

## MIDAZOLAM DAYTIME RESIDUAL EFFECT EVALUATED BY THE MULTIPLE SLEEP LATENCY TEST

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**SUMMARY** — Daytime sleepiness after ingestion of midazolam as a hypnotic was quantitatively studied employing the Multiple Sleep Latency Test (MSLT). We evaluated 20 healthy volunteers, 10 of which received a single oral dose of midazolam (15 mg, one tablet) and 10 of which received placebo, in a double-blind design. Tablets were administered at 2200 h, bedtime. On the following day, all subjects were submitted to a clinical evaluation, a subjective checklist and the MSLT. The mean age was  $34.7 \pm 8.9$  years in the midazolam and  $38.0 \pm 10.6$  years in the placebo groups (n.s.). Sex and weight distributions were similar in both groups (n.s.). Clinical evaluation and subjective symptom checklist did not make evident significant differences between midazolam and placebo groups (n.s.). The MSTL was performed at 0900, 1100, 1300, 1500 and 1700 h. Mean sleep latencies were 12.0, 12.7, 8.0, 13.5, 17.0 min in the midazolam group; mean sleep latencies were 13.8, 9.0, 6.9, 9.5, 13.6 min in the placebo group (n.s.). In the single dose, double-blind design here evaluated, midazolam did not show differences in relation to placebo on the following day, detectable by the MSLT.

**KEY WORDS:** sleep, midazolam, multiple sleep latency test.

**Midazolam e o efeito residual do dia seguinte avaliado utilizando o teste das latências múltiplas do sono**

**RESUMO** — O objetivo foi avaliar quantitativamente a sonolência no dia seguinte após dose única de midazolam, utilizado como hipnótico ao deitar. Avaliamos 20 voluntários saudáveis, 10 dos quais receberam midazolam, por via oral (15 mg, um comprimido) e 10 receberam placebo, em esquema duplo-cego. Os comprimidos eram administrados às 22:00 h, ao deitar. No dia seguinte todos os probandos foram submetidos a avaliação clínica, questionários e o Teste das Latências Múltiplas do Sono (TLMS). A média de idade foi  $34,7 \pm 8,9$  anos no grupo com midazolam e  $38,0 \pm 10,6$  anos no grupo com placebo (n.s.). Sexo e peso tiveram distribuições semelhantes em ambos os grupos (n.s.). A avaliação clínica e o questionário não mostraram diferenças entre os grupos midazolam e placebo (n.s.). O TLMS permitiu quantificar as latências de sono 5 vezes consecutivas durante o dia. Mostrou no grupo com midazolam as seguintes médias de latências do sono, 12,0, 12,7, 8,0, 13,5, 17,0 min; no grupo com placebo, as médias foram 13,8, 9,0, 6,9, 9,5, 13,6 min (n.s.). O protocolo utilizado, duplo-cego com dose única de midazolam ou placebo ao deitar, não revelou diferenças mensuráveis pelo TLMS.

**PALAVRAS-CHAVE:** sono, midazolam, teste das latências múltiplas do sono.

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The clinical use of benzodiazepines as hypnotics may produce the residual effect of daytime sleepiness on the following morning. Midazolam (1,4-imidazobenzodiazepine), a water-soluble ultrarapidly eliminated benzodiazepine, is often imputed to lack such a residual effect, but most of the studies focusing on this aspect deal with subjective reports<sup>4,10,12</sup>. The Multiple Sleep Latency Test (MSLT)<sup>2,3,16,20</sup> is an objective, standardized, quantitative and reliable tool for the daytime sleepiness evaluation.

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The present study was designed to address the possibility of daytime sleepiness using the MSLT after ingestion of midazolam as a hypnotic, at bedtime.

#### METHODS

The subjects were 20 healthy volunteers, 10 of which received a single oral dose of midazolam (15 mg, one tablet) and 10 received a placebo, in a double-blind paradigm. Midazolam and placebo tablets were identical in appearance. The tablets were administered at bedtime, which was fixed at 2200 h. On the following day, all subjects were submitted to the MSLT, clinical evaluation and symptom checklist.

Table 1. Sleep latencies measured by the Multiple Sleep Latency Test (MSLT) the day after a single dose of midazolam (15 mg) or placebo at bedtime (2200 h).

MSLT time (h)	Sleep latency (min)		Mann-Whitney test (U)
	Midazolam	Placebo	
0900	12.0 ± 6.94	13.8 ± 6.78	59.5 (n.s.)
1100	12.7 ± 5.98	9.0 ± 5.83	32.5 (n.s.)
1300	8.0 ± 6.57	6.9 ± 4.72	50.5 (n.s.)
1500	13.5 ± 6.26	9.5 ± 6.69	34.0 (n.s.)
1700	17.0 ± 4.14	13.6 ± 6.83	35.5 (n.s.)

The mean age was 34.7 ± 8.9 years in the midazolam group and 38.0 ± 10.6 years in the placebo group (Student's t test,  $t=0.719$ , n.s.). The mean weight was 61.9 ± 11.2 kg in the midazolam group and 57.8 ± 14.4 kg in the placebo group (Student's t test,  $t=0.747$ , n.s.). In the midazolam group, there were 6 women and 4 men, while in the placebo group 9 women and 1 man (Fisher test,  $p>0.05$ , n.s.).

The MSLT was applied using the standardized technique recommended by Carskadon & col. 2,3,6. This test was performed allowing the subject to sleep, at 2 h intervals, starting at 0900 h, for a total of 5 consecutive times, that is at 0900, 1100, 1300, 1500 and 1700 h. The test was conducted at the Sleep Disorders Center in a pleasant bedroom, which is light-proofed, sound-attenuated, controlled at a constant temperature (21°C) and furnished with a comfortable bed. As the objective of the test was to quantify the tendency to sleep, any external factor that could impair the results was avoided. The subjects wore comfortable everyday clothes. During the intervals between tests they stayed out of the bedroom and did not sleep.

The MSLT polygraph program included electroencephalogram in central derivations (C3 or C4) and occipital derivations (O1 or O2), with reference to the auriculars (A1 or A2); electroculogram with two horizontal or oblique derivations or verticals; submental electromyogram; electrocardiogram. The records were analysed measuring two latencies; (a) Sleep latency, the time from lights off to the onset of sleep; (b) REM latency, the time from sleep onset to the beginning of stage REM.

#### RESULTS

Clinical evaluation just previous to the 0900, 1100, 1300, 1500 and 1700 h MSLT tests did not show any sign of sleepiness in the midazolam group. One subject of this group reported mild and another reported moderate sleepiness at 900 h. In the placebo group, one showed mild sleepiness at 0900, 1100, 1300 and 1500 h, as evaluated by the clinician and the same subject reported mild sleepiness at all 5 MSLT times. No other side effects were observed in the midazolam as well as in the placebo group.

The MSLT showed in the midazolam group mean sleep latencies of 8.0-17.0 min (Table 1). In the placebo group, mean sleep latencies were 6.9-13.6 min. There were no significant differences between both groups (Mann-Whitney test, n.s.). Stage REM occurred in only one subject, from the placebo group, at 1300 h; it was not present in the midazolam group.

#### COMMENTS

The MSLT is an objective and quantitative way of evaluating the degree of daytime sleepiness. It is used to verify the impairment of excessive daytime sleepiness patients, including those with sleep apnea, narcolepsy, periodic limb movement disorder, and depression. It is also employed to differentiate between the complaint of fatigue and sleepiness, which may be difficult at times, based exclusively on patients reports. The MSLT has been also used in the evaluation of daytime alertness impairment due to sleep deprivation, and in that secondary to hypnotics ingestion at bedtime<sup>19</sup>.

In the present study, a single oral dose of midazolam (15 mg) or placebo were administered to healthy subjects at bedtime, in a double-blind design. The subjective evaluation by the clinician, as well as by the subjects checklist did not demonstrate significant differences between midazolam and placebo groups. The absence of subjective residual effects of this drug has been reported in several publications<sup>4,10,12,18</sup>.

The MSLT, as an objective tool, did not show significant differences between midazolam and placebo in our sample. This finding may be attributed to its ultrashort half-life of  $1.9 \pm 0.4$  h with recommended dose range of 7.5-15.0 mg<sup>4,6,7,11,13-15</sup>, and the absence of significant long acting metabolites. Our data agree with the lack of residual effects 7 or more hours after midazolam administration described in other publications using such distinct objective tools as the digit symbol substitution test<sup>12</sup>, complex reaction time task<sup>12</sup>, body sway<sup>8,9</sup>, choice reaction time<sup>5</sup>, critical flicker threshold<sup>5</sup>, and auditory evoked responses<sup>9</sup>.

The tendency for shorter sleep latencies detected in the early afternoon, which was present in the midazolam group, as well as in the placebo group, corresponds to the well documented semicircadian pattern of sleepiness oscillation observed in normal subjects<sup>1,17</sup>.

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