

SLEEP-INDUCING EFFECTS OF CARBAMAZEPINE (TEGRETOL) AND CLORAZEPATE (TRANXENE) IN THE PRIMARY PERSISTENT INSOMNIA

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Summary. Primary persistent insomnia (PPI) occurs independently of any known physical or mental condition and is among the most difficult problems in sleep disorders. For the treatment of PPI, comedication of clorazepate (Tranxene) in dosage 1 capsule of 10 mg and carbamazepine (Tegretol) in dosage 1 tablet of 200 mg in 32 out-patients for 30 days was applied. Normalization of sleep was achieved in 29 patients (90,63%). Side effects were few (5 patients) and of little importance, and the treatment was well tolerated.

Key words: *primary persistent insomnia, clorazepate (Tranxene), carbamazepine (Tegretol)*

INTRODUCTION

Insomnia is difficulty in initiating or maintaining sleep [7]. It is the most frequent sleep disturbance [6].

Insomnia may be transient and persistent. Transient insomnia is most often associated with anxiety (an examination, for example) and specific treatment for this condition is usually not required.

Persistent insomnia may be primary or secondary. The term "primary": indicates that the insomnia occurs independently of any known physical or mental condition [7]. "Secondary" insomnia occurs in relation to different medical conditions (for example any painful condition, neoplastic or other diseases, direct substance effects, substance interactions etc.), and in relation to psychiatric or envi-

ronmental conditions (for example circadian–rhythm sleep disorder). According to DSM-IV-1994 [2], the predominant complaints in primary insomnia are difficulty in initiating or maintaining sleep or nonrestorative sleep, for at least one month. The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational or other important areas of functioning [2]. Treatment of primary insomnia is among the most difficult problems in sleep disorders and is commonly treated with benzodiazepine hypnotics [7].

The consequences of prolonged sleep deprivation are dangerous. In experiments with rats, sleep deprivation produces a syndrome that includes weight loss, skin lesions, decreased temperature and dead. Sleep deprivation in humans provokes easy irritability, decreased memory and hallucinations.

AIM

The aim of treatment was to study the effectiveness of clorazepate (Tranxene) in combination with the carbamazepine (Tegretol) for normalization of the sleep in patients with persistent primary insomnia.

Patients and Methods

The combination was studied in 32 out-patients with persistent primary insomnia. Demographic characteristics of patients and their professions are shown on Table 1 and Table 2.

Table 1. Demographic characteristics of 32 out-patients with primary persistent insomnia

Age (years)	Number	Sex	
		women	men
21 – 30	3	3	–
31 – 40	7	6	1
41 – 50	12	8	4
51 – 60	8	2	6
61 – 70	2	1	1
Total	32	20	12

Table 2. Professions of patients

Profession	Patients	Sex	
		women	men
Teachers	9	6	3
Unemployed	13	7	6
Journalists	4	4	–
Lawyers	3	1	2

Pensioners	2	1	1
Secretaries	1	1	–
Total	32	20	12

Duration of insomnia was different: more than 1 month to 6 months – 10 patients, 7 months to 1 year – 19 patients, more than 1 year – 3 patients.

Sleep disturbances show difficulty of falling asleep in 16 patients, multiple brief awakenings during the night – 6 patients, combined complaints – 10 patients. Main contraindications observed for both medicaments before treatment were: allergy to benzodiazepine and respiratory insufficiency for Tranxene and atrioventricular block and use of tricyclic antidepressant for Tegretol.

Both drugs were taken orally in dosage 1 capsule of 10 mg for Tranxene and 1 tablet of 200 mg for Tegretol. Time of intake was 1 hour before going to bed. Duration of treatment was restricted to 30 days. Treatment was stopped gradually, during one-week period.

Results and discussion

Normalization of sleep was achieved in 29 patients (90.63%). The combination was without effect in 3 patient (9.37%) suffering from severe depression. Side effects were observed in 5 patients (17.24%): sleepiness – in 2 patients, fatigue – in 1 patient and dizziness – in 2 patients.

The benzodiazepine clorazepate (Tranxene) was chosen because this benzodiazepine has sedative, hypnotic and some antiepileptic effects. Tranxene has fast absorption (time of peak level is 2 hour), and it is a long-acting benzodiazepine (elimination half-life as 30 hours).

Carbamazepine (Tegretol) is a drug of first choice in the treatment of epilepsy [3]. But this drug has also sleep-inducing effect [1], positive psychotropic effects on depression and anxiety and some analgesic effect [3]. Its time of peak level is 4-5 hours and its elimination half-life is 5-6 hours (but very variable) [3].

Tranxene and Tegretol are not real hypnotics but in combination their hypnotic effects might increase.

Sleep serves a restorative, homeostatic function and is probably crucial for normal thermoregulation and energy conservation [11]. Most investigators conclude that there is not a simple sleep control center but a small number of interconnecting systems or structures that are chiefly located in the brainstem and that mutually activate and inhibit one another [7]. Main structures involved in the sleep regulation include: Locus ceruleus (located immediately underneath the floor of the fourth ventricle in the rostral part of the pons), lateral brainstem tegmentum, dorsal raphe nucleus of the brainstem, pontine reticular formation, suprachiasmatic nucleus of the hypothalamus, pineal gland and possibly other structures. Sleep is associated with a variety of physiological changes, including cardiac function, blood pressure, respiration, muscle tone and hormone secretion. Biochemical regulations of sleep are very complex and the interrelationships between biogenic amine neu-

rotransmitters (dopamine, norepinephrine, epinephrine, serotonin, acetylcholine, histamine) are incompletely understood [9]. It was found that prolonged periods of sleep deprivation lead to decreased body temperature and to endocrine changes including decreased plasma thyroxine and increased plasma norepinephrine [7]. The catecholamines (norepinephrine, epinephrine and dopamine) play an important role in the sleep regulation. The major concentration of noradrenergic (i.e. norepinephric) neurons is in the locus ceruleus (the most important noradrenergic nucleus in the brain) and also in the lateral brainstem tegmentum [5]. In these neurons, dopamine converts to norepinephrine. Evidence shows that dopamine has an alerting effect and drugs that increase brain dopamine tend to produce arousal and wakefulness [7]. Drugs that increase the firing of norepinephrine-containing neurons, located in the locus ceruleus, produce also an increase in wakefulness [13]. These neurons project to many areas in the forebrain, the amygdaloidal body, the cerebellum and the hypothalamus [5]. It is possible the hypnotic effect of benzodiazepines (i.e. Tranxene) to be linked with their action on the noradrenergic neurons in the Locus ceruleus and the lateral brainstem tegmentum [4].

Serotonine, another neurotransmitter, has an important role in sleep regulation and sleep disorders, including insomnia. The major sites of serotonergic cell bodies are in the upper pons and the midbrain and include dorsal and medial raphe nuclei, the caudal locus ceruleus, the area postrema and the interpeduncular area [5]. Their neurons project to the cerebral cortex, the limbic system and the basal ganglia [5]. Prevention of serotonin synthesis or destruction of the dorsal raphe nucleus (which contains nearly all the brain's serotonergic cell bodies) reduce sleep for a considerable time [7].

Acetylcholine (located mainly in nucleus basalis of Meynert and in the reticular formation) and many other neurotransmitters and substances (like melatonin for example) are also involved in sleep regulation and sleep disorders. It is possible the sleep-inducing effect of carbamazepine (i.e. Tegretol) to be linked with its influence on a restricted pontine area that include nucleus reticularis pontis caudalis and locus ceruleus [3].

Studies on the action of carbamazepine in REM sleep behavior disorder [1] support this probability.

When treatment with hypnotic drugs is indicated, the physician and the patient should both be clear that some symptoms, including a brief recurrence of the insomnia, may be expected when the medication is discontinued [8]. Hypnotic drugs should be used with care and no longer than 30 days. Long-term use of hypnotics is not well tolerated by the patients who begin to complain of sleep disturbances, most often of multiple brief awakenings during the night [7]. That's why the treatment with Tranxene and Tegretol was restricted to 30 days.

With the sustained use of benzodiazepine tolerance increases and the drugs lose their hypnotic effects, then patients often increase the dosage [7]. On sudden

discontinuation of the sleep-inducing drugs, the rebound phenomena such as insomnia, fear, agitation and other withdrawal effects may occur [12]. That's why the treatment with Tranxene and Tegretol was stopped gradually.

Various nonspecific measures can be helpful in improving sleep. This is the so called "sleep hygiene", who may increase the effect of the treatment with sleep-inducing drugs. These nonspecific measures include 10 advices [10]:

- Arise at the same time daily;
- Limit daily in-bed time to the usual amount present before the sleep disturbance;
- Discontinue CNS – acting substances (caffeine, nicotine, alcohol, stimulants);
- Avoid daytime naps (except when sleep chart shows they induce better night sleep);
- Establish physical fitness by means of a graded program of vigorous exercise early in the day;
- Avoid evening stimulation; substitute radio or relaxed reading for television;
- Try very hot, 20-minute, body temperature-raising bath soaks near bedtime;
- Eat at regular times daily; avoid large meals near bedtime;
- Practice evening relaxation routines such as progressive muscle relaxation or mediation;
- Maintain comfortable sleeping conditions.

CONCLUSIONS

Persistent insomnia is more frequent in women than in men. Psychosocial factors are the most common causes of insomnia. Co administration of Tranxene and Tegretol combines hypnotic effects with sedative, antidepressive and positive psychotropic effects. Combination of Tranxene and Tegretol normalizes the sleep in 90.63% of patients. Side effects are few and of little importance and the treatment is well tolerated.

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