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Treatment of Narcolepsy with Codeine

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Summary: The effectiveness of codeine as a treatment for the excessive daytime sleepiness of narcolepsy was studied in two experimental trials. In an open trial of codeine in five narcoleptic subjects, dramatic clinical improvement was reported. However, all-night polysomnography and maintenance of wakefulness tests before and after codeine showed no significant differences. A double-blind placebo-codeine trial was conducted in which eight narcoleptic subjects received codeine for 1 week and placebo for 1 week in a random order. During the week they kept a diary, and on the sixth evening and for 10 h following awakening on the seventh day they were monitored by radiotelemetry in the sleep laboratory for electroencephalogram, electro-oculogram, and electromyogram. The results were analyzed for sleep stages as well as four levels of wakefulness. The results showed no significant differences in any of the objective sleep or wakefulness parameters. However, the diaries showed significantly fewer naps during the week on codeine as compared with the placebo week. Eighteen of 27 narcoleptic patients treated with codeine report clinical improvement. Codeine consistently results in subjective clinical improvement. However, this is not reflected in the objective measures generally used to assess daytime sleepiness. **Key Words:** Narcolepsy—Opiates—Codeine—Excessive daytime sleepiness.

The current treatment for the excessive daytime sleepiness (EDS) of narcolepsy consists of stimulants such as pemoline, methylphenidate, and amphetamines (1). However, these drugs are often unsatisfactory because of variable response, undesirable side effects, and tolerance (2–7).

In a case report, Harper (8) described a 55-year-old narcoleptic patient whose EDS and associated symptoms were relieved by either codeine phosphate or pentazocine, which were prescribed for control of pain and diarrhea of Crohn's disease. The response to these medications suggested that another class of drugs, opiates, might be useful in the treatment of the EDS of narcolepsy. It also implies that the endorphin system is involved in the neurochemical lesion of narcolepsy.

We report here the results of an open trial of codeine (9), a double-blind placebo-codeine trial, and the results of our clinical experience with 27 narcoleptic patients treated with codeine.

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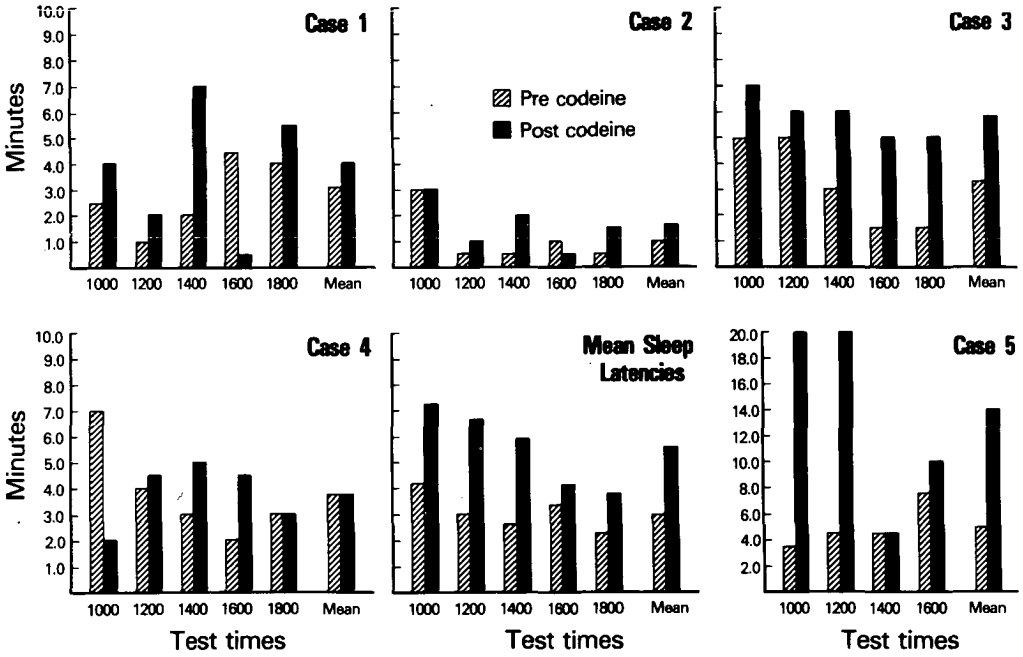

FIG. 1. Comparison of maintenance of wakefulness test (MWT) latencies before and during treatment with codeine.

STUDY 1: AN OPEN TRIAL OF CODEINE

Patients and methods

The subjects were five narcoleptic patients, aged 34–55 years, with definite cataplexy. Stimulant drugs were discontinued ≥1 week prior to an all-night polysomnographic recording that ruled out the possibility of other sleep disorders contributing to EDS. The polysomnogram was followed by the maintenance of wakefulness test (MWT) (10). The MWT consisted of polysomnographic monitoring during five 20-min trials of the ability to remain awake at 2-h intervals throughout the day. The patient was seated in a comfortable reclining chair in a darkened room and instructed to sit quietly and stay awake for as long as possible. Sleep onset was defined as three consecutive 30-s epochs of stage 1 sleep or one 30-s epoch of stage 2, 3, 4, or REM sleep as defined by standard criteria (11). The trial was terminated after 20 min if no sleep occurred or after 10 min if sleep did occur. The subjects were not allowed to nap between test times.

Following these recordings the subjects were given codeine, 30-mg tablets p.o. A 30-mg dose was taken ~30 min after awakening in the morning and then every 3–4 h during the day until a total of five doses of codeine were taken per day. After receiving codeine for ≥2 weeks, the subjects returned to the Sleep Disorders Center for repeat recordings and to report any changes in their symptoms.

Results

Figure 1 shows the results of the MWT before and during codeine treatments. Prior to codeine, all subjects had sleep latencies well within the range of pathological daytime sleepiness (<5-min sleep latency). In the first four subjects, although the tendency was to increase the MWT, the changes were small and most tests tended to remain within the

range of pathological sleepiness. In the fifth subject, sleep latencies increased to within the range of normal daytime alertness. As a group, the increase in sleep latencies did not reach statistical significance.

However, all subjects reported dramatic clinical improvement in daytime sleepiness. Three of the subjects also noted a decrease in the frequency of cataplectic attacks. Two subjects who had frequent amnestic periods and automatic behaviors reported a complete resolution of these symptoms. Four of the five subjects preferred codeine over all previously used stimulant medications because of both the effectiveness and the lack of side effects. The only side effect noted was constipation, which was fairly well controlled by stool softeners and mild laxatives.

STUDY 2: DOUBLE BLIND PLACEBO-CODEINE

Patients and methods

The subjects were eight narcoleptic patients with a mean age of 45 ± 8.9 years. All subjects had definite cataplexy and diagnostic polysomnograms and multiple sleep latency tests (MSLT). All subjects were free of stimulants for at least 2 weeks prior to administration of codeine or placebo. Throughout the study, subjects kept a daily diary of naps, cataplectic attacks, nocturnal sleep, and the time medications were taken. Each subject received placebo for 1 week and codeine for 1 week. The order was randomly determined. On the night of the sixth day of each week, the subjects slept in the sleep laboratory monitored by radiotelemetry (Telefactor Model TM 100-8R). The following parameters were monitored; electroencephalogram (EEG) (C_4-A_1,A_2, O_1-A_1,A_2), electro-oculogram (right and left outer canthi), and electromyogram (bilateral mentalis muscle). On the seventh day, monitoring by radiotelemetry was continued for 10 h after the morning awakening. Subjects remained in the laboratory area and were permitted to engage in quiet activities, including sleeping and eating, as they wished. The radiotelemetered parameters were recorded on a polygraph. This procedure was repeated on the sixth and seventh days of each week. The polygraphic record was sleep stage scored by standard criteria (11). In addition, the waking EEG was subdivided into four stages: active alertness with movement, active alertness without movement, quiet alertness, and drowsiness. In addition to the usual scoring of 30-s epochs, the record was scored in real time to include any microsleeps. Any intrusion of sleep stages or of the drowsy wake stage that lasted ≥3 s was scored and tallied separately.

The daily diaries were also analyzed for the number of naps, number of cataplectic attacks, amount of nocturnal sleep, and adherence to the drug schedule.

Results

An analysis of the nocturnal sleep parameters and the nine daytime levels of alertness and sleep failed to show any significant differences when compared by paired *t* tests.

However, an analysis of the diary data with paired *t* tests showed a significant reduction in the number of reported daily naps from 3.2 ± 1.8 to 1.9 ± 1.8 ($t = 3.4$, $p < 0.007$). The other variables were not significantly different.

REVIEW OF CLINICAL EXPERIENCE

Patients and methods

Twenty-seven diagnosed narcoleptic patients with a mean age of 45.4 ± 10.7 years (range 19–62 years) were treated with codeine. For patients who had discontinued codeine the reasons for discontinuation and the length of time taken were determined. All patients

taking codeine were interviewed during a follow-up visit or by telephone. They were asked to describe their current medications, their present dosage of codeine, how effective codeine was, how they would compare codeine with their previous stimulant medications, and any side effects they experienced with codeine treatment.

Results

Eighteen of these 27 patients have continued codeine and have been taking it for 10–33 months. Of the nine patients who discontinued, eight discontinued within 6 weeks. The reasons for discontinuation include ineffectiveness in seven cases, worsening of a preexisting depression in one case, and an allergic rash in one case. Among the 18 patients who continue to use codeine, eight report no side effects, seven report mild constipation, two report severe constipation, and 1 reports "slowed thinking." The amount of codeine taken is 90–180 mg/day in divided doses for 14 patients and 30–90 mg/day 1–3 days/week for the other four patients. All 18 patients reported that the codeine was definitely effective for reduction of daytime sleepiness. The four patients who do not take codeine every day have mild EDS and take codeine only during situations when they are especially prone to sleepiness or on days when they are unable to take regular naps. These patients reported that codeine taken as needed results in a dependable reduction in EDS. All of the 14 patients who take codeine daily (with 2–4 drug holidays per month) are employed and/or attending college. These patients reported improvement in daily performance due to reduction in EDS and amnestic episodes. Of the 18 patients who continued taking codeine, 14 had previously taken stimulant medications. Of these 14 patients, eight preferred codeine because previously taken stimulants caused intolerable side effects, three because stimulants were less effective, and the remaining three for both reasons. Thus, clinical evidence suggests that codeine is useful for the treatment of excessive daytime sleepiness of narcolepsy.

DISCUSSION

The dramatic clinical improvement of the subjects in both studies as well as patient satisfaction provides evidence for the usefulness of opiates in the treatment of the EDS of narcolepsy. The advantage of codeine over analeptic medications is that the side effects of codeine are generally limited to constipation, whereas stimulants produce a variety of side effects, including irritability, nervousness, insomnia, and cardiovascular symptoms (2–7).

The MSLT has objectively documented changes in alertness following sleep deprivation or sleep extension and has been reported to be significantly correlated with subjective alertness (12–14). However, previous studies of treatment efficacy of stimulant drugs in narcolepsy have often produced a pattern of subjective improvement without change in objective measures such as the MSLT and MWT as reported here. During the discussion of a report of the failure of the MSLT to document subjective improvement in alertness in treated sleep apneic patients, Roth et al. (15) also noted an attempt to document improvement in daytime alertness in five narcoleptic patients with the MSLT. These narcoleptic patients reported subjective improvement in alertness following treatment, but showed no change with the MSLT. The type of treatment was not indicated. Hartse et al. (16) reported on five narcoleptic patients treated with dextroamphetamine 30 mg, pemoline 37.5 mg, protriptyline 20 mg, or protriptyline 10–20 mg plus pemoline 37.5–75 mg. These patients reported subjective improvement in alertness that was not documented with the MSLT. Mitler et al. (10) reported on eight narcoleptic patients with improvement in their subjective alertness but with no change on the MWT following treatment with pemoline and/or protriptyline. A subsequent noncontrolled study of 12 narcoleptic patients by Mitler et al. (17)

documented an increase in MWT latencies following treatment. Patients were treated with pemoline, methylphenidate, or dextroamphetamine and/or an anticataplectic drug such as protriptyline or imipramine. The type of drug and the doses were selected by the treating physician on a patient-by-patient basis. Followup testing with the MWT was done when patients reported at least 25% improvement. Mitler et al. (18), in a treatment efficacy study of methylphenidate, pemoline, and protriptyline at different doses in narcoleptic patients, documented a significant increase in the mean MWT latency only at the highest dose of methylphenidate, 60 mg. Thus, the MSLT and MWT inconsistently document subjective improvement of alertness in narcoleptic patients after treatment with stimulants.

The problem appears to be in the lack of appropriate tests that detect or respond to the subjective improvement. The MSLT, the state-of-the-art measure for sleepiness, is thought to measure the baseline level of sleepiness or latent sleepiness (19). The MWT involves the motivation to remain awake and thus was thought to be a good measure of manifest sleepiness (10). The use of radiotelemetry in study 2 of this report was an attempt to avoid structured testing situations, which are conducive to sleep, and to measure variations in alertness in a more normal environment in which subjects were not prevented from sleeping when they wanted to and in which sleepiness could be measured during wakefulness. The failure of this method to detect any differences suggests either that polysomnographic recording and/or analysis techniques are inadequate or that the improvement reported by narcoleptic patients does not reflect the quantity of sleepiness, but rather an improvement in the quality of alertness. This explanation is supported by the findings of Mitler et al. (18) that narcoleptic patients improved significantly on performance tests with various doses of stimulants that did not result in significantly increased MWT latencies.

The symptomatic improvement reported by the majority of patients treated with codeine suggests that opioids are involved in the pathophysiology of narcolepsy. Harper (8) suggested that narcolepsy could result from excess firing of locus ceruleus neurons because of inappropriate acetylcholine excitatory effect or diminished adrenergic inhibitory effect. Opiates might inhibit this excessive firing and allow the normal sequence of wakefulness and sleep. This theory is supported by studies showing that the locus ceruleus appears necessary for the REM state to occur and by the very high density of opiate receptors found there (20). Iontophoretic application of opiates to the locus ceruleus produces marked and prolonged depression of spontaneous activity (21).

In two recent single case reports, the administration of the opiate antagonist naloxone appeared to decrease the symptoms of narcolepsy (22,23). This suggests that narcolepsy symptoms may be related to excess activity of the endogenous opiate system. However, a study now in progress in this laboratory suggests that low-dose naloxone does not affect subjective alertness in narcoleptic subjects.

The evidence reported suggests that codeine and other opiates may be useful for the treatment of the EDS of narcolepsy. An entirely different class of drugs with significantly fewer side effects may thus become useful for the treatment of the major symptoms of narcolepsy, EDS.

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