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Melatonin Niosome Gel vs. Chloral Hydrate for Sedation in Children Undergoing Auditory Brainstem Response: a Randomized Controlled Trial

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ABSTRACT

OBJECTIVE: To compare the success rate of auditory brainstem response (ABR) testing after the application of melatonin niosome gel (MNG) versus chloral hydrate in children aged 1 to 6 years.

METHODS: A double-blinded, randomized, controlled trial was conducted. Participants in the MNG group were given 250 mg of MNG (5 mg melatonin) for sedation prior to the ABR test, and those in the chloral hydrate group were given chloral hydrate syrup, 50 mg/kg with an additional dose of 25 mg/kg if they didn't fall asleep within 30 min. The study was conducted in the morning; all the participants were prepared in accordance with protocols similar to the regular ABR protocols.

RESULTS: Twenty-four children were enrolled, and 16 participants passed the screening and were randomized into 2 groups. The success rate of ABR in the MNG group was 25.0% compared to 100.0% in the chloral hydrate group (p-value = 0.01). Twenty-five percent of the subjects in the chloral hydrate group required a second dose of choral hydrate. The average sleep onset latency of the chloral hydrate group was 25.1 min, which was approximately the same as the MNG group (25.4 min). The average sleep duration of the chloral hydrate group was 89.3 min, which was significantly longer than the MNG group (45.6 min), with a mean difference of 43.6 min (p-value = 0.01). There were minor adverse events in both groups, including vomiting (12.5 – 25.0%) and irritability (25.0%), without any serious adverse events reported.

CONCLUSION: The sedative effect of trans-mucosal MNG was unfavorable comparing with the chloral hydrate. The sublingual delivery was intolerance for uncooperative children and sedation for neurodevelopment disordered children were challenging. However, the sleep onset latency by behavioral observation induced by MNG tended to be comparable to chloral hydrate. Further adjustment of trans-mucosal administration and dosage could provide adequate pediatric sedation.

KEYWORDS: auditory brainstem response, chloral hydrate, melatonin niosome gel, pediatric sedation

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INTRODUCTION

The auditory brainstem response (ABR) test is a diagnostic tool used to detect retro-cochlear pathology, and estimate hearing threshold. During the ABR test, muscle movements affect the electrical wave forms that are recorded. Therefore, it is recommended for patients to be asleep during the procedure. Sedative agents are usually administered to children aged between 6 months and 6 years to induce calmness during the test. For children, younger than 6 months, ABR testing can be performed while the patient sleeps naturally[1].

Sedative agents used for children include chloral hydrate, fentanyl, opioids, ketamine, midazolam, and nitrous oxide[2]. Chloral hydrate is commonly used for ABR testing. According to Valenzuela and Reynold's studies[1,3], the success rates of the ABR test after chloral hydrate administration in children older than 6 months were 66.0% and 95.0%, respectively. Sleep onset latency ranged from 20.0 to 49.0 min (with an average of 30.0 min)[3]. The adverse events of chloral hydrate are prolonged sleepiness lasting more than 8 hours (11.0%)[4], vomiting (15.0%)[4] and agitation (34.0%)[5]. Some patients with chronic neurological abnormalities such as cerebral palsy and developmental abnormalities are difficult to sedate with chloral hydrate and cannot fall asleep through the procedure as reported in a pediatric electroencephalogram study[6].

Oral melatonin is also a sedative agent for pediatric non-invasive procedures, with the advantage of the low side effects of central nervous system (CNS) suppression. This agent is also used for ABR testing with success rates of 65.0 – 86.7%[7] and a mean ABR examination time of 52.0 min[8]. The limitation of oral formulation is variation of gastrointestinal absorption and poor bioavailability (< 33.0%) due to extensive first-pass hepatic metabolism[9-11]. The melatonin niosome gel (MNG) is the muco-adhesive gel providing strong affinity for mucosal surface contributed by molecular interaction between gel and mucin/mucosa[12] to increase contact time, improve absorption and prolonged release of medication. Trans mucosal MNG provides direct absorption of melatonin through the oral mucosa, bypassing the first pass metabolism, resulting in high bioavailability with prolonged effect[11]. The MNG has 6 times higher maximal plasma concentration (C-max) than the oral formulation and mean half-life of 1.2-1.5 hour covering the routine ABR testing duration[11,13]. In addition, the trans-mucosal MNG in young adults' study reported no significant local and systemic adverse events[11]. The dosage of MNG was formulated according to the pharmacokinetic study of MNG in young adults applied to the oral melatonin dose [11,14-15]. This study aimed to evaluate the efficacy of MNG for ABR testing. The secondary outcomes were to study the effects of both medications on daytime sleep induction, including sleep onset latency and sleep duration, in addition to drug safety and any adverse events.

METHODS

This research was designed as a double-blinded, randomized controlled trial for children in an otorhinolaryngology clinic who undergo ABR testing at a university hospital. The study was conducted at the clinical research ward (Academic Clinical Research Office; ACRO) of Srinagarind Hospital, Faculty of Medicine, Khon Kaen University. Inclusion criteria were 1) aged between 1 and 6 years old. 2) No abnormalities of pinna and external auditory canal, craniofacial anomalies, or cleft palate conditions that contribute to conductive hearing loss and require additional air conduction testing. 3) No history of allergic reactions to melatonin or chloral hydrate, as determined by medical records. 4) No history of gastric ulcer[16]. 5) No use of medications interacting with sedative agents, such as warfarin[16], carbamazepine[16], cimetidine[16], fluvoxamine[16], furosemide[17], nifedipine[18], rifampicin[19], fluconazole[19], ketoconazole[19], and quinolone[20]. 6) No use of medications with CNS suppressing effects, such as opioids, benzodiazepines, and barbiturates[16].

7) No history of severe adverse events during previous sedation, including respiratory arrest and upper airway obstruction. Exclusion criteria were 1) Participants with the American Society of Anesthesiologist physical status classification of class III or below, such as patients with severe systemic disease and definitely restricted function[21]. 2) Participants who had a previous history of arrhythmias, arrhythmia detected on physical examination, or taking tricyclic antidepressants[19]. 3) Patients with severe renal impairment, indicated by a glomerular filtration rate less than 50 ml/min/1.73m^2 (according to KDIGO 2012 criteria) calculated by the Schwartz equation to estimate glomerular filtration rate in children[22]. 4) Patients with severe liver dysfunction, including those with cirrhosis or acute hepatitis[16]. 5) Participants who had abnormal blood test results, including blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, and direct bilirubin.

The sample size calculation was based on the previous studies of ABR when the success rate of chloral hydrate and oral melatonin sedation were 65.8%[3] and 86.7%[14], respectively. The two-sided test for a superior clinical trial was used with a statistical power level of 80.0% and error level (α) of 0.05. The calculated number of participants for each group was 64.

The parents or caregivers were informed about the testing procedures, including advice for preparations before the ABR test (fasting from food, water, and milk for at least 2 hours prior, avoiding falling asleep before the test, and the signs of illness that are contraindications for sedation), the medication given before the ABR test and the potential risks or side effects of both sedative agents. For the participants with an unsuccessful ABR test, an additional ABR test was scheduled with chloral hydrate sedation, according to the institutional standard. Subsequently, the research assistants obtained consent from the parents and caregivers of the participants.

The participants were categorized according to the presence of neuro-developmental disorders, including autistic spectrum disorder[23], Down's syndrome[24], attention deficit hyperactivity disorder (ADHD)[25], and cerebral palsy[26]. Stratified randomization was employed by using a permutated block randomization method (block of four) (figure 1). The codes for each participant were kept in sealed opaque envelopes, concealed from sleep assessors, audiologists and physicians, and were given to the 1st research assistant nurse who administered the sedative medication.

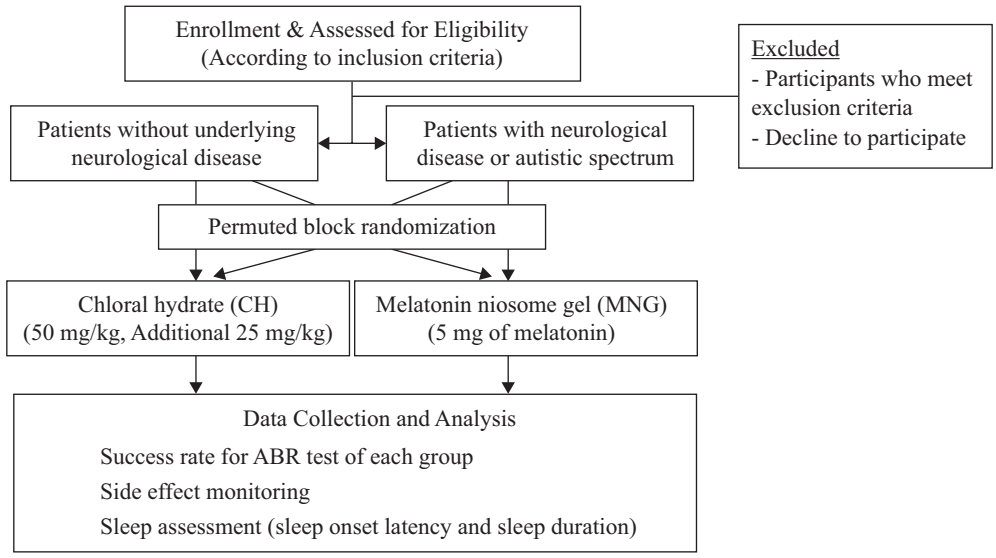

Figure 1 The consort flow diagram of study populations.

This study was a double-blinded randomized controlled trial. The researchers, sleep assessors, audiologists, and all parents were blinded from the intervention given to the participants.

The MNG was stored at a temperature of 2-8°C throughout the study period. The stability of the substances was assessed every 3 months. The MNG included melatonin, 0.08% w/w cholesterol, 0.08% w/w sorbitan monostearate, 9.0% w/w polyvinylpyrrolidone, 9.0% w/w hydroxypropyl methylcellulose, 8.0% w/w poloxamer 407, and 3.0% sucralose (flavoring agent). Glygerine, polyethylene glycol 400, and water were used as the solvents of the melatonin in muco-adhesive niosome gel.

The reference dose of oral melatonin adjusted by age[14-15] prior to the ABR testing was as the following:

- Children aged up to one year received 5 mg of oral melatonin
- Children aged between 1 and 6 years received up to total 10 mg of oral melatonin
- Children aged older than 6 years old received up to total 20 mg of oral melatonin

The study included participants aged between 1 and 6 years old which met the total dose of 10 mg oral melatonin by age range. Although the pharmacokinetic of melatonin in children were different from adult in drug metabolism and elimination, the MNG has bypassed the first pass metabolism and exclude the issue of different hepatic clearance between children and adults[11,27]. Therefore, the MNG dose were calculated from young adult pharmacokinetics data. According to the study of trans-mucosal melatonin, the MNG (5 mg) provided maximum plasma concentration (C-max) of 3 times greater than 10 mg oral formulation[11,13]. Another trans-mucosal buccal application study provided (C-max) of 2.3 times greater than same dose of oral formulation[28]. Therefore, trans-mucosal MNG (5 mg dose) would provide C-max at least 1.2-3 times as 10 mg oral formulation and prolonged effect covering ABR testing duration (mean $T_{1/2}$ of 1.5 hour). The MNG (5 mg) was administered before the ABR test. Participants received 5 mg of melatonin (in 250 mg of the melatonin niosome gel) administered at the sublingual area or the mucosal area between the gum and the inner cheek (buccal mucosal area). This method is referred to as trans-mucosal drug delivery. According to British medical association[16], the recommended maximal daily dose was 10 mg oral melatonin for children. In addition, the studies by Schmidt et al.[14] and Guerlain et al.[15] also applied total dose up to 10 mg oral melatonin for children aged between 1 and 6 years old prior to ABR test. As a result, a single dose of trans-mucosal MNG (5 mg) which provided higher C-max than 10 mg oral formulation reached the maximum dosage recommended for this age range and no additional dose applied.

The chloral hydrate syrup (100 mg/ml) was stored in amber glass bottles; each bottle contained 10 ml of the drug and was stored at a temperature of 15°C–25°C. The first dose of chloral hydrate syrup (100 mg/ml) was 50 mg/kg per oral, not exceeding 1 gram[16]. The participants were observed for 30 min (corresponding to the time of maximal effect)[29]. The second dose of chloral hydrate (25 mg/kg) was administered if the participants were not sedated or could not complete the test. The total doses of chloral hydrate did not exceed 100 mg/kg[16].

A successful ABR test was defined as the participants could complete the test on both ears after the sedation. If the participants could not initiate the test (within 60 min after the first dose of sedation), or could not complete the test, they were recorded as failed ABR tests.

Evaluation of sleep parameters and daytime sleep induction was conducted through direct observation and a sleep monitoring device (Philips Respironics Actiwatch 2) for the objective parameters. In direct observation, the sleep onset latency (SOL) was recorded from the time of drug administration until the onset of sleep (observed through the behaviors of eye closing, decreased body movements and consistent, rhythmic breathing for 5 min). Sleep duration was recorded

from the onset of sleep until the time of waking, which was observed through the behaviors of eye opening and increased body movements.

The sleep monitoring device contains acceleration-responsive piezoelectric sensors to record the intensity, frequency, and duration of movement that could assist in the evaluation of a patient's sleep. The devices were attached to the non-dominant wrist of participants and monitored their movement in order to interpret whether participants were asleep or awake. The devices reported SOL, sleep duration, and wakefulness after sleep onset (WASO) as outcomes. The adverse events were monitored from the drug administration until the post-test monitoring period, and were classified as common terminology criteria for adverse events (CTCAE) version 5.0[30].

Data were analyzed using descriptive statistics for continuous data, reported as means and standard deviations, while categorical data were presented as numbers and percentages. Statistically, the Independent T-Test was used to compare the sleep parameters and Fisher's Exact Test was used to compare the success rate of the ABR test, with a p-value of < 0.05 considered statistically significant. Statistical analysis was performed using IBM SPSS statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, Released 2021).

This study underwent an ethical review conducted by the Human Research Ethics Committee at Khon Kaen University (reference number HE621458) and was registered in the Thai Clinical Trial Registry (TCTR) (reference number TCTR20211121003).

RESULTS

The study was conducted between July 21, 2020 and October 5, 2020 and included a total number of 24 participants. Four participants were excluded due to abnormal laboratory tests. The number of participants who met the research criteria was 20. The research was suspended by the Data and Safety Monitoring Board to investigate cases that couldn't complete the test due to overall success rate obtained from the study which was lower than routine practice (62.5% and 70.0%, respectively). Among the included participants, 1 case was lost to follow-up, and the ABR schedule was suspended in 3 cases. Sixteen participants were investigated, including 8 children in each study group. The average ages were 2.6 and 2.1 years in the MNG group and the chloral hydrate group, respectively (table 1). There were 2 cases with neuro-developmental disorders (autistic spectrum disorder and ADHD) in the MNG group. The laboratory parameters and vital signs,

Table 1 The baseline characteristics of the participants in both study groups

Characteristic	Number of cases (%)	
	Melatonin niosome gel (N = 8)	Chloral hydrate (N = 8)
Male	6 (75.0)	7 (87.5)
Female	2 (25.0)	1 (12.5)
Age (μ ± SD)	2.6 ± 0.9 yr	2.1 ± 1.1 yr
Weight (μ ± SD)	15.0 ± 0.7 kg	12.3 ± 1.2 kg
Height (μ ± SD)	93.8 ± 2.8 cm	87.8 ± 3.7 cm
Neurological disorder	2 (25.0)	0
Underlying disease	5 (62.5)	3 (37.5)
Drug allergy	0	0
Current medication	3 (37.5)	2 (25.0)
Non-dominant hand	Left 7 (87.5) Right 1 (12.5)	Left 8 (100.0) Right 0

Abbreviations: cm, centimeter; kg, kilogram; N, number; SD, standard deviation; yr, year old; μ, means

except systolic blood pressure (SBP), were in the age-appropriate range for all participants[31] (table 2). The rise of SBP was temporary and didn't indicate a health issue. The mean dose of chloral hydrate was 652.0 mg and the additional dose of chloral hydrate was administered in 2 cases (25.0 %) with the mean dose of 357.0 mg (table 3). The success rate of the chloral hydrate group (100.0 %) was greater than the MNG group (25.0 %) (table 4) with a statistically significant difference (p-value = 0.01).

The effects on daytime sleep induction (table 4) include: The average SOL was 25.4 min and 25.1 min in the MNG group and the choral hydrate group, respectively, without any statistically significant differences between the groups. The sleep onset latency from the sleep monitoring device (table 4) were 21.3 min and 6.8 min in the MNG group and the choral hydrate group, respectively. However, the mean difference of 14.5 min was not statistically significant. According to the time gap between drug administration and starting of record by the devices which affected the SOL parameter, the author prioritized behavioral observation method for the SOL assessment.

Table 2 Physical examination of the participants

Variable		Number of cases (%)	
		Melatonin niosome gel (N = 8)	Chloral hydrate (N = 8)
Breath Sound		Normal 8 (100.0) Abnormal 0	Normal 8 (100.0) Abnormal 0
Heart Sound		Normal 8 (100.0) Abnormal 0	Normal 8 (100.0) Abnormal 0
Anterior Rhinoscopy		Normal finding 7 (87.5) Clear nasal discharge 1 (12.5)	Normal finding 7 (87.5) Clear nasal discharge 1 (12.5)
Retrognathia		1 (12.5)	1 (12.5)
Right Tonsil	Grade 1	4 (50.0)	2 (25.0)
	Grade 2	3 (37.5)	3 (37.5)
	Grade 3	0	3 (37.5)
	Grade 4	1 (12.5)	0
Left Tonsil	Grade 1	3 (37.5)	4 (50.0)
	Grade 2	3 (37.5)	3 (37.5)
	Grade 3	2 (25.0)	1 (12.5)
	Grade 4	0	0
Body Temperature (μ ± SD)		36.6 ± 0.3 °C	36.4 ± 0.2 °C
Blood Pressure (μ ± SD)		SBP 126.1 ± 12.1 mmHg DBP 68.4 ± 7.1 mmHg	SBP 131.1 ± 13.9 mmHg DBP 81.0 ± 11.3 mmHg
Pulse Rate (μ ± SD)		87.0 ± 24.6 BPM	121.8 ± 13.6 BPM
Respiratory Rate (μ ± SD)		20.5 ± 4.0 per min	26.1 ± 5.5 per min

Abbreviations: BPM, beats per minute; °C, degree Celsius; DBP, diastolic blood pressure; min, minute; mmHg, millimeter of mercury; N, number; SBP, systolic blood pressure; SD, standard deviation; μ, means

Table 3 Dosage and volume of the administered medication

Dose	Mean drug dose in mg (μ ± SD)	
	Melatonin niosome gel (N = 8)	Chloral hydrate (N = 8)
1st Dose	250.0	652.0 ± 184.0
2nd Dose	0	357.0 ± 106.0 Second dose administration 2 (25.0%)

Abbreviations: mg, milligram(s); N, number; SD, standard deviation; μ, means

Table 4 The sleep parameters among the study groups by direct observation and sleep monitoring device and the success rates of ABR testing

Variable	Duration in min (μ ± SD (range))		Mean difference (min)	P-value*
	Melatonin niosome gel	Chloral hydrate		
Sleep onset latency	25.4 ± 19.6 (10.0 – 59.0)	25.1 ± 19.5 (9.0 – 60.0)	0.3	0.98
Sleep duration	45.6 ± 33.8 (0 – 96.0)	89.3 ± 24.2 (55.0 – 126.0)	43.6	0.01
Sleep onset latency (By Actigraphy)	21.3 ± 22.7 (3.0 – 51.0)	6.8 ± 9.6 (2.0 – 30.0)	14.5	0.14
Sleep duration (By Actigraphy)	30.3 ± 37.1 (0 – 89.0)	77.5 ± 20.4 (36.0 – 100.0)	47.3	0.01
WASO (By Actigraphy)	3.1 ± 0.9 (1.3 – 4.3)	4.6 ± 3.2 (1.5 – 8.8)	1.5	0.38
Duration of ABR test	71.5 ± 3.5 (69.0 – 74.0)	63.3 ± 26.7 (19.0 – 91.0)	8.3	0.69
Success rate	25.0 %	100.0 %	Risk Ratio 0.25	0.01**

Abbreviations: ABR, auditory brainstem response; min, minute; SD, standard deviation; WASO, wakefulness after sleep onset; μ, means
*Independent T-Test
** Fisher's Exact Test

The average sleep duration by observation was 45.6 min and 89.3 min in the MNG group and the chloral hydrate group, respectively. The mean difference in sleep duration was 43.6 min and showed statistical significance (p-value = 0.01). According to Actiwatch, sleep duration was 30.3 min and 77.5 min in the MNG group and the chloral hydrate group, respectively. The mean difference of 47.3 min was statistically significant (p-value = 0.01).

WASO, measured by Actiwatch, were 3.1 min and 4.6 min for the MNG group and the chloral hydrate group, respectively, without any statistically significant difference. There were several minor adverse events (CTCAE grade 1) in both groups (table 5). Vomiting (1 case) and irritability (2 cases) were reported in the MNG group and resolved during the post-test monitoring period. In the chloral hydrate group, vomiting (2 cases) and irritability (2 cases) were also reported. There was no significant difference in the adverse events between groups.

DISCUSSION

Our study applied the current trend of melatonin trans-mucosal delivery for children in order to improve absorption, bioavailability, and more prolonged effect. It was designed to compare MNG sedation with the routine practice. However, the preliminary analytic results were

Table 5 Adverse events after the administration of medication

Adverse events	Number of cases (%)		P-value*
	Melatonin niosome gel (N = 8)	Chloral hydrate (N = 8)	
Nausea	0	0	-
Vomiting	1 (12.5) **	2 (25.0) **	0.99
Headache	0	0	-
Irritability	2 (25.0) **	2 (25.0) **	0.99
Total	3 (37.5)	4 (50.0)	-

Abbreviation: N, number
* Fisher's Exact Test
** CTCAE grade 1

not as effective as expected. The small number of sample size might not represent the entire ABR testing population. The previous studies of oral dosage including, Casteil et al.[8] reported a 65.0% ABR success rate in 29 children aged 1 to 6 years. Chaouki et al.[32] administered 5 mg melatonin (with a repeated dose if necessary) in children aged 5 months to 4 years and reported a 72.7% ABR success rate. Hajjij et al.[33] administered 2-5 mg melatonin for children aged 6 months to 3 years and 5-10 mg for children aged 3 to 6 years resulted in 83.4% success rate. The systematic review by Behrman et al.[7] also reported a 65.0% - 86.7% success rate in children aged 1 month to 14.5 years. In our study, the factors associated with unsuccessful test was the sublingual administration was intolerance for uncooperative participants. The proper adjustment of MNG administration could improve the efficacy such as aiming for buccal administration which was more tolerable for children. Moreover, the neuro-developmental patients, including autism spectrum disorders and ADHD, were also difficult cases for sedation as it could lead to chronic insomnia[24,26]. In terms of daytime sleep induction effect, MNG induced comparable sleep onset latency to chloral hydrate (approximately 25.0 min by behavioral observation). However, the sleep duration of MNG (average 45.6 min) was not sufficient for the ABR testing duration (69.0 – 74.0 min). According to oral formulation, Casteil et al.[8] reported average sleep onset latency of 41.0 min and a sleep duration of 33.0 min in children aged 1 to 6 years. Guerlain et al.[15] report 35.0 min of sleep onset latency and 23.0 min of sleep duration in children aged 1 to 13 years. Compared with the oral dosage, MNG tended to induce earlier onset of sleep with comparable sleep duration. The adjustment of MNG administration and dosage are also needed to facilitate pediatric sedation.

CONCLUSION

The sedative effect of trans-mucosal melatonin niosome gel in pediatric auditory brainstem response test was unfavorable comparing with chloral hydrate. The contributing factors including sublingual administration which was intolerance for uncooperative children and neurodevelopmental disordered children were also challenging for sedation. Nevertheless, the sleep onset latency by behavioral observation tended to be comparable with the chloral hydrate. The adjustment of drug administration and dosage would provide adequate sedation and ensure its suitability for clinical applications.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, SL, upon reasonable request.

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