Sleep Induction by Intranasal Application of Melatonin

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ABSTRACT

The sleep inducing potency of melatonin was tested in a double-blind study against placebo. The application form was a nasal spray with a 0.85 % solution of melatonin in ethanol. 70 % of the subjects fell asleep after treatment with the hormone.

KEYWORDS

Melatonin; nasal spray; sleep.

INTRODUCTION

Several groups of investigators have given melatonin to human subjects in doses of 50 mg intravenously (Cramer and co-workers, 1974), and 250 mg (Nordlund and Lerner, 1977) or 1.2 g (Anton-Tay and co-workers, 1971) orally. The effects were mild sedation or sleep for a short time. These large amounts administered for a longer period of time showed no apparent toxicity other than drowsiness in some of the subjects. Other investigators have also noted the non-toxicity of melatonin (Reiter, 1975; Burns, 1973).
Because these amounts of melatonin were very high in comparison with the concentrations found in urine and pineal gland, we wanted to investigate the effects by using another form of application and particularly by administering a smaller dose. Intranasal application of other hormones to human subjects seems to be an appropriate method, because the enterohepatic circuit can be avoided and side effects are less frequent for the smaller concentrations used.

MATERIALS AND METHODS

The sleep inducing potency of melatonin was tested in a double-blind study against placebo. The application form was a nasal spray with a 0.85 % solution of melatonin in ethanol. The dose administered was 1.7 mg (0.85 mg/nostril). The study was made using a sample of ten healthy volunteers (6 males, 4 females). One female subject suffered from a hyperthyreosis and irregularities in menstruations.
The average age of the females was 26.5 years and of the males 28.8 years. The study was designed as a double-blind crossover experiment with each volunteer serv-

ing as his or her own control. Neither the patients nor the experimenters were aware whether melatonin or placebo was being given. The placebo was the ethanol solution without melatonin. The time (9.00 - 10.00 hours) of treatment for all subjects was during day-time with one exception at 22.00 hours. The experiments were carried out in March 1979, and melatonin and placebo, or inversely, were given 1 week apart. In 8 of the subjects the experiments were repeated 2 weeks later. Following application the patients were asked about their tiredness every ten minutes and the time of falling asleep and waking up again was noted on a special ruled sheet with a 100 mm line including the range from "I am fully awake" to "I am very tired". Before starting the experiment the pulse and the blood pressure (lying and standing) was controlled. Side-effects were noted on a special list.

RESULTS

After administration of melatonin 70 % of the subjects investigated fell asleep, mostly within 40 to 60 min, in two instances after 120 and 130 min respectively. The volunteer with a hyperthyreosis showed no effect at all. The remainder reported a feeling of mild sedation or mild tiredness. After administration of placebo one of the subjects investigated fell asleep and slept for 2 hours.
The duration of sleep after administration of melatonin was 50 to 90 min when the experiments had been carried out in the morning and 11 hours in the one instance when melatonin had been given late in the evening.
In the first experiment the first signs of tiredness occurred at 30 min after melatonin administration. In a second experiment two weeks later the subjects reacted in a similar manner.
All the subjects that responded to melatonin reported feelings of well-being and felt emotionally well-balanced after melatonin-induced sleep. One subject reported a feeling of mild depression.

CONCLUSION

Our results indicate that melatonin, in the small dosage used, appears to be a potent tranquillizer and sleep inducer. Perhaps the short way between the nasal cavities and the brain explains that 1.7 mg of the substance can be effective. Some workers concluded that melatonin probably plays a role in modulating via the preoptic region the state of wakefulness and sleep (Marczynski and co-workers, 1964). In the present study the sensitivity and the unsensitivity for melatonin was constantly present in the same subjects. Cramer and co-workers (1974) have shown when subjects, reacting to melatonin treatment, were distributed according to their neurasthenia ratings, a subgroup which scores of a moderate degree of neurasthenia showed a positive influence on emotional stability as a trend.
Furthermore it is interesting that the volunteer suffering from a hyperthyreosis was the only subject with no reactions to the application of melatonin. Based on the present experiments which confirm previous results on sleep induction (Cramer and co-workers, 1974; Nordlund and Lerner, 1977; Anton-Tay and co-workers, 1971) we conclude that one of the functions of the pineal may be to act as a tranquillizing organ (see Romijn, 1978).

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