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# MORPHINE-LIKE INSOMNIA FROM HEROIN IN NONDEPENDENT HUMAN ADDICTS

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**1** This study was performed because dose-related effects of heroin on human sleep had not been described previously, and to discover if heroin produces a morphine-like insomnia.

**2** After three adaptation nights, the sleep of seven male nondependent opiate addicts was studied following i.m. doses of heroin (3, 6, 12 mg/70 kg), morphine (10, 20 mg/70 kg) or placebo at weekly intervals in a randomized double-blind crossover design.

**3** Heroin produces a dose-related increase in wakefulness, drowsiness episodes, muscle tension, and shifts in sleep-waking states.

**4** Heroin produces a dose-related decrease in total sleep, sleep efficiency, delta sleep and REM sleep (REMS).

**5** Heroin is about twice as potent as morphine in producing this type of insomnia.

**6** 'Morphine insomnia' appears to be a characteristic initial effect of several opioids, at least in nondependent opiate addicts, and might serve as a model insomnia for evaluation of hypnotics.

## Introduction

Heroin was introduced in 1898 as an antitussive superior to morphine (Eddy, Halbach & Braenden, 1957). Among its several clinical uses it was early tried as a substitute for morphine in addicts—and slowly recognized by the medical profession for its serious abuse potential. Although careful evaluation of heroin (c.f., Martin & Fraser, 1961) has found it almost identical to morphine except for its greater potency (2:1), there have been recent claims that it is more attractive to addicts than morphine or methadone (Brecher, 1972; Lidz, Lewis, Crane & Gould, 1975; Johnson, 1977). This study examines whether heroin causes a morphine-like insomnia in man.

Morphine produces a dose-related insomnia in nondependent opiate addicts when single doses are administered just prior to sleep (Kay, Eisenstein & Jasinski, 1969). Persistence, although attenuated, of this arousal effect is seen during chronic administration of morphine (Kay, 1975b). Methadone produces a comparable dose-related insomnia in nondependent opiate addicts (Pickworth, Neidert & Kay, 1981), with almost complete tolerance developing during chronic administration of methadone (Kay, 1975a). Heroin (diacetylmorphine) effects on sleep have not been studied as extensively as those of morphine or methadone. Three consecutive bedtime doses of subcutaneous heroin (7.5 mg) did tend to arouse 4 nonaddict subjects: it decreased REM sleep and increased sleep latency; it increased stage 2 and tended to increase drowsiness and stage shifts during early night (Lewis, Oswald, Evans, Akindele & Tompsett, 1970). Chronic heroin abusers have been reported to have a longer REM sleep latency than a nonaddict control group (Davison & Osselton, 1973). The current study was designed to compare heroin and morphine in their initial effects on the sleep of nondependent opiate addicts.

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## Methods

### *Subjects*

Seven male nondependent opiate addicts participated in this study after giving their informed consent, and with prior approval of the ARC scientific ethics committee. These men were federal prisoners who had volunteered for such research, and then received standard prison compensation for participation. Their ages ranged from 28 to 43 (mean 36.0) years; three were white and four were black. They had histories of 3–25 (mean 10.9) years of recurrent abuse of heroin and other drugs. Apart from one subject (2 months after chronic buprenorphine) they had been withdrawn from chronic opioid use 6–64

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(mean 25.8) months prior to participation in this study. None had received any psychoactive drug for at least 7 days prior to the first adaptation night in this study.

*Design*

After three initial weekly adaptation (placebo) nights, each subject participated in weekly sleep studies with a double-blind crossover design and a randomized order. Placebo (saline), morphine (10, 20 mg/70 kg) or heroin (3, 6, 12 mg/70 kg) was administered in a 2.0 ml intramuscular injection just prior to lights out. Two observers verified the labeled (man and date) but unnamed injection. Subjects maintained daily diaries of sleep–waking activities during the study, and on occasion participation in an experiment was delayed for a week because of concurrent illness or accident.

*Setting*

Each subject slept in one of two dimly lit and sound attenuated rooms that were maintained at a temperature of optimal subject comfort. White noise was introduced into each room sufficient to block perception of experimenters' voices, and an intercom and emergency signal were available for separate communication with each subject. A closed-circuit infrared TV system permitted monitoring of subject posture when body movement or muscle tension was increased.

*Measures*

Time in each experiment was coded on all records to the nearest second by a Systron-Donner 8120 time-code generator. A Grass 78 polygraph was used to record several parameters from each subject: two measures of the electroencephalograph (EEG), P3-A2 (mastoid process) and Fz-Oz; two measures of the electro-oculograph (EOG), between each lateral epicanthus and A2; the submental electromyograph (EMG); the respiratory pattern, detected by transthoracic impedance; and the finger plethysmograph response (FPR), detected by indirect light reflectance from an index finger. Computer analyses from tape recordings of some of these data are reported elsewhere (Kay, Pickworth, Neidert, Falcone, Fishman & Othmer, 1979).

*Scoring*

The scoring of the paper strip chart was blind to drug condition, and used techniques described by Kay, Jasinski, Eisenstein & Kelly (1972). Briefly, each sleep–waking state was defined to the nearest 2-s epoch, and had to persist for at least 10 s to be so identified, although drowsiness prior to spindle sleep might persist for less than 10 s. Waking state (stage 0), drowsiness (stage 1), spindle sleep (stage 2), delta sleep (stages 3 + 4), and REM sleep were all identified and tabulated for two durations: 360 min after the first sleep spindle (standard sleep time: ST) and 450 min after lights out (standard night: SN). If the 360 min duration of ST was unattainable (when sleep onset was delayed), the ST in that night consisted of all recorded time after the first sleep spindle; such a situation existed in 3 nights in this study. A sleep base (total of spindle sleep, delta sleep and REM sleep) was calculated for both ST and SN, and sleep stages were also calculated as a percentage of the appropriate sleep base. Sleep efficiency was the expression of the appropriate sleep base as a percentage of ST or SN. For each sleep–waking state, calculations included the total accumulated time, the number of episodes, and the mean episode duration (until a shift in state). Sleep latency (from lights out to first sleep spindle) was also measured, and the number of state shifts (new sleep–waking state episodes in ST or SN) were counted. Within REM sleep, time with (EMI) and without (ASI) rapid eye movements were calculated, as well as REM density, REM sleep latency (time from first sleep spindle to onset of first REM sleep episode) and REM sleep cycle (Kay *et al.*, 1972). REM sleep disruptions were divided into waking state disruptions and non-REM sleep (NREM sleep) disruptions; these were calculated only for SN.

In addition to the above measures of sleep-waking states, several episodic phenomena were also evaluated: K-complexes (Loomis, Harvey & Hobart, 1938; Johnson & Karpan, 1968) were defined as EEG slow wave bursts (2–10 s in duration) with synchronous parallel deflections in EEG and both EOG channels; often this EEG pattern was followed by a vasoconstriction response (FPR) within 4–8 s. K-complexes with and without FPR were tabulated separately and together for the entire SN. Each K-complex was tabulated by duration in every 20 s epoch during SN, with calculation of total number and mean duration of K-complexes in SN. Twenty 1 min samples of spindle sleep in the latter part of the night were used to estimate the incidence of sleep spindles (bursts per minute) and of K-complexes during spindle sleep.

Muscle tension was defined as an increase in muscle activity in at least three of the five EEG, EOG or EMG channels for at least 2 s. The number and duration of each episode of muscle tension was tabulated for every 20 s epoch during SN, with calculation of total duration of muscle tension, total number of episodes and mean episode duration in SN.

*Analysis*

For each measure, two two-way (subject-dose)

analyses of variance (Snedecor & Cochran, 1976) were utilized: (1) From the three heroin doses plus placebo, the between-dose component was partitioned into three comparisons: Placebo-drug difference, linear regression, and deviations from linearity. (2) From the two morphine doses plus three heroin doses plus placebo, a bioassay was performed (Finney, 1971). The between-dose component was partitioned into five comparisons: Placebo-drug difference, linear regression, non-comparable preparations, nonparallelism of the two regression lines, and nonlinearity of the common regression line. Potency of morphine relative to heroin (with 95% confidence limits) was calculated for measures with a valid bioassay (i.e., significant placebo-drug difference plus significant linear regression, but *no* significant preparations difference, nonparallelism or nonlinearity).

## Results

Some subjects in this study appeared to eagerly anticipate receiving their bedtime drug doses, with complaints the next morning that the dosage was insufficient. TV monitoring was used to inhibit excessive sitting or standing during the night, which some addicts use to promote enjoyment of opiates. The effects of heroin and morphine were comparable in both ST and SN measures; only the SN measures are tabulated in this report, with illustration of selected drug effects.

### *Heroin*

This congener of morphine produced significant insomnia (Table 1): It increased total wakefulness (Figure 1) by increasing the number of episodes without increasing the mean duration of each episode, and also increased drowsiness episodes. Thus, there was regular interruption of wakefulness by drowsiness and sleep episodes (Figure 2). Heroin increased number of awakenings (Figure 3c), and increased the number of stage shifts in the night (Figure 3a), while decreasing total sleep and sleep efficiency (Figure 3b), and not significantly affecting sleep latency (Figure 3d).

**Table 1** Heroin and morphine effects on arousal measures in 450 min.

| | *Saline* | *Heroin* | | | *ANOVA*§ | | | *Combined ANOVA*‡ |
|---|---|---|---|---|---|---|---|---|
| *Measures* | *Placebo* | *3 mg* | *6 mg* | *12 mg* | *P/D* | *LIN* | *DEV* | *Relative potency (95% confidence limits)*† |
| Total waking state (min) | 72.8 | 93.8 | 117 | 174 | *b* | *c* | — | 1.71 (0.90–2.74) |
| Total waking episodes (number) | 26.9 | 40.0 | 52.1 | 75.4 | *d* | *d* | — | 1.67 (1.15–2.26). *xa.* |
| Mean waking episodes (min) | 4.17 | 3.63 | 2.63 | 2.42 | — | — | — | *ve. vf.* |
| Total drowsiness (min) | 39.1 | 32.0 | 41.4 | 42.1 | — | — | — | *xb.* |
| Total drowsy episodes (number) | 29.1 | 39.9 | 51.9 | 74.9 | *d* | *d* | — | 1.63 (1.10–2.23). *xa.* |
| Mean drowsy episodes (s) | 78.0 | 46.0 | 46.8 | 34.2 | *b* | — | — | *vf.* |
| Total muscle tension (min) | 15.4 | 12.2 | 16.7 | 28.6 | — | *d* | — | *ve.* |
| Total muscle episodes (number) | 197 | 157 | 180 | 268 | — | *d* | — | *ve.* |
| Mean muscle episodes (s) | 9.43 | 9.40 | 11.3 | 12.4 | *a* | *c* | — | *ve.* |
| Sleep latency (min) | 32.8 | 51.5 | 52.8 | 27.7 | — | — | — | *ve. vf.* |
| Sleep base (min) | 338 | 324 | 292 | 234 | *b* | *d* | — | *xb.* |
| Total stage shifts (number) | 85.7 | 121 | 148 | 205 | *d* | *d* | — | 1.74 (1.19–2.39) |
| Total K-complexes (number) | 382 | 487 | 466 | 249 | — | *b* | — | *ve.* |
| Mean K-complex (s) | 4.42 | 6.65 | 6.19 | 6.19 | *d* | — | — | 3.05 (*vg.*) |

*a.* F-ratio with $P < 0.10$.
*b.* F-ratio with $P < 0.05$.
*c.* F-ratio with $P < 0.01$.
*d.* F-ratio with $P < 0.005$.
§ Analysis of variance within responses of seven subjects to placebo and three doses of heroin, including placebo/drug difference (P/D), linear regression (LIN) and deviations from linearity (DEV).
‡ Analysis of variance within responses of seven subjects to placebo and both opiates, including relative potency in the bioassay. Invalid bioassays (absence of relative potency) are explained in *v, x, y* and *z*.
† Relative potency of heroin in comparison to morphine (i.e., X.XX mg of morphine equals 1.00 mg of heroin). Calculated only for valid bioassays (a significant placebo/drug difference and linear regression in the combined ANOVA, with no significant ($P <$ 0.05) source of unwanted variance). 95% confidence limits are included for the relative potency in each valid bioassay.
*v.* Bioassay invalid because (*ve*) placebo-drug difference was not significant, or (*vf*) regression of dose-effect line was not significantly linear. Some 95% confidence limits (*vg*) could not be estimated.
*x.* Significant difference in preparations (mean effects) between the two drugs. Significance as in *a* and *b*.
*y.* Significant nonparallelism (slopes of the two dose-effect lines) between the two drugs. Significance as in *a* and *b*.
*z.* Significant nonlinearity in the slope of the common regression line of the two drugs. Significance as in *a* and *b*.

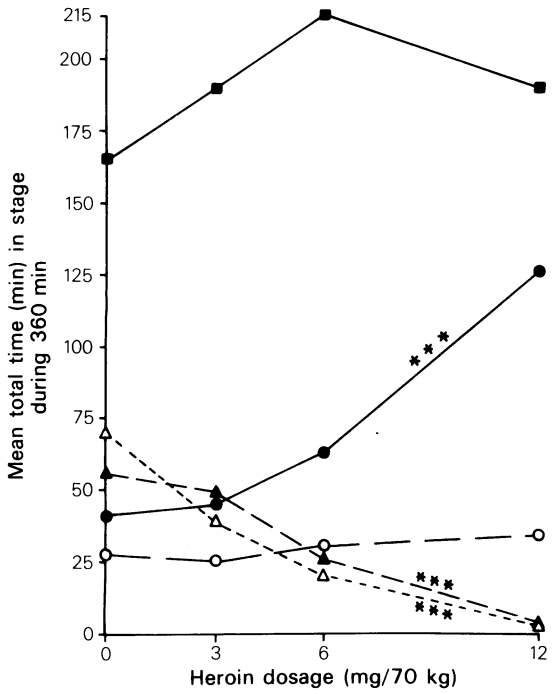


**Figure 1** The effects of heroin and placebo on sleep–waking states ( ■ spindle sleep, ● waking state, ○ drowsiness, ▲ delta sleep △ REM sleep). Values on the abscissa are dosages (mg/70 kg) of heroin. Each point represents the mean ($n = 7$) duration (min) of the specific state during the first 360 min after sleep onset. Significant linear regression of the dose-effect relationship is indicated (*** = $P < 0.005$).

In measures of NREM sleep (Table 2), heroin increased percentage (and number of episodes) of spindle sleep and decreased the mean duration of each spindle sleep episode, without significantly increasing total spindle sleep (Figure 1). Heroin significantly decreased total delta sleep (Figure 1), percentage delta sleep, and number and mean duration of delta sleep episodes. Heroin decreased sleep spindles and increased K-complexes (Table 2), but not in a dose-related way.

In measures of REM sleep (Table 3), heroin showed several significant dose-related changes: It increased latency to REM sleep: it decreased total (Figure 1) and percentage REM sleep, number and duration of REM sleep episodes, and REM density with REM sleep. At 12 mg/70 kg of heroin, REM sleep was greatly inhibited, with intermediate effects on REM sleep patterns at lower doses (Figure 4).

*Potency relative to morphine*

Comparable to prior findings (Kay *et al.*, 1969; Pickworth *et al.*, 1980), morphine increased wakefulness and drowsiness episodes, and decreased both delta sleep and REM sleep. Morphine increased number of state shifts in the night, while decreasing total sleep below placebo. The nocturnal pattern of morphine insomnia (Pickworth *et al.*, 1980) was comparable to that of heroin (Figure 2).

The potency of morphine relative to heroin (X.XX mg of morphine equals 1.00 mg of heroin) in the valid measures of arousal (Table 1) ranged from 1.39 (wakefulness in ST) to 3.05 (mean K-complex duration in SN). The 95% confidence limits of all valid relative potency estimates overlapped two times equipotency (2:1).

**Table 2** Heroin and morphine effects on non-REM sleep measures in 450 min.

| | *Saline* | *Heroin* | | | *ANOVA*§ | | | *Combined ANOVA*‡ |
|---|---|---|---|---|---|---|---|---|
| *Measures* | *Placebo* | *3 mg* | *6 mg* | *12 mg* | *P/D* | *LIN* | *DEV* | *Relative potency (95% confidence limits)*† |
| Total spindle sleep (min) | 165 | 191 | 216 | 190 | *a* | — | — | *ve. vf.* |
| % spindle sleep (%) | 58.7 | 66.4 | 81.3 | 96.7 | *d* | *d* | — | *xd.* |
| Total spindle sleep episodes (number) | 23.3 | 34.9 | 40.4 | 54.7 | *d* | *d* | — | 2.08 (1.32–3.13) |
| Mean spindle sleep episode (min) | 9.17 | 6.80 | 6.25 | 4.63 | *d* | *b* | — | 1.53 (0.61–2.67) |
| Total delta sleep (min) | 58.6 | 60.6 | 28.2 | 5.11 | *c* | *d* | — | *xb.* |
| % delta sleep (%) | 17.9 | 18.9 | 9.11 | 1.98 | *c* | *d* | — | *xb. yb.* |
| Total delta sleep episodes (number) | 4.57 | 5.29 | 3.00 | 0.57 | *a* | *d* | — | *xb.* |
| Mean delta sleep episodes (min) | 13.3 | 12.3 | 6.72 | 2.25 | *d* | *d* | — | 1.97 (1.21–2.99) |
| Spindle burst rate* (number/min) | 8.14 | 6.59 | 6.45 | 6.28 | *d* | — | — | *vf.* |
| K-complex rate* (number/min) | 1.62 | 1.91 | 2.03 | 1.74 | — | — | — | *ve. vf.* |
| Sleep efficiency (%) | 75.1 | 72.1 | 64.9 | 52.0 | *b* | *d* | — | *xb.* |

Explanation is the same as in Table 1.
* Spindle bursts or K-complexes per minute in spindle sleep.

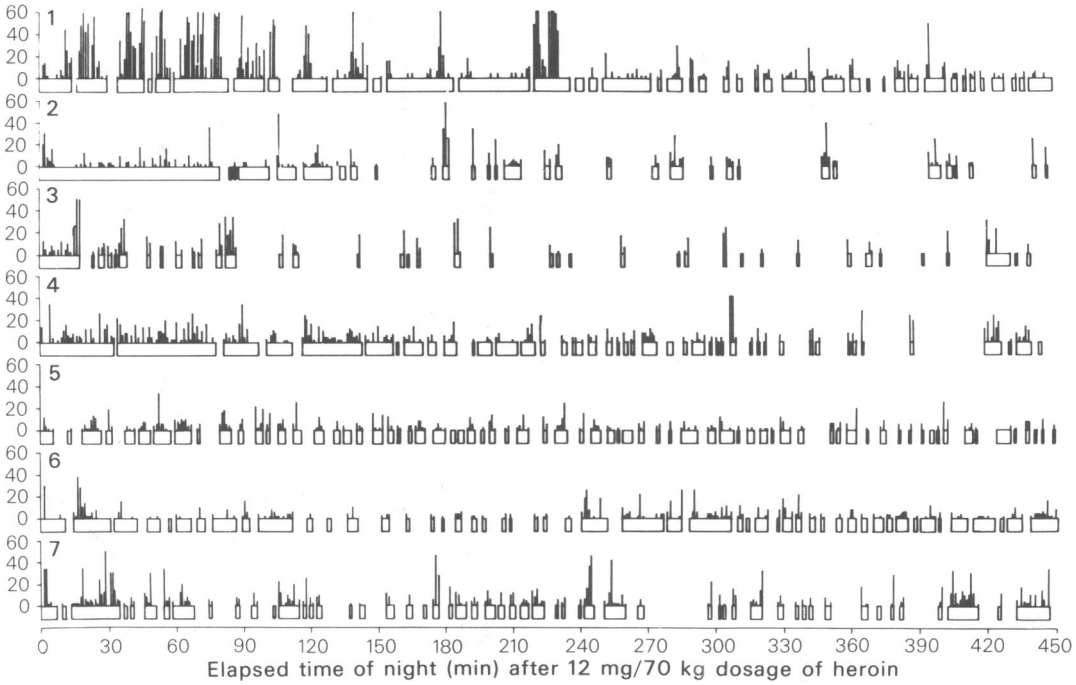


**Figure 2** Wakefulness and muscle tension after heroin. For each of seven subjects, the presence of wakefulness (lower open blocks) and duration (0–60 s) of muscle tension (upper solid lines) is illustrated for each minute of the night after administration of 12 mg/70 kg of intramuscular heroin. Wakefulness is identified with each minute in which it occurs, regardless of relative proportion of the minute occupied by waking; therefore, the multiple short episodes of drowsiness which interrupted waking cannot be adequately illustrated.

**Table 3** Heroin and morphine effects on REM sleep measures in 450 min.

| | *Saline* | *Heroin* | | | *ANOVA*§ | | | *Combined ANOVA*‡ |
|---|---|---|---|---|---|---|---|---|
| *Measures* | *Placebo* | *3 mg* | *6 mg* | *12 mg* | *P/D* | *LIN* | *DEV* | *Relative potency (95% confidence limits)*† |
| Total REM sleep (min) | 80.1 | 46.7 | 29.0 | 3.88 | *d* | *d* | — | 1.85 (1.35–2.44) |
| % REM sleep (%) | 23.4 | 14.6 | 9.56 | 1.37 | *d* | *d* | — | 1.90 (1.48–2.39) |
| Total REM sleep episodes (number) | 2.86 | 2.29 | 1.29 | 0.43 | *d* | *d* | — | 1.94 (1.30–2.76) |
| Mean REM sleep episodes (min) | 29.0 | 20.7 | 18.4 | 1.29 | *d* | *d* | *b* | *zb.* |
| Waking disruption (min) | 3.10 | 1.64 | 0.92 | 0.18 | *d* | *b* | — | 2.09 (1.14–3.57) |
| NREM disruption (min) | 1.18 | 0.39 | 0.25 | 0.00 | *b* | — | — | *vf.* |
| Total ASI* (min) | 63.4 | 38.7 | 24.6 | 3.40 | *d* | *d* | — | 1.89 (1.41–2.46) |
| Total EMI* (min) | 12.3 | 5.99 | 3.21 | 0.30 | *d* | *b* | — | 1.58 (0.59–2.84) |
| REM density (%) | 15.1 | 14.2 | 7.71 | 1.18 | *d* | *d* | — | *xb.* |
| REM sleep latency (min) | 141 | 148 | 287 | 418 | *d* | *d* | — | 1.87 (1.35–2.50) |
| REM sleep cycle (min) | 102 | 134 | 120 | — | — | — | — | *ve. vf.* |

Explanation is the same as in Table 1.

* Activated Sleep Index (ASI) is REM sleep without eye movements; Eye Movement Index (EMI) is REM sleep with eye movements.

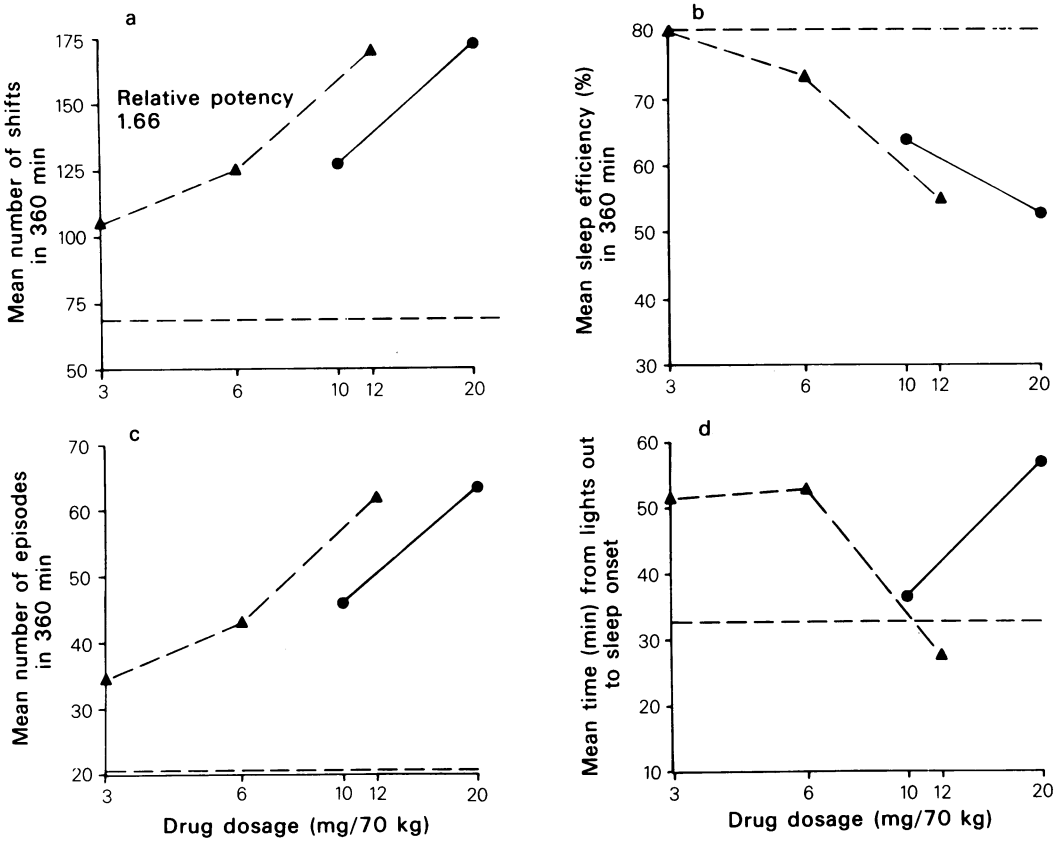


**Figure 3** Effects of heroin (▲) relative to morphine (●) in four measures of insomnia. Values on the abscissa are dosages (mg/70 kg) on a log scale, so placebo is indicated by a horizontal line. Each point represents either the mean ($n$ = 7) total number of shifts in sleep-waking states in 360 min (a); sleep efficiency (%) in 360 min (b); number of awakenings in 360 min (c); or minutes from lights out to first sleep spindle (d). Relative potency of morphine is indicated for measures with a valid bioassay.

Several ST and SN measures of NREM sleep showed comparable valid bioassays. Relative potency in these measures ranged from 1.42 (mean spindle sleep episode in ST) to 2.08 (number of spindle sleep episodes in SN), with the confidence limits of all relative potency estimates overlapping 2:1.

Several ST and SN measures of REM sleep also showed comparable valid bioassays. Relative potency ranged from 1.53 (total EMI in ST) to 2.09 (waking state disruptions of REM sleep in SN), with the confidence limits of all relative potency estimates overlapping 2:1.

*Pattern of insomnia*

The pattern of insomnia after 12 mg of heroin (Figure 2) showed increased wakefulness with variable amounts of muscle tension. This illustration resulted from defining every minute containing wakefulness as being waking state. With a finer differentiation (reflected in Table 1), wakefulness could be seen to be regularly interrupted by episodes of drowsiness (or sleep). Such fluctuating insomnia is associated with a delay and disturbance of the regular nocturnal pattern of REM sleep (Figure 4) and differs greatly from placebo (Figure 5), which induces fewer, briefer and less tense waking episodes. The frequency of K-complexes during sleep was changed little in the latter part of the night after opiates, but the number of K-complexes was observed to increase in the early part of the night in the sleep between episodes of wakefulness and drowsiness.

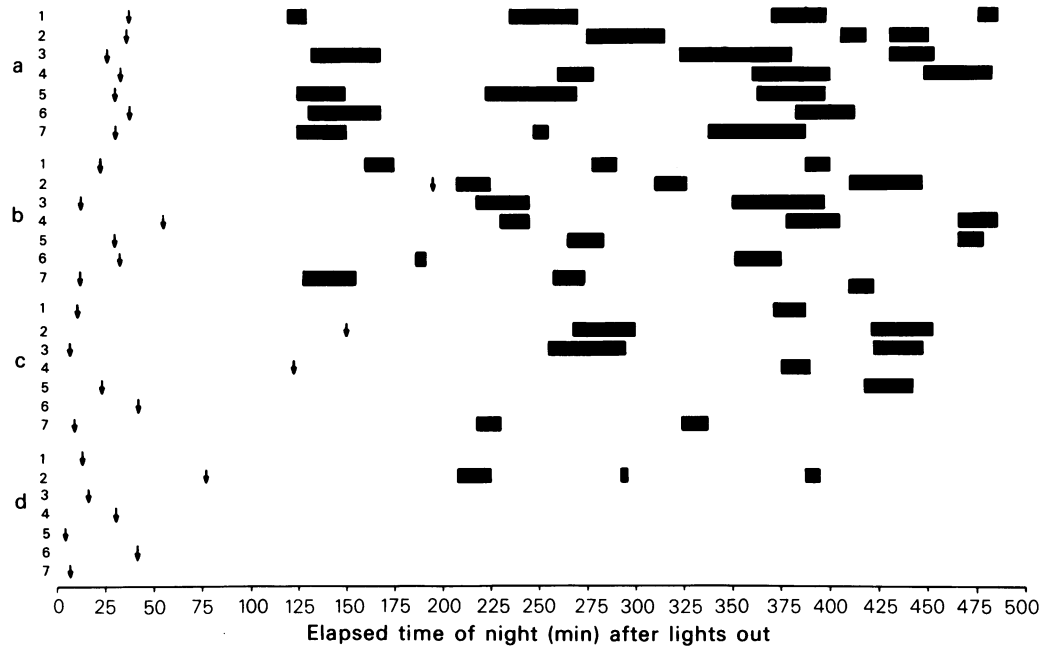


**Figure 4** The actual pattern of sleep onset (↓) and REM sleep episodes (■) is graphically represented for the night of each of seven subjects under four drug conditions: a) placebo; b) 3 mg heroin; c) 6 mg heroin; and d) 12 mg heroin. All dosages are mg/70 kg.

## Discussion

### *Baseline arousal in addicts*

As part of their informed consent, the subjects in this study knew that the only active drugs which they would receive would be opioids, some dosages of which would be euphorigenic. This probably led to more arousal during this drug study than in sleep studies with other types of drugs. Arousal similar to that seen in the subjects of this study has been reported previously in opiate addicts just prior to the onset of chronic morphine administration (Kay, 1974). Subjects in the current investigation demonstrated somewhat more nocturnal insomnia (Figure 5) than that seen after placebo in prior studies with other nondependent opiate addicts: In comparison with the average weekly placebo night of 33 other addicts (Kay, 1974), placebo nights in this study showed more waking (72.8 *v* 58.7 min/SN), greater drowsiness (39.1 *v* 7.9 min/SN), and less total sleep (338 *v* 382 min/SN). Such nocturnal wakefulness in addicts is greater than that (48.3 min) reported in a nonaddict population of comparable age (Williams, Karacan & Hursch, 1974). Much of the wakefulness during placebo condition in this study was seen in one subject (Figure 5).

Although the arousal seen during placebo nights in these addicts could be considered a learned (or conditioned) response, evidence exists that some individuals are more liable to stimulation by opiates. Harley (1868) found two types of response to opium in both humans and dogs. In one type, opium induced sleep easily, even to the point of narcotism; while in the other it was very difficult to induce sleep or narcotism. 'In this latter class, opium produces the most distressing symptoms—faintness, prolonged nausea and retching, with intervals of dreamy, delirious somnolency, rarely or never deepening into sleep.' Kreuger, Eddy & Sumwalt (1941) in their review of early literature, noted several examples of behavioural arousal after morphine, but explained these as common variants from the usual quieting effect on humans. Hill, Haertzen, Wolbach & Miner (1963) and Haertzen (1966) have found that morphine shares several characteristics with the stimulant amphetamine, as measured by the ARC Inventory in addicts.

There is evidence that nondependent addicts differ from the general population in response to morphine. Andrews (1941) noted marked behavioural effects in normal individuals: 'Nausea, even to the point of vomiting, lassitude and general depression were common experiences and there was

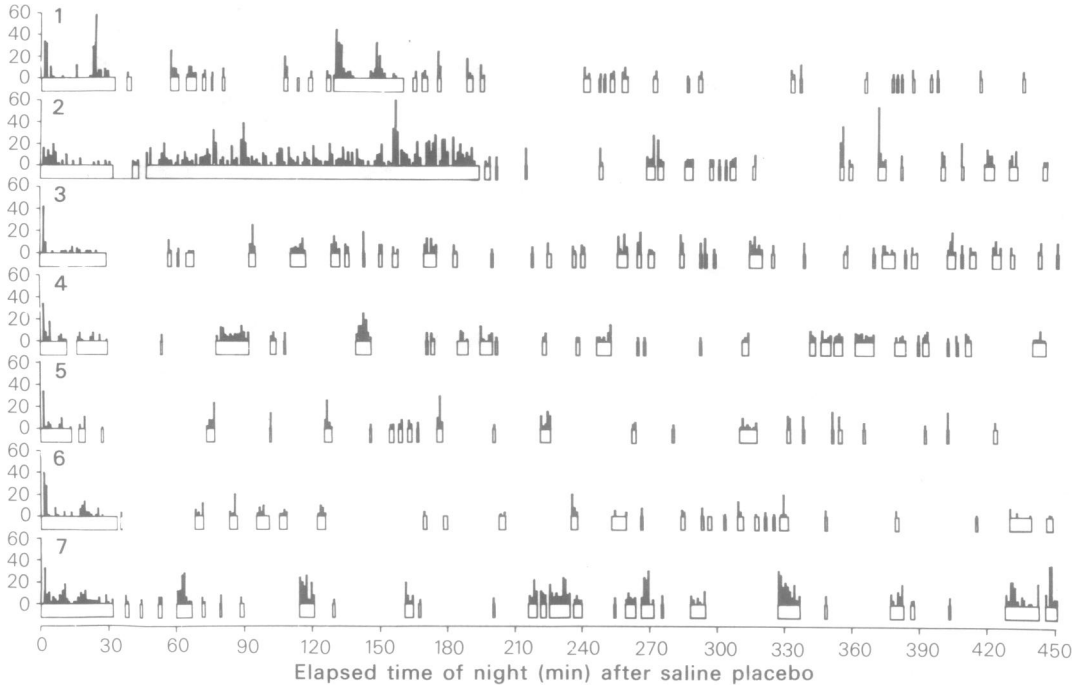


**Figure 5** Wakefulness and muscle tension after placebo. For each of seven subjects, the presence of wakefulness (lower open blocks) and duration (0–60 s) of muscle tension (upper solid lines) is illustrated for each minute of the night after administration of saline placebo. Except for one subject ($S_2$), waking episodes were relatively short and most (except for $S_2$ and $S_7$) had little muscle tension in them.

no evidence of the excitement phase (which has been) observed in those who had been previously addicted.' When Wikler (1954) studied morphine effects in non-dependent addicts he also emphasized the uniform pattern of arousal, 'thrill' and euphoria in these subjects as contrasted to the variety of behavioural effects seen in normal individuals. Lasagna, von Felsinger & Beecher (1955) and Beecher (1959) found that nondependent addicts tended to experience mental stimulation and euphoria after opiates, in contrast to the 'mental clouding' and dysphoria seen in typical college students. Von Felsinger, Lasagna & Beecher (1955) described the atypical college student (who became euphoric after opiates) as immature, impulsive, self-centred and emotional. They found these individuals to 'use excessive fantasy to handle their strong but diffuse striving for achievement which was beyond their capabilities'. This description also fits many addicts. Recent data collected by Hewett & Martin (1980) support the concept that both the childhood and adult life of an addict are characterized by significantly more sleep disturbances than in nonaddicts. The baseline insomnia seen in our subjects thus could be an expression of this basic sleep disorder, as well as their anticipation of potential opiate drug effects.

*Comparability of heroin and morphine*

*Behaviour and subjective effects* The behavioural effects of heroin are similar to those of morphine after subcutaneous (Fraser, Van Horn, Martin, Wolbach & Isbell, 1961) and intravenous (Martin & Fraser, 1961) administration in nondependent opiate addicts. Both (Fraser *et al.*, 1961) produce a typical pattern of physiological signs (miosis, analgesia, bradypnea, hypothermia), behaviour (talkativeness, scratching, vomiting, nodding), and subjective effects (euphoria, 'coasting', internal energy, itchy, 'turning' of stomach). Intravenous morphine does produce more skin tingling and conjunctival reddening than heroin (Martin & Fraser, 1961).

*EEG* No clear differences between heroin and morphine are evident in effects on the EEG (Martin & Kay, 1977). Both morphine (Hawkes, Brunt, Prescott & Horn, 1973) and heroin produce EEG slowing. After an extremely large intravenous dose of

heroin (mean 22.9 mg) to 63 opiate addicts, increased alpha amplitude, decreased alpha frequency and occasional alpha spindles were seen within 2 min (Volavka, Zaks, Roubicek & Fink, 1970). After 5 min, alpha activity was replaced by theta activity, which itself increased in amplitude and decreased in frequency over time; in most subjects, this was replaced with delta activity, and 19 subjects then showed EEG paroxysmal activity—with two men experiencing clonic seizures (promptly antagonized by naloxone). This EEG slowing was associated with omission errors in performance tasks, increased reaction time, bradypnea, miosis, tachycardia, and euphoria—all of which were antagonized by naloxone (Volavka, Levine, Feldstein & Fink, 1974). Morphine also slows alpha frequency and produces slower frequencies in some humans at a 20 mg i.m. dosage (Andrews, 1941; 1943). Both heroin and morphine are known to be convulsants at higher dosages, so this EEG slowing probably does not represent sedation alone.

*Sleep* The effects of single doses of morphine on human sleep seen in the current study replicate the results of investigations by Kay and associates (Kay *et al.*, 1969; Pickworth *et al.*, 1981). Morphine (7.5, 15, 30 mg/70 kg) produces a dose-related increase in insomnia and muscle tension in nondependent opiate addicts (Kay *et al.*, 1969); it also produces a dose-related decrease in REM sleep and delta sleep. In the current investigation, morphine increased arousal and decreased REM sleep in a dose-related fashion, and decreased delta sleep below placebo. Morphine has also been found to decrease REM sleep in rabbits (Khazan & Sawyer, 1964) and to decrease both REM sleep and NREM sleep in rats (Khazan, Weeks & Schroeder, 1967) and cats (Echols & Jewett, 1972). However, while morphine decreases REM sleep, it increases a catatonic state and NREM sleep slow waves in a dose-related fashion during a 2-h experiment in the dog (Pickworth & Sharpe, 1979); possibly during a longer experiment a hyperarousal response would also be seen in the dog, comparable to the stupor-arousal pattern in the rat (Colasanti, 1977). Although not previously described in humans, heroin was found in the current study to produce insomnia, increase muscle tension, and decrease both REM sleep and NREM sleep in a dose-related fashion.

### *The character of morphine insomnia*

The pattern of opioid insomnia can be appreciated in part by comparing Figures 2 and 5, where each minute was defined by whether it contained *any* waking state. Furthermore, when sleep–waking states are defined to the nearest 2 s after lasting at least 10 s (as in Table 1–3) it becomes evident from the *number* of sleep–waking state episodes that the wakefulness produced by morphine and heroin is regularly broken by episodes of drowsiness or sleep. It also can be seen in Figure 2 that muscle tension during wakefulness after heroin consists of several highly variable episodes. Anecdotal reports from the subjects in this and other studies would support the idea that this fluctuating drowsy–waking state is not dysphoric, even when morphine-like symptoms are not detected by the subjects. Such a pattern of insomnia (wakefulness and episodic muscle tension regularly punctuated with drowsiness) might be contrasted with other potential patterns of insomnia: prolonged wakefulness punctuated only with marked muscle tension; or, sleepfulness punctuated with brief episodes of waking and/or muscle tension. Also, this pattern of morphine insomnia in humans does not appear to be the same in all species: equivalent dosages of morphine produce prolonged arousal in the cat (Echols & Jewett, 1972) while much higher dosages of morphine produce stupour and then prolonged arousal in the rat (Colasanti, 1977); in the dog, morphine does not appear to initially produce insomnia (Pickworth & Sharpe, 1979).

### *Opiate insomnia as a model*

Current study of insomnia is complicated by the highly variable sleep of individuals who suffer from chronic insomnia (Karacan, Williams, Littell & Salis, 1973). It therefore would be quite helpful to have an experimental insomnia with which to test the hypnotic effects of drugs in normal subjects (Kay, Blackburn, Buckingham & Karacan, 1976). Besides insomnia induced with physical stimuli such as noise (Okuma & Honda, 1978), drug-induced insomnias can provide the basis for discovering different mechanisms (and treatments) for insomnia. Morphine insomnia in cats has already been used to evaluate diazepam, flunitazepam, glutethimide and DSIP (Scherschlicht, Schneeberger, Steiner & Haefely, 1979). Opiate insomnia in humans might also provide a unique model in which to test hypnotics.

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