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Evaluation of Chronosensitivity and Chronopharmacology of some centrally acting potential drugs in albino wistar rats

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ABSTRACT

Many of the drugs leave the market due to their adverse effects than their therapeutic effects. If the pharmacology of the drug and its adverse effect is Circadian Time (CT) dependent, it can be modulated by altering the time of administration of drugs. Chronopharmacology describes the effect of drugs in terms of time of administration. Its main objective is chronotherapy (time based treatment). Here the psychopharmacological drug such as Diazepam, Chlorpromazine and Phenobarbitone undergoes circadian investigation by using Latin square design. Male albino wistar rats were selected, divided into four groups, each group consist of six animals and subjected for investigation. Animals are acclimatized for 12 h L/D cycle in laboratory condition and animals were given access to feed and water ad libitum. Rats were treated with Diazepam (4 mg/kg b.w, orally), Chlorpromazine (3 mg/kg b.w, orally) and Phenobarbitone (16 mg/kg b.w, orally) at CT 0200, CT 0800, CT 1400 and CT 2000 respectively. Anxiolytic effect, skeletal muscle relaxant effect and locomotor effect were recorded by using Actophotometer, Rota rod apparatus, Elevated plus maze and Mirror chamber apparatus at different circadian time mentioned above. The effect of drug was determined by using chronogram. Based on the observation it was concluded that the rhythmic activity of rats was not influencing the pharmacology of Diazepam, Phenobarbitone but circadian pattern influences the activity of Chlorpromazine.

Keywords: Chronopharmacology, Psychopharmacology, CNS activity, Circadian time

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INTRODUCTION

Chronopharmacology involves the study of changes in the pharmacology of drugs with reference to the time of administration. Chronosensitivity involves variation in sensitivity, response and behavior of animals at different times of circadian cycle (ζ= 24 h).

"The investigation of drug effects as a function of biological timing as well as their effects upon rhythmic characteristics (is) has been the concern of developing discipline called Chronopharmacology".

It has been known for decades that circadian rhythms occur within all organisms; ranging from bacteria to humans [1]. These patterns have been shown to influence homeostasis, which in many cases is caused by time related variations [1, 2]. These patterns extend to the fields of pharmacokinetics and pharmacodynamics; the study of these temporal variations is generally termed as Chronopharmacology [2, 3].

Chronopharmacology is a vast term which encompasses three branches viz.,
1. The Chronokinetics of a drug. This term includes rhythmic changes in the drug(s) bioavailability, pharmacokinetic and its excretion.
2. The Chronesthesy of a biosystem to a drug. i.e. circadian changes in the susceptibility of any biosystem to a drug.
3. The Chronergy which includes its chronokinetic and the chronesthesies of the involved organisms biosystem [4].

Chronopharmacology is useful to solve problems of drug optimization, i.e. to enhance the desired efficiency or to reduce its undesired effects. In the humans (among other animal species) the metabolic fate of a pharmacologic agent (as well as that of a nutrient) is not constant but it is a function of time.

Thus, the chronopharmacologic approach involves a lesser risk of errors and/or false information than the conventional homeostatic approach. Many psychopharmacological drugs are useful in seasonal affective disorders. Though diazepam has fewer adverse effects, other selected drugs such as Phenobarbitone and Chlorpromazine also have many adverse effects, because of which they are leaving the market even though their pharmacological actions are potent. The need of the hour is to design strategies to ameliorate the side effects and make them more acceptable.

If the pharmacology and adverse effects of these drugs is CT (Circardian time) dependent, it can be modulated by altering the time of administration of the drugs. Any dependence of these drugs on the circadian time may provide a clue to ameliorate the major drawback of drugs. It was studied here to investigate, if any circardian factor in the pharmacological effect of drugs such as Diazepam, Chlorpromazine, and Phenobarbitone exist. This circardian pattern inturn may reveal the chronosensitivity of the receptors, which will also finally end up in chronotherapy. Hence, this study was designed to identify the chronopharmacological clue that may lead to chronotherapy.

MATERIALS AND METHODS

Preparation of drug samples

Drug samples of Diazepam in 4 mg/kg b.w, Chlorpromazine 3 mg/kg b.w and Phenabarbitone 16 mg/kg b.w were prepared by mixing with 0.3% CMC Suspension, drug samples were administered orally.

Experimental animals and acclimatization

Wistar albino rats of either sex weighing 180-200g were used for this study. Those animals were grouped in polyacrylic cages and maintained under standard laboratory conditions (temperature 25 ± 2ºC) and relative humidity (50 ± 5%) with dark and light cycle (12h/12h). They were

allowed free access to standard dry pellet diet and water ad libitum. The rats were acclimatized to laboratory condition for 10 days before commencement of the experiment. The Institutional Animal Ethics Committee (LAP/KMCP/MPHARM/2628/08-09) has approved the experimental protocols and care of animals was taken according to CPCSEA guidelines.

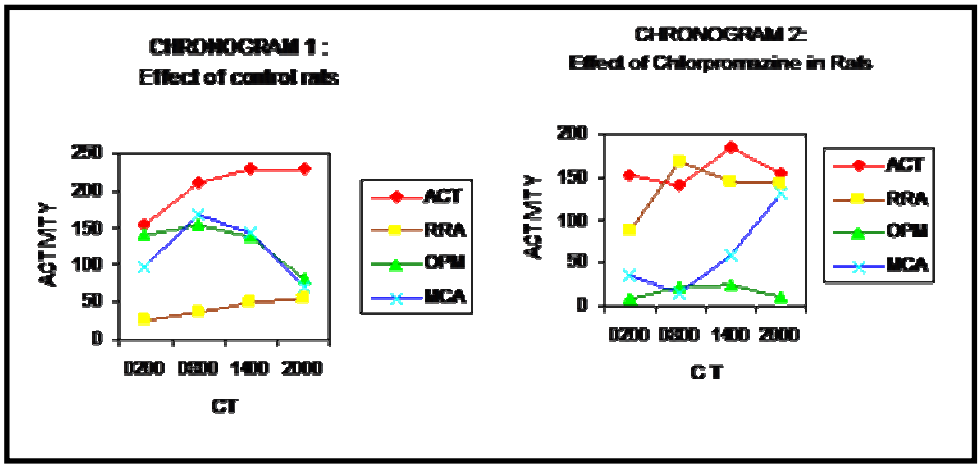
Four groups of 6 animals each were selected. Group 1 served as a normal control received vehicle 0.3% CMC suspension. Group 2, 3, 4 served as a treatment group in which diazepam (4 mg/kg), chlorpromazine (3mg/kg), phenobarbitone (16 mg/kg) was administered orally half an hour before commencement of study respectively.

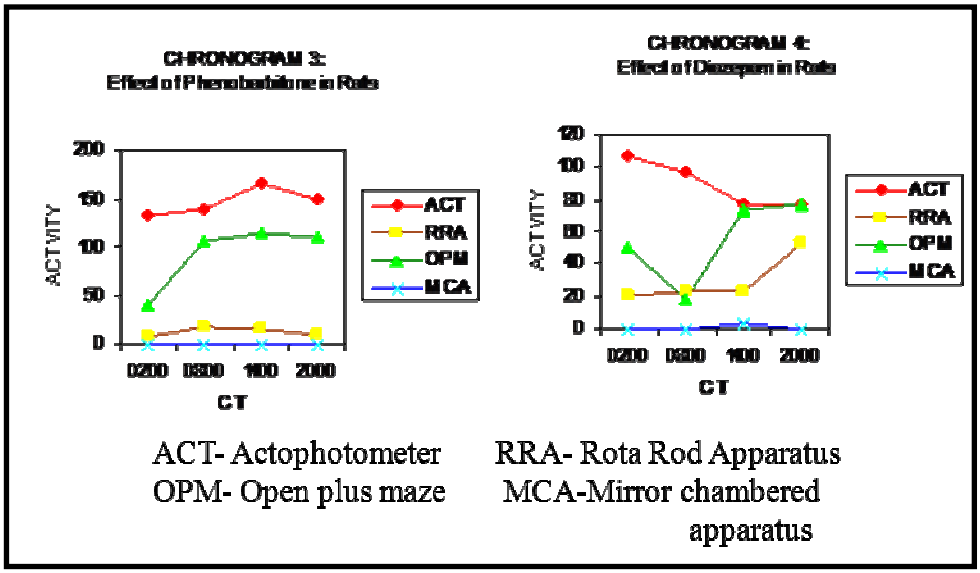
Apparatus used

Actophotometer was used to determine the locomotor activity, Rota Rod Apparatus was used to determine the skeletal muscle relaxant property, Elevated plus maze apparatus was used to determine the anxiolytic property and Mirror chamber apparatus was used to determine the anxiolytic property at different circadian time.

Circadian Time Selection

Chronosensitivity was studied by recording the responses before and after drug treatment at different circadian time such as 0200 CT (8 am), 0800 CT (2 pm), 1400 CT (8 pm) , and 2000 CT (2 am). Latin square design has been followed to determine the psychopharmacological response.





ACT- Actophotometer RRA- Rota Rod Apparatus
OPM- Open plus maze MCA-Mirror chambered apparatus

RESULTS AND DISCUSSION

The results of chronopharmacological study of Diazepam, Chlorpromazine and Phenobarbitone and the chronosensitivity of the animals have been depicted as chronogram 1-4. While looking into the chronopharmacological effect of diazepam using various instruments (viz open plus maze, Mirror chamber apparatus, Actophotometer, and Rota rod apparatus), no stastistically significant differences were observed when recorded at different circadian times.

However, when the depressant effect of Phenobarbitone was assessed using the above mentioned apparatus, a statistically significant difference was observed with an instrument viz elevated plus maze i.e., the reaction time recorded at CT 0200(8 am) was significantly lower, against the time recorded at CT 0800(2 pm), CT 1400(8 pm), and CT 2000 (2 am). Hence, the responses recorded using other instruments did not show any significant difference.

In case of Chlorpromazine, the responses recorded using mirror chamber apparatus, Rota rod apparatus and actophotometer showed statistically significant differences at different circadian times. However, the responses recorded using other instrument did not show any significant differences.

In case of control rats; which have not been treated with any of these drugs, only the responses were recorded at different circadian times using these instruments. The responses recorded using actophotometer showed significant differences. The response recorded at CT 2000(2 am), with respect to Mirror chamber apparatus, was significantly lower against the value recorded at CT 0800(2 pm). In case open plus maze and Rota rod apparatus, the responses at CT 2000(2 am) were significantly different when compared with the responses at CT 0800(2 pm).

The results of the control group clearly imply that the rats were maximally active at CT 2000(2 am), and least active around CT 0200(8 am). This might possibly explain the highest values in Actophotometer and Rota rod apparatus and lowest values in Mirror chamber apparatus. Thus these observations are explicit regarding the activity and rest spans of the animals.

But the observations with the Phenobarbitone and Diazepam imply that the rhythmicity in animal behaviour did not alter the pharmacology of these drugs means no rhythmicity in the drug responses was observed.

However in case of chlorpromazine, such rhythmicity was observed obviously when examined for its effect using Actophotometer and Rota rod apparatus. The animals were most active at CT 2000(2 am)

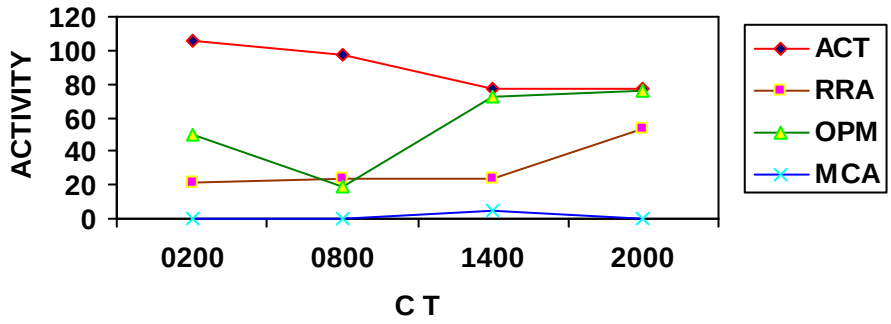
It is well known that liver is the key organ to drug chronokinetics and circadian rhythmicity is documented in hepatic drug metabolizing enzymes[5]. In rats and mice of either sex, the enzymatic activity of enzymes like Aminopyrine-N-demethylase, 4- dimethyl aminobenzene reductase, was greatest during second half of the rest span.

Jori et al[6] have shown in rats that circadian changes in the hepatic microsomal activity is synchronized by 12 h light / 12 h dark cycle and the crest time of the enzyme occurred during the course of the activity span. Probably this might be the reason of the fast metabolism of chlorpromazine and hence the mild pharmacological effect. Moreover the CT 2000(2 am) response in Actophotometer of the chlorpromazine treated rats did not statistically vary from that of CT 2000(2 am) reading of control rats.

But in case of Rota rod apparatus, the CT 2000(2 am) response of chlorpromazine treated rats was statistically less than that of control rats but the rhythm was preserved.

From these observations it can be concluded that the rhythmic activity of rats were not influencing the pharmacology of Diazepam, Phenobarbitone but that of Chlorpromazine. Further investigation with chlorpromazine may throw light on chronopharmacology of chlorpromazine, chronosensitivity of its receptors and hence the chronotherapy with chlorpromazine. Based on the observation it was concluded that the rhythmic activity of rats was not influencing the pharmacology of Diazepam, Phenobarbitone but circardian pattern influences the activity of Chlorpromazine.

CHRONOGRAM 4:
Effect of Diazepam in Rats



ACT- ACTOPHOTOMETER; EPM – ELEVATED PLUS MAZE; RRA – ROTA ROD APPARATUS; MCA – MIRROR CHAMBER APPARATUS

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