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Safety and effectiveness of chloral hydrate in outpatient paediatric sedation for objective hearing tests

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ABSTRACT

Objectives: Chloral hydrate is a sedative that has been used for many years in clinical practice and, under proper conditions, gives a deep and long enough sleep to allow performance of objective hearing tests in young children. The reluctance to use this substance stems from side effects reported over time that can vary, depending on dose, procedure settings and immediate life supporting intervention when needed. Our study adds to those that have appeared in recent years, showing that chloral hydrate is an effective and safe substance when is used in proper conditions.

Methods: The study included 322 children who needed sedation for objective hearing tests, from April 2014 to March 2018. Parents were instructed to bring the child tired and fasted for at least 2 h before sedation. The sedative was administered by trained staff in the hospital, and the child was monitored until awaking.

Results: In our study group, over half of the children were in the age 1–4 years group, and only 15% were older than 4 years. The dose of chloral hydrate ranged between 50 and 83 mg/kg body weight, with an average of 75 mg. Successful sedation occurred in 94.1% of children; 0.9% of children awoke during testing and required supplemental sedation or rescheduling of the testing. The most common side effects were vomiting, agitation, prolonged sleep, and failure to fall asleep.

Conclusions: Comparing the side effects of chloral hydrate in our study with those from other studies, ours were similar to those described in the literature. In our study chloral hydrate was effective and had only limited adverse effects. The use of chloral hydrate under hospital conditions with proper monitoring could be a practical and safe solution for outpatients or those with short-term hospitalisation.

1. Introduction

Hearing loss is a sensory disorder that needs to be diagnosed early in life to provide these children proper developmental conditions. Diagnosis requires a battery of tests including objective hearing assessments, such as auditory brain stem responses (ABR) and auditory steady-state responses (ASSR), which set hearing thresholds in young children. However, in young children, collaboration with these tests is more difficult. The electrophysiological tests require the child to be as quiet and motionless as possible, to reduce the myogenic activity that may interfere with the recordings of the auditory evoked potentials [1]. Tests can be done either in spontaneous sleep, especially in young children, in induced sleep, with the help of drugs, or under general anaesthesia [2].

Sedation with drugs is a method commonly used in electrophysiological assessment (ABR and ASSR) of hearing in young children. It aims to reduce physical and mental discomfort, to reduce anxiety and, in particular, in case of ABR responses, to reduce unwanted movements that could influence the results [3]. The majour advantage of sedation is that it can also be performed outside of the operating room [4].

Sedative drugs can be administered orally, nasally, intravenously, intramuscularly, subcutaneously, or by inhalation [5]. Of these, the most commonly used in paediatric sedation are a mixture of nitrous oxide and oxygen, administered by inhalation; or midazolam, a benzodiazepine, administered by the intramuscular, intravenous, oral, rectal, sublingual, or nasal route. Ketamine can be administered intravenously or intramuscularly; propofol is administered intravenously; and sevoflurane can be administered via inhalation or intravenously. Fentanyl can be administered parenterally, transdermally, nasally, or

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orally. Sufentanil, chloral hydrate, can be administered orally or intrarectally, with more sedative and less analgaesic effect. Hydroxyzine and promethazine, administered orally or intramuscularly, are often associated with chloral hydrate, pentobarbital, metohexital, or thiopental. Barbiturates are administered orally or rectally. Melatonin is administered orally. Dexmedetomidine, an imidazole compound, can be administered intravenously or nasally [6].

Regardless of the type of sedative used, adverse effects may occur [7], the most common being vomiting (55.5%), agitation (17.9%), hypoxia (14.8%), and apnoea (7.1%) [8].

The type of sedative and route of administration are chosen depending on the child, on the type of procedure, and on the desired effect. If the procedure is not painful and it requires only a patient's immobilisation, simple sedation can be used, preferably non-parenteral, such as chloral hydrate, promethazine, midazolam, melatonin, or barbiturates (e.g., pentobarbital, methohexital, thiopental, or dexmedetomidine) [9].

Chloral hydrate was discovered in the 19th century and was used primarily until barbiturates and benzodiazepines displaced it. It is administered both orally and rectally and is rapidly absorbed into the gastrointestinal tract, then metabolised by alcohol dehydrogenase in the liver and erythrocytes, in trichlorethanol and trichloroacetic acid, the active metabolites [10]. Chloral hydrate is an easy to administer sedative with a high success rate and a low prevalence of adverse effects, unlike other traditional sedative agents that may have more significant respiratory or cardiovascular adverse effects [11,12]. Some of the adverse effects are abdominal distension, vertigo, ataxia, headache, paradoxical agitation, cancer (in case of prolonged use), hallucinations, nightmares, seizures, vomiting, hypotension, unpleasant taste, and cardiac arrhythmia [13]. Studies in rodents have shown that it would have genotoxic and carcinogenetic effects [14,15], but these effects cannot be extrapolated to humans [16,17]. Severe adverse effects reported by the Institute for Safe Medication Practice were largely due to dosage errors, unmonitored oversedation, and accidents of venous administration of oral solution [18].bib18

The adverse effects most commonly reported in the literature were in very young children, less than 6 months of age, including apnoea, desaturation, hypotension, vomiting, and prolonged sedation [19].

Chloral hydrate is recommended in painless procedures in children who cannot cooperate; for neurophysiologic diagnostic procedures, such as ABR; electroencephalography; electrocardiography; imaging evaluations; ophthalmologic manoeuvers; and in some procedures in cardiovascular intensive therapy [20–23].

The purpose of this study was to evaluate incidents and adverse effects arising from the administration of chloral hydrate. The safe administration of chloral hydrate allows the testing of children in the outpatient department, relieving the hospital of a series of costs involving general anaesthesia and hospital admission.

2. Material and methods

The study was conducted between July 2014 and April 2018, and it was approved by the Ethics Committee of the University of Medicine and Pharmacy and by the Ethics Committee of the hospital, in compliance with the Declaration of Helsinki. Informed consent was obtained from every family to use the child's data.

The group consisted of 323 children who required sedation with chloral hydrate to perform objective hearing tests with ABR and ASSR, with the purpose of establishing an audiological diagnosis.

The study group included children between 5 months and 7 years of age requiring sedation with chloral hydrate to perform electrophysiological auditory tests. In children less than 1 year of age, the testing was performed during natural sleep, with a few exceptions. Older children, over the age of 4–5 years, were sedated only in cases in which they would not cooperate for behavioural assessment or when they did not sit quietly to be tested for ABR and ASSR, usually in the case of neuropsychiatric disorders. Children who could be tested in natural sleep and did not require sedation were excluded from this study. No sedative was administered to children with fever or to those with acute infection of the upper or lower respiratory tract. Prior to the procedure the child was evaluated by the otolaryngologist. The assessment included health history, allergies, other diagnostic tests, airway assessment, previous sedation and/or analgesia and anaesthesia history, and other relevant details. In medically complex cases an anaesthesiologist was asked to evaluate the patient [24].

Parents were instructed to make sure the children fasted at least 2 h before coming to the hospital, and to awake them early and not let them sleep on the way to the hospital, so that they would be as tired as possible.

After a consultation with an Ear, Nose, and Throat (ENT) specialist, the chloral hydrate was administered by a trained nurse, by the oral route, in a dose of 50–100 mg/kg body weight, without exceeding the total dose of 2.5 g [25]. In the case of vomiting, depending on the amount administered, the dose was further supplemented. Also, if sedation was not obtained after 45–60 min, the dose was supplemented by 20–40 mg/kg body weight. After the sedative was administered, the child was placed in a quiet and soundproofed room, together with the parent, to fall asleep, under the supervision of the nurse. During the sleep, the children were monitored with a pulse oximeter and the reading of dates was at every 10 min.

After sleep onset, surface electrodes were placed: inverting electrodes (−) on each mastoid, noninverting electrode (+) on the high forehead, on the midline, and the ground electrode on the forehead, 3 cm from the noninverting electrode.

According to our protocol, we started with the tympanogram and otoacoustic emissions after which the auditory evoked potentials and the ASSR were performed. The testing was done with the Interacoustics Titan device for wideband tympanometry and otoacoustic emissions and with the SmartEP Intelligent Hearing System (IHS) equipment (Miami, Florida USA), with insert earphones in most cases, or with headphones for atretic ears, for electrophysiological measurements. For conductive hearing loss we used a B-71 bone conduction transducer held by one finger on the mastoid.

After completion of the testing, the child was stimulated to wake up. Children who did not wake up immediately after the completion of the testing were further monitored until they woke up, and all of them remained at the hospital until awake.

The data collected between June 2014 and May 2018 were studied retrospectively. In the study group were included only the patients who received chloral hydrate for sedation, with the age of up to 18 years. Patients who were tested in spontaneous sleep or under general anaesthesia, as well as adult patients, were not included in the study.

Patient consultation sheets containing the history, child weight, age at the time of evaluation, the amount of chloral hydrate administered, the period of time until sleep onset, sleep duration, adverse effects of the sedative (vomiting, agitation, failure to fall asleep, prolonged sleep), as well as cardiorespiratory parameters before and after sleep induction were analysed. Related diseases and the audiological diagnosis have also been taken into account. The collected data were kept secure and were analysed, keeping the privacy of the personal data.

The collected data were processed with the Statistical Package for Social Science (SPSS Statistics 21.0) program.

3. Results

The group was made up of 323 children aged between 5 and 83 months (7 years old), the average age being 28.18 ± 18.10 months, a median of 26 months [95% confidence interval (CI); 26.20–30.16). In the studied group, 26% were children between 5 months and 1 year of age; 58.8% were between 1 year and 4 years of age; and 15.2% were older than 4 years of age.

In the study were included children who required sedation with

chloral hydrate for objective hearing testing during sleep, young children who did not fall asleep spontaneously, or older children who were not able to cooperate long enough to perform the tests, which are, otherwise, noninvasive.

The group of children were 40.2% girls and 59.8% boys; 43.3% were from rural areas, and 56.7% were from urban areas.

In the studied group, 50.5% of the patients did not have other known associated conditions. Of 323 tested children, 21 were diagnosed with various syndromes such Bartter (2), BOR (1), Down (5), Treacher-Collins (5), Goldenhar (4), Hunter (2), West (1) and Wolf-Hirschorn (1). 24 children had craniofacial dysmorphism: five had Treacher-Collins features, five had cleft palates, four had craniofacial malformations without any known syndrome and ten children had unilateral auricular malformation. Four of those with unilateral auricular malformation had Goldenhar syndrome, the rest did not have any other syndrome features. 56 (17.3%) children were tested because of premature birth and because they did not pass the screening. 41 (12.7%) children presented with neuropsychiatric conditions such as autism spectrum disorders and attention deficit/hyperactivity disorder. Eight (2.5%) children had cardiac malformations and three had kidney malformations. Two children were diagnosed with CMV intrauterine infection, one child had a history of encephalitis, one had hydrocephalus and one had tetraparesis. Of all tested children, 118 (36.5%) had normal hearing; the rest had unilateral (4.3%) or bilateral (10.3%) conductive hearing loss, unilateral (1.5%) or bilateral (44.2%) sensorineural hearing loss, or mixed hearing loss (3.2%).

The dose of chloral hydrate administered ranged from 0.50 to 0.83 mL/kg body weight, with an average of 0.75 mL kg body weight [95%CI: 0.74–0.75, standard deviation (SD) = 0.52].

Sleep onset occurred within 10–75 min of administration. The success rate, defined as children who fell asleep and slept during the entire testing, was 94.1%. When we grouped the children by age (under one year, between 1 and 4 years and children older than 4 years), the success rate varied between 96.4% and 89.8%, without significant differences. Inadequate sedation ranged between 3.6% and 6.1% but also with no statistical differences. When compared, rates of sedation failure were significantly different between the group of children between 1 and 4 years and the group of children older than 4 years, p = .046. (Fig. 1).

There were only three children (0.9%) who did not fall asleep even after the initial dose of chloral hydrate was supplemented by 20–40 mg/kg body weight. These children were subsequently tested with chloral hydrate, in one case (0.3%) and, in two cases, under general anaesthesia (0.6%). Several children woke up during testing (5.0%) before the completion of the protocol and required supplementation of the chloral hydrate dose, or were rescheduled for testing. These children were either left quiet to fall asleep again, or the solution dose was supplemented (Table 1).

Table 1
Adverse effects of chloral hydrate in our study group.

	Frequency	Percent
No complications	254	78.6
Vomiting	37	11.5
Inadequate sedation	16	5.0
Paroxistical hyperactivity	10	3.1
Prolonged sedation	3	0.9
Failed sedation	3	0.9
Total	323	100.0

Administration of the 10% chloral hydrate solution was sometimes difficult, because the taste of the solution is very bitter, causing nausea and vomiting reactions (14.5%) that followed the administration of the solution. Vomiting was more commonly seen in older children and in those who did not respect the time interval between the last meal and the drug administration.

Some children (3.1%) experienced a state of agitation after administration of the solution, and sleep onset was slower; however, no changes in cardio-respiratory parameters were noted (Figs. 2 and 3).

Patients were monitored with the pulse oximeter during testing, and O_2 saturation did not decrease to below 95%; the pulse was within normal limits for all children. No patient required oxygen administration or other manoeuvres to maintain cardio-respiratory functions.

The test duration varied between 45 and 100 min. Most patients woke up immediately after the testing, upon the removal of electrodes. Others woke up after 10–30 min. In the studied group, only three (0.9%) patients experienced prolonged sleep (more than 4 h after the first drug administration), but without cardio-respiratory changes. Those patients remained in the hospital until the next day, were monitored, and subsequently discharged without further complications (Figs. 2 and 3).

4. Discussions

Objective hearing assessment in young children is extremely important for establishing an early diagnosis. To assess hearing and determine neurophysiological hearing thresholds, it is necessary to perform the ABR and the ASSR, which require a quiet, preferably sleeping

Fig. 1. The success rate was greater than 94% in children under the age of 4 years, and slightly less than 90% in children older than 4 years of age. There was no statistically significant difference between the age groups either in the success rate or the rate of inadequate sedation. As for the failure rate, the difference between the 1–4 years age group and the over 4 group had statistical significance, p = .046.

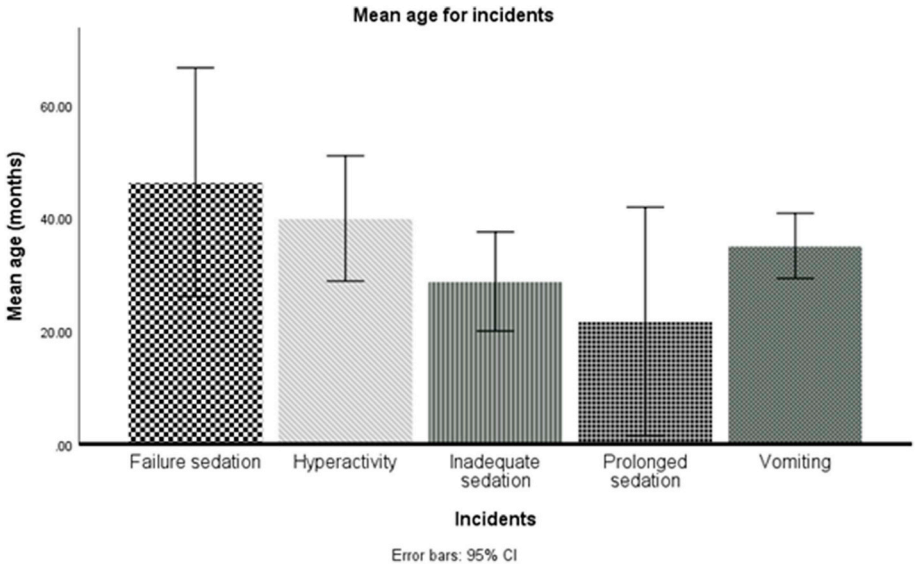

Fig. 2. The mean age of children for each incident and complication that occurred after the administration of chloral hydrate and the 95% confidence interval. Hyperactivity and sedation failure were more often in older children and the mean age in the study group was between 3 and 4 years. Vomiting was often around the age of 3 years while prolonged sedation occurred in younger children, about the age of 2.

patient, to minimise artifacts. The investigation can be done either in natural sleep or in drug-induced sleep or under general anaesthesia. Each method has its advantages and disadvantages both in terms of time and cost.

The study group was composed of 323 children aged between 5 months and 7 years; more than half of them (58.8%) were between 1 and 4 years old. The children were sedated with chloral hydrate to be tested for neurophysiological auditory thresholds. Our auditory assessment protocol comprises the otoacoustic emissions, the tympanogram, the ABR, and the ASSR. Approximately half of the children in the group experienced associated conditions such as craniofacial dysmorphism, external ear malformations, cardiac or kidney malformations, or neuropsychiatric disorders. The mean dose of chloral hydrate was 75 mg/kg and, in some cases, it was necessary to supplement it by 20–40 mg/kg to obtain the proper sedation. The success rate was 94.1% with a single dose of chloral hydrate and 99.1% if we consider the cases that required dose supplementation. The value obtained by us was similar to that reported by Avlonitou et al. (2011), of 99.7% [26], whereas West et al. (2013) [22] reported a success rate of 92.79% in a group of 1509 sedations at a single dose of 80 mg/kg and 96.69% when a top-up dose was used. Studies in which lower doses were used, 50–75 mg/kg, reported lower success rates, ranging from 64% to 89.4% [27–29].

There were no incidents or majour complications in the studied group. The most frequent incident was vomiting, followed by inappropriate sedation and hyperactivity. In three cases, the children could not be sedated, even after the dose was supplemented; and, in the other three cases, sedation was prolonged and lasted more than 6 h. During sedation, patients were monitored for oxygen saturation and heart rate with a pulse oximeter and there were no cases requiring oxygen therapy.

From our point of view, the advantage of testing under chloral hydrate sedation was that we could benefit from the soundproof room, without the noises specific to the operating room. Another advantage was that we did not invoke the cost of operating room use, and we could prolong the testing as long as necessary, without supplementing drug doses and additional increases of costs. The most unpleasant aspect of solution administration was the nausea reaction caused by the bitter, unpleasant taste, followed by vomiting.

In a systematic review and meta-analysis of the incidence of adverse effects due to child sedation procedures in the emergency department, Bellolio et al. (2016) noticed that the most commonly reported adverse

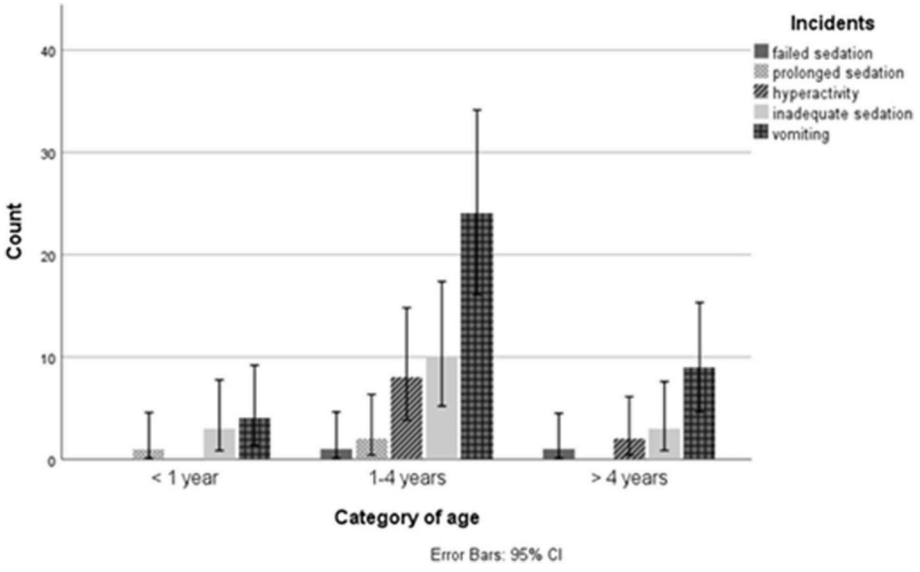

Fig. 3. Adverse effects, by age group, and their incidence. In every group, vomiting was the primary side effect, followed by inadequate sedation and hyperactivity.

effect was vomiting, followed by agitation, hypoxia, and apnoea. Vomiting had a higher incidence in studies in which sedation was done with ketamine (80.7 per 1000 sedations), whereas agitation was more common in studies with midazolam. Hypoxia has been reported more often in the studies with etomidate, and apnoea has been associated particularly with propofol [8].

Vomiting was more common in our group than in other studies (11.5%). West et al. (2013), in a study conducted on 1509 sedations, reported a lower incidence of vomiting, 0.53% [22], compared with other studies in which the incidence was higher. In the study conducted by Lee et al. (2018) in a group of 1590 patients, the incidence of vomiting was 6.5% [30]. In a study reported by Avlonitou et al. (2011) [26], the incidence was 11.4, similar to what we noticed.

In our study, the second most common adverse effect was inadequate sedation. Of the 323 children, 16 (5%) woke up during the testing and required dose supplementation or rescheduling. West et al. (2013) reported inadequate sedation in 7.2% of children, at a dose of 80 mg/kg of chloral hydrate, with dose supplementation by 40 mg/kg [22]. In another study, Abulebda et al. (2017) reported, in a group of 73 children, 14% of children required supplementation of the initial dose of chloral hydrate of 33.4 mg/kg [20]. In their study, Avlonitou et al. (2011) reported an initial dose of 40 mg/kg of chloral hydrate, with additional 40 mg/kg for those who required it. The success rate after the first dose was 72% for children older than six months and 100% for those younger than six months; and only 5 (0.3%) could not be sedated with chloral hydrate [26]. In a group of 148 children, Hijazi et al. (2005) reported a success rate which increased from 79% to 95%, with the initial average dose of chloral hydrate being 56.9 ± 9.3 mg/kg and a second dose of 18.5 ± 6.4 mg/kg [31].

Failure to fall asleep was often due to the parents' failure to awake the child early on the morning of the procedure and not keeping the child awake on the way to the hospital. In our study, there were only three children who could not be sedated with chloral hydrate, even after dose supplementation.

Agitation or hyperactivity after administration of the chloral hydrate occurred in 3.1% of cases. In the study conducted by Avlonitou et al. (2011), the percentage was 8% [26], whereas in the study conducted by Wandalsen et al. (2016), the percentage was just 1.3% [32]. As in the study reported by West et al. [22], the incidence in our group was between the two values, close to that reported by Valenzuela et al. (2016), of 5% [33]. As a matter of fact, agitation is a complication found with other types of sedatives, as shown by the review performed by Bellolio et al. (2016), in which agitation was reported in 18.2 of 1000 cases. Studies with midazolam report the highest incidence of agitation [8].

Prolonged sedation occurred in three patients (0.9%) in our study, whereas Wandalsen et al. (2016) reported 0.4% of cases with prolonged sedation [32], and 1.33% was reported in the study reported by West et al. [22]. All cases required only supervision, without any other interventions, and the children were hospitalised overnight, without complications.

No greater incidence of adverse effects was observed in patients with cardiac malformations, and there were no cases of anoxia, bradycardia, or other majour adverse effects in our study. The data are consistent with other studies in which chloral hydrate was administered to cardiac patients without majour adverse effects [23,34].

The limitations of the study are due to the lack of a standardised protocol for the administration of chloral hydrate as well as the limited monitoring possibilities of patients in an outpatient setting. Comparisons with other studies are relative, given that the doses administered were variable. However, it is obvious that adverse effects are not significant unless the admissible doses are exceeded. However, the carcinogenetic and genotoxic risk outlined by older studies remains, and further studies are needed to address the problem, even if it appears that such effects occur only due to high doses administered for a long time. It would also be useful to compare the effect of chloral hydrate with other sedatives that could be used in outpatient conditions.

After a period when chloral hydrate was used less due to the fear of carcinogenetic and genotoxic effects that could not be demonstrated with certainty [35], and due to accidents caused by improper administration or excessive doses, studies on large groups of children, published in recent years, come to show that there are no higher risks in chloral hydrate use than in other substances currently used in paediatric sedation, when it is used in the proper dose. The majour advantage of chloral hydrate in audiology, unlike many other substances, is the duration of sedation, which allows performing painless tests that can last more than an hour.

5. Conclusions

Our study confirms what studies have shown in recent years about chloral hydrate, that sporadically administered, without exceeding the permissible doses, adverse effects are not more common or more severe than in the case of other substances used for sedation. Like any substance administered, it has its advantages and disadvantages, and the use of chloral hydrate should be done judiciously, in appropriate conditions, by observing the doses to achieve effective and risk-free sedation. Besides the low costs, the big advantage is that it can be administered outside the operating room but under specialised supervision.

Declarations of interest

None.

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