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Ketotifen and nocturnal asthma

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ABSTRACT Patients with asthma often wheeze at night and they also become hypoxic during sleep. To determine whether ketotifen, a drug with sedative properties, is safe for use at night in patients with asthma, we performed a double blind crossover study comparing the effects of a single 1 mg dose of ketotifen and of placebo on arterial oxygen saturation (SaO_2), breathing patterns, electroencephalographic (EEG) sleep stage, and overnight change in FEV_1 in 10 patients with stable asthma. After taking ketotifen, the patients slept longer and their sleep was less disturbed than after taking placebo, true sleep occupying 387 (SEM 8) minutes after ketotifen and 336 (19) minutes after placebo ($p<0{\cdot}02$). On ketotifen nights the patients had less wakefulness and drowsiness (EEG sleep stages 0 and 1) and more non-rapid eye movement (non-REM) sleep than on placebo nights, but the duration of REM sleep was similar on the two occasions. Nocturnal changes in SaO_2, the duration of irregular breathing, and overnight change in FEV_1 were unaffected by ketotifen.

Patients with asthma often become wheezy at night,[1] with an overnight fall in forced expiratory flow rates.[2] They also sleep less well, become more hypoxaemic during the night, and have more irregular beathing during sleep than do healthy people of similar age.[3 4]

Drowsiness is a recognised side effect of ketotifen (Zaditen, Sandoz),[5] and, since sleep is associated with hypoxaemia and irregular breathing in asthmatic patients we were concerned that ketotifen might have an adverse effect on patients with nocturnal asthma. We have therefore studied the effects of a single 1 mg dose of ketotifen on oxygenation, sleep quality, breathing patterns, and overnight change in one second forced expiratory volume (FEV_1) during nocturnal sleep in 10 patients with stable asthma.

Methods

We made non-invasive measurements of electroencephalographic (EEG) sleep stage, breathing patterns, arterial oxygen saturation (SaO_2), and overnight change in FEV_1 in 10 adult patients with stable asthma during nocturnal sleep in a double blind crossover trial of ketotifen. The trial was designed so that half the patients received placebo before ketotifen and half received ketotifen first. The patients slept in a quiet, darkened room on two pairs of two consecutive nights (the first serving as an acclimatisation night) separated by two to four weeks. The patients (nine men and one woman, aged 18–55 years) all had airways obstruction that was reversible and varied spontaneously. During the two years before the study the lowest FEV_1 recorded in each subject at the outpatient clinic ranged from 0·5 to 1·9 l and the highest spontaneous FEV_1 from 1·7 to 4·2 l. Eight of the patients had positive skinprick test responses to at least two common allergens, including *Dermatophagoides pteronyssinus,* and six had a family history of atopy. All the patients inhaled a $beta_2$ agonist, six inhaled beclomethasone dipropionate, and three took regular oral prednisolone in a dose of 5 mg daily. None of the patients was receiving sodium cromoglycate, antihistamines, theophyllines, hypnotics, or sedatives.

On the night of the study $beta_2$ agonists were withheld from 5.00 pm. The patients arrived in the laboratory at 9.30 pm and, after the apparatus had been set up and the FEV_1 measured, they were given one tablet of either placebo or ketotifen 10 minutes before the lights were switched off. During the night the EEG sleep stage was measured with an electroencephalogram, electro-oculogram and electromyogram, chest wall movement was measured

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semiquantitatively by magnetometers at the level of the third intercostal space anteriorly, air flow at the nostrils and mouth was detected by thermocouples mounted on nasal prongs, and SaO_2 was measured by a Hewlett-Packard 4720A ear oximeter.[6] In the morning the FEV_1 was measured when the patient woke up.

EEG sleep stages were determined by standard criteria.[7] Apnoea was defined as an episode in which air flow at the nose and mouth stopped for at least 10 seconds and each episode of apnoea was classified as central or obstructive.[8] Hypopnoea was defined as an episode lasting at least 10 seconds in which the amplitude of chest wall movement fell to less than half the amplitude during the preceding period of regular breathing. As most episodes of apnoea and hypopnoea during sleep occur repetitively,[3] we identified *periods* of irregular breathing, each of which is defined as starting with either apnoea or hypopnoea and ending at the onset of the next full two minute period of regular breathing.[3]

Differences between placebo and ketotifen nights were analysed by the paired Student's *t* test. Values are given as means with standard error of the mean in parentheses.

Results

EEG SLEEP STAGES

The lights were switched off on average at 11.36 pm (SEM 8 min) on the placebo nights and at 11.35 pm (6 min) on ketotifen nights. The total time of study—total recording time from "lights off' to "lights on"—averaged 409 (9) minutes on ketotifen nights, slightly longer than the 394 (10) minutes on placebo nights ($p<0.04$). True sleep—EEG sleep stages 1, 2, 3, and 4 and rapid eye movement (REM) sleep—occupied 387 (8) minutes on ketotifen nights but only 336 (19) minutes on placebo nights ($p<0.02$). When expressed as a percentage of total recording time, this true sleep occupied 95% (1·1%) of total recording time after ketotifen but only 85% (3·8%) after placebo ($p<0.04$). The patients took on average 28 minutes to fall asleep on placebo nights compared with 12 minutes on ketotifen nights, but this was not a significant difference. After ketotifen less time was spent in wakefulness and light sleep (EEG sleep stages 0 and 1) and more time in non-REM sleep (EEG sleep stages 2, 3, and 4) than after placebo (fig 1). The duration of REM sleep on the other hand was similar after drug and placebo, averaging 55 minutes a night.

IRREGULAR BREATHING

The cumulative duration of apnoea and hypopnoea after onset of sleep was the same after ketotifen and placebo, averaging 42 (12) minutes after the active drug and 37 (7) minutes after placebo. Most (99%) of this irregular breathing was hypopnoea. In all 10 subjects only nine episodes of apnoea occurred after placebo and 11 after ketotifen. All the apnoeic episodes were of central type.

ARTERIAL OXYGEN SATURATION

SaO_2 during sleep was also unaltered by ketotifen. The change in SaO_2 from the level before sleep (ketotifen nights 96·4% (0·7%); placebo nights 95·6% (0·9%)) to the lowest level during sleep (ketotifen 88·4% (1·2%); placebo 88·1% (1·6%)) was the same after the drug (8·0% (1·1%)) and after placebo (7·8% (1·2%)). Significant episodes of hypoxaemia (defined as falls in SaO_2 of at least 4% from the immediately preceding stable SaO_2) occurred in six patients from once to nine times (mean 2·4 times) a night on placebo. The number of episodes was not significantly different on ketotifen nights, when six patients had from one to 12 (mean 2.6) hypoxaemic episodes a night.

OVERNIGHT CHANGE IN FEV_1

The FEV_1 before sleep averaged 2·9 (0·4) l on ketotifen nights and 2·9 (0·4) l on placebo nights. In all patients the lower of these values was within 30% of the higher. After taking ketotifen none of the patients asked to use an inhaler during the night. After taking placebo, however, four of the 10 patients required their $beta_2$ agonist inhalers before going back to sleep ($p<0.1$, χ^2 test for small numbers).[9] Three of these awakenings occurred between 3.00 and 3.30 am and the other at 5.35 am. The FEV_1 recorded at these times was on average 1.0 l (range 0.3–1·7 l) lower than the FEV_1 before sleep. In the other six patients the FEV_1 was on average 0·6 l lower after sleep than before sleep when they had taken placebo, compared with a fall of 0·9 l with ketotifen. This difference (fig 2) was not significant.

Discussion

Ketotifen had no significant adverse effect on oxygenation and breathing patterns during sleep or on overnight change in FEV_1 when given as a single 1 mg dose to our 10 adult patients with stable asthma at night. Furthermore, our patients slept longer and spent more time in the deeper stages of sleep after taking ketotifen than after taking placebo.

It is not clear how ketotifen helps asthmatic patients to sleep. The drug has both antiallergic and antihistaminic properties.[10] We do not know whether it affects bronchoconstriction during sleep

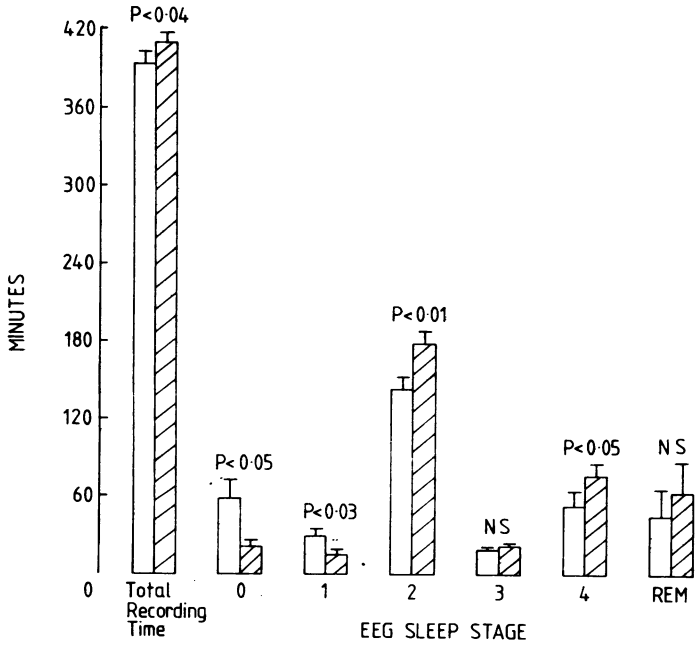

Fig 1 *Total recording time and duration of different EEG sleep stages (means and 1 SEM) in 10 adults with stable asthma studied during sleep after taking placebo (open columns) or 1 mg ketotifen (hatched columns).*

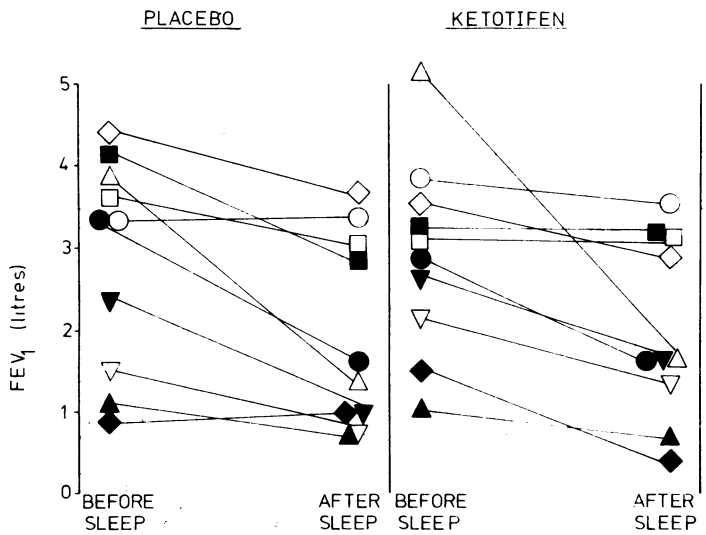

Fig 2 *FEV_1 before sleep and after sleep on placebo nights (left) and when the patients had taken 1 mg ketotifen (right). With ketotifen all the FEV_1 measurements after sleep were those made at the time of final awakening. After placebo six of the "after sleep" FEV_1 measurements were made at the time of final awakening and four were made when the patients woke during the night (see text for details).*

in asthmatic patients as there is no satisfactory method of measuring airways obstruction without waking the patient. Antihistamines in therapeutic dosage often cause somnolence,[11] but their effect on EEG sleep stages is poorly documented. Diphenhydramine, in contrast to ketotifen in our study, suppresses REM sleep, but we do not know whether other antihistamines do the same.[11]

$Beta_2$ agonists were withheld on the nights of our study, to separate the effects of ketotifen from those of sympathomimetic drugs. We do not know whether ketotifen would have the same effects on EEG sleep stage when given in combination with $beta_2$ agonists.

Ketotifen has been described as protecting against acute antigen challenge[12] and histamine challenge[13] in asthmatic patients but there is debate whether it provides effective prophylaxis against asthmatic attacks in clinical practice.[14–17] The cause of nocturnal asthma is not known, but a rise in plasma histamine has been associated with bronchoconstriction at 4 am[18] and early morning peak expiratory flow rate has been reported to improve with allergen avoidance.[19] Ketotifen failed to improve the overnight change in FEV_1 in our patients. This, however, could reflect the fact that we gave only a single 1 mg dose, for a protective effect of ketotifen has been described with prolonged administration of 2 mg a day.[20]

The morning fall in peak expiratory flow in asthma can be reduced by long acting $beta_2$ agonists[21] and theophyllines.[21 22] Both are stimulants of the central nervous system, however, and can interfere with sleep.[23–25] We would recommend that drugs used in the treatment of nocturnal asthma should be assessed not only for their effects on nocturnal bronchoconstriction but also for their therapeutic value in treating the disturbed sleep experienced by these patients.

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