Drug Testing in Children with Excessive Daytime Sleepiness During Multiple Sleep Latency Testing

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Study Objective: To determine the incidence of positive drug screens in children undergoing a multiple sleep latency test (MSLT) for evaluation of excessive daytime sleepiness (EDS).

Methods: A retrospective analysis was performed in children evaluated at the Boston Children's Hospital Sleep Center between 1998 and 2013 who underwent MSLT for EDS with a concurrent urine and/or serum drug screen.

Results: A total of 210 MSLTs were accompanied by drug testing. Children were 12.7 ± 3.7 years old (mean $\pm$ SD), 43% were female, and 24% had narcolepsy. Positive tests were obtained in 32% for caffeine, 5% for prescription medications, and 4% for over-the-counter drugs. No drugs of abuse were identified. Children testing positive for caffeine were older (13.8 ± 3.5 vs. 12.4 ± 3.7) and more likely female (59% vs. 36%), but did not differ in MSLT or overnight polysomnographic parameters compared to children without caffeine detected.

Overall, only 14% had specific documentation regarding caffeine intake, though 90% were referred from a sleep clinic. Of the children testing positive for caffeine, 5% acknowledged use, 3% denied use, and 92% did not have a documented caffeine intake history during their sleep clinic visit.

Conclusions: Routine drug testing for drugs of abuse during an MSLT for EDS yielded no positive results over a 15-year period, indicating that this routine practice is unnecessary in our pediatric population without specific concerns. However, objective evidence for caffeine exposure was found in 32% of tested children undergoing an MSLT. Sleep physicians rarely documented the caffeine intake history during clinic visits for EDS.

Keywords: narcolepsy, hypersomnia, caffeine

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Excessive daytime sleepiness (EDS) is reported in over 40% of adolescents, and is associated with poor school performance, inattention, and mood disorders.¹⁻³ The etiology of EDS is often multifactorial, including obesity, medications, chronic insufficient sleep, poor sleep hygiene, delayed sleep phase syndrome, excessive caffeine use, and less commonly, narcolepsy. Approximately 90% of 12- to 18-year-old children obtain less than the recommended 8 hours of nightly sleep.⁴ Nearly all children ingest some caffeine daily, mostly caffeinated beverages^{5,6}; the average is two soda drinks per day.^{7,8} In addition, though rare overall, narcolepsy typically presents in childhood. Establishing the specific cause of EDS is crucial to instituting the correct treatment regimen, which may be behavioral or pharmacological. When narcolepsy is suspected, an overnight polysomnogram (to exclude sleep apnea or periodic leg movements) followed by a multiple sleep latency test (MSLT) is performed.

Caffeine is rapidly absorbed after oral intake, peaks at 15 to 45 minutes, and has a plasma half-life of 3 to 12 hours. Caffeine alters alpha EEG activity in the wake state⁹ and has direct adverse effects on sleep quality.¹⁰ Caffeine in the evening increases sleep latency, decreases sleep efficiency, and decreases sleep duration.¹¹ Similarly, caffeine use in the morning also affected nocturnal sleep with a decreased sleep efficiency and total sleep time, and suppression of delta EEG activity.¹² Caffeine abstinence overnight may result in withdrawal symptoms including headache, fatigue, irritability,

BRIEF SUMMARY

Current Knowledge/Study Rationale: Caffeine is widely available in beverages used by children, and consumption increases with age. Caffeine temporarily enhances alertness, but also has adverse effects on sleep quality, and may contribute to excessive daytime sleepiness.

Study Impact: Children presenting with excessive daytime sleepiness are ingesting considerable amounts of caffeinated beverages that may adversely affect sleep. In addition, many of these children deny caffeine usage, and physicians frequently omit explicit documentation of caffeine intake during clinic visits.

diminished alertness, and anxiety, which may promote daily usage to alleviate symptoms.^{13,14} Consequently, increases in daytime alertness in daytime caffeine users may be more accurately considered "withdrawal-reversal" rather than enhanced vigilance per se.^{15,16} Tolerance to the effects of caffeine has also been reported,^{17,18} leading to escalating doses.

Early guidelines for performing the MSLT in adults suggested avoidance of caffeine beforehand and a drug of abuse screen during the test.¹⁹ The rationale for these recommendations was that surreptitious sedative drug use could shorten the sleep latency enough to achieve a diagnosis of narcolepsy, resulting in a prescription for stimulants. Conversely, caffeine usage, dependence, or withdrawal might influence sleepiness sufficiently to obscure the diagnosis of narcolepsy. The utility of drug testing and caffeine avoidance instructions during an MSLT in children have not been evaluated. The present study

documents drug testing in a large sample of children with EDS referred for an MSLT.

PATIENTS AND METHODS

The database of the Boston Children's Hospital Sleep laboratory was retrospectively queried to identify all MSLTs performed between 1998 and 2013. The electronic medical records of the patients having MSLTs were reviewed and the clinical, polysomnographic, and MSLT data was extracted into a Microsoft Excel spreadsheet as follows: (1) Clinical: Age, race, gender, sleep clinic visit (yes/no), presenting symptoms, reported regular caffeine usage (no documentation, yes, no), diagnosis; (2) MSLT: Average sleep latency; (3) Drug testing: type of test, drugs identified. Children with EDS undergoing an MSLT with contemporaneous urine and/or serum drug testing were included in this study. Obstructive sleep apnea syndrome (OSAS) was defined as mild, moderate, or severe, with an apnea/hypopnea index of 1-5, 5-10, or > 10/h, respectively. Periodic leg movement disorder was defined as mild, moderate, or severe with a periodic leg movement index of 1-5, 5-10, or > 10/h, respectively. This study was approved by the Institutional Review Board at Boston Children's Hospital.

Multiple Sleep Latency Test

The MSLT was performed using standard techniques¹⁹ in a dark, quiet room usually following an overnight polysomnogram. Patients were instructed to arrive in the sleep laboratory at 7 PM. If possible, it was advised that medications known to effect sleep latency or REM latency be discontinued 2 weeks prior to the study. The MSLT consists of a series of 5 nap opportunities (10:00, 12:00, 14:00, 16:00, 18:00) lasting up to 20 min, starting 2 h after awakening in the morning. Breakfast and lunch was provided that did not include any caffeinated products. For the MSLT, the following data were acquired: left and right electro-oculogram; C3-A1/C4-A2/02-A1 electroencephalogram; mental/submental electromyography; electrocardiogram; and audio-video recordings. The MSLT was scored by standard techniques¹⁹ and interpreted by a board-certified sleep medicine physician. *Sleep latency* is the elapsed time from lights out to the first epoch of sleep. A *SOREM* period was scored if REM sleep was achieved within 20 min of sleep onset for each nap opportunity. Normative data are scant in children, but the consensus is that mean sleep latency < 5 min is pathological, 5-12 min is suggestive of hypersomnia, and > 12 min is considered normal. The presence of ≥ 2 SOREM periods is suggestive of narcolepsy.

Drug Testing

There were 3 separate options for drug testing that were available during the study interval: (1) Boston Children's Hospital (Boston, MA) drug of abuse screen immunoassay screen in urine (marijuana, cocaine, phencyclidine [PCP], opiates); (2) Quest Diagnostics (Cambridge, MA) drug of abuse immunoassay screen in urine (marijuana, cocaine, PCP, opiates); (3) UMass Memorial Medical Center (Worcester, MA) qualitative gas chromatography/mass spectroscopy (GC/MS) screen of urine and serum. The testing by GC/MS enabled the detection

of many drugs including over-the-counter, prescription, and illicit drugs (e.g., caffeine, cotinine, ibuprofen, antidepressants [serotonin reuptake inhibitors, tricyclics], anticonvulsants, antipsychotics, antihistamines, decongestants, sympathomimetic amines, cocaine, PCP, opioids). In addition to a GC/MS screen, serum samples were also tested by immunoassay for barbiturates, benzodiazepines, acetaminophen, and salicylate, by gas chromatography for ethanol, methanol, isopropanol, and acetone. Both urine and serum drug testing was routinely performed at noon to 1 PM during the MSLT.

Data Analysis

Differences between groups for continuous variables (including age, overnight polysomnographic indices, and average sleep latencies from the MSLT) were analyzed with an un-paired *t*-test. Differences in proportions (for race, gender, and caffeine positivity) were analyzed with χ^2 analysis. In all cases, a *p*-value of < 0.05 was considered significant.

RESULTS

A total of 224 MSLT studies in 217 participants (7 had 2 studies) were performed during the study interval. Ten patients were referred for evaluation of isolated cataplexy and were excluded from this analysis. Two hundred fourteen of the MSLT studies were performed with an indication of EDS, and 210 of these were paired with at least one urine or serum drug screen. These 210 patients constitute the sample used for evaluating the incidence of detecting drugs of abuse. A total of 189 children were tested using techniques suitable to identify the presence of caffeine in the urine.

The average age of the 210 children was 12.7 ± 3.7 years, and 43% were female. The self-reported racial background was 62% Caucasian, 16% African American, 2% Hispanic, and 20% Other/unknown. Most (90%) children were referred from the sleep disorders clinic, and an overnight polysomnogram was performed on the night before 96% of MSLT studies. Obstructive sleep apnea was observed in 13% (mild 10%, moderate 2%, severe 1%) and periodic leg movements in 31% (mild 17%, moderate 7%, 7% severe). Overall, 24% of children had narcolepsy; the remainder were given a clinical diagnosis of hypersomnia due to a combination of sleep disruption, delayed sleep phase syndrome, chronic insufficient sleep, idiopathic hypersomnia, and/or poor sleep hygiene.

Screening for drugs of abuse was performed in 99.5% of patients using urine specimens. All of these tests were negative. GC/MS screening for prescription medications, over-the-counter medications, and caffeine was performed in 90% using urine (189 patients), and 98% using serum specimens. Caffeine testing was positive in 32% of urine tests and 4% of serum tests. Overall, 32% of children who were tested for caffeine were positive in either urine or serum. Children screening positive for caffeine were older and more likely to be female than those without caffeine detected (**Table 1**). There was no difference between any of the PSG or MSLT parameters between the 2 groups (**Table 1**). Of the first 95 patients tested for caffeine (before November 2009), 19% were caffeine positive, compared to a 45% positivity rate in the most recently tested 94 patients (after November 2009; *p* = 0.0001). Seven children

Table 1—Demographic, MSLT and polysomnographic variables

	Caffeine Positive (n = 60)	Caffeine Negative (n = 129)	p-value*
Age	13.8 ± 3.5	12.4 ± 3.7	0.02
Gender (% female)	59%	36%	0.0008
Race (% African American)	16%	13%	0.58
Overnight sleep latency (min)	22 ± 23	19 ± 26	0.43
Sleep efficiency (%)	87 ± 10	84 ± 13	0.19
Sleep maintenance (%)	90 ± 9	88 ± 10	0.16
REM latency (min)	121 ± 72	113 ± 81	0.53
Wake after sleep onset (min)	52 ± 43	64 ± 51	0.10
Stage 1 (% of TST)	8 ± 5	8 ± 7	0.58
Stage 2 (% of TST)	48 ± 12	45 ± 12	0.18
REM (% of TST)	22 ± 7	23 ± 7	0.59
Slow wave (% of TST)	22 ± 12	23 ± 11	0.70
Arousal index (events/h)	9.1 ± 3.9	8 ± 5	0.36
MSLT mean sleep latency (min)	11.2 ± 6.2	11.1 ± 6.4	0.96

PSG, polysomnogram; REM, rapid eye movement; TST, total sleep time; MSLT, multiple sleep latency test. *p-value is Caffeine positive vs. Caffeine negative. The data include only children tested for caffeine in the urine.

had 2 MSLTs, and in 5 of these there was a positive caffeine screen on one of the studies. In one instance, a child had a sleep latency of 12.2 min with 2 SOREMs while testing positive for caffeine. A repeat MSLT 4 weeks later, while testing negative for caffeine, revealed a sleep latency of 2.5 min with 2 SOREMs, confirming the diagnosis of narcolepsy.

Overall, 90% of children were evaluated in the sleep medicine clinic prior to the MSLT. The clinical history omitted a notation to caffeine usage altogether in 86% of visits. Caffeine intake was documented in 14% of children, with 8% acknowledging using caffeine regularly, and 6% denying usage. Twenty-one percent of children reporting regular caffeine intake had drug tests positive for caffeine; 20% of children who denied caffeine intake tested positive for caffeine. Prescription drugs (SSRI's) and over the counter medications (diphenhydramine, pseudoephedrine, acetaminophen) were identified in 5% and 4% of children tested, respectively.

DISCUSSION

This is the first study to report urine and serum drug testing results in children undergoing an MSLT for EDS. We observed a very high incidence (32%) of caffeine-positive drug tests despite the fact that samples were taken at least 18 hours after arriving at the sleep laboratory. In addition, the incidence of caffeine positivity increased over time in our population, and positive caffeine tests were observed in 20% of children who denied caffeine usage. Surprisingly, the caffeine intake history was not documented in 86% of clinic visits for EDS. In addition, unreported prescription or over-the-counter medications that may interfere with sleep were identified in approximately 8% of patients. Street drugs such as marijuana, cocaine, PCP, and opiates were never identified in this population. These data suggest that routine screening for drugs of abuse is not indicated in children in our population of children who are referred with EDS for MSLT, but screening for SSRI's, antihistamines, and caffeine may have a higher yield. Further, this study indicates

that urine is the preferred testing specimen to detect any drug use. It should be noted that there may be regional differences in the prevalence of drugs of abuse, and individual sleep laboratories need to adjust their screening practices appropriately. Future work should focus on refining structured screening tools for caffeine usage and elucidation of the role of caffeine in contributing to EDS.

The MSLT was introduced as a clinical test to quantitate sleepiness in the 1960s, and there have been several consensus statements published on the proper methodology.¹⁹⁻²³ Normative data for the MSLT in children have been reported to be 17.5 ± 3.5 minutes (n = 46, age 9.2 ± 1.5 years)²⁴ and 17.1 ± 2.4 minutes (n = 25, age 8.7 ± 1.1 years).²⁵ The determinants of sleep latency include prior sleep time before the MSLT, sleep fragmentation, circadian phase, pubertal status, and caffeine usage.^{22,26} Contemporaneous caffeine intake increases sleep latency during MSLT in individuals with normal and restricted sleep by approximately 4 minutes.²⁷ Initially, concern was raised that amphetamine-seeking malingerers would surreptitiously use various drugs to appear excessively sleepy. Thus, a recommendation for routine drug testing during MSLT was instituted, but has never been adequately tested. This practice of routine drug testing during MSLT remains common in pediatric laboratories. However, a survey of adult sleep centers in Europe reported that only 17% of laboratories routinely perform drug testing during an MSLT.²⁸ Our pediatric data indicate that routine testing for drugs of abuse during an MSLT is a waste of resources. However, the yield for caffeine and unreported prescription/over-the-counter medications was considerably higher and resulted in a change in clinical management in several cases.

The “gold standard” gas chromatography combined with mass spectrometry, was used for identifying caffeine in the urine. The results were reported qualitatively as a binary outcome, positive or negative, rather than determining the concentration. In general, drugs may be detectable for approximately 5 half-lives. In the case of caffeine, given the plasma half life

is 3-12 hours, it may be detected in plasma for approximately 15-60 hours after consumption and slightly longer in urine. Given the wide intra- and inter-individual variability in plasma and urine caffeine concentrations reported during steady-state dosing, concentrations have limited utility with reference to determining dose or dosing regimen. It is known that caffeine metabolism has considerable variability between individuals related to age, genetics, renal function, and medication usage. The specific enzymes involved with caffeine degradation include cytochrome P450 (CYP1A2), N-acetyltransferase 2 (NAT2), xanthine oxidase (XO). Thus, some children may be particularly vulnerable to the effects of caffeine. Nevertheless, we cannot determine from our data whether children screening positive for caffeine were chronic users, slow metabolizers, had ingested caffeine on the night of the study, or surreptitiously used caffeine during the MSLT.

Caffeine is ingested daily by approximately 90% of adolescents, taking an average of 59-144 mg/day.^{29,30} Importantly, caffeine use was reported to occur late in the day (between 3 and 5 PM in 25.3% and in 21.3% between 6 and 8 PM), increasing the likelihood of adversely affecting sleep. Several studies have reported a relationship between caffeine use in children and shortened sleep.^{4,31} Calamaro et al. reported that 33% of adolescents fall asleep at school, and caffeine consumption is 76% higher in these children.³⁰ Caffeine intake may vary considerably from day to day related to dietary choices and brewing strength of coffee or tea. However, in adults, there is no significant relationship between self-reported caffeine use serum caffeine levels after overnight abstinence.³² In the present study, an acknowledgement of caffeine usage was rarely elicited in sleep clinic visits. Whether this represents deception on behalf of the patient or a failure of the clinical history taking needs further study.

The primary limitations of this study stem from the retrospective nature of the data. A standardized screening questionnaire for caffeine was not used; therefore, future research is necessary to determine whether a structured clinical history is predictive of children testing positive for caffeine. However, the lack of documentation of caffeine use that was observed in the majority of clinic visits suggests that caffeine is under-recognized by physicians as a contributor to EDS. A potentially false negative MSLT was observed in at least one patient with narcolepsy who screened positive for caffeine. Nevertheless, the majority of MSLTs were not repeated, despite testing positive for caffeine; therefore, the incidence of this interaction is unknown. Whether the caffeine identified was related to excessive ingestion on the day prior to the MSLT, surreptitious use during the MSLT, or a genetic/environmental predisposition towards caffeine accumulation cannot be determined from this data. It should also be emphasized that as a group we did not observe differences in any MSLT or polysomnographic variables between the children testing positive or negative for caffeine. The likely explanation for this is that these data were obtained retrospectively from clinical studies without strict control of sleep schedules, which may affect sleep latency and sleep state distribution. Finally, the cross-sectional nature of our data does not permit determination of whether caffeine use was contributing to the EDS, or being used as a mitigating strategy by the children. Finally, future research should elucidate the

optimal protocol for weaning a child off caffeine in preparation for an MSLT.

CONCLUSION

In summary, in children with EDS referred for an MSLT, we observed that approximately 32% of children tested for caffeine were positive. Caffeine-positive children were older and more likely to be female than children without caffeine detected. Most often the caffeine use was not suspected, despite a preceding sleep clinic visit and admonitions to avoid caffeinated beverages before and during the study. The variability in the metabolism of caffeine may be an under-recognized cause of sleep disruption leading to EDS. Additionally, largely unreported prescription and over-the-counter medications were identified in 9% of patients. Thus, it appears that there was substantial merit to screening children undergoing an MSLT for EDS for these compounds. By contrast, there was not a single positive test for drugs of abuse over the 15-year interval of this study, indicating that the routine screening for these drugs is not indicated unless there are specific concerns. Goals for future research include (1) evaluating whether caffeine was contributing to the EDS in these children or mitigating the reported sleepiness; (2) developing a well-validated clinical questionnaire suitable for screening for caffeine intake; (3) developing practice guidelines that determine the optimal MSLT drug screening protocol and mandate documenting drug screens in the MSLT report. The use of caffeine in children is increasing, and there are many concerns regarding the effects on sleep and daytime function.

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