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Effects of Nonsedating Histamine H_1-Antagonists on EEG Activity and Behavior in the Cat

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MARZANATTI, M., A. MONOPOLI, M. TRAMPUS AND E. ONGINI. *Effects of nonsedating histamine H_1-antagonists on EEG activity and behavior in the cat.* PHARMACOL BIOCHEM BEHAV **32**(4) 861–866, 1989.—The central effects of the newly-developed antihistamines (H_1-receptor antagonists) loratadine, astemizole, mequitazine and terfenadine were evaluated by studying brain electrical activity (EEG), sleep-waking patterns and behavior in the cat. The different stages of the sleep-waking cycle, i.e., wakefulness (W), spindle sleep (SS), slow wave sleep (SWS) and REM sleep (REM) were evaluated. The power spectrum analysis of the EEG was obtained by a computerized technique. For comparison, the sedating agent diphenhydramine was examined. Given at 3 mg/kg orally, a dose slightly above that effective therapeutically, diphenhydramine markedly affected behavior and all sleep stages. In particular, it depressed REM and increased SS (drowsiness). The EEG showed occasional spikes typical of subconvulsive states. Loratadine did not modify either sleep patterns or behavior over the 3–30 mg/kg dose range orally, which is far above that used clinically. The EEG, evaluated either visually or by spectral power analysis, was unaffected. Astemizole at 10 and 30 mg/kg PO reduced REM, markedly altered behavior at 30 mg/kg, but did not modify EEG activity. Mequitazine, at low doses (1–10 mg/kg PO), enhanced SS and decreased SWS and REM. Like diphenhydramine, mequitazine induced EEG changes typical of subconvulsive states and affected EEG power over the frequency range of 0.1–15.0 Hz. Terfenadine did not change sleep patterns and slightly affected behavior only at the high dose of 30 mg/kg orally; EEG activity was not influenced. These data show that: a) diphenhydramine and mequitazine appear to produce CNS effects by altering basic processes within the brain; b) astemizole and terfenadine seem to cross the blood-brain barrier at high doses only; c) loratadine has the lowest liability to produce central side effects. Of the sleep features examined, REM appeared to be the most sensitive stage to blockade of central H_1-receptor pathways.

H_1-antagonists Loratadine Sedation REM sleep EEG activity Cat

A major limitation of conventional antihistamines, H_1-receptor antagonists, is their liability for a variety of undesirable side effects (6,23). Among these, the most common are concerned with the central nervous system (CNS) and include both sedation and stimulation (6). Consequently, there has been an effort to develop new antihistamine agents free of central effects. One such, loratadine (SCH 29851), has been found to possess a promising therapeutic effectiveness without side effect liability (2,27). In laboratory animals, loratadine exhibits antihistamine activity and inhibits responses mediated by other autacoids which are involved in allergic reactions (2,10). Clinical studies have largely confirmed that loratadine given at 10 mg once a day is effective for treatment of rhinitis, conjunctivitis and other allergic disorders (3, 5, 22). Studies in different animal species including man have demonstrated that the compound does not interfere with CNS functions and therefore meets the criteria for being classified as a "nonsedating" antihistamine (2–4, 18, 24). Over the last few years, other compounds have been discovered whose structures prevent penetration into the CNS. In addition, compared with classic antihistamines, the new compounds have relatively higher affinity for H_1-receptors than for other receptor systems (11, 21, 26). Those currently used include astemizole (21), terfenadine (26) and mequitazine (12,15).

The present studies were designed to assess the central effects of loratadine and other "nonsedating" antihistamines in the cat, an animal species highly sensitive to central actions of a variety of drugs including antihistamines (7, 8, 17, 18). To provide an objective comparison of drug effects on the CNS, measurements of brain electrical activity (EEG), as associated with related behavioral states, were used as major descriptors of effects on the sedation-arousal continuum. Visual interpretation of EEG recording was supplemented by frequency analysis which had proved useful in the quantification of bioelectrical patterns of drugs effective on the CNS (9).

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METHOD

Behavior

Adult male drug-naive cats (2.5–3.5 kg), Savo-Ivanovas strain, supplied by Charles River, Italia (Calco, Como), were housed in the experimental environment and allowed to grow accustomed to it for 1 month prior to the experiments. The cats were handled several times a week to assess their baseline behavior and responses to stimuli.

Gross behavior changes as well as indices of neurologic and autonomic involvement were investigated by following a modification of the method of Irwin (8). The cats were observed at hourly intervals, starting 1 hr before treatment and continuing for 4 hr afterward. A late observation was made 24 hr after drug administration. The information was recorded on a sheet by raters who were unaware of the treatment schedule. Behavior was scored for locomotor activity (ability to walk and occurrence of spontaneous locomotion), muscle tone (abdominal tone and posture), response to observer approach (fearfulness or playfulness), approach to food (refusal), salivation and vomiting. Any divergent responses from the baseline state of the animals were noted. Each deviation from baseline behavior was scored as "1" for each of the 6 measures examined. The observations were collected at selected time points (1, 2 and 4 hr) and scores were averaged to have the mean score for each cat. Then, the data from the 5 animals that received the same treatment were grouped together and the mean group score was calculated. After completion of the study, ANOVA with Dunnett's test was carried out to compare drug treatments. Post hoc individual comparisons were also performed to compare each drug with loratadine.

Sleep-Waking Cycle and EEG Activity

A second group of cats was prepared with electrodes chronically implanted for the measurement of the cortical and hippocampal electroencephalographic (EEG) activity and neck electromyogram (EMG) as described elsewhere (17). The cats were habituated to stay periods of 8 hr in a Plexiglas box located in a sound-attenuated, electrically-shielded room until sleep-wakefulness measures were relatively constant. The animals were kept under a normal light/dark cycle and experiments were conducted during the light period. At least 2 months elapsed between surgery and the beginning of recordings.

EEG activity was recorded on a Battaglia Rangoni BP8 electroencephalograph and scored visually to assess whether drugs produced changes in the electrical activity. Concomitantly, during the experiments, the animals were observed by means of a monitor to match EEG patterns with behavioral states and allow the classification of wakefulness (W), spindle sleep (SS) slow wave sleep (SWS) and REM sleep (REM). This was made by experienced observers, who were unaware of the treatment schedule, according to concomitant evaluation of behavioral, EEG and EMG changes. Evaluation of all 1-min epochs for periods of 8 hr was made on the basis of standard criteria and fed on-line in a minicomputer (Brain Surveyor, Basis Trade, Verona, Italy) programmed to develop hypnograms and separate the varying features of the sleep-waking cycle. For each measure, statistical analysis was made using ANOVA and comparison among treatment groups were made by multiple comparison procedures (Dunnett's test). Data from the diphenhydramine group were compared with the control group by Student's *t*-test.

Two channels (left fronto-parietal cortex and dorsal hippocampus) were also analyzed on-line by a computer (BFA 3364, Ote Biomedica connected with Brain Surveyor, Basis) which was programmed for the processing of the EEG activity by the Fast Fourier Transform (FFT). This was done on segments of 8 sec in the frequency range of 0.1–32.0 Hz with a resolution of 0.1 Hz. Artifacts appearing on the background activity were automatically suppressed by a preset artifact rejection algorithm (elimination of sudden peaks having an amplitude greater than 128 μV). Spectral arrays for 8-sec samples were plotted on-line on a monitor with an overlap of 7/8 sec to evaluate visually the major changes occurring on spectral power. The samples were then automatically averaged to obtain one power spectrum for every min and stored in a file on disc. Every 1-min power spectrum up to 8 hr was automatically associated with the corresponding sleep stage. Then, cumulative values within each sleep stage were averaged to give the mean power for each experiment. The program also calculated the relative power of selected frequency bands. These were defined on the basis of pilot experiments which provided information on the frequency range where drug effects appeared to be more evident. Specifically, three bands were selected: (A) 0.1–8.0; (B) 10.0–15.0; (C) 16.0–32.0 Hz. For each stage of sleep, mean power values were analyzed statistically by ANOVA with Dunnett's test. Data were also transformed into a standard score (Z-score) to express features of EEG changes produced by each drug treatment (mean power after treatment minus mean power of control)/standard deviation (9).

Treatment Schedule and Drugs

Behavior and sleep-waking patterns were studied in separate experiments with different groups of cats.

On the basis of data described elsewhere (18) for each antihistamine except diphenhydramine, we selected the dose of 30 mg/kg for behavioral studies and 10 mg/kg for effects on the sleep-waking cycle. This latter dosage did not dramatically influence sleep patterns for the drugs tested. For diphenhydramine, a lower dose (3 mg/kg) was considered to be more appropriate in order to avoid marked behavioral and neurological effects.

Drugs were administered orally at 10 a.m. immediately prior to starting the experiments. They were placed in gelatin capsules containing a standard amount of corn starch and lactose; capsules with only excipient were used in control animals. The compounds used were obtained from the following sources: loratadine (Schering-Plough, USA), diphenhydramine (Recordati, Italy), astemizole (Janssen, Belgium), mequitazine (Rorer, Italy) and terfenadine (Dow-Lepetit, Italy).

Except for studies on diphenhydramine which were conducted separately, experiments were designed to ensure that each cat received each treatment once, according to a 5×5 latin square crossover design. A single 5×5 design was used for behavioral studies, whereas two separate 5×5 designs, which were then grouped together, were used for EEG studies. A period of 2 weeks elapsed between the sessions. Since mequitazine produced severe changes at 10 mg/kg, separate experiments were undertaken to evaluate whether it produced dose-dependent effects (0.6–5 mg/kg).

RESULTS

Behavior

Diphenhydramine (3 mg/kg) potently affected all of the behavioral measures in most of the cats. The effects were evident within 30 min, reached a maximum at 1–2 hr and lasted more than 4 hr. Periods of hyperactivity alternated with immobility, food refusal, salivation and vomiting were the most obvious behavioral changes, followed by tremors, fearfulness and muscle rigidity (Table 1). Quantification of behavioral changes provided a mean group score

TABLE 1

EFFECTS OF LORATADINE, DIPHENHYDRAMINE, ASTEMIZOLE AND TERFENADINE ON SOME MEASURES OF BEHAVIOR IN THE CAT

Measures for Altered Behaviors	Control (n=5)	Diphenhydramine 3 mg/kg (n=5)	Loratadine 30 mg/kg (n=5)	Astemizole 30 mg/kg (n=5)	Terfenadine 30 mg/kg (n=5)
Altered locomotion	0	5	0	4	5
Muscle tone (rigidity)	0	2	0	2	0
Tremors	0	3	1	0	1
Responses to observer approach (fearfulness)	0	3	0	4	2
Approach to food	0	5	2	3	3
Salivation and vomiting	0	5	0	2	2
Mean group score	—	4.6±0.4†	0.6±0.2	3.0±0.7†	2.6±0.2*

Observations were made at hourly intervals commencing 1 hr before oral administration of either drugs or placebo and continuing for 4 hr afterward. Values are number of animals displaying selected altered behaviors over the observation period. Each deviation from normal was scored as "1" for each measure. The mean group score was calculated by averaging data from the 5 animals of each group.

*$p<0.05$; †$p<0.01$ compared to loratadine (Dunnett's test).

of 4.60±0.40, $F(3,16)=13.88$, $p<0.01$.

Loratadine (30 mg/kg) produced few or no behavioral changes with a mean group score of 0.60±0.24. The results of the crossover design indicate that loratadine caused significantly fewer behavioral changes than did all the other antihistamines examined (Table 1).

Astemizole (30 mg/kg) produced evident signs of general discomfort, such as vocalization, vomiting and food refusal, changes of spontaneous activity with muscle rigidity. Fearfulness and agitation were also present (Table 1). Behavioral changes appeared at 1–2 hr and were still marked 4 hr after drug administration with some residual effects after 24 hr. The resulting mean group score was 3.00±0.70 ($p<0.01$ vs. loratadine).

Terfenadine (30 mg/kg) had a mild influence on behavioral profile. Locomotion was the most affected measure and there was also a tendency to food refusal, while the other measures were modified to a lesser extent (Table 1). The resulting mean score was 2.60±0.24 ($p<0.05$ vs. loratadine).

Sleep-Waking Patterns

The reference sedating agent diphenhydramine (3 mg/kg) markedly influenced the sleep-waking parameters when compared with the control group. Duration of the different phases of sleep was significantly altered, with an increase of SS and a decrease of SWS and REM ($p<0.01$; Fig. 1). There was increased wakefulness in 3 out of 5 animals. The onset of REM sleep was significantly delayed (350±10 vs. 117±58 min of controls: $p<0.01$). Moreover, the cats assumed unusual postures during sleep.

Loratadine (10 mg/kg) produced no significant changes of the different features of the sleep-waking cycle. Neither the duration of sleep stages nor latency of the first episode of each stage was affected (Fig. 1; Table 2).

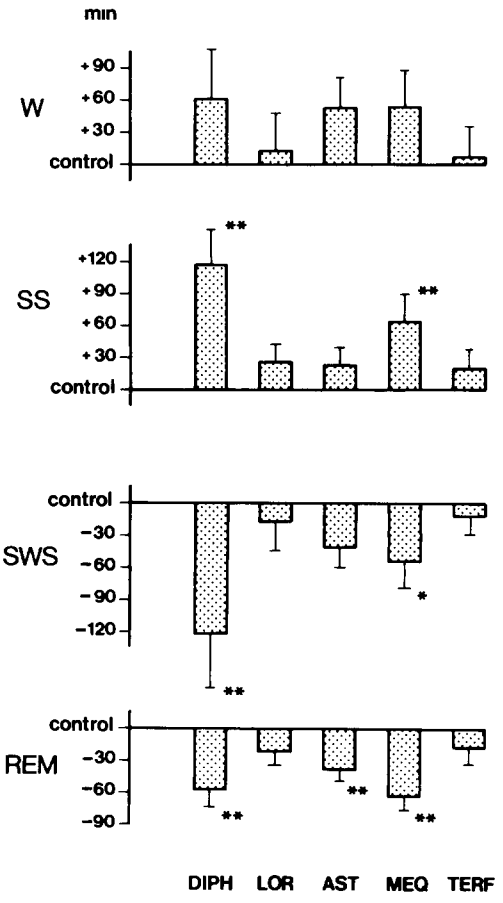

FIG. 1. Effects of H_1-antagonists on the duration of different phases of the sleep-waking cycle in the cat. Behavior and EEG activity were monitored for 8 hr after treatment. Data for astemizole, loratadine, mequitazine and terfenadine are from 2 crossover 5×5 latin square experiments. Data for diphenhydramine were obtained in separate studies on a group of 5 animals. All drugs were given at 10 mg/kg orally with the exception of diphenhydramine which was administered at 3 mg/kg. Columns represent changes in stage duration (min) as compared with the respective control values. *$p<0.05$; **$p<0.01$ compared to controls (Dunnett's test).

Astemizole (10 mg/kg) altered the sleep-waking patterns. Duration of REM was significantly reduced, $p<0.01$ (Fig. 1) and the onset of REM sleep was delayed, $p<0.1$ (Table 2). Although mean duration of W did not significantly increase when compared with control values, some of the cats showed agitation and assumed unusual postures during the brief periods of sleep.

Like loratadine, terfenadine (10 mg/kg) did not affect the varying features of the sleep-waking cycle (Fig. 1; Table 2).

Mequitazine (10 mg/kg) markedly altered the sleep-waking features. Significant increases of SS, $p<0.01$, and evident reductions of both SWS, $p<0.1$, and REM ($p<0.01$) were observed (Fig. 1). The onset of REM was also significantly delayed ($p<0.01$; Table 2). Moreover, signs of marked agitation and unusual postures occurred during sleep. In dose-response experiments, there was a tendency toward an increase of waking, $F(3,6)=4.55$, $p<0.1$ (Table 3). SS was significantly enhanced by the doses of 1.25, 2.5 and 5 mg/kg, $F(3,6)=21.26$, $p<0.01$. Duration of SWS tended to diminish reaching significance at 5 mg/kg, $p<0.01$. REM sleep was significantly reduced at 2.5 and 5 mg/kg, $p<0.05$ (Table 3).

TABLE 2

EFFECTS OF LORATADINE, ASTEMIZOLE, MEQUITAZINE AND TERFENADINE ON THE LATENCY IN ONSET OF PRINCIPAL STAGES OF SLEEP IN THE CAT

Treatment	Dose mg/kg PO	Spindle Sleep Latency (min)	Slow Wave Sleep Latency (min)	REM Sleep Latency (min)	Number of REM Episodes
Control	—	32 ± 6	51 ± 8	73 ± 10	12 ± 1
Loratadine	10	16 ± 5	52 ± 9	101 ± 17	8 ± 1
Astemizole	10	38 ± 11	79 ± 15	188 ± 29*	6 ± 1†
Mequitazine	10	15 ± 4	35 ± 6	287 ± 67†	2 ± 1†
Terfenadine	10	29 ± 7	56 ± 11	73 ± 12	11 ± 1

Behavior and EEG activity were monitored for 8 hr after either placebo or drug administration. Values are the mean ± S.E. of 2 crossover 5 × 5 latin square experiments. Note the delayed onset of REM sleep after both astemizole and mequitazine.

*$p<0.1$; †$p<0.01$ compared to controls (Dunnett's test).

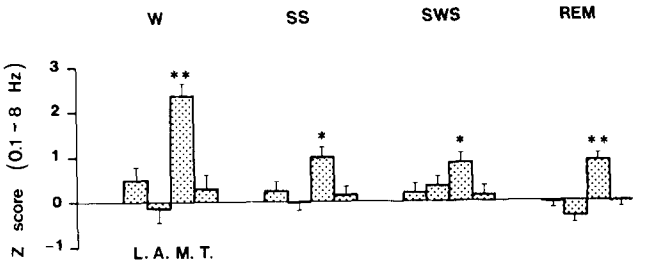

FIG. 3. Effects of antihistamines loratadine (L), astemizole (A), mequitazine (M) and terfenadine (T) on EEG spectral power in the selected frequency band of 0.1–8 Hz. Drugs were given at the dose of 10 mg/kg orally. The Z-transformation for interdrug comparisons was used (see the Method section). Mean Z-score (±S.E.) for each sleep-waking stage refers to 8-hr period from crossover experiments with 10 cats. Note that mequitazine produced significant changes of EEG power density, particularly evident during waking states. This is related to the occurrence of spikes and slow wave patterns typical of subconvulsive states. *$p<0.05$; **$p<0.01$ (Dunnett's test).

EEG Activity

When the EEG was scored visually, loratadine, astemizole and terfenadine (10 mg/kg) did not produce noticeable changes as compared with typical patterns occurring during the spontaneous sleep-waking cycle. Conversely, both diphenhydramine (3 mg/kg) and mequitazine (10 mg/kg) induced spikes and slow wave patterns similar to those produced by lower doses of convulsant agents (14). These were observed occasionally in most of the cats especially during W and SS. The effects were evident at 2–4 hr postadministration (Fig. 2).

EEG spectral analysis showed that only mequitazine, but not loratadine, astemizole and terfenadine, was able to significantly modify the power content in 2 out of 3 selected frequency bands (0.1–8.0 and 10.0–15.0 Hz). This reflected the occurrence of spikes and slow wave patterns induced by mequitazine in the EEG. Relative power values for mequitazine were significant in the low frequency range (0.1–8.0 Hz) over the stages of waking, $p<0.01$, spindle sleep, $p<0.05$, and REM, $p<0.01$. The Z-score transformation is represented in Fig. 3. In the frequency range of 10.0–15.0 Hz, changes of relative power were significant only during W and REM, $p<0.05$. No significant changes occurred in the frequency range of 16.0–32.0 Hz.

DISCUSSION

The reference antihistamine diphenhydramine and the "nonsedating" antihistamines mequitazine and astemizole produced varying degrees of CNS effects. They altered behavior and affected sleep architecture, in particular they suppressed REM sleep. Mequitazine and diphenhydramine also affected the bioelectrical activity of the brain as evidenced by signs of cortical excitation similar to those induced by subconvulsive doses of central convulsant drugs (14). Terfenadine did not alter the various behavioral and EEG parameters in the cat. Clinical studies corroborate these findings by showing that the drug produces few or no central

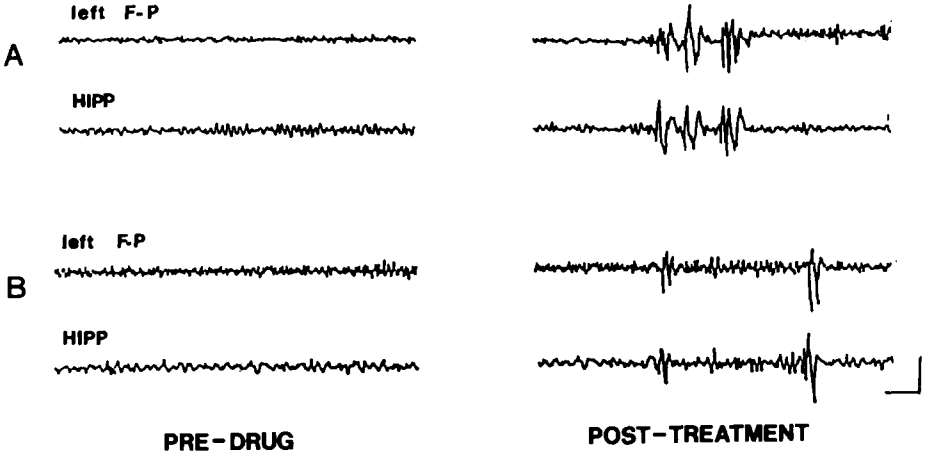

FIG. 2. Slow wave patterns and spikes induced by diphenhydramine, 3 mg/kg (A) or mequitazine, 10 mg/kg (B) on EEG activity recorded during wakefulness. Drugs were given orally. Note that EEG tracings show typical patterns of subconvulsive states. These changes were recorded between 2–4 hr posttreatment. F-P = Fronto-parietal cortex; HIPP = Hippocampus; Calibration: 1 sec, 100 μV.

TABLE 3

DOSE-RESPONSE EFFECT OF MEQUITAZINE ON DURATION OF EACH SLEEP-WAKING STAGE IN THE CAT

Treatment	Dose mg/kg PO	Waking (min)	Spindle Sleep (min)	Slow Wave Sleep (min)	REM Sleep (min)
Mequitazine	0.62	182 ± 43	107 ± 8	137 ± 33	52 ± 10
	1.25	155 ± 26	150 ± 21†	126 ± 15	48 ± 13
	2.5	147 ± 34	216 ± 17‡	99 ± 28	17 ± 5*
	5	248 ± 21	198 ± 10‡	29 ± 16‡	4 ± 2†

Behavior and EEG activity were monitored for 8 hr after drug administration. Values are the mean ± S.E. of a crossover 4×4 latin square experiment.

Note the inverse correlation between Spindle Sleep and REM by increasing the dose.

*$p<0.1$; †$p<0.05$; ‡$p<0.01$ (Dunnett's test).

effects in man (26). However, previous experiments based on a higher dose (30 mg/kg) showed that terfenadine affects sleep patterns and reduces REM (18), a finding also described in the dog (28).

Under the same conditions, loratadine was essentially devoid of effects on the CNS. Sleep patterns and the varying features of the EEG activity were not influenced by treatment with an oral dose of 10 mg/kg, which is at least 50-fold that effective in standard tests in animals and therapeutically (2, 3, 5, 22, 24). Support for this finding is provided by similar results obtained through a variety of experimental procedures in rodents, dogs, and monkeys (2,4). This has been confirmed further in the clinical setting by measures of central activity such as multiple sleep latency test (24) or sleep patterns (3). The absence of CNS effects of loratadine has been attributed to difficulty in crossing the blood-brain barrier, as shown by the results of whole body autoradiography in mice and monkeys (Zampaglione, personal communication), and the weaker affinity for central H_1-receptors as compared to the more potent affinity for those in periphery (1). Further, the compound does not substantially interact with alpha-adrenergic or cholinergic receptors which also control CNS functions (2).

The comparison of therapeutic potency of the drugs examined allows to determine which drug has the better safety margin for adverse CNS effects. The clinically recommended doses of loratadine, astemizole and mequitazine are similar and in the range of 0.1–0.2 mg/kg daily (5, 15, 21, 22), whereas terfenadine and diphenhydramine possess weaker activity and are used therapeutically at 1–2 mg/kg per day (6,26). In the cat model, the standard H_1-antagonist diphenhydramine produced marked CNS effects at a dose (3 mg/kg) close to that used therapeutically and reported to be sedating (6). Mequitazine and astemizole showed CNS effects at doses about 10- and 50-fold those used in man. Terfenadine and loratadine appeared to be free of central effects at doses 10 and 50 times higher than those used in therapy respectively. Thus, although the new compounds differ for their potential to cause CNS effects, when comparison is made with a reference older drug, it is evident that a substantial improvement has been made in the direction of developing "nonsedating" H_1-antagonists. Of the compounds examined, loratadine has shown the lowest liability for producing central effects.

In addition to having defined the profile for central effects of the new "nonsedating" antihistamines, these findings provide a contribution to the current debate on the possible functions of H_1-pathways in the CNS (19,20). This is based on the notion that central actions produced by H_1-antagonists depend upon interactions with H_1-receptors located on neural pathways which are involved in the modulation of various physiological events (13, 19, 20).

Central effects of conventional antihistamines are usually identified with the sedative side effects encountered during therapy. However, in animals, these drugs also produce stimulatory effects (4, 7, 8, 18). Specifically, in the cat model, diphenhydramine, astemizole and mequitazine produced periods of behavioral excitation and increased waking [Fig. 1; (18)]. Such a stimulatory response was not uniform in all the cats and alternated with periods of sedation. However, the overall duration of non-REM sleep (spindle and slow-wave sleep) appeared not to be modified by the compounds, even though spindle sleep seemed to increase (Fig. 1). In addition, like high doses of other antihistamines (7), diphenhydramine and mequitazine produced EEG patterns which are typically observed with drugs that induce cortical excitation and ultimately lead to EEG seizures (14). Thus, in the cat, H_1-receptor blockade appears to be more associated with arousal rather than sedation. This is difficult to reconcile with the recent findings by Lin *et al.* (13) who found that the state of arousal is induced by activation of H_1-neurons, whereas it is depressed by blockade of H_1-pathways. Since in their studies H_1-receptors were blocked by mepyramine, which also interacts with other receptors within the brain, it is likely that other factors may have contributed to the decrease of arousal. In interpreting all these findings it has to be considered that other mechanisms, beyond blockade of H_1-receptors, may underlie the variety of CNS effects produced by these drugs. In fact, some H_1-antagonists have also relatively high affinity for other receptors which have a role in the regulation of sleep patterns and physiological processes underlying EEG activity. In particular, diphenhydramine blocks cholinergic, alpha-adrenergic and serotonin receptors (11,16), mequitazine interacts with cholinergic receptors (11,12) and astemizole has some affinity in vitro for serotonin and alpha-adrenergic receptors (21).

A major finding emerging from our data is that REM is more sensitive than other sleep stages to the central actions of H_1-antagonists. This is also supported by a variety of findings with other antihistamines in animals (13, 18, 28) and man (15). This does not directly imply that histaminergic pathways are involved in the control of REM sleep. Both diphenhydramine and mequitazine may alter sleep processes through their interaction with central cholinergic pathways which have a firmly established role in the control of REM (25). It is therefore likely that the anticholinergic properties that several H_1-antagonists possess may underlie their effects on REM (11). However, this appears not to be the case for astemizole and terfenadine which instead poorly interact with acetylcholine receptors within the brain (11, 21, 26). In our studies in the cat, REM duration was reduced by astemizole dose-dependently and by high doses of terfenadine (18). In the dog, Wauquier *et al.* (28) have shown that REM is reduced by terfenadine and ketotifen, which also has relatively high affinity for H_1-receptors (11). Altogether, the data available lend support to the suggestion that REM processes might be influenced by the specific blockade of central H_1-pathways.

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