COMPARATIVE EFFECTS OF HYOSCINE BUTYLBROMIDE AND ATROPINE SULPHATE ON SLEEP ARCHITECTURE IN HEALTHY HUMAN VOLUNTEERS

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Abstract : The changes in sleep architecture, heart rate and respiratory rate to hyoscine butylbromide (HBB), a peripherally acting anticholinergic was studied. These effects were compared with that of atropine sulphate, a drug known to cross the blood brain barrier. The study followed a single blind cross over design with a one week washout period. Atropine sulphate (0.4 mg) and HBB (10 mg) were given intravenously to ten adult healthy male volunteers before sleep onset. Normal saline was used as control. All night sleep polysomnography was done with the standard montage for sleep staging. Respiration and airflow were also monitored. Rapid eye movement (REM) latency was significantly increased with both the drugs whereas the duration of REM sleep was decreased only with atropine. Slow wave sleep (SWS) was also increased significantly by atropine. There was no change in heart rate, or respiratory rate during any of the sleep stages. HBB affects the initiation of REM sleep whereas atropine affects both its initiation and maintenance.

Key words : sleep   polysomnography   sleep stages
     atropine   hyoscine butylbromide

INTRODUCTION

Acetylcholine (ACh) has an important role in wakefulness and vigilance. Cholinergic agonists elicit cortical activation and arousal while anticholinergic agents produce a decrease in vigilance. ACh is the main neurotransmitter implicated in Rapid Eye Movement (REM) sleep (1). During sleep, sympathetic activity decreases while parasympathetic activity increases (2). Anti cholinergic drugs given prior to the onset of sleep could be expected to tilt the balance towards an increased sympathetic drive.

Hyoscine butylbromide (HBB), an anticholinergic agent which does not cross the blood brain barrier (BBB) is commonly used as an antispasmodic and as premedication prior to surgery (3, 4). However, the effect of this drug on sleep is not known. HBB was administered to young,

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healthy male volunteers prior to sleep onset with the aim of studying the alterations in sleep architecture, heart rate and respiratory rates during the various stages of sleep. These effects were compared with atropine sulphate which is known to cross the BBB.

METHODS

The study was conducted in ten adult healthy male volunteers. Subjects in the age group of 18–31 years were included. All the volunteers were free from any systemic disease, including sleep or breathing disorders. All subjects were non-smokers and did not take alcohol on a regular basis. None of the volunteers had consumed alcohol for 48 hours before the study nor were they taking any medication. Written informed consent was obtained from the volunteers prior to the study. The study was approved by the JIPMER Ethics Committee.

The study followed a single blind crossover design, where the subjects were blind to the nature of the drug. All subjects received placebo and the two drugs in a manner which eliminated bias due to order of treatment. A washout period of one week was given between each treatment.

Atropine sulphate (N. I. Pharmaceutical Works Private Ltd, Calcutta) was given in a dose of 0.4 mg intravenously, hyoscine butylbromide (German Remedies Ltd, Goa) was given in a dose of 10 mg intravenously and normal saline was used as the placebo. All drugs were injected in a volume of 0.5 ml into the median cubital vein prior to lights off.

All night sleep polysomnography was done using a computerized polysomnography equipment from Healthdyne Technologies, Marietta, United States of America. The system was connected to an IBM 486 Personal Computer. All sleep data were stored on magneto-optical disks with a capacity of 1.3 Gigabytes. Alice 3 version 1.19 software supplied by Healthdyne was used for analysis of sleep records.

Electroencephalography (EEG), electro-oculography (EOG), air-inflow, chest movements, abdominal movements, oxygen saturation and snoring sounds were recorded during all night sleep. EEG, EOG and EMG were used to stage sleep. ECG was used for calculating heart rate while respiratory rate was recorded from air-inflow, chest and abdominal movements.

Each subject was studied for 4 nights in a split-type air-conditioned, partially sound-proof room, while the recording was done in an adjacent room. The first night was an acclimatization night, where the subjects slept with all electrodes, respiratory belts and microphone fixed. No data was collected on this night since it is known that many subjects suffer from a "first night effect" (5). Data was collected only on subsequent nights. Subjects came to the Sleep Disorders Laboratory at 8.45 P.M. after a light dinner at 8 P.M. The selection of sites for placement of electrodes, and the number of electrodes used for the study were according to the standardized procedure for cardiopulmonary sleep studies as accepted by the Americal Thoracic Society (6).

After the electrodes, thermistor and other measurement belts were fixed to the subject, he was made to lie down on the bed. Ten minutes later, baseline parameters

such as heart rate, respiratory rate, temperature and blood pressure (by sphygmomanometer method) were recorded. Immediately after this the drugs or placebo were injected using standard aseptic techniques. The heart and respiratory rates were once again determined five minutes after the injection. This was calculated directly from the polysomnographic tracing so that the subject would not be disturbed. Lights were switched off immediately after this and the subjects were allowed to sleep undisturbed until 5 A.M. in the morning when lights were switched on. After waking the volunteers up, the heart rate, respiratory rate, blood pressure and temperature were measured again while they were still in bed.

Sleep scoring was done according to guidelines and criteria for staging normal human sleep as given in the standard sleep staging manual (7). An epoch by epoch scoring method was followed with an epoch length of 30 seconds. Each sleep record was manually scored at the end of the study. The results were analyzed using Student's paired "t" test. A statistical software package called "STATISTIX" was used for the calculation. Probability value ≤0.05 was considered to be significant.

Time in bed (TIB) is the total time spent from lights out to lights on while the subject is on the bed. Sleep period time (SPT) is the total time spent from sleep onset to last sleep stage. Total Sleep Time (TST) is the total time spent in REM plus NREM plus body movement during sleep period time. Sleep efficiency is TST divided by TIB multiplied by 100.

RESULTS

The mean (S. D.) age and weight were 22.0 (4.76) years and 58.6 (4.81) kg respectively. There was no difference in the TST and the SPT between the two drug treatments and the placebo. The sleep efficiency was 94.98% for saline, 96.33% for atropine and 92.73% for HBB. These changes were not statistically significant. There was a statistically significant (P<0.01) increase in total time spent in NREM sleep (NREM time) when the subjects received atropine but not HBB when compared to the saline treatment (Fig. 1). The NREM time (total time spent in Stage I, II, III & IV during the whole night) also reflected a significant (P<0.05) increase in the slow wave sleep (SWS) component (Stages III & IV) and a concomitant decrease in time spent in REM sleep (REM time) with atropine treatment (Fig. 1). However, the number of individual REM episodes counted throughout the night was the same for all treatments. On calculating total REM time
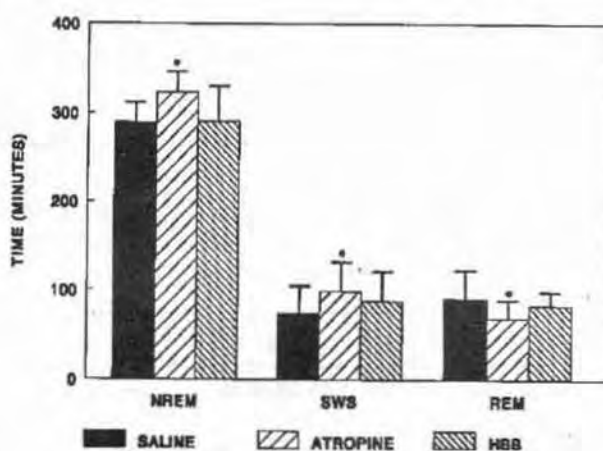

Fig. 1 : Effect of saline, atropine and hyoscine butylbromide on sleep architecture in ten healthy volunteers.

Values are mean ± S.D. *P<0.05 when compared to saline.

as a percentage of total sleep time (mean ± S.D.), it was found that while there was no difference between saline (23.46 ± 8.18) and HBB (21.99 ± 4.57), the percentage was significantly decreased (P<0.03) during atropine treatment (17.28 ± 5.17). There was no change in sleep onset latency (elapsed time from lights out until the first three consecutive epochs of stage I or the first epoch of any other stage) between the various treatments. REM latency (elapsed time from sleep onset to the first epoch of REM sleep) was significantly (P<0.05) prolonged with both atropine and HBB when compared to normal saline (Fig. 2).

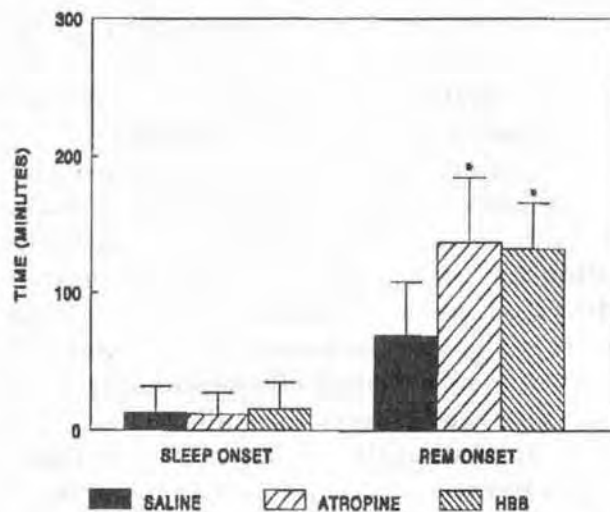There was a significant increase (P<0.001) in heart rate five minutes after

Fig.2 : Effect of saline, atropine and hyoscine butylbromide on sleep latencies in ten healthy volunteers.
Values are mean ± S.D. *P<0.05 when compared to saline.

TABLE I : Effect of normal saline, atropine sulphate and hyoscine butylbromide on heart rate and respiratory rate, during wakefulness, before and after injection of drugs.

Drugs	Heart Rate/min		Respiratory Rate/min	
	Before	After	Before	After
Saline 0.5 ml iv	76.30±11.06	76.67±11.92	22.20±3.82	18.82±4.25
Atropine 0.4 mg iv	71.60±10.62	72.89±10.57	22.90±2.84	20.13±3.06
Hyoscine 10 mg iv	75.00±11.79	102.20±8.99*	23.10±3.60	18.65±3.21

Values are mean ± S.D. in 10 normal human volunteers.
*P< 0.001 compared to normal saline as well as basal value (before injection).

TABLE II : Effect of normal saline, atropine sulphate and hyoscine butylbromide on heart rate during various sleep stages in normal human volunteers.

Drugs	Respiratory Rate/min						
	Baseline	Stage I	Stage II	Stage III	Stage IV	REM	NREM
Saline 0.5 ml iv	76.30±11.06	68.52±9.18	66.21±11.31	66.86±9.28	68.08±10.65	63.87±6.84	65.56±8.49
Atropine 0.4 mg iv	71.60±10.62	66.11±12.00	61.45±8.27	64.09±8.34	66.60±9.02	62.27±8.57	62.94±7.95
Hyoscine 10 mg iv	75.00±11.79	73.58±15.83	65.08±10.77	66.00±10.45	66.07±10.60	65.15±8.48	65.74±10.02

Values are mean ± S.D. in 10 subjects.

TABLE III : Effect of normal saline, atropine sulphate and hyoscine butylbromide
on respiratory rate during the various stages of sleep.

Drugs	Respiratory Rate / min				
	Stage I	Stage II	Stage III	Stage IV	REM
Saline 0.5 ml iv	16.24±3.70	16.44±2.70	16.00±2.48	16.64±2.36	16.64±2.04
Atropine 0.4 mg iv	16.10±3.92	16.04±2.44	16.30±2.26	16.80±2.08	16.60±2.54
Hyoscine 10 mg iv	15.64±3.80	16.04±3.10	15.94±2.12	16.60±2.72	17.54±3.56

Values are mean ± S.D. in 10 subjects.

the injection of HBB but not with atropine when compared to the saline controls (Table I). However, once sleep onset occurred there was no difference in heart rate (Table II) or in the respiratory rates (Table III) with either of the two treatments during any stage of sleep.

DISCUSSION

Anticholinergics are known to decrease total REM time and increase REM latency (8). Our results show that total REM time is decreased with atropine but not with HBB whereas both drugs increased REM latency. Atropine which crosses the BBB, probably affects mechanisms which control the maintenance of REM sleep. Since HBB does not cross the BBB there was no appreciable effect on the duration of total REM sleep. There was no modification of the sleep pattern in man when they used methscopolamine bromide, a quarternary ammonium antimuscarinic compound, which does not cross the BBB (9). This further reiterates the fact that mechanisms for the initiation and maintenance of REM sleep may be separate, independent and in different parts of the CNS. It is possible to hypothesize that the mechanism or stimuli which initiates REM sleep is probably situated at a site outside the BBB, while the site which maintains REM sleep is probably protected by the BBB to a certain extent. At the present time the site for initiation and maintenance of sleep have not been precisely located, though it has been postulated that an extrinsic cholinergic input "primes" the cholinoceptive REM sleep neurons in the medial pontine reticular formation. These neurons in turn may trigger the discrete nuclei individually responsible for the various components of REM sleep such as muscle atonia, eye movements etc., (8).

In the present study, SWS is increased significantly in the atropine treated group. This is contrary to an earlier finding where the percentage of SWS was decreased in a segment of sleep timed to fall between 2 and 4 hours from sleep onset (10). However, in the same study, when the whole night was considered, there was no difference. Since SWS is abundant only in the early part of the night, a segmental division of the night into 2 hour slots may not reveal any increase in this stage in the second hour slot. The implications of prolonged SWS may be twofold. Firstly, SWS is closely linked with the secretion of growth hormone (11). Would this prolongation result in longer periods of GH secretion? Secondly, SWS is a stage associated with dual autonomic tone

(12). The association of SWS with dual autonomic tone is derived from observations in animals that cardiac arrhythmias are more common and abundant in this period (12). It is possible that the increase in SWS caused by an anticholinergic drug like atropine may put those subjects who are vulnerable to cardiac rhythm abnormalities at a greater risk towards the development of arrhythmias. From this study we could conclude that HBB does not modify sleep architecture significantly and therefore may be preferred over atropine as an anticholinergic agent in patients with cardiac disease.

The injection of clinical doses of atropine into humans are known to cause an initial bradycardia without changes in BP or cardiac output. This vagal effect was due to blockade of M1 receptors on postganglionic parasympathetic neurons, thereby relieving the inhibitory effects of synaptic ACh on release of transmitter (13). In our study, injection of HBB but not atropine caused a very significant increase in heart rate prior to the onset of sleep. This may mean that the dose of atropine necessary to produce an increase in heart rate needs to be higher whereas the dose of HBB is sufficient. This is in accordance with an earlier study using 3 different doses of atropine (10). A dose of 0.25 mg of atropine failed to elicit a change in heart rate whereas larger doses of 5 mg and 10 mg caused an initial bradycardia and a tachycardia which lasted till the next morning. The effect of HBB seems to be very transient and is probably related to the high plasma levels reached immediately after the injection of the drug intravenously.

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