

A STUDY TO EVALUATE THE EFFECT OF SPARFLOXACIN ON PENTOBARBITONE INDUCED SLEEP IN MICE

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ABSTRACT

Objective: To evaluate the effect of sparfloxacin on pentobarbitone induced sleeping time.

Methods: animals were divided into 3 groups of 6 mice each. Group 1 served as control where as group 2 and 3 were sparfloxacin treated. All the drugs were suspended in gumacasia and given orally once daily for 10 days. Sleep was induced to animals by injecting pentobarbitone at the dose of 35mg/kg. Two parameters latency of sleep and duration of sleep were noted by observing righting reflex on day 1 and day 10 of treatment

Results: in acute study there was no significance change in latency of sleep and sleep duration when compared to control whereas after 10 days of treatment animals did not show any significance change in sleep latency but duration of sleep decreased significantly when compared to control group (56.388±4.48) at both the dose of sparfloxacin(21.006±6.70, 29.400±6.59).

Conclusion: sparfloxacin at the dose of 25mg/kg and 50mg/kg significantly decreases pentobarbitone induced sleep duration when given for 10days without affecting latency of sleep.

Keywords: sparfloxacin, pentobarbitone induced sleep

INTRODUCTION

Sparfloxacin belong to the group of fluoroquinolones which is a commonly used antimicrobial agent in the treatment of various infectious diseases because of their broad and strong antibacterial activities with excellent tissue penetrability. These classes of drugs are generally well-tolerated and considered as relatively safe drugs.^[1] Various adverse effects have been reported along with increase in the usage of new-generation fluoroquinolones.

The most commonly occurring adverse effects are GI upset (7%). Less common effects may include central nervous system (CNS) events (less than 5%), blood disorders (approximately 5%), renal disturbances (approximately 4.5%), and skin hypersensitivity and photosensitivity effects (approximately 2%).^[2,3] Fluoroquinolones have been shown to possess excitatory side effects on central nervous system, such as headache, dizziness, insomnia, impairment of concentration and dexterity, convulsions, psychosis and tendinitis.^[4,5] However, some of these events may not be directly attributable to fluoroquinolone therapy per se, and other underlying conditions of the patient, including additional drug therapy unrelated to the antimicrobial, may contribute to the reporting of side effects.

Sparfloxacin differ from other fluoroquinolones because of considerable differences in the pharmacokinetic profile of various fluoroquinolones such as bioavailability, inhibition of hepatic microsomal enzyme, tissue distribution particularly penetration into

the brain tissue, central diffusion and the affinity for the receptors responsible for the central excitatory activity^[6]. Based on above data the present study is undertaken to evaluate the effect of sparfloxacin a second generation difluorinated quinolone on latency of sleep and total sleeping time induced by pentobarbitone in mice.

MATERIALS AND METHODS

Experimental animals

Swiss albino mice of either sex, weighing between 25 – 30 g, were used in this study. The animals were housed in polypropylene cages maintained at standard conditions of 12 h light

/12 h dark cycle; 24 ±2 °C, 45 – 55 % relative humidity) and had free access to standard rat feed and water *ad libitum*. All the animals were acclimatized to laboratory conditions for a week prior to commencement of experiments. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) and Committee for the Purpose of Control and Supervisions on Experimentation on Animals (CPCSEA) guidelines were followed.

Grouping

Animals were divided into three groups. Each group contained 6 animals. Drugs were suspended in 1% gum acacia and were administered orally. Group 1 was control and received gum acacia 10ml/kg. Group 2 received sparfloxacin at a dose of 25 mg/kg. Group 3 received sparfloxacin at a dose of 50 mg/kg.

Table 1: Grouping and dosing schedule

Group no	Group	Treatment given
Group I	Control	1% gumacasia at the dose of 10ml/kg
Group II	Test 1	Sparfloxacin at the dose of 25mg/kg
Group III	Test 2	Sparfloxacin at the dose of 50mg/kg

For acute study drug was given 45min prior to the pentobarbitone injection where as for chronic study all drugs were administered once daily for 10 days.

Pentobarbital induced –sleep test ^[7]

All the animals were injected with sodium pentobarbitone at the dose of 35mg/kg intraperitoneally after 45min of the drug treatments in acute study and after 10 days of treatments in chronic study.

Time taken for induction of sleep and total duration of sleep were noted down. Righting reflex is used to assess whether or not animals are asleep. The time when animal loses its righting reflex it is noted as onset of sleep and the time between loss of righting reflex and regaining of righting reflex was considered as duration of sleep

Statistical analysis

All results are expressed as MEAN±SE. All the group were analyzed using one way ANOVA followed by

Dunnet's multiple comparison test using SPSS software version 17. P<0.05 was considered significance.

RESULTS AND DISCUSSION

Sparfloxacin is a second generation fluoroquinolone used for treatment of various bacterial infections. As such fluoroquinolone group of drugs are well tolerated but still an incidence of adverse effect related to GIT, CNS, renal, blood disorder and skin hypersensitivity is observed. Out of all the adverse effect of Fluoroquinolones 5% of adverse effects are related to the central nervous system.. CNS associated adverse

effects include mainly insomnia, anxiety, altered behavior, hallucinations, convulsions.^[3,4] Binding of fluoroquinolones to brain gamma-aminobutyric acid (GABA) receptor appears to be the main mechanism of any CNS activity produced by fluoroquinolones.^[8] GABA is an inhibitory neurotransmitter of brain. Fluoroquinolones with GABA like ring substitute acts as an antagonist and prevent normal binding of GABA with their receptors causing an increase in CNS activity. There are reports on fluoroquinolones directly activating N-methyl-d-aspartate (NMDA) and adenosine receptors present in the hippocampus and excitatory potential increases in dose dependent manner.^[9,10] Sparfloxacin reportedly have poor tissue distribution in CNS also decreased GABA inhibitory propensity.^[11]

However under specific conditions of sufficient CNS penetration, associated with antagonism of inhibitory pathways (GABA) and stimulation of excitatory pathways (NMDA, adenosine), observable CNS symptoms are manifested.^[12]

Table 2: Effect of sparfloxacin on pentobarbitone induced sleeping time on day 1

Group	Latency of sleep(in min)	Total sleeping time (in min)
Control	5.89±0.41	45.02±2.55
Sparfloxacin 25mg/kg	5.15±0.88	52.15±2.59
Sparfloxacin 50mg/kg	6.50±0.70	47.25±6.69

All the values were expressed as mean ± standard error of mean. * P<0.05

Table 3: Effect of Sparfloxacin on latency of sleep and total sleeping time in mice on day 10

GROUP	LATENCY OF SLEEP(in min)	TOTAL SLEEPING TIME (in min)
Control	6.338±0.95	56.388±4.48
Sparfloxacin 25 mg/kg	4.173±0.075	21.006±6.70*
Sparfloxacin 50 mg/kg	6.496±1.518	29.400±6.59*

All the values were expressed as mean ± standard error of mean. * P<0.05

Was considered statistically significant.

As shown in table 3 in the chronic study i.e. on day 10 of treatment sparfloxacin treated group did not show any significance difference in onset of sleep when compared to control group but there was significance decrease in total duration of sleep (p<0.05). The total duration of sleep being 21.006±6.70min, 29.400±6.59min and 56.388±4.48min for sparfloxacin treated group at 25mg/kg, 50mg/kg and control group respectively.

After administering sparfloxacin animals were observed for changes in motor activity. There were no considerable change in the locomotor activity of the animal indicating that sparfloxacin has no effect on motor activity

In the present study which was conducted to evaluate the effect of sparfloxacin on pentobarbitone induced sleeping time shows that there is significant reduction in total sleep duration without affecting the onset of sleep in mice fed with sparfloxacin at 25 mg/kg and 50 mg/kg for about 10 days .

The pharmacokinetic difference of sparfloxacin from other fluoroquinolones did not alter central nervous system adverse effect insomnia. But results of acute study show that there is no significance difference between control and sparfloxacin treated group in both the parameters. This may be because at acute dose sparfloxacin may not be able to penetrate or attain sufficient concentration to produce CNS effects. Fluoroquinolones are enzyme inhibitors but this activity is less with sparfloxacin. Therefore, the reduction of pentobarbitone effect cannot be correlated to its enzyme inhibitory activity.

CONCLUSION

To conclude sparfloxacin at the dose of 25 mg/kg and 50 mg/kg significantly decreases pentobarbitone induced sleep duration when given for 10days without affecting latency of sleep. However further comparative studies of fluoroquinolones on sleeping time and other CNS activity are needed to select a drug with least action on central nervous system.

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