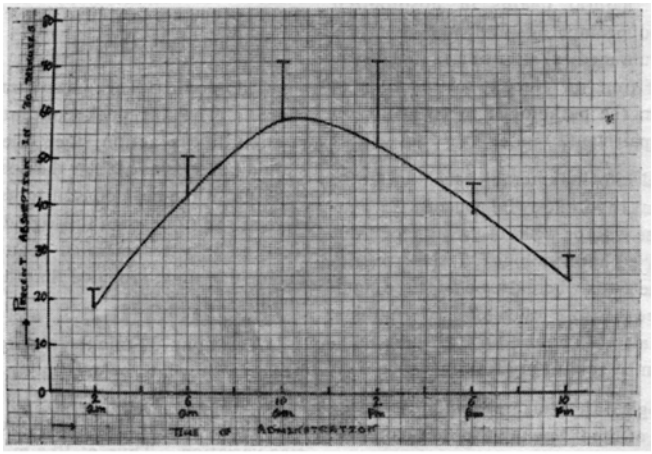

Fig. 1

Showing the serum concentration of penicillin 30 minutes after oral administration of 1-2 m units of phenoxymethyl-penicillin on an empty stomach at various times in a 24-hour period. The absorption is the most rapid when the drug is administered at 10 a.m. and very poor when administered at 10 p.m. or 2 a.m.

This could be of great therapeutic significance. Thus, if peak concentration has any relation to its action, then the dose at night should be twice as high as the dose in the morning. Or, if the peak concentration is related to adverse reactions, then the high dose at night is likely to be better tolerated than a similar dose during day time, provided that the tissue sensitivity is same.

A similar 30 minute absorption difference has been shown to be present in the absorption of iodine tracer studies (Fig. 2). This absorption variation is parallel to the thyroidal concentration variation. Thus, at 10 a.m. there is 3 times more thyroidal concentration when administered at 10 a.m., as compared to 10 p.m. administration. But there is no difference in the 6 hour thyroidal concentration indicating similar total absorption.

My colleague Dr. Doshi failed to find any differences in serum concentration of tetracycline after administration on an empty stomach at 8 a.m. and 8 p.m.

It therefore appears that the absorption rates of rapidly absorbed drugs are variable with the time in 24 hour period but slowly-absorbed drugs are not significantly affected. One could use this knowledge to determine appropriate doses and the time of administration to derive maximum benefit with minimum adverse reactions.

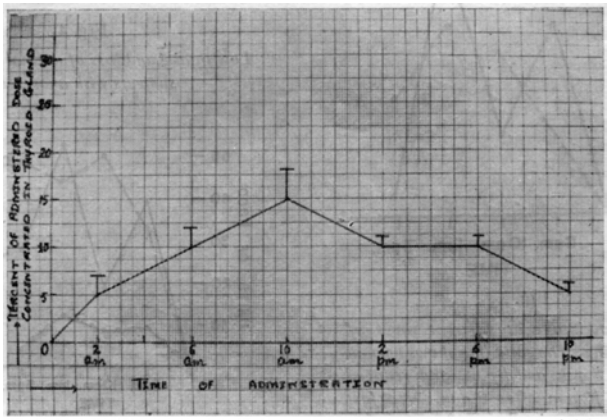

Fig. 2

Showing the per cent of orally-administered dose of radio-iodine concentrated in thyroid gland in 30 minutes. Here also the most rapid concentration occurs when the drug is administered at 10 a.m. and the least when administered at 10 p.m. and 2 a.m.

Phenoxymethyl-penicillin is an important antibiotic and serum concentrations are determined microbiologically. My colleague Salma Motiwala recently investigated the circadian sensitivity of the test organism – *S. aureus,* as also the circadian changes in growth rates. This possibility was suggested from the commentary of Franz Halberg on a very old observation. The methodology she used initially suggested some kind of cyclic change in growth rates which was later found out to be a methodological artefact. After rigidly controlling the initial bacterial growth rates for *S. aureus* and *E. coli* were very constant and these sensitivity to penicillin and tetracyclin was unaltered. My colleague Dr. Walwaikar investigated last year the circadian periodicity of Sulfamoxole absorption and metabolism. He found strong circadian variations in total sulfonamide in blood but not in the free sulfonamide levels. This indicates that the acetylation of sulfonamides is time dependant, being maximum at 8 p.m. and minimum at 4 a.m. Body temperature shows circadian changes. Even in fevers, the morning temperature is usually lower than the evening temperature. Blood pressure has also been shown to vary with time in 24 hours, both in normal subjects and hypertensive patients. It is common knowledge that asthmatic attacks are frequent at night. During night, with lowered respiratory rate, mild acidosis occurs and during acidosis, adrenaline effects are reduced. Is this the reason why asthmatic attacks are more common at night? My colleague Dr. Doshi has been studying the adrenergic beta receptor sensitivity in human beings. By following a study design permitting standardisation of fasting and resting status at each of 5 study times, she could confirm the temperature rhythm and demonstrate parallel charges in diastolic blood pressure and pulse rate. The data which is presented in this Conference is too small to draw firm conclusions but is indicative of altered sensitivity of β receptors to adrenaline depending on time.

CHRONOBIOLOGIA AND AYURVEDA

Emphasis on time of the day for medication and other 'Karmas' is well known in Ayurveda. It also lays great stress on 'Dincharya'. Though it is not stated in so many words in any of the ancient works on Ayurveda, it seems very obvious to me that biological rhythms were considered very important. Did they also realise that disturbed rhythm could be a cause of disease and therefore the stress on 'Dincharya' to reinforce these rhythms so as to avoid disturbances? If this be so, they seem to have noticed the origin of disease in the disturbed rhythm. It is then not surprising that many herbal remedies which have stood the test of time are devoid of the acute pharmacodynamic effects.

We studied this problem in relation to hunger and satiety rhythms. It is common knowledge that one feels hungry at the usual meal time and can eat and digest a meal. Soon after the meal, the food ceases to be attractive. If you miss a meal, hunger gradually disappears. Several hours later, one cannot eat the same meal and one feels heavy. We studied this phenomena in school children and by assigning scores to food articles, we could quantify the intake at breakfast and lunch (Fig. 3).

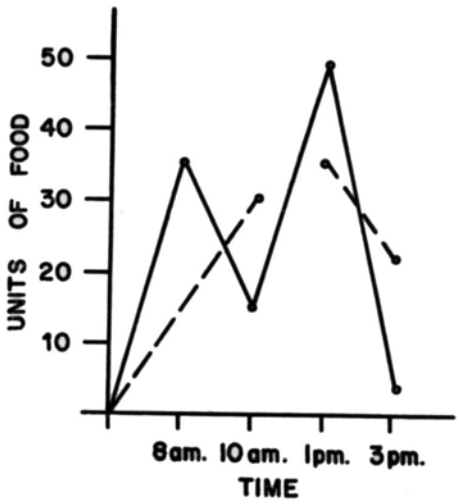

Fig. 3

Shows food intake at different times of the morning. The solid line shows normal intake at 8 a.m. and 1 p.m. and reduced intake at 10 a.m. after 8 a.m. breakfast and very poor intake at 3 p.m. after normal meal at 1 p.m. The broken line shows relatively less intake, if breakfast is delayed to 10 a.m. and further reduced intake at 3 p.m. when lunch is similarly delayed. Delayed breakfast also reduces lunch intake at normal time.

The results looked very interesting when cases of anorexia were similarly studied. Out of 26 cases of anorexia in adults, 23 showed complete loss of appetite and no satiety phase could be elicited (Fig. 4). Out of these 23 cases, 12 were treated with Liv.52 and 11 were treated with Cyproheptadine. The food intake increased in 11 out of 12 cases on Liv.52 and 12 out of 12 cases on Cyproheptadine (Fig. 3). However, the satiety phase could be clearly demonstrated in Liv.52 treated group but not in the Cyproheptadine-treated group. The mechanism of Cyproheptadine is probably by suppressing hyperactive satiety centre but Liv.52 seems to normalise the appetite satiety rhythm (Fig. 4). This indicates that large majority of anorexia cases are due to loss of the basic rhythm of appetite and satiety and Liv.52 acts to correct this defect rather than stimulating the appetite centre or suppressing the satiety centre (Fig. 5).

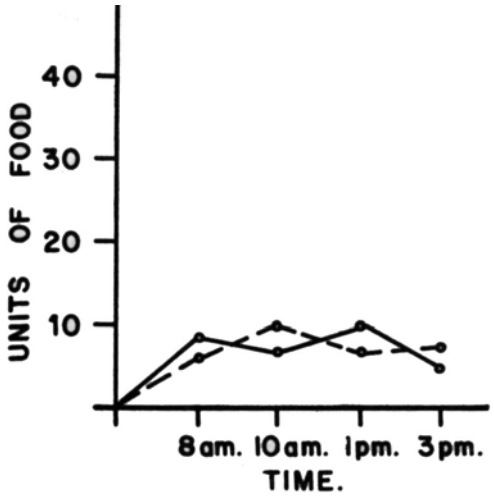

Fig. 4

Low intake and loss of normal rhythm in subjects with anorexia.

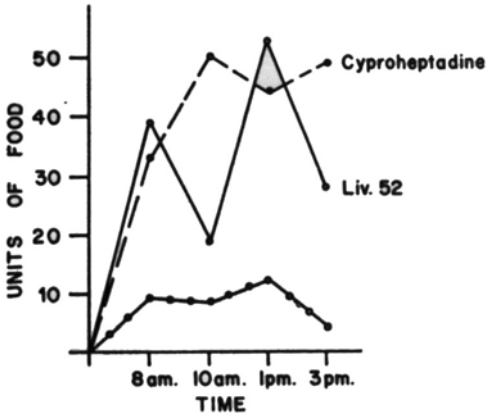

Fig. 5

Shows marked increase in appetite by cyproheptadine but lack of normal rhythm in subjects with anorexia. Liv. 52 produces less pronounced increase in food intake but a normal rhythm.

Thus, it is obvious that biological rhythms have a great significance in medicine and better knowledge of chronobiology would help in the use of potent drugs with reduced adverse reactions. Even Ayurvedic drugs need to be re-evaluated from this point of view and there is a good chance that we may acquire a better understanding of drug action in general.