Drug and Alcohol Dependence, 6 (1980) 247 - 262

ACUTE HEROIN ABSTINENCE IN MAN
III. EFFECT UPON WAKING AND SLOW WAVE SLEEP*

RICHARD C. HOWE, JERRY L. PHILLIPS and FREDERICK W. HEGGE†

Department of Physiology, Eastern Virginia Medical School, Norfolk, Virginia 23501, and †Department of Military Medical Psychophysiology, Walter Reed Army Institute of Research, Washington, DC 20012 (U.S.A.)

(Received May 20, 1980; in revised form July 3, 1980)

Summary

The purpose of this study was to evaluate the effects of acute heroin withdrawal on waking behavior and slow wave sleep. Data were collected from drug-dependent patients who were using pure heroin and from drug-free controls. All data were recorded on a 24-hour per day basis for 5 - 7 consecutive days. EEG records were manually scored according to standard criteria. The heroin-dependent patients during withdrawal showed approximately a 26% decrease in slow wave sleep and an 18% increase in waking behavior. The awake state in the heroin-dependent patients during withdrawal also displayed an increase in number of episodes and number of state shifts, and a decrease in duration and sleep onset latency. In addition, the slow wave sleep categories during withdrawal generally showed an increase in sleep onset latency and interstate interval and a decrease in number of episodes. These results indicate that heroin withdrawal is associated with a marked disruption of the central nervous system mechanisms responsible for maintenance of the normal sleep–waking cycle. Analyses of the pattern of this disruption will further aid in understanding the withdrawal syndrome.

Introduction

Several investigators have noted the effect of opiate drugs on the electroencephalogram (EEG) and sleep in animals [1 - 11]. The effect of morphine and/or narcotic withdrawal on rapid eye movement (REM) sleep has been examined in several studies [1 - 6, 8, 10 - 13]. In general, these animal studies have shown a suppression of REM sleep during the acute withdrawal phase.

*Send reprint requests to: Dr. Richard C. Howe, Department of Physiology, Eastern Virginia Medical School, P.O. Box 1980, Norfolk, Virginia 23501, U.S.A.

However, detailed information regarding the effects of opiate withdrawal on slow wave (non-REM) sleep in experimental animals is not readily available. One study noted a decrease in the mean EEG voltage output for slow wave sleep during morphine withdrawal [2]. Khazan [4] reported that during withdrawal, slow wave sleep increased in the first 4 - 6 hours then progressively decreased and was finally replaced by an hyperirritability stage. Another investigator noted that cocaine caused a significant decrease in non-REM sleep [9].

Some of the effects of opiates on sleep in experimental animals have also been reported in humans. Kay [14] reported that during chronic morphine administration, early delta (slow wave) sleep decreased and waking increased. Lewis *et al.* [15] noted that heroin administration resulted in more frequent appearances of drowsiness or wakefulness and an increased delay to the onset of the first stage II of the night. However, these studies only reported on the changes in slow wave sleep during morphine or heroin administration and not during the withdrawal phase. In recent reports from this laboratory, acute heroin withdrawal was associated with a general suppression of total sleep [16] and a greater suppression of REM sleep [17].

The data in this study are unique in that they were collected from young military personnel who were addicted to pure heroin, had short heroin use histories, used few other drugs concurrently, and were generally in good health [18 - 20]. Thus, the setting of this study provided an excellent experimental model to evaluate heroin withdrawal without the numerous complications associated with stateside drug users. The purpose of this particular study was to examine the effects of acute heroin abstinence on waking behavior and slow wave sleep in humans. This study is part of a comprehensive investigation using the same subjects as reported on in previous papers [16, 17, 20 - 22].

Methods

The electrophysiological data were obtained from twenty heroin-dependent patients and five drug-free control subjects as previously reported [16, 17]. All data were recorded on a 24-hour per day basis for 5 - 7 continuous days and totaled 2602 hours of recording time. Several heroin-dependent patients voluntarily withdrew from the study after one or two days. The heroin use history for the drug users has already been published [16, 17, 20, 21]. These patients were selected from heroin users identified in the Army drug screening program. All patients were covered by the provisions of the Army Exemption Policy which established voluntary rehabilitation programs for drug users. No drugs were given throughout this study. Informed consent was obtained from all patients and matched controls who voluntarily participated in this project.

The electrophysiological parameters recorded in this study included the electroencephalogram (EEG), electrooculogram (EOG), electrocardiogram

(EKG), electropneumogram (EPG), and electrogastrogram (EGG). The EEG and EOG electrodes were standard EEG electrodes (Grass) and were attached to the skin by a small gauze patch covered with collodion. The EEG electrode was placed over the occipital cortex in the standard 0–2 position and the EOG lead was located one centimeter beyond the lateral orbital ridge of the right eye.

The recording environment was a typical hospital ward and all subjects were permitted freedom of movement within the confines of the ward. Blood drawings and clinical evaluations were performed on all subjects three times daily at 0600, 1000, and 2200 hours for other aspects of this study [20 - 22]. Continuous behavioral observations were also noted on "subject log sheets" throughout the entire recording time (5 - 7 days). The results concerning these behavioral observations have been published previously [16].

All EEG records were manually scored into the standard awake and sleep states [23] in one-minute epochs. During the analysis, it became necessary to add another behavioral category which we called "awake-with-alpha" state. This state was associated with the heroin-dependent patients lying in bed with their eyes closed attempting to sleep, but remaining awake and thus producing long trains of alpha rhythm. Each recording day was defined from midnight to midnight, day 0 being the day the subjects entered the study and day 1 the first complete 24-hour day. The raw minute by minute EEG data were smoothed for certain data analyses (see below). In the smoothed files, all intervals of four minutes or less were removed via a low-pass redistribution technique [24]. The raw minute-by-minute EEG data were used to calculate total minutes and number of state shifts. Smoothed EEG data files were used for determination of average state durations, number of state episodes, latencies of the various states from sleep onset (first occurrence of stage II sleep) and interstate intervals. Only complete 24-hour days were included in the data analysis. A two-tailed *t*-test between heroin users and control subjects for days 2 - 5 was applied to all data (population variances unknown but assumed equal). Additional methodological details have been reported previously [16, 17].

Results

The data presented below have been divided into several sections, each section concerning a particular sleep parameter across all the awake and slow wave sleep categories for both the heroin-dependent patients during withdrawal and the control subjects. As mentioned earlier, each recording day was defined from midnight to midnight. On day 1, the control subjects showed a general disruption of sleep associated with the "first night effect". However, the heroin users did not begin withdrawal until approximately half way through day 1, after they had slept and/or "nodded out" through the initial part of day 1. Over-all, the heroin-dependent patients showed the

largest total amount of sleep on day 1. Therefore, in order to avoid these first day effects, the mean data values below were from recording days 2 through 5.

General sleep patterns

The heroin-dependent patients during withdrawal showed a disruption of sleep and frequent attempts at sleeping throughout the 24-hour day. Figure 1 shows a typical 24-hour sleep–waking plot for a heroin-dependent patient on withdrawal day 4. More severely disrupted patterns were observed for the heroin-dependent patients on days 2 and 3 of withdrawal. Figure 2 shows a 24-hour EEG plot for a control subject on day 4. The controls commonly slept in a solid block of time starting sometime after midnight to approximately 1000 hours in the morning. The awake period around 0600 was associated with the clinical evaluation performed on all subjects for other aspects of the study.

Total minutes

The heroin-dependent patients during withdrawal days 2 - 5 showed a 15.4% increase in waking behavior as compared to controls (1135.8 *vs.* 984.1 mins). The mean total minutes presented at the bottom of Table 1 were reported previously [16]. The heroin-dependent patients also showed a 79.8% increase in awake-with-alpha per day during withdrawal (71.2 *vs.* 39.6 mins). Combining both awake categories, the heroin-dependent patients displayed a total of 1207.0 minutes of waking behavior per day during withdrawal, compared to 1023.7 minutes in the control subjects. The slow wave sleep categories showed a general reduction in total minutes during withdrawal days 2 - 5. Stage II was significantly reduced by 25.1% in the heroin-dependent patients during withdrawal relative to the controls (175.9 *vs.* 234.8 mins). Combining slow wave sleep stages II, III and IV, the heroin-dependent patients during withdrawal averaged 217.5 total minutes compared to 294.5

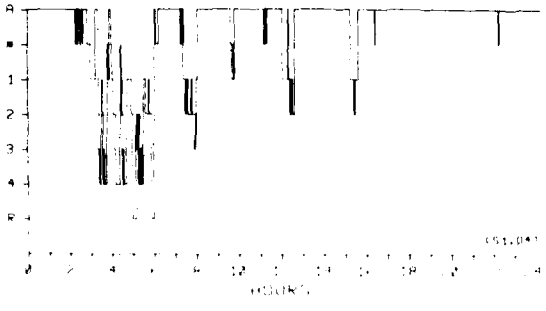

Fig. 1. Twenty-four hour plot of sleep–waking states for a heroin-dependent patient during withdrawal. A = awake; * = awake-with-alpha; 1-4 = slow wave sleep stages I - IV; R = rapid eye movement (REM) sleep.

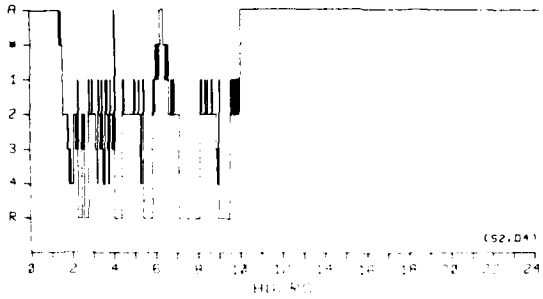

Fig. 2. Twenty-four hour plot of sleep–waking states for a control subject. Abbreviations are the same as described for Fig. 1.

total minutes of slow wave sleep in the controls. This represents a 26.1% decrease in slow wave sleep during withdrawal.

On recording day 1, the control subjects showed 1025.5 minutes of awake *versus* 878.7 minutes in the heroin-dependent patients. The heroin-dependent patients on day 1 also displayed more total minutes in all slow wave sleep categories than the controls. These differences on day 1 are due to the "first night effect" in the control subjects and to the "narcotic high" or "nodding out" condition in the heroin-dependent patients.

Duration

The heroin-dependent patients during withdrawal days 2 - 5 showed an average awake duration of 141.8 minutes compared to 229.7 minutes in the controls (Table 2). The awake-with-alpha category displayed an increase in duration over control values to approximately 12.4 minutes during withdrawal days 2 - 4. The heroin-dependent patients also showed a small decrease in duration of stage II sleep to 24.5 minutes *versus* 26.6 minutes in the control subjects. No significant differences were observed in the other behavioral categories during days 2 - 5. On day 1, the duration of awake and awake-with-alpha was shorter in the heroin-dependent patients as compared to average control values.

Number of state episodes

This category examined the number of distinct occurrences of each behavioral category per 24-hour day. The heroin-dependent patients during withdrawal days 2 - 5 averaged 7.5 awake and 4.8 awake-with-alpha episodes per day (Table 3). The control subjects showed 4.0 awake and 3.6 awake-with-alpha episodes per day for this same time period. During slow wave sleep, 8.0 and 1.9 episodes were observed for the heroin-dependent patients during withdrawal for stages II and III, respectively, compared to 9.4 and 2.8 episodes for the controls. Slow wave sleep stage IV similarly tended to occur less frequently in the heroin-dependent patients during withdrawal. By contrast, all slow wave sleep stages in the heroin-dependent patients showed a higher number of occurrences on day 1 during the "narcotic high" or "nodding out" phase as compared to the controls.

TABLE 1

Effect of heroin withdrawal on waking and slow wave (non-REM) sleep in humans
All values are total minutes per 24-hour day. The mean total minutes values were reported previously [16].

Day	Awake		Awake-with-alpha		Stage I		Stage II		Stage III		Stage IV	
	C	E	C	E	C	E	C	E	C	E	C	E
1	1025.5	878.7	25.0	53.7	61.3	82.5	240.8	305.4	19.0	49.3	32.7	50.0
2	1023.7	1149.2	50.0	84.3	69.7	64.6	226.7	167.8	26.7	22.2	19.7	10.2
3	963.0	1139.8	31.0	86.2	67.7	64.8	258.3	178.1	30.3	19.7	29.3	14.4
4	996.7	1129.1	39.0	70.9	65.3	54.2	204.3	177.1	36.0	30.1	23.3	18.8
5	953.0	1125.0	38.3	43.4	65.5	47.9	250.0	180.5	30.3	23.8	43.3	27.0
Mean[†]	984.1	1135.8***	39.6	71.2*	67.1	57.9°	234.8	175.9**	30.8	24.0°	28.9	17.6
S.D.	32.3	10.9	7.8	19.7	2.1	8.3	24.4	5.6	3.8	4.4	10.4	7.2

C = control subjects; E = drug users.
[†] Days 2 - 5.
$^{\circ}p < 0.10$.
$^{*}p < 0.05$.
$^{**}p < 0.01$.
$^{***}p < 0.001$.

TABLE 2

Effect of heroin withdrawal on duration of waking and slow wave sleep states in humans
Values are average state durations (in minutes) per 24-hour day.

Day	Awake		Awake-with-alpha		Stage I		Stage II		Stage III		Stage IV	
	C	E	C	E	C	E	C	E	C	E	C	E
1	287.7	105.8	10.8	7.8	13.3	8.1	29.6	24.6	7.5	10.3	20.8	20.9
2	225.7	137.4	9.5	12.2	10.4	9.3	26.9	23.8	9.4	12.4	13.3	26.7
3	280.4	122.7	10.3	12.4	7.9	8.4	26.4	23.4	10.0	9.8	15.3	10.5
4	240.5	142.6	11.5	12.7	8.0	8.6	27.6	25.1	12.8	10.1	11.6	12.1
5	172.1	164.5	10.5	10.1	9.1	7.8	25.4	25.8	7.0	10.6	12.5	15.4
Mean[†]	229.7	141.8[**]	10.5	11.9[°]	8.9	8.5	26.6	24.5[*]	9.8	10.8	13.2	16.2
S.D.	44.8	17.3	0.8	1.2	1.2	0.6	0.9	1.1	2.4	1.3	1.6	7.3

C = control subjects; E = drug users.

[†]Days 2 - 5.

[°]$p < 0.10$.

[*]$p < 0.05$.

[**]$p \leq 0.02$.

TABLE 3

Effect of heroin withdrawal on number of episodes of waking and slow wave sleep states
Values are average number of occurrences of a state per 24-hour day.

Day	Awake		Awake-with-alpha		Stage I		Stage II		Stage III		Stage IV	
	C	E	C	E	C	E	C	E	C	E	C	E
1	4.0	8.7	1.5	3.3	2.5	5.4	10.0	14.7	1.5	4.1	1.5	2.4
2	4.3	7.9	4.7	5.2	4.0	4.7	9.3	8.0	2.7	1.6	1.3	0.3
3	3.3	8.7	2.3	6.0	5.3	4.8	10.7	8.7	2.7	1.4	2.0	1.5
4	4.0	7.5	3.7	4.6	4.0	3.8	8.0	7.9	3.0	2.7	1.7	1.6
5	4.3	5.9	3.7	3.3	2.3	2.7	9.7	7.5	2.7	1.9	4.0	1.5
Mean[†]	4.0	7.5**	3.6	4.8	3.9	4.0	9.4	8.0°	2.8	1.9*	2.3	1.2
S.D.	0.5	1.2	1.0	1.1	1.2	1.0	1.1	0.5	0.2	0.6	1.2	0.6

C = control subjects; E = drug users.

[†] Days 2 - 5.

° $p < 0.10$.

* $p < 0.05$.

** $p < 0.01$.

Latency from sleep onset

Latency from sleep onset was defined as the time between the first occurrence of stage II sleep and the next occurrence of a state. The awake category showed a latency from sleep onset of 77.5 minutes in the heroin-dependent patients during withdrawal and 175.8 minutes in the control subjects (Table 4). Latency from sleep onset for the awake-with-alpha category was 87.3 minutes in the drug users during withdrawal compared to 202.3 minutes in the controls. Slow wave sleep stages III and IV displayed a sleep onset latency of 55.8 and 85.2 minutes in the heroin-dependent patients on withdrawal days 2 - 5. For this same time period, the control subjects showed a latency of 19.4 and 30.5 minutes for stages III and IV, respectively. No significant differences in sleep onset latency were observed for stages I and II, although both categories tended to show longer latencies in the heroin-dependent patients than in the control subjects.

Interstate intervals

Analysis of the interstate intervals revealed no distinct differences between the heroin-dependent patients and control subjects for all behavioral categories except stage II sleep (Table 5). The heroin-dependent patients during withdrawal days 2 - 5 showed an average interstate interval for stage II of 87.9 minutes compared to 59.6 minutes in the control subjects. Analysis of the data in this section was particularly difficult due to the large variations observed in the interstate intervals in both control and heroin-dependent patients. Stage II slow wave sleep showed the least amount of variation of all the behavioral categories. In general, the heroin-dependent patient during withdrawal tended to display shorter interstate intervals in the awake and awake-with-alpha categories and longer intervals in the slow wave sleep states when compared to the control subjects.

Number of state shifts

The data in this section represent the number of times a subject entered and/or left each behavioral category. The control subjects averaged 17.4 awake and 20.9 awake-with-alpha shifts per 24-hour period for recording days 2 - 5 (Table 6). During this same period, the heroin-dependent patients undergoing withdrawal showed an average of 48.9 awake and 48.7 awake-with-alpha shifts per day. An average of 53.1 stage I shifts were observed for the heroin-dependent patients during withdrawal compared to 63.7 shifts in the control subjects. Stage II also tended to show a smaller number of shifts in the heroin-dependent patients than in the controls, although not statistically significant. Slow wave sleep stages III and IV showed no significant differences in state shifts between the control subjects and heroin-dependent patients.

On recording day 1, the control subjects showed a greater number of state shifts in awake, awake-with-alpha, stage I and stage II as compared to their averaged values for days 2 - 5. The heroin-dependent patients on day 1 showed no differences in number of state shifts in the awake and awake-

TABLE 4

Effect of heroin withdrawal on latency from sleep onset
Values are average latency from sleep onset (in minutes) calculated from first occurrence of stage II sleep.

Day	Awake		Awake-with-alpha		Stage I		Stage II		Stage III		Stage IV	
	C	E	C	E	C	E	C	E	C	E	C	E
1	288.0	110.9	223.5	265.7	45.3	19.9	31.3	18.5	13.0	85.3	23.0	120.4
2	220.3	42.1	178.7	52.7	15.0	11.8	17.0	12.2	17.7	42.9	38.0	88.8
3	216.7	47.5	306.0	94.2	13.3	16.4	14.3	25.7	17.3	88.1	24.3	89.3
4	94.3	98.4	134.0	64.2	16.7	26.6	8.0	20.8	29.7	28.6	40.7	59.3
5	172.0	122.0	190.3	138.1	14.3	31.5	15.3	19.2	12.7	63.4	19.0	108.6
Mean[†]	175.8	77.5[*]	202.3	87.3[*]	14.8	21.6	13.7	19.5	19.4	55.8[*]	30.5	85.2[**]
S.D.	58.6	39.0	73.3	38.1	1.4	9.1	3.9	5.6	7.3	25.9	10.5	22.8

C = control subjects; E = drug users.

[†] Days 2 - 5.

[*] $p < 0.05$.

[**] $p < 0.01$.

TABLE 5

Effect of heroin withdrawal on interstate intervals
Values are average intervals (in minutes) calculated from onset of a particular state episode to onset of the next episode.

Day	Awake		Awake-with-alpha		Stage I		Stage II		Stage III		Stage IV	
	C	E	C	E	C	E	C	E	C	E	C	E
1	283.5	201.5	253.0	250.0	272.0	141.3	72.8	70.3	0	98.9	14.0	118.3
2	186.3	205.2	174.0	178.1	150.1	113.2	56.6	98.5	92.3	154.0	89.0	91.0
3	214.7	139.0	176.0	103.7	60.4	147.8	55.7	100.9	90.4	96.8	31.7	53.6
4	287.7	194.6	156.3	191.1	96.0	140.5	68.0	80.4	141.0	65.3	78.1	68.1
5	203.0	152.3	219.0	117.0	120.8	167.1	57 9	71.7	81.3	140.4	77.9	81.4
Mean†	222.9	172.8	181.3	147.5	106.8	142.2	59.6	87.9**	101.3	114.1	69.2	73.5
S.D.	44.7	32.1	26.6	43.5	38.0	22.3	5.7	14.1	26.9	40.7	25.5	16.3

C = control subjects; E = drug users.

†Days 2 - 5.

**$P < 0.01$.

TABLE 6

Effet of heroin withdrawal on number of state shifts of waking and slow wave sleep states
Values are the average number of entries to and exits from each state per 24-hour day.

Day	Awake		Awake-with-alpha		Stage I		Stage II		Stage III		Stage IV	
	C	E	C	E	C	E	C	E	C	E	C	E
1	21.0	55.7	30.5	54.0	75.0	80.1	74.5	95.0	20.7	43.4	14.0	19.3
2	18.0	61.3	22.0	60.8	58.0	56.1	60.7	61.7	24.0	30.0	11.3	7.4
3	18.3	54.4	21.0	54.5	68.0	61.3	72.0	56.3	28.0	19.8	14.0	10.9
4	15.0	46.8	21.7	47.5	66.7	47.4	60.0	53.5	25.3	27.2	15.3	15.8
5	18.3	32.9	18.7	32.1	62.0	47.4	59.3	51.2	29.3	21.6	20.0	10.7
Mean[†]	17.4	48.9**	20.9	48.7**	63.7	53.1*	63.0	55.7°	26.7	24.7	15.2	11.2
S.D.	1.6	12.2	1.5	12.3	4.6	6.9	6.0	4.5	4.8	4.8	3.6	3.5

C = control subjects; E = drug users.
[†] Days 2 - 5.
° $P < 0.10$.
* $P < 0.05$.
** $P < 0.01$.

with-alpha categories when compared to the averaged values for days 2 - 5. The heroin-dependent patients also displayed the greatest number of state shifts for slow wave sleep stages I - IV on day 1 during the "narcotic high" condition.

Discussion

Several animal studies have reported a general decrease in slow wave sleep associated with morphine and/or cocaine withdrawal [2, 4, 9]. Previous human studies have reported changes in slow wave sleep only during morphine or heroin administration and not during withdrawal [14, 15]. The results of this study have shown a significant reduction of slow wave sleep associated with heroin withdrawal in humans.

The decrease in slow wave sleep during heroin withdrawal was related primarily to a decrease in total minutes of stages II, III, and IV. Stage II sleep also showed a decrease in duration and an increase in interstate interval during withdrawal from heroin. A decrease in number of state episodes and an increase in sleep onset latency was also observed for slow wave sleep stages III and IV together. These results suggest that the heroin-dependent patients during withdrawal were unable to maintain the sleep condition, thus displaying a disruption of the sleep–waking cycle. The inability to maintain the sleep state would similarly disrupt REM sleep, as was reported recently from this laboratory [17].

Simultaneously with the decrease in slow wave sleep, the heroin-dependent patients during withdrawal also showed an increase in wakefulness. The awake category increased by approximately 15% and awake-with-alpha increased almost 80%, whereas both awake categories together increased by approximately 18%. Khazan [4] reported an increase in wakefulness in rats during morphine withdrawal. However, specific data on total minutes or percentage changes in either wakefulness or slow wave sleep were not included in that study. These results are consistent with the disruption of sleep and increase in wakefulness associated with morphine withdrawal in experimental animals [2, 4, 9].

Even though the heroin-dependent patients during withdrawal showed an increase in total waking, the duration of individual awake episodes decreased. Additionally, the awake state during withdrawal displayed an increase in number of episodes and number of state shifts, and a decrease in interstate interval and latency from sleep onset. These results suggest that the normal pattern of waking behavior is similarly being disrupted. Indeed, the heroin-dependent patients in this study showed frequent attempts at sleeping throughout the 24-hour day, whereas the controls generally slept during one major block. This disruption of normal waking patterns is probably secondarily related to the disruption of sleep and the resultant attempts by the heroin-dependent patients to "regain" some of the lost sleep.

Several of the results reported in this study associated with heroin withdrawal are similar to those observed during morphine and/or heroin administration. In the cat, morphine administration has been shown to increase wakefulness [3]. The initial phase of morphine administration in the rat decreased slow wave sleep and almost eliminated REM sleep [25]. Kay [14] reported an increase in waking and a decrease in slow wave sleep during administration of morphine in humans. Heroin administration was associated with an increased frequency of shifts to stage I sleep (drowsiness) or wakefulness [15]. In this study, the acute phase of heroin withdrawal showed a decrease in slow wave sleep and an increase in wakefulness. In a related report, we also noted that REM sleep was markedly reduced during heroin withdrawal [17]. Thus, it appears that the disruptive effects of morphine upon the central nervous system may be of a similar nature during both the initial administration phase and acute withdrawal phase.

In addition to the results concerned with the withdrawal phase, several interesting observations were also noted in this study on recording day 1. This day was associated with the "first night effect" in the control subjects and the "narcotic high" or "nodding out" phase in the heroin-dependent patients. Most of these patients entered the study shortly after taking their last dose of heroin and subsequently "nodded out" and/or went to sleep (distinction between these two conditions at this phase was not possible). Thus, the heroin-dependent patients displayed the largest amount of total sleep on day 1. In these patients, slow wave sleep stages III and IV were particularly high during this period. In man, single doses of opioids have been reported tc produce an increased delta activity in the EEG [26]. Chronic morphine administration in humans has been shown to increase the number and total minutes of delta EEG activity [14]. Similarly, morphine injections in the rat were followed by stuporous behavior and high-voltage slow waves in the EEG [5, 25]. Prolonged episodes of slow wave sleep and REM sleep also predominated in the time interval before injection of morphine in dependent rats [25]. Thus, the increased amount of slow wave sleep reported in this study on day 1 may be related to the increase in drowsiness and increase in EEG delta activity associated with administration of opiates.

In addition, the heroin-dependent patients on day 1 displayed an increase in the number of state episodes and number of state shifts for all slow wave sleep categories. Total minutes of awake, duration of awake episodes and duration of awake-with-alpha episodes were also reduced in these patients on day 1. These results further indicate that the heroin-dependent patients had less waking and more sleep on day 1 and, thus, had more opportunities for a greater number of state shifts and interstate intervals to occur.

In general, the results of this study showed a significant reduction of slow wave sleep and an increase in waking behavior associated with heroin withdrawal in humans. These results are particularly important in the overall understanding of the withdrawal syndrome as the drug-dependent pa-

tients in this study were using pure heroin. Analyses of the sequential pattern of sleep–waking changes associated with heroin withdrawal are needed to further our understanding of this phenomenon.

Acknowledgements

This research was supported by National Institute of Drug Abuse Grant DA01613 and U.S. Army Medical Research and Development Command Contract DAMD-17-75-C-5030.

References

1 B. K. Colasanti, Involvement of brain biogenic amines in the electroencephalographic and behavioural effects of morphine in post-addict rats. *Neuropharmacology, 16* (1977) 235 - 240.
2 B. Colasanti, A. Kirchman and N. Khazan, Changes in the electroencephalogram and REM sleep time during morphine abstinence in pellet-implanted rats. *Res. Commun. Chem. Pathol. Pharmacol., 12* (1975) 163 - 172.
3 S. D. Echols and R. E. Jewett, Effects of morphine on sleep in the cat. *Psychopharmacologia, 24* (1972) 435 - 448.
4 N. Khazan, The implication and significance of EEG and sleep–awake activity in the study of experimental drug dependence on morphine. In S. Ehrenpreis and A. Neidle (eds.), *Methods in Narcotics Research*, Marcel Dekker, New York, 1975, pp. 173 - 215.
5 N. Khazan and B. Colasanti, EEG correlates of morphine challenge in post-addict rats. *Psychopharmacologia, 22* (1971) 56 - 63.
6 N. Khazan and B. Colasanti, Protracted rebound in rapid eye movement sleep time and electroencephalogram voltage output in morphine-dependent rats upon withdrawal. *J. Pharmacol. Exp. Ther., 183* (1972) 23 - 30.
7 N. Khazan and C. H. Sawyer, Mechanisms of paradoxical sleep as revealed by neurophysiologic and pharmacologic approaches. *Psychopharmacologia, 5* (1964) 457 - 466.
8 P. Nash, B. Colasanti and N. Khazan, Long-term effects of morphine on the electroencephalogram and behavior of the rat. *Psychopharmacologia, 29* (1973) 271 - 276.
9 R. M. Post, Clinical aspects of cocaine: Assessment of acute and chronic effects in animals and man. In S. J. Mule (ed.), *Cocaine: Chemical, Biological, Clinical, Social, and Treatment Aspects*, CRC Press, Cleveland, 1976, pp. 203 - 215.
10 G. A. Young, J. E. Moreton, L. Meltzer and N. Khazan, REM sleep distributions in post-addict rats relapsing to morphine self-administration: Effects of Naloxone subcutaneous pellets. *Res. Commun. Chem. Pathol. Pharmacol., 11* (1975) 355 - 363.
11 G. A. Young, J. E. Moreton, L. T. Meltzer and N. Khazan, L-Alpha-acetylmethadol (LAAM), methadone and morphine abstinence in dependent rats: EEG and behavioral correlates. *Drug Alcohol Depend., 2* (1977) 141 - 148.
12 B. Colasanti and N. Khazan, Antagonism of the acute electroencephalographic and behavioral effects of morphine in the rat by depletion of brain biogenic amines. *Neuropharmacology, 12* (1973) 463 - 469.
13 B. Colasanti and N. Khazan, Agonistic properties of narcotic analgesics and antagonists on the electroencephalogram and behavior in the rat and their reversal by naloxone. *Neuropharmacology, 12* (1973) 619 - 627.
14 D. C. Kay, Human sleep during chronic morphine intoxication. *Psychopharmacologia, 44* (1975) 117 - 124.
15 S. A. Lewis, I. Oswald, J. I. Evans, M. D. Akindele and S. L. Tompsett, Heroin and human sleep. *Electroencephalogr. Clin. Neurophysiol., 28* (1970) 374 - 381.

16 R. C. Howe, F. W. Hegge and J. L. Phillips, Acute heroin abstinence in man: I. Changes in behavior and sleep. *Drug Alcohol Depend.*, 5 (1980) 341 - 356.
17 R. C. Howe, F. W. Hegge and J. L. Phillips, Acute heroin abstinence in man: II. Alterations in rapid eye movement (REM) sleep. *Drug Alcohol Depend.*, *6* (1980) 149 - 161.
18 S. L. Baker, U. S. Army heroin abuse identification program in Viet Nam: Implications for a methadone program. *Am. J. Public Health*, *62* (1972) 857 - 860.
19 L. N. Robins, A follow-up of Viet Nam drug users. *Special Action Office for Drug Abuse Prevention Monograph, Series A*, Number 1, Executive Office of the President, Washington, DC, 1973.
20 M. G. Robinson, H. W. Siegel, R. C. Howe, N. W. Ream and F. W. Hegge, Biochemical and clinical findings during acute heroin withdrawal in Viet Nam: A preliminary report. In J. M. Singh and H. Lal (eds.), *Drug Addiction*, Vol. 4, Futura Publishing Company, Mount Kisco, New York, 1974, pp. 79 - 95.
21 M. G. Robinson, R. C. Howe, N. W. Ream, H. W. Siegel and F. W. Hegge, Acute heroin withdrawal in Viet Nam. An immunochemical evaluation of excretion. *Clin. Pharmacol. Ther.*, *16* (1974) 303 - 309.
22 M. G. Robinson, R. C. Howe, J. G. Varni, N. W. Ream and F. W. Hegge, Assessment of pupil size during acute heroin withdrawal in Viet Nam. *Neurology*, *24* (1974) 729 - 732.
23 A. Rectschaffen and A. Kales (eds.), *A Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects, (NIH Publication* No. 204), U.S. Government Printing Office, Washington, DC, 1968.
24 R. C. Howe, L. E. Byrd and J. L. Phillips, A method for transition smoothing of sleep–waking states, *Sleep*, *1* (1979) 445 - 449.
25 N. Khazan, J. R. Weeks and L. A. Schroeder, Electroencephalographic, electromyographic and behavioral correlates during a cycle of self-maintained morphine addiction in the rat. *J. Pharmacol. Exp. Ther.*, *155* (1967) 521 - 531.
26 J. H. Jaffe and W. R. Martin, Narcotic analgesics and antagonists. In L. S. Goodman and A. Gilman (eds.), *The Pharmacological Basis of Therapeutics*, 5th edn., Macmillan, New York, 1975, pp. 245 - 283.