ORIGINAL ARTICLE

A STUDY OF THIOPENTAL SODIUM-INDUCED SLEEP IN WISTAR RATS IN DOSES OF QUININE AND ARTESUNATE

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Background: Full knowledge of the actual central nervous system properties of both quinine and artesunate is still hazy and far from very clear. There are no scientific data to support the suggestion that either of these drugs possess properties that modify the functioning of central nervous system. It was the aim of this study to evaluate the patterns of thiopental sodium-induced sleep in separately administered doses of quinine and artesunate in Wistar rats. **Method:** Healthy adult rats of comparable size, weight and age were employed to examine the onset time (latency) and duration of thiopental sodium-induced sleep in separate pretreated doses of quinine and artesunate. The time of the Onset and Duration of the induced sleep were computed in varying doses of each of the drugs. The results were expressed as Mean±SEM, and values of $p \leq 0.05$ were regarded as statistically significant. **Results:** The onset time of the induced sleep were significantly decreased in higher doses of quinine ($p \leq 0.05$) while the sleep duration were prolonged ($p \leq 0.05$; $p \leq 0.01$) in higher doses of both drugs, indicative that the animals sleep quicker with corresponding longer sleeping time in high doses in both quinine and artesunate. **Conclusion:** Both quinine and artesunate possess some central properties that account for the observed potentiating influence on the induced sleep. The promoting effects on the induced sleep may be linked to serotonergic mechanism or the GABA mechanism in the brain.

Keywords: Thiopental sodium sleep, Wistar rats, Potentiating effects, Quinine, Artesunate

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INTRODUCTION

Most scientific reports in the past have focused on psychoactive compounds. Very often however, very little is known as regards the actual or potential central nervous system effects of some of these compounds, including total lack of scientific data on the psychoactive properties of the compounds. Meanwhile, humans consume a wide range of drugs and dietary supplements some of which may have constituents and properties that can modify the functioning of the central nervous system. For example, it was reported that artesunate may have dual behavioural modulating properties of both excitatory and sedative effects in Wistar rats.[1] A report from one other study noted that ascorbic acid dose-dependently antagonized pentobarbitone-induced sleep in rats[2], and behavioural excitatory effects were also reported in low doses of ascorbic acid in Wistar rats[3].

Both quinine and artesunate have been the treatment for malaria since the discovery of the Cinchona tree bark to European medicine in 1638[4], and these drugs have remained part of the main ingredients in most drugs formulations for the treatment of severe malaria in African countries. In spite of the complaints and claims of some side effects in both the quinine and artesunate treatments for malaria, information on the actual or potential central nervous system activities of these compounds is not yet fully defined, and since these drugs are also known to easily cross the blood-brain barrier, knowledge about possible behavioural modulating properties of these drugs are yet to be ascertained.

Essentially, sleep is a behavioural state in the animal. One obvious assumption by most workers recognized that a change in the behavioural output of a normal animal must result from alteration in the central nervous system activity. For example, it was reported that artesunate prolonged hexobarbital sleeping time in mice[5], and there were suggestions that both quinine and artesunate may have sedative properties in the study considered as the most reliable method of assessing agents with central nervous system depressant activity.[5] The role of neurotransmitter systems that traditionally mediate the arousal and waking states functions of the brain is implicit in the physiology of sleep, thus, one of the reliable methods in which it is possible to study the central regulatory mechanism of consciousness and waking states, is by examining sleep.

This study was designed to produce sleep using a short acting barbiturate, and the overall aim was to evaluate and compare the induced sleep in Wistar rats in varying doses of separately administered quinine and artesunate.

MATERIAL AND METHOD

A total of sixty-five (65) Wistar rats of comparable age, size and weight, were kept in animal house for a period of two weeks to acclimatize to the laboratory environment before the commencement of the experiments. The animals had free access to standard feeds and water throughout the period of the

experiments. The animals were separated by the use of body markings for group identification and were also kept in separate transparent cages according to the sex.

Known quantity of the drug (artesunate or quinine) was dissolved in a known quantity of physiological saline, and the resultant mixture was left to stand for about one hour before filtration to remove any debris. A stock solution of either quinine or artesunate was then obtained, from which the various doses (4, 8, 16, 32, 64 and 128 mg/Kg) in respect of each drug was then determined.

An animal from an experimental group was given one of the doses of either quinine or artesunate prior to the 40 mg/Kg dose of thiopental sodium, intraperitoneally (i/p), to obtain the sleep data by close observation and recording of the Onset Time and Duration of the induced sleep using a stop watch. Animals of the control group received 40 mg/Kg dose of thiopental sodium only, to obtain and record the time course of the induced sleep. All experiments were conducted between the hours of 9 AM–1 PM GMT+1 daily. The sleep data in each experiment were pooled and subjected to statistical analysis using graphpad prism statistical package[6] and One Way Anova. Test results were compared with those of the control group using the Dunnet Multiple Comparison post hoc test. The results were expressed as Mean and Standard Error of the Mean (SEM), and $p \leq 0.05$ was considered as statistically significant.

RESULTS

Results are illustrated in Tables: 1-2, and Figures: 1-2.

Table-1: Pattern of Thiopental sodium-induced sleep in Wistar rats in varying doses of Quinine

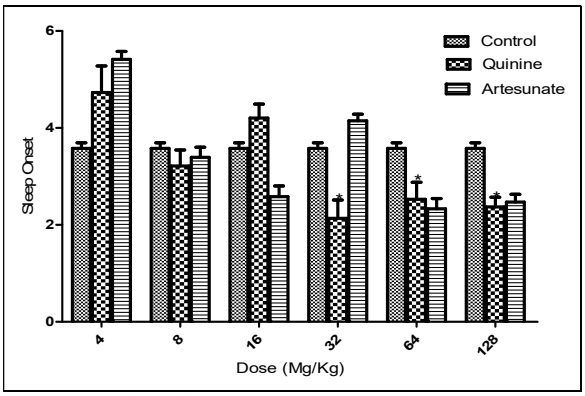
DOSE (mg/Kg, i/p)		Pattern of sleep (Min.)	
Quinine	Thiopental sodium	Onset of Sleep	Duration of sleep
Control	40	3.58±0.51	59.97±3.57
4	40	4.73±0.45	59.53±1.06
8	40	3.22±0.53	62.92±1.60
16	40	4.20±0.28	75.34±3.05*
32	40	2.13±0.08*	92.85±1.18**
64	40	2.53±0.15*	87.43±2.79**
128	40	2.37±0.20*	89.76±2.33**

*Significant, Mean±SEM, compared to baseline control (n=5)

Table-2: Pattern of Thiopental sodium-induced Sleep in Wistar rats in doses of Artesunate

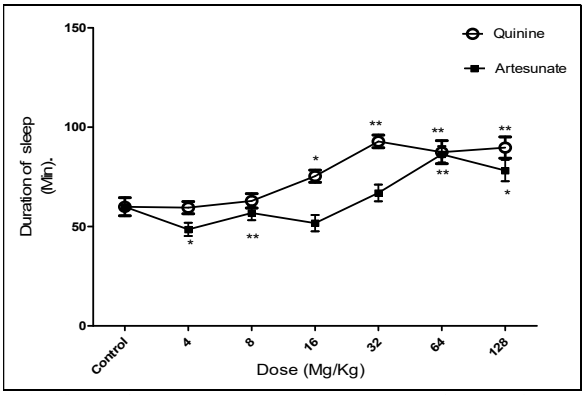
Dose (mg/Kg, i/p)		Pattern of sleep (Min)	
Artesunate	Thiopental sodium	Onset of Sleep	Duration of sleep
Control	40	3.58±0.51	59.97±3.57
4	40	4.42±0.76	48.58±2.34
8	40	3.39±0.41	56.83±2.61
16	40	2.58±0.22	51.72±4.13
32	40	4.15±0.44	66.94±3.22.
64	40	2.33±0.11	86.34±3.13**
128	40	2.47±0.16	78.19±4.33*

*Significant, Mean±SEM, compared to baseline control (n=5)



*Significant compared to control (n=5)

Figure-1: Time Course of the Onset of thiopental sodium-induced Sleep in Wistar rats in different doses of quinine and artesunate



*Significant values are Mean±SEM ($p \leq 0.05$), compared to control (n=5)

Figure-2: Comparison of duration of thiopental sodium-induced sleep in Wistar rats in pretreated separate doses of Quinine and Artesunate

DISCUSSION

The mean values of the thiopental sodium-induced sleep data showed that the onset time (latency) of the induced sleep decreased significantly ($p \leq 0.05$) in higher doses (32–128 mg/Kg) of quinine, in concomitant increases in the duration of the induced sleep ($p \leq 0.05$, $p \leq 0.01$), also in the larger doses (16–128 mg/Kg). This showed that the animals sleep quicker and stay longer in the induced sleep in higher doses of quinine. The sleep data showed that duration of the thiopental sodium-induced sleep increased significantly ($p \leq 0.05$, $p \leq 0.01$), mainly in larger doses (64–128 mg/Kg) of artesunate. In the light of these observations, it can be deduced that both quinine and artesunate significantly prolonged or potentiated thiopental sodium-induced sleep in rats. Although the pattern of latency of the induced sleep in respect of artesunate administration was not clearly determinable, it nevertheless observably (but not statistically significant) decreased in the larger doses of artesunate.

Since both quinine and artesunate have been shown to cross the blood-brain barrier[7], and since there

have been suggestions that both compounds may have some definable central activity[8,9], it is noteworthy that one major implication of the present observations is the clear indication that, some central transmitter systems traditionally involved in the regulatory mechanism of sleep must be linked with the potentiating effects of quinine and artesunate on thiopental sodium-induced sleep observed in this study. Specifically, the neurotransmitter systems in the brain implicated in the central regulatory mechanism of sleep includes: Serotonin, reported to facilitated the central mechanism for sleep onset[10]; GABA, reported to mediate the central inhibitory processes, hence, inhibits the arousal regions of the brain thereby potentiating sleep and increasing total sleep time[11,12].

In the light of the observations in this study, and in view of these reports and other observations by various workers, it is strongly suggestive that both quinine and artesunate may have properties capable of exerting some promoting influences on the central mechanism of sleep. A number of reports have earlier speculated on possible sedative properties of quinine and artesunate.[1,7,13] Notably among these is a report which noted potentiating and anaesthetic effects of quinine on sodium pentobarbital sleep in mice[14], the report which held that hexobarbital-induced sleeping time in mice was prolonged in doses of artesunate[5].

CONCLUSION

The results of this study are largely consistent with the earlier notion of possible sedative properties of quinine and artesunate. The potentiating influences on thiopental sodium sleep may have been mediated through serotonin mechanism or the central GABA transmitter system mechanism, or both.

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