

EFFECT OF PROLONGED ADMINISTRATION OF NITRAZEPAM ON SLEEP CYCLES IN RATS

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The effect of nitrazepam given as a single dose or by prolonged intraperitoneal injection, on sleep cycles in male Wistar rats was studied. In a dose of 1 mg/kg nitrazepam had no significant effect on sleep cycles whether given as a single or by prolonged injection. In a dose of 10 mg/kg a single injection of nitrazepam reduced the duration of paradoxical sleep and the number of sleep cycles during 5 h of recording, whereas prolonged (7-14 days) administration of the drug led to an increase in these indices. Withholding the drug after its prolonged administration was followed by a further increase in the number of sleep cycles and the duration of paradoxical sleep. No correlation was found between the hypnotic and muscle-relaxing action of nitrazepam during its prolonged administration.

KEY WORDS: nitrazepam; sleep cycles; muscle relaxation; withdrawal syndrome.

According to some observations [1, 4, 7, 8, 14, 16] nitrazepam substantially reduces the duration of paradoxical sleep, whereas according to others [2, 10, 15, 18], like flunitrazepam and diazepam, it increases its duration. Other workers [5, 6, 9, 12, 13] found no action in general of tranquilizers of the benzodiazepine series on desynchronized sleep.

Sleep cycles were investigated in rats following a single injection and prolonged administration of diazepam in different doses and the dynamics of its muscle-relaxing effect also was studied.

EXPERIMENTAL METHOD

Sleep cycles in male Wistar rats were studied by the methods of Bauer and Sur [3] and Kadlecova et al. [11]. Bipolar electrodes were implanted in the hippocampus and neck muscles under ether anesthesia. Sleep was recorded before administration of nitrazepam (on the 5th day after the operation) and on the first, second, fourth, seventh, tenth and 14th days after the beginning of its daily intraperitoneal injection in doses of 1 and 10 mg/kg. The duration of recording was 5 h. Sleep cycles were assessed from changes in the EEG and EMG, analyzed visually [17] with determination of the duration of periods of wakefulness, the number of sleep cycles, and the two phases of sleep - slow-wave (synchronized) and paradoxical (desynchronized). The muscle-relaxing action of nitrazepam after intraperitoneal injection in a dose of 10 mg/kg was assessed from the inability of the rats to hold on with their paws to an overturned network platform for 30-60 sec.

EXPERIMENTAL RESULTS

After a single and prolonged injection, nitrazepam in a dose of 1 mg/kg had no appreciable effect on the sleep cycles of the rats. Only a very slight increase was observed in the duration of slow-wave sleep and in the number of sleep cycles (Table 1).

A single injection of nitrazepam in a dose of 10 mg/kg increased the duration of slow-wave sleep by

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TABLE 1. Effect of a Single Injection and Prolonged Administration of Nitrazepam on Sleep Cycles in Rats (mean values and confidence limits at $P = 0.05$)

Experimental conditions	sec				Total duration of sleep	Total number of sleep cycles
	Duration of periods of wakefulness	Duration of slow-wave sleep	Duration of paradoxical sleep			
Control	7 033 (6 120—7 946)	9 514 (8 706—10 322)	1 509 (1 240—1 778)	11 024 (10 128—12 060)	24 (19.6—28.4)	
Injection of nitrazepam (10 mg/kg):						
single	4 940 (3 153—6 727)	11 688 (10 318—13 058)	1 167 (679—1 655)	12 855 (11 118—14 521)	16 (2.3—29.7)	
4 days	4 957 (1 144—8 770)	11 414 (7 363—15 465)	1 589 (1 166—2 012)	13 003 (9 369—16 637)	29 (12.3—46.7)	
7 days	4 808 (2 842—6 774)	11 398 (9 134—13 662)	1 869 (797—2 941)	13 267 (11 301—15 233)	32 (11.2—52.8)	
10 days	5 170 (3 326—7 026)	10 892 (9 925—11 775)	1 934 (898—2 970)	12 820 (10 976—14 676)	30 (11.9—48.1)	
14 days	5 235 (4 254—5 777)	10 154 (8 192—12 116)	2 611 (1 791—3 431)	12 765 (11 606—13 924)	38 (14.8—61.2)	
one day after administration for	6 516 (3 657—9 375)	8 520 (6 375—10 665)	2 973 (948—4 998)	11 494 (7 801—15 187)	42 (20.0—64.0)	
7 days after administration for	6 585 (4 740—7 830)	8 920 (7 784—10 056)	2 418 (1 691—3 145)	11 338 (9 749—12 929)	35 (18.7—51.3)	
14 days after administration for	8 110 (3 473—12 747)	7 861 (4 561—11 261)	2 039 (523—3 555)	9 900 (2 765—17 035)	30 (0.6—59.4)	
Injection of nitrazepam (1 mg/kg):						
single	5 903 (3 545—8 261)	10 477 (4 715—16 239)	1 620 (1 301—5 041)	12 097 (9 739—14 455)	30 (22.2—82.2)	
12 days	4 911 (3 573—6 249)	11 688 (10 550—13 026)	1 415 (524—2 306)	13 103 (11 763—14 439)	39 (21.2—56.8)	
one day after administration for	7 147 (2 420—11 874)	8 798 (6 747—10 849)	2 055 (1 081—2 929)	10 853 (8 713—12 993)	45 (27.2—62.8)	
12 days after administration for	6 953 (2 583—11 323)	8 489 (5 992—10 986)	2 513 (729—4 297)	11 002 (6 631—153 771)	53 (14.7—91.3)	

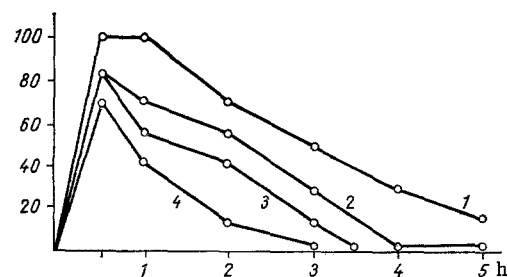


Fig. 1. Dynamics of muscle-relaxing effect of nitrazepam after prolonged administration (10 mg/kg intraperitoneally) to rats: 1) single injection of nitrazepam; 2) for 3 days; 3) for 10 days; 4) for 18 days. Abscissa, time of recording effect; ordinate, percentage of animals with muscle-relaxing manifestations.

21% and shortened paradoxical sleep by 24%; the number of sleep cycles was reduced by one-third.

During prolonged administration of nitrazepam in a dose of 10 mg/kg the total duration of sleep and the duration of its slow-wave stage were unchanged compared with the effect of a single injection of the drug, but the duration of paradoxical sleep and the number of sleep cycles increased. On the seventh day of administration of the drug, for instance, the duration of paradoxical sleep was 23% longer than in the control, and on the 14th day it was 73% longer. The total number of sleep cycles was increased by 1.6 times after administration for 14 days. The dynamics of onset and rhythm of appearance of paradoxical sleep during each hour of recording were undisturbed.

Withdrawal of nitrazepam, after injection for 12-14 days (in doses of 1 or 10 mg/kg) was followed by a further increase in the total number of sleep cycles and in the duration of paradoxical sleep compared with the last day of administration. These indices remained at a high level for 7 or even 14 days after withdrawal of the drug.

The results suggest that differences in the duration of administration and in the doses of the drug could be among the causes of the contradictory estimates of the effect of nitrazepam on sleep cycles in man and animals [1-15].

Parallel with changes in sleep cycles, movement coordination and the gait of all the animals were disturbed after receiving nitrazepam in a dose of 10 mg/kg and the rats could no longer hold on to an overturned network platform. Prolonged administration of nitrazepam in the same dose led to gradual weakening of the muscle-relaxing phenomena and to a decrease in their duration (Fig. 1). These results indicate an absence of correlation between the

hypnotic and muscle-relaxing action of nitrazepam, and they thus suggest that the mechanisms of formation and manifestation of these effects are different.

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