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Chronic Morphine Administration in Cats: Effects on Sleep and EEG

ISABEL DE ANDRÉS[1] AND AMELIA CABALLERO

Depto. Morfología, Fac. Medicina, Universidad Autónoma de Madrid, Madrid, 28029, Spain

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DE ANDRÉS, I. AND A. CABALLERO. *Chronic morphine administration in cats: Effects on sleep and EEG.* PHARMACOL BIOCHEM BEHAV 32(2) 519–526, 1989.—Sleep-wakefulness and EEG responses to a chronic morphine treatment (2 mg/kg/day, IP, during 15 days) were studied in 8 cats provided with electrodes for EEG, EMG and EOG records. Results indicated that, in contrast to a resistance of the cats to exhibit overt signs of tolerance in the immediate behavioral and EEG responses to morphine, tolerance developed in sleep since: 1) there was a reduction in its onset latency after the initial insomnia period; 2) despite that the initial insomnia period was present throughout the treatment, compared to the effects of the first MS day, the total amount of both NREM sleep and REM sleep significantly increased in subsequent drug days, the total amount of REM sleep reached similar placebo values from day 5; 3) the restoration in the total amount of both sleep states was due to significant increases that occurred from day 5 after the first 6 hours of the MS injection. During the 19–24 hours after MS injections, increases of NREM and REM also resulted statistically significant compared to placebo values. A biphasic depressed and aroused response occurred during early withdrawal. REM sleep rebound was present after MS discontinuation and in the following week. Similarities with effects of opiate chronic administration in other species are discussed. These results support the potential use of the cat for the study of neural mechanisms involved in sleep chronic effects of opiates.

Morphine Sleep-wakefulness Cat Tolerance Withdrawal

IN spite of the wide use of the cat in neuroscience and sleep research, this species has been commonly disregarded as an experimental subject to investigate acute and chronic actions of morphine and other opiates. This fact may be due to the strong excitatory effects produced in the cat ("feline mania") by the administration of relatively high customary doses of morphine (4, 5, 18, 26) and to the high mortality rate of cats undergoing chronic administration of such doses (16). However, in more recent studies—using relatively low doses of morphine—we were able to assess the suitability of the cat for the study of the behavioral effects of morphine: single morphine injections in the cat, in a range of 0.5 to 3 mg/kg IP, elicit a characteristic quantifiable and reproducible pattern of behavioral responses. We were also able to disclose CNS sites of drug action involved in the expression of these effects (2, 29, 30). On the other hand, two weeks of daily administration of these low morphine doses produce mild signs of tolerance in the behavioral responses of cat, together with strong withdrawal manifestations precipitated by naloxone (6).

Single injections of morphine within the abovementioned range produce a dose-dependent suppression of both non-Rem (NREM) and Rem sleep (REM) which is followed by sleep rebound (especially NREM) in this species (3). Latency to onset of this latter rebound effect is likewise dose-dependent. The immediate behavioral wakefulness state induced by morphine was accompanied by a characteristic EEG pattern with high voltage, slow frequency bursts (3). Since sleep deprivation and EEG/behavioral dissociation during the initial insomnia period are peculiar phenomena under morphine reported in other species, including man (11–14, 20, 21, 23), it seems probable that the cat shares, together with other species, the basic features produced by morphine on EEG and the sleep-wakefulness cycle (SWC).

The EEG and the continuum SWC have proven to be useful tools for assessing physical dependence properties of morphine and other opiates (13). The present study was designed to examine the EEG and sleep responses of the cat following chronic administration of low doses of morphine, considering that the single administration of low doses of morphine has validated the use of the cat for the study of behavioral and electroencephalographic effects of opiates. Considerable information about wakefulness and sleep mechanisms has been accumulated in this species. We therefore believe that the knowledge of such responses could be of particular interest for further examination of the neural basis of opiate tolerance and physical dependence within the framework of SWC.

METHOD

Under general anaesthesia (Ketolar 7 mg/kg, IM and Nembutal 22 mg/kg., IP) 8 adult cats were implanted with

[1]Requests for reprints should be addressed to Dr. Isabel de Andrés, Depto. Morfología, Fac. Medicina, UAM, C/ Arzobispo Morcillo s/n, Madrid, 28029, Spain.

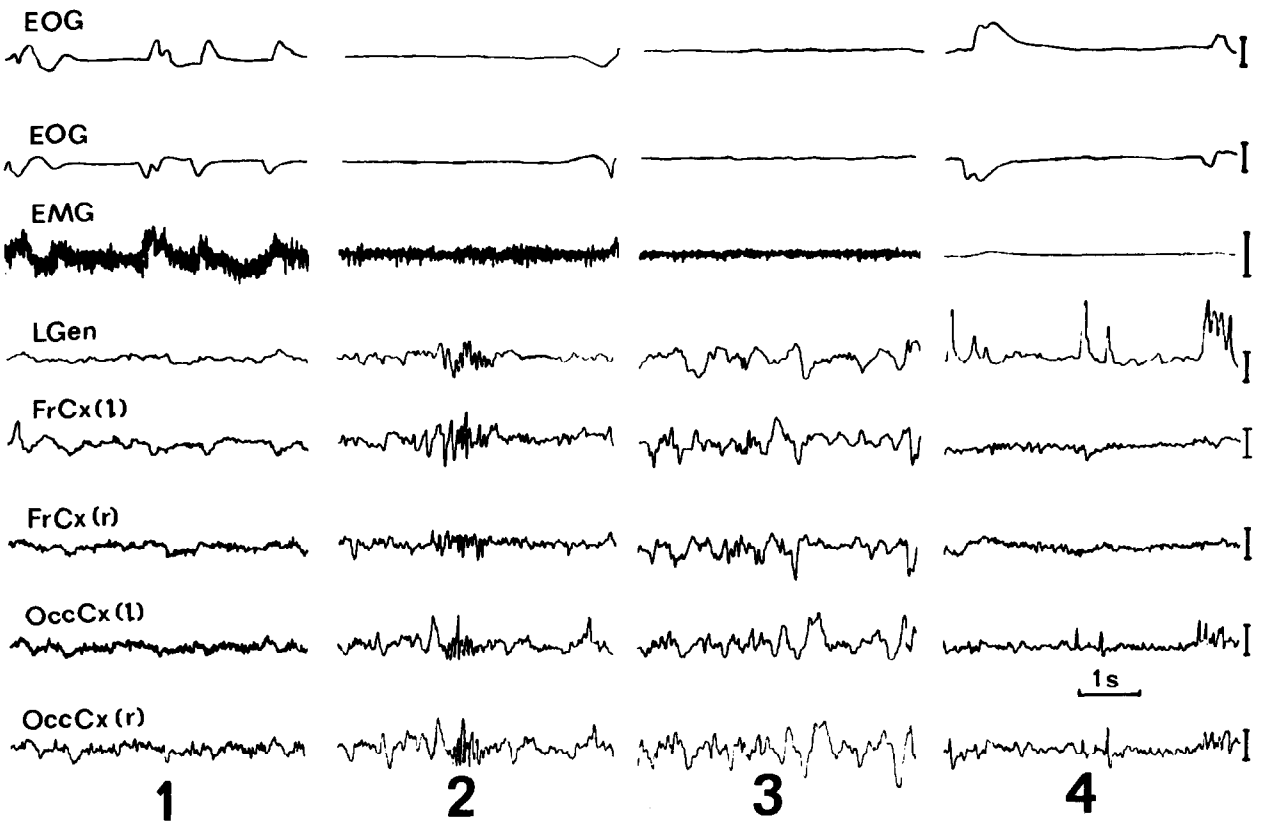

FIG. 1. Polygraphic patterns of SWC states in the cat during baseline placebo records. 1: Wakefulness (W), 2: Drowsiness (D), 3: Nonrapid-eye-movement sleep (NREM), 4: Rapid-eye-movement sleep (REM). Key: EOG=electrooculogram; EMG=electromyogram; LGen=EEG, lateral geniculate body; FrCx=EEG, frontal cortex; OccCx=EEG, occipital cortex; l=left; r=right. All records are bipolar with the reference electrode.

neocortical, lateral geniculate, orbital and neck muscle standard electrodes to record EEG, EOG and EMG respectively. An additional reference electrode was placed in the midline of the frontal sinus. All electrodes were terminated in an Amphenol connector and secured in a pedestal of dental cement.

After 8 to 10 days from surgery, each cat was acclimatized for 3 or more days to the recording conditions. The animal was placed in a sound-attenuated, ventilated recording chamber, with food and water ad lib, where it could be observed through a one-way mirror. After habituation, the cats received placebo injections (saline vehicle) that were followed by two 24-hr polygraphic records to be used as baseline controls.

Chronic treatment of morphine consisted of the administration of 2 mg/kg/day of morphine sulfate (MS) IP during 15 days. All injections were given between 9.30 a.m.–10.30 a.m. Sleep was continously monitored for 24 hr on days 1, 5, 10 and 15. Sleep records were extended for the following 3 days (early withdrawal) after discontinuation of MS administration and with placebo injections. In 4 animals, 24-hr sleep records were also obtained between the 6th and 10th days after the last MS dose (late withdrawal). Naloxone (1 mg/kg, IP) was administered two hours after the last MS dose (on the 15th day) in 3 animals.

Sleep records were scored visually, according to polygraphic criteria (Fig. 1) for wakefulness (W), relaxed wakefulness or drowsiness (D), NonRem sleep (NREM) and Rem sleep (REM) of the cat (25,28). Behavioral observations of the cats were also performed on the different recording days for the first 6–7 hr after MS. These observations were also taken into account when scoring the polygraphic records.

Initially, sleep records were blocked in 1-hr intervals. The percentage spent in each SWC state was calculated, and the results were accumulated into 24-hr or 6-hr intervals. In the three cats in which naloxone was administered on the 15th day of treatment, values of the two following hours after administering the antagonist were excluded from the data. *t*-Tests for paired samples were used to assess the MS effects in the onset latencies of both NREM sleep and REM sleep and in their total 24-hr proportions during chronic treatment. The time course of the MS effects in the different testing days was examined. Two-way ANOVAS (days and time) were used to compare the average of 6-hour samples throughout MS treatment. Multiple pair contrasts were carried out using the Tukey test, comparisons were concentrated between baseline and first day values and those of subsequent drug days.

During early and late withdrawal periods, changes in the four SWC states proportions during the whole 24-hr records were examined using one-way ANOVAS. Six-hour block values of the three first days after MS discontinuation were also included in the two-way ANOVAS for examination of the time course of changes during early withdrawal.

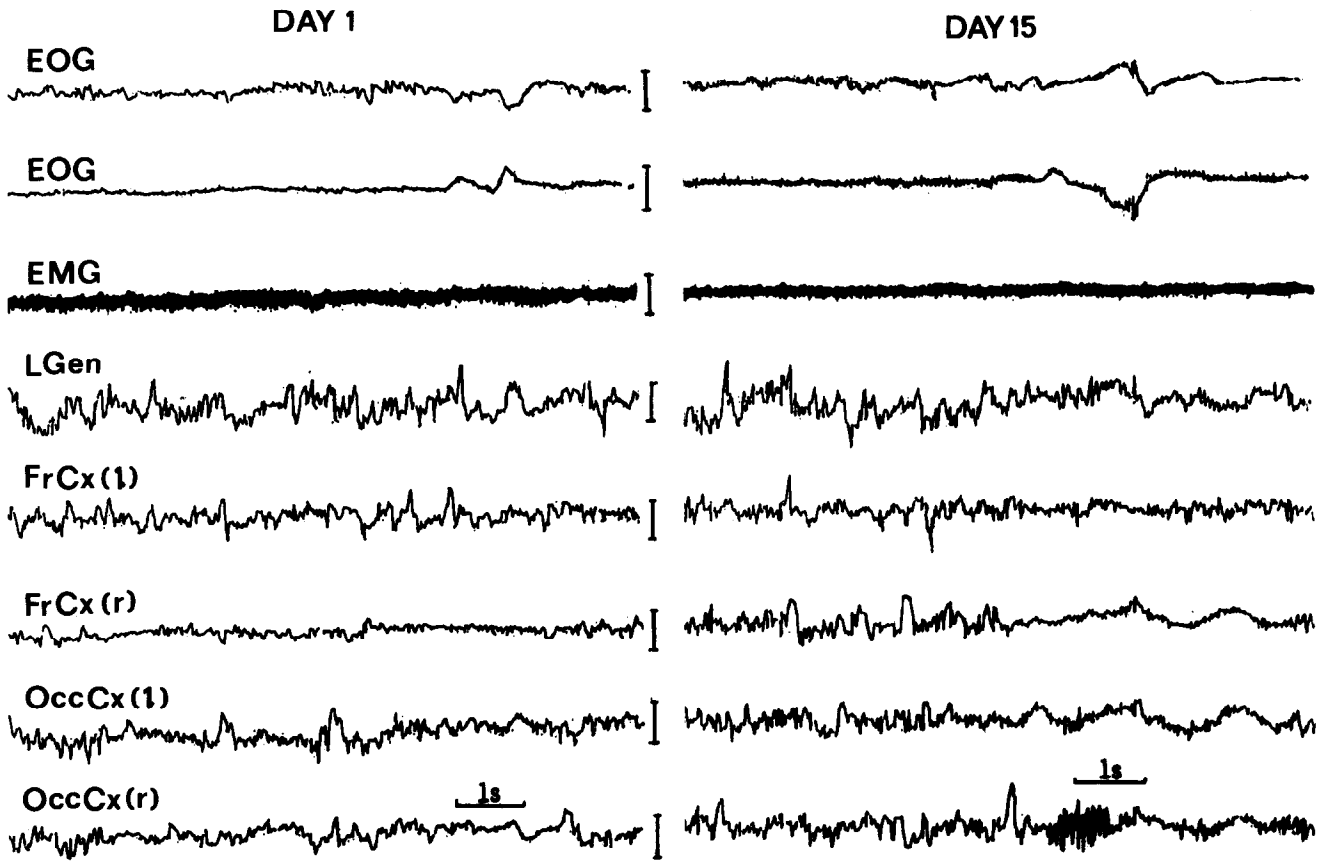

FIG. 2. Polygraphic records taken from a cat 20 minutes after injection of morphine sulfate in the first and the last day of chronic treatment. Lettering as in Fig. 1. Note, in both days, the similar slow pattern in the EEG while the cat was behaviorally awake (see EOG, EMG).

RESULTS

Chronic Treatment

Chronic treatment with 2 mg/kg/day of MS during 15 days did not produce substantial variations in the animal's body weight, nor other signs that could indicate an overall deterioration of the physical status of the cats.

Through the behavioral observations that were performed in the course of the first 6–7 hours after MS administration in the different testing days, it was possible to assess that the immediate response of the cats to chronic administration of low doses of MS was similar throughout the whole treatment. MS administration was invariably followed by the peculiar behavioral state of wakefulness already described after similar single MS doses (29,30) from the first to the last days. That is, during each day of the chronic treatment, when behaviorally aroused, the cat presented, the stage of "autonomic signs," the alert "quiet stage" and finally the "head movement" stage. The EEG was also found to be similar on the first and last day of the chronic treatment during these stages (Fig. 2). As in the case of single doses (3), and in spite of the aroused behavior of the cats, the EEG slowed up during quiet periods, but it had a detectable tendency to present a decrease in voltage and an increase in frequency when the cats presented bouts of body or head movement (Fig. 2).

With regard to the sleep-wake continuum, the onset latencies of both NREM and REM sleep decreased in the course of the treatment. As shown in Table 1, comparisons between the effects on day 1 and subsequent drug days indicated that diminution of the onset latency for REM reached significant values from day 5, while the decrease for NREM was statistically significant on day 15. However, as indicated above, the initial insomnia period produced by MS was still present on the last drug day (day 15) when compared with baseline values.

This effect tended to be compensated during the MS treatment as proven by the changes undergone in the total proportions for both NREM and REM in the different drug days (Fig. 3). REM sleep reached similar placebo values already from day 5, while full NREM sleep restoration was achieved only on day 15. Comparisons between day 1 values and those of subsequent drug days showed that increases in the total amount of both NREM and REM on days 5, 10 and 15 were statistically significant.

A more particularized analysis on the SWC effects of the MS chronic treatment was provided by comparisons among the six-hour block proportions of each SWC state in the different testing days. Two-way ANOVAS indicated that the day-dependency of all SWC states changed significantly throughout the course of the treatment and subsequent early withdrawal period, as shown by the interaction effects between day × time for wakefulness, $F(21,244)=11.745$, $p<0.0001$, drowsiness,

TABLE 1

DEVELOPMENT OF TOLERANCE IN THE ONSET LATENCIES OF NONRAPID-EYE-MOVEMENT SLEEP (NREM) AND RAPID-EYE-MOVEMENT SLEEP (REM) AFTER MORPHINE (2 mg/kg/day) INJECTIONS

	Baseline	Day 1	Day 5	Day 10	Day 15
NREM mean[a]	0.8	9.5	7.6	7.2	5.0
t			0.2	0.2	2.4*
REM mean[a]	3.1	11.7	11.0	11.6	8.9
t			4.9†	2.2*	2.8*

[a]Mean latency values for the experiments with saline placebo (Baseline) and for the different days of the chronic morphine treatment.
t=*t*-test for paired samples between day 1 and subsequent drug days.
*$p \leq 0.05$, †$p \leq 0.01$.

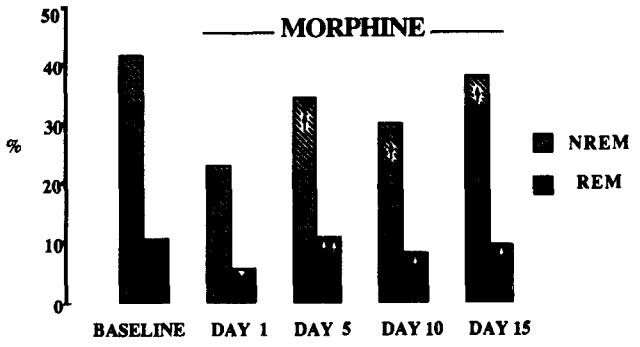

FIG. 3. Nonrapid-eye-movement sleep (NREM) and rapid-eye-movement (REM). Whole day (24 hr) mean percentages during placebo (Baseline) and morphine days (Morphine). $\Delta\Delta p \leq 0.01$, $\Delta p \leq 0.05$ (comparisons with baseline values. *t*-Test for paired samples). $\uparrow\uparrow p \leq 0.01$, $\uparrow p \leq 0.05$ (comparisons with the first morphine day. *t*-Test for paired samples).

$F(21,244)=3.182$, $p<0.0001$, NREM sleep, $F(21,244)=8.808$, $p<0.0001$, and REM sleep, $F(21,244)=4.046$, $p<0.0001$.

Details of SWC effects on the different days of the chronic treatment are shown in the histograms of Fig. 4 (Morphine), where the percent time spent in each SWC state during the 24 hr of the experiments is plotted. Changes in each 6-hr period were examined with multiple comparison tests.

W was significantly increased ($p<0.01$) at the expense of both sleep states and drowsiness for at least 12 hr after MS during the different testing days of the chronic treatment, compared to baseline placebo values. Moreover, comparisons of the values of the first block (0–6 hr after MS) indicated that W increases, with a practically total suppression of both sleep states, were similar in days 1, 5 and 10 of treatment. However, in day 15, although W was still significantly increased compared to baseline values, it was significantly decreased ($p<0.01$) compared to the values reached in all preceding days of treatment. This W decrease correlated with a significant increase ($p<0.05$) of NREM sleep values compared to NREM sleep of previous days under MS treatment. The appearance of REM sleep also took place in the initial six-hour block of day 15 (see also Fig. 4, Morphine).

A tendency to diminish the insomnia produced by the drug also occurred during hours 7–12 (2nd block) starting from the 5th day of MS administration. Total REM sleep suppression was prolonged until this period in the first day, but this effect was not observed in subsequent drug days. Moreover, compared to the effects observed in day 1, a significant decrease ($p \leq 0.01$) of W occurred in days 5, 10 and 15. Decrease of W paralleled with both NREM and REM statistically significant increases on days 5 ($p \leq 0.05$) and 15 ($p \leq 0.01$).

In hours 13–18 (3rd block, Fig. 4, Morphine), W was still significantly increased in the first day of MS administration ($p \leq 0.05$), but this effect was not present in the remaining drug days. In general for sleep states—except for REM sleep that was significantly increased on day 5—only slight differences occurred during this period with respect to the corresponding baseline values. However, when compared to the values reached in the first day, during the third 6-hr block, sleep increases reached statistically significant values on days 5 (NREM $p \leq 0.05$ and REM $p \leq 0.01$) and 15 (NREM $p \leq 0.05$).

The tendency to present sleep increases with MS chronic administration was even more detectable in the following 19–24 hours (4th block, Fig. 4, Morphine). Significant changes from day 5 and during the rest of the chronic treatment differed to both baseline and day 1 values. With regard to baseline placebo values, these changes consisted of a significant increase in both NREM ($p \leq 0.01$) and REM ($p \leq 0.05$ or $p \leq 0.01$) sleep at the expense of both W and D. Increase of NREM, together with decrease of W on days 5, 10 and 15, were statistically significant ($p \leq 0.05$) when compared to day 1.

Withdrawal Period

In chronically-treated cats, discontinuation of MS administration did not produce overt signs of spontaneous behavioral discomfort. Only whole body or body segment "wet dog shakes" were occasionally observed. However, in animals administered with naloxone two hours after the last MS dose as described by Harris *et al.* (6), clear precipitated withdrawal signs were detected. During the 30–40-minute period in which the cats had strong precipitated withdrawal manifestations (salivation, panting, tachypnea, vocalizations, escape behavior) the EEG was totally desynchronized.

In spite of the scarce spontaneous behavioral withdrawal manifestations exhibited by the cats, there were changes in

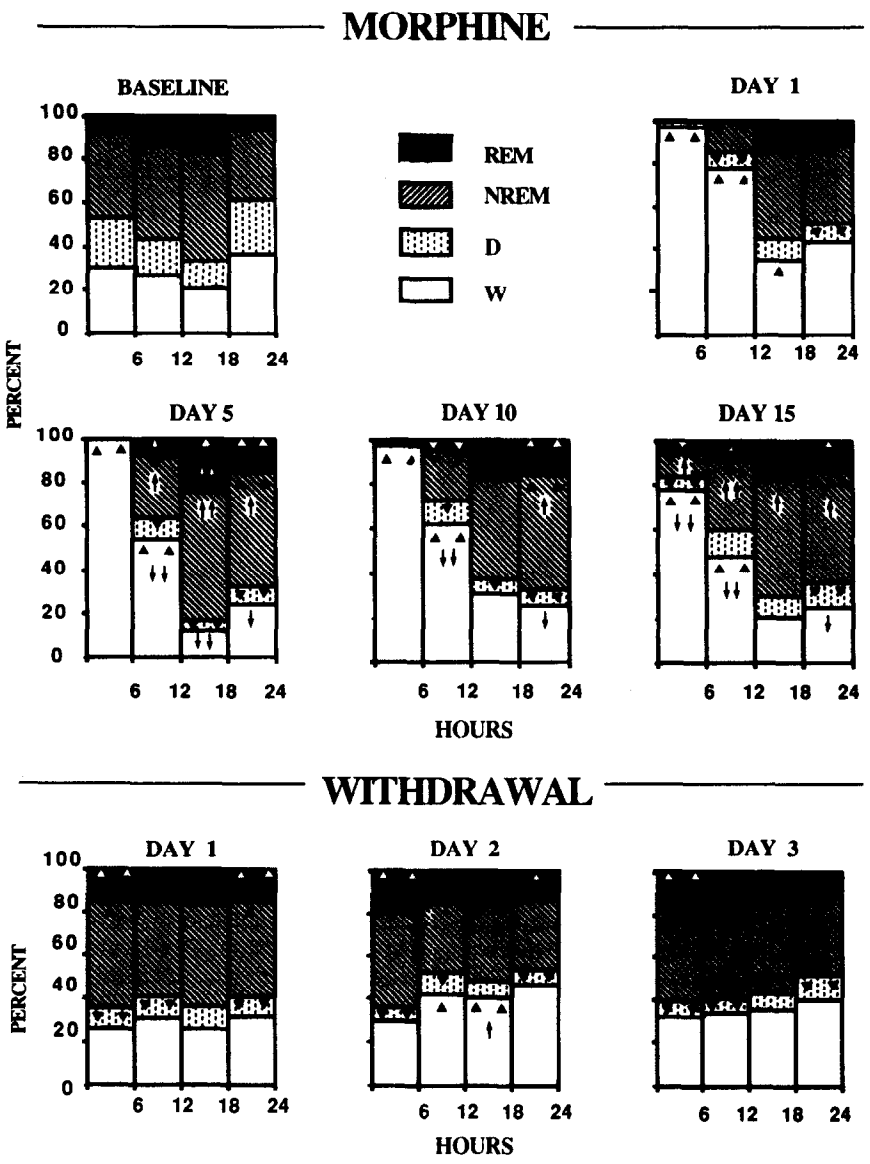

FIG. 4. Frequency histograms of mean percent values of sleep-wakefulness stats during 6-hr periods recorded after the administration of saline placebo (Baseline), after morphine in different days of the chronic treatment and during early withdrawal. Key: REM=rapid-eye-movement sleep; NREM=nonrapid-eye-movement sleep; D=drowsiness, W=wakefulness; Percent=cumulative percentage of the four behavioral states for each 6-hr period. The individual percentage for each of the states is indicated by different shadings in each of the bars. $\Delta\Delta p \leq 0.01$, $\Delta p \leq 0.05$ (comparions with baseline values). $\uparrow\uparrow p \leq 0.01$, $\uparrow p \leq 0.05$ (comparisons with first morphine day).

the SWC during early and late withdrawal periods. There was a rebound in the total time spent in REM sleep during the early withdrawal period that was maintained in the records taken in the following week (late withdrawal, Table 2). REM sleep increases occurred in both withdrawal periods at the expense of D. Neither total amount of W nor NREM were significantly different from the baseline in early or late withdrawal. However, six-hour block comparisons between the three days of the early withdrawal period (Fig. 4, Withdrawal) indicated that besides changes in REM sleep and D, there were moderate but significant changes in W and NREM which occurred during specific 6-hr periods of the second withdrawal day. The time course of SWC states throughout the 3 days following MS discontinuation was as follows: Both NREM and REM sleep augmented with respect to the corresponding baseline values, mainly at the expense of D, during day 1 and the first 6 hours of day 2 (NREM, $p \leq 0.05$, first and fourth blocks of day 1 and REM $p \leq 0.01$ during the same periods and during the first 6 hours of day 2). During the following 12 hours (2nd and 3rd 6 hr blocks of day 2) a statistically significant increase of W occurred. This W increase was due to a decrease of either D or

TABLE 2

SLEEP-WAKEFULNESS STATES DURING MORPHINE WITHDRAWAL

	Baseline	Early Withdrawal (days 1–3)	Late Withdrawal (days 7–10)	F (2,42)
REM	10.5 (±4.9)	15.0 (±3.3)	16.0 (±5.4)	6.54*
NREM	41.7 (±8.5)	41.6 (±9.3)	43.3 (±7.2)	0.12 n.s.
D	18.9 (±5.5)	8.6 (±2.3)	8.0 (±2.9)	33.67†
W	28.9 (±8.5)	34.8 (±9.8)	32.7 (±10.1)	1.72 n.s.

Values are mean and standard deviations of 24-hr experiments with saline placebo in the days prior to the chronic morphine treatment (baseline) and in the first and second weeks (early and late withdrawal respectively) after morphine discontinuation.

F=F-test (One-way ANOVAS). *$p \leq 0.01$; †$p \leq 0.001$; n.s., not statistically significant differences.

NREM sleep. REM sleep maintained similar values to those observed during the equivalent 6-hr periods of baseline records. A significant increase ($p \leq 0.01$) of REM sleep took place during the last 6-hr period of day 2 and continued to day 3 ($p \leq 0.01$, first block). Comparisons between early withdrawal days showed that the increase of W in third 6-hr block of day 2 was statistically significant to the corresponding values of day 1.

DISCUSSION

Tolerance

Previous studies on animal models for opiate tolerance and physical dependence have been carried out mainly in the rat (13–15, 24, 31). These studies—using multiple MS injections at increasing doses—report that by the third day of the treatment, the immediate stupor period produced by MS in the rat is reduced and the total amount of sleep and REM sleep approached normal values. However, to establish further comparisons with results in the cat found in the present study, is interesting to point out that in rats under a state of self-administration of the drug, sleep predominated in the period before injections, while wakefulness prevailed during the first 30 or 60 minutes after an injection (13,14).

In the cat, even on the fifteenth day of treatment, the immediate sleep-suppressing effects of MS can be observed. Each MS injection was invariably followed by a behaviorally active period. When compared to baseline values in all drug days, insomnia was present during the first 6 hours after MS injections as shown by the proportions reached by W and the delayed onset latencies for both NREM sleep and REM sleep. However, in comparison to the effects obtained in the first day, NREM and REM sleep onset latencies were reduced throughout the treatment. Furthermore, when compared to the first day, amount of NREM sleep was significantly increased during the first 6 hours of the last day of the treatment. The appearance of REM sleep in this period of time also took place in some of the cats. There was a trend to restore the total amount of the two sleep states in spite of the initial insomnia during the MS chronic treatment. When comparing the values reached in the first day with those of subsequent drug days, there was a significant increase of both NREM sleep and REM sleep. When compared to baseline values, REM sleep reached similar placebo values from day 5, while NREM sleep full restoration took longer (on day 15).

It therefore seems that the basic facts indicating development of tolerance are similar in the cat and in rat, the prolonged time required by the cat might not reflect a different response of this species to chronic morphine, rather it could be due to the distinct procedures used in MS administration: multiple increasing injections each day in the case of the rat (abovementioned studies) and a single constant dose, administered daily in our cats. On the other hand, our results—indicating a slow development of tolerance in the immediate sleep suppression produced by MS, but a prompt trend back to control values in the total percentage of REM sleep—are similar to the results found in nonaddicted men under administration of a constant single dose of heroin during 3 or 7 consecutive nights (17).

The delayed increases in REM sleep (13,14) and in NREM sleep that occurs between the administration of two doses during chronic MS treatment are well documented in our study. In the cat, compared to the effects observed on the first day, the amount of both NREM sleep and REM sleep increased during the 7–12-hr period after MS from the 5th day of the treatment. The same trend, though less prominent on day 10, occurred in the following 6-hr block. Finally, also from the 5th day, rebound of both NREM sleep and REM sleep occurred at the end of each day before the following MS injection with respect to placebo values. Concerning this last point, it is interesting to mention that in a previous study (3), where single MS injections at different low doses were administered to the cat, sleep rebound appeared within the first 24 hr with only the smallest dose (0.5 mg/kg), while single doses of the range used in the present chronic treatment produced NREM sleep rebound in the following day after MS administration.

Accordingly, our study shows that in the cat, the analysis of changes in sleep provides a more sensitive index of tolerance than the visual examination of the EEG patterns produced by the drug. Slow frequency EEG bursts associated with the peculiar wakefulness behavior—previously described in the cat under low single MS doses (3, 29, 30)—invariably followed MS from the first to the last day of the chronic treatment. In the rat—using computer analyzed EEG—tolerance effects have been described under chronic treatment of multiple MS injections (24,27). Also, single dose

delayed tolerance to morphine EEG effects has been reported in this species (19). However, slow frequency bursts still prevail immediately after an MS injection, even when the rat is in a dependent state with self-administration of the drug (13). In man (10), effects of partial tolerance have been described in sleep. There is a reduction of the initial wakefulness produced by morphine and other opiates, but in spite of the tendency to develop tolerance in the sleep-wake continuum, slow frequency bursts were still present 3 weeks after initiation of a period of induction of dependence with administration of increasing doses of morphine (10).

Therefore, it seems to be a common fact among the studied species that, independently of the procedure used for chronic administration of morphine, there are specific time course differences in the development of tolerance of the distinct actions produced by opiates.

This fact seems to be especially so in the cat. Within sleep for the various parameters examined, this study shows differences between NREM sleep and REM sleep. On the other hand, Labrecque and Domino (16) indicated a fast development of tolerance for the gastrointestinal actions of the drug, with a chronic treatment of multiple increasing doses of morphine. However, pupil midriasis and general behavioral excitatory effects only presented diminished signs when almost lethal doses of the drug were reached. More recently, Harris *et al.* (6), with a chronic MS treatment similar to that of the present study, reported clear tolerance signs in the hyperthermic effects produced by morphine in the cat. However, as corroborated in this study, and extending observations to the associated EEG, it was difficult to detect tolerance development in the peculiar behavioral manifestations under the drug exhibited by intact cats without brain lesions.

Given the difficulty to reach tolerance development in behavioral actions produced by morphine in the cat—even in the strong excitatory effects ("feline mania") evoked by relatively high doses (1)—it is not surprising that there is a generalized opinion as to the unsuitability of the cat for experimental studies on chronic effects of opiates. However, our study demonstrates that in a not very long period of time and with a simple procedure of chronic morphine administration, tolerance signs related to sleep states can easily be detected in this species. Moreover, no mortality problems were observed.

Abstinence

The presence of rebound of REM sleep is common during the period of abstinence of drugs that produce addiction (22). In our cats, increases of both NREM sleep and REM sleep have been detected during specific periods of time in the three days immediately after MS discontinuation. A protracted REM sleep rebound could also be identified in the following week. In cats with a chronic MS treatment similar to the present study, definite naloxone-precipitated behavioral manifestations took place not only in the last day of MS administration, they were still obvious 15–30 days after MS discontinuation (6).

Changes in sleep related to the suppression of opiate administration are well-documented in other species. In man an immediate and long-lasting REM rebound (up to two months) followed discontinuation of daily administration of a constant single dose of heroine over a short period (17). In humans with a long dependency history, however, irritation and decrease of both NREM and REM sleep are associated to the early withdrawal syndrome (7–9). On the other hand, in morphine-dependent rats, a protracted REM sleep rebound followed an earlier biphasic depressed and aroused pattern of behavior (14,15). This biphasic response of the rat was restricted mainly to the first 24 hours after abrupt morphine suppression and consisted of an initial increase of sleep followed by wakefulness in which clear behavioral withdrawal signs were manifested (13). The profile of the changes in the sleep-wake continuum of our cats during the first 72 hours after morphine discontinuation closely resembles the immediate biphasic response of the rat. In the cat, increase of both NREM and REM sleep occurred during the first withdrawal day and the latter remained enhanced during the first 6 hours of the second day. Increase of wakefulness was observed during the following 12 hours of the second day. There are further similarities between cat and rat before the protracted sleep rebound starts. The early biphasic pattern of response was followed in both species by a period in which the sleep-wake continuum tended to reach normal placebo values. This was the case in the third day for the cat, in NREM sleep and wakefulness. However, some increases of REM sleep already occurred during the same day.

Concerning behavioral signs of morphine withdrawal, once again it seems that the measure of the SWC can dispense a more sensitive index of morphine addiction than the examination of overt behavior. In contrast to rats treated with multiple increasing doses (13,14), our cats, after discontinuation of the daily constant low dose MS treatment, did not present overt signs of spontaneous behavioral discomfort during abstinence period. Nevertheless, a clear withdrawal syndrome could be precipitated with naloxone administration associated with a fully desynchronized EEG.

Finally, taking into account previous studies (2, 3, 29, 30), we believe that the results found in the present investigation, which in part can be matched to the results found in other species, provide further support to the validity of the cat as an experimental model for the study of neural mechanisms involved in chronic effects of opiates.

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REFERENCES

1. Borrel, J.; Borrel, S. Chronic administration of morphine in cats: Effects on adrenal and urinary catecholamines. Eur. J. Pharmacol. 32:337–343; 1975.
2. De Andrés, I.; Villablanca, J. R.; Olmstead, C. E. Caudate lesions change the behavioral effects of morphine in cats. Soc. Neurosci. Abstr. 4:489; 1978.
3. De Andrés, I.; Villablanca, J. R.; Burgess, J. W. Reassessing morphine effects in cats: II. Protracted effects on sleep-wakefulness and the EEG. Pharmacol. Biochem. Behav. 21:923–928; 1984.
4. Dhasmana, K. W.; Dixit, K. S.; Jaju, B. P.; Gupta, M. L. Role of central dopaminergic receptors in maniac response of cats to morphine. Psychopharmacologia 24:380–383; 1972.

5. Fertziger, A. P.; Stein, A.; Lynch, J. J. Suppression of morphine induced mania in cats. Psychopharmacologia 36:185–187; 1974.
6. Harris, C. M.; Villablanca, J. R.; Burgess, J. W.; de Andrés, I. Reassessing morphine effects in cats: III. Responses of intact, caudate nuclei-lesioned and hemispherectomized animals following chronic administration and precipitated withdrawal. Pharmacol. Biochem. Behav. 21:929–936; 1984.
7. Howe, R. C.; Hegge, F. W.; Phillips, J. L. Acute heroin abstinence in man: I. Changes in behavior and sleep. Drug Alcohol Depend. 5:341–356; 1980.
8. Howe, R. C.; Hegge, F. W.; Phillips, J. L. Acute abstinence in man: II. Alterations in rapid eye movement (REM) sleep. Drug Alcohol Depend. 6:146–161; 1980.
9. Howe, R. C.; Phillips, J. L.; Hegge, F. W. Acute heroin abstinence in man: III. Effect upon waking and slow wave sleep. Drug Alcohol Depend. 6:247–262; 1980.
10. Kay, D. C. Human sleep during chronic morphine intoxication. Psychopharmacologia 44:117–124; 1975.
11. Kay, D. C.; Eisenstein, R. B.; Jasinski, D. R. Morphine effects on human Rem state, waking state and NREM sleep. Psychopharmacologia 14:404–416; 1969.
12. Kay, D. C.; Pickworth, W. B.; Neidert, G. L.; Falcone, D.; Fishman, P. M.; Othmer, E. Opiod effects on computer derived sleep and EEG parameters in nondependent human addicts. Sleep 2:175–191; 1979.
13. Khazan, N. The implication and significance of EEG and sleep-awake activity in the study of experimental drug dependence on morphine. In: Ehrenpreis, S.; Heidle, A., eds. Methods in narcotic research. New York: Marcel Dekker; 1975:173–215.
14. Khazan, N.; Weeks, J. R.; Schroeder, L. A. Electroencephalographic, electromyographic and behavioral correlates during a cycle of self-maintained morphine addiction in the rat. J. Pharmacol. Exp. Ther. 155:521–531; 1967.
15. Khazan, N.; Colasanti, B. Protracted rebound in rapid eye movement sleep time and electroencephalogram voltage output in morphine-dependent rats upon withdrawal. J. Pharmacol. Exp. Ther. 183:23–30; 1972.
16. Labrecque, G.; Domino, E. F. Tolerance to and physical dependence on morphine: Relation to neocortical acetylcholine release in the cat. J. Pharmacol. Exp. Ther. 191:189–200; 1974.
17. Lewis, S. A.; Oswald, I.; Evans, J. I.; Akindele, M. O.; Tompsett, S. L. Heroin and human sleep. Electroencephalogr. Clin. Neurophysiol. 28:374–381; 1970.
18. Loewe, S. Influence of chlorpromazine, reserpine, dibenzyline and desoxycorticosterone upon morphine-induced feline mania. Arch. Int. Pharmacodyn. 108:453–456; 1956.
19. Nakamura, J.; Winters, W. D. Attenuation of the morphine EEG continuum following a repeat dose within 16 days: Delayed tolerance in the rat. Neuropharmacology 12:607–617; 1973.
20. Navarro, G.; Elliott, H. W. The effects of morphine, morphinone and thebaine on the EEG and behavior of rabbits and cats. Neuropharmacology 10:367–377; 1971.
21. Novack, G. D.; Winters, W. D.; Nakamura, J. EEG and behavioral effects of morphine in dogs. Proc. West Pharmacol. Soc. 19:239–242; 1976.
22. Oswald, I. Human brain protein, drugs and dreams. Nature 223:893–897; 1969.
23. Pickworth, W. B.; Neidert, G. L.; Kay, D. C. Morphinelike arousal by methadone during sleep. Clin. Pharmacol. Ther. 30:796–804; 1981.
24. Steinfels, G. F.; Young, G. A.; Khazan, N. Opiod self-administration and Rem sleep EEG power spectra. Neuropharmacology 19:69–74; 1980.
25. Sterman, M. B.; Knauss, T.; Lehmann, D.; Clemente, C. D. Circadian sleep and waking patterns in the laboratory cat. Electroencephalogr. Clin. Neurophysiol. 19:509–517; 1965.
26. Sturtevant, F. M.; Drill, V. A. Tranquilizing drugs and morphine mania in cats. Nature 179:1253; 1957.
27. Tortella, F. C.; Moreton, J. E.; Khazan, N. Electroencephalographic and behavioral tolerance to and cross-tolerance between D-Ala^2-methionine-enkephalinamide and morphine in the rat. J. Pharmacol. Exp. Ther. 210:174–179; 1979.
28. Ursin, R.; Sterman, M. B. A manual for standardized scoring of sleep and waking states in the adult cat. Los Angeles: Brain Information Service/Brain Research Institute, University of California, Los Angeles; 1981:103.
29. Villablanca, J. R.; Olmstead, C. E.; de Andrés, I. Striatal lesions change the behavioral effects of morphine in cats. Brain Res. 248:159–167; 1982.
30. Villablanca, J. R.; Harris, C. M.; Burgess, J. W.; de Andrés, I. Reassessing morphine effects in cats: I. Specific behavioral responses in intact and unilaterally brain-lesioned animals. Pharmacol. Biochem. Behav. 21:913–921; 1984.
31. Young, G. A.; Moreton, J. E.; Meltzer, L. T.; Khazan, N. l-alpha acetylmethadol (LAAM), methadone and morphine abstinence in dependent rats: EEG and behavioral correlates. Drug Alcohol Depend. 2:141–148; 1977.