Is Orally Administered Pentobarbital a Safe and Effective Alternative to Chloral Hydrate for Pediatric Procedural Sedation?

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OBJECTIVES Chloral hydrate had been extensively used for children undergoing sedation for imaging studies, but after the manufacturer discontinued production, pediatric sedation providers explored alternative sedation medications. Those medications needed to be at least as safe and as effective as chloral hydrate. In this study, we examined if pentobarbital is a suitable replacement for chloral hydrate.

METHODS Subjects who received pentobarbital were recruited from a prospectively collected database, whereas we used a retrospective chart review to study subjects who received chloral hydrate. Sedation success was defined as the ability to provide adequate sedation using a single medication. We included electively performed sedations for subjects aged 2 months to 3 years who received either pentobarbital or chloral hydrate orally. We excluded subjects stratified as American Academy of Anesthesiologists category III or higher and those who received sedation for electroencephalogram. The data collected captured subject demographics and complications.

RESULTS Five hundred thirty-four subjects were included in the final analysis, 368 in the chloral hydrate group and 166 in the pentobarbital group. Subjects who received pentobarbital had a statistically significant higher success rate [136 (82%) vs 238 (65%), $p < 0.001$], but longer sleeping time (18.1% vs 0%, $p < 0.001$) in all age groups. Subjects who received chloral hydrate had a higher risk of airway complications in the <1 year of age group (6.5% vs 1.8%, $p = 0.03$).

CONCLUSIONS For pediatric patients younger than 3 years of age undergoing sedation for imaging studies, oral pentobarbital may be at least as effective and as safe as chloral hydrate, making it an acceptable and practical alternative.

ABBREVIATIONS ASA, American Academy of Anesthesiologists; EEG, electroencephalography; UMSS, University of Michigan Sedation Scale

KEYWORDS chloral hydrate; oral administration; pediatrics; pentobarbital; procedural sedation

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Introduction

Infants and children often need sedation during imaging studies to prevent motion artifact and assure quality imaging with minimal radiation exposure. Oral chloral hydrate was considered by many pediatric sedation providers the drug of choice for sedation of infants under 3 years of age undergoing electroencephalography (EEG) or radiological procedures, such as computed tomography or magnetic resonance imaging.^{1–3} However, chloral hydrate was discontinued by the manufacturer in April 2012 for financial reasons as it was no longer profitable for the manufacturer. Pediatric sedation providers have been searching for a safe, yet effective, alternative that can be administered orally or intranasally.

Many authors have suggested the use of intrana-

sal dexmedetomidine as an alternative medication and few have considered pentobarbital as a viable alternative.^{3,4} Although the older literature comparing pentobarbital to chloral hydrate is conflicted, in many cases those studies had evaluated it intravenously rather than orally.^{5,6} Administering pentobarbital via the intravenous route limits its practical use in a sedation setting, owing to the availability of more efficient and safer medications (e.g., propofol). Because of its fast onset of action and short recovery time, intravenous propofol is the main sedation medication used by pediatric sedation providers, but insertion of an intravenous catheter is time consuming and emotionally distressing for both the child and family. For that reason, when it is possible, sedation providers prefer oral or intranasal routes of administration. Therefore, oral administration of pentobarbital is still of value for sedation providers.

Table 1. University of Michigan Sedation Scale (UMSS)

Score	Level of Sedation
0	Awake and alert
1	Minimally sedated: tired/sleepy, appropriate response to verbal conversation and/or sound
2	Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated: deep sleep, arousable only with significant physical stimulation
4	Unarousable

One study by Mason et al⁴ demonstrated the superiority of pentobarbital versus chloral hydrate for sedation of infants during imaging studies. The primary objective of this study was to evaluate the relative efficacy and safety of oral pentobarbital compared to oral chloral hydrate when used as the primary sedative agent for noninvasive pediatric procedures. We hypothesized that pentobarbital, when administered orally for pediatric procedural sedation, would be at least as effective and as safe as chloral hydrate, making it an appropriate alternative medication.

Materials and Methods

As chloral hydrate is no longer available commercially, prospective data review was not possible. In this study, we retrospectively reviewed sedation records of subjects previously sedated using chloral hydrate. We used a prospective database to review the use of oral pentobarbital at our institution. The primary objective was to compare the safety profile and effectiveness in providing adequate sedation for both chloral hydrate and pentobarbital when used as primary agents for sedation. The primary outcome measure was the success rate of providing moderate to deep sedation, as defined by the University of Michigan Sedation Scale (UMSS) (Table 1),⁷ using pentobarbital or chloral hydrate as the primary sedating agent. If a second (rescue) agent was used, the sedation was considered unsuccessful. The need for a rescue medication was determined by the sedation provider if the subject did not achieve the desired level of sedation. The secondary outcome measure was the rate of complications associated with the use of these medications. The retrospective database spanned from 2009 to 2012. The prospectively

collected database spanned from 2013 to 2016. The study was performed in a single institution and included only outpatient imaging studies.

Subjects in the prospectively collected database presented to the pediatric outpatient procedure suite at our tertiary care hospital on the day of their scheduled procedure, at which time they were evaluated for participation in the study. Assessment was performed by a pediatric nurse followed by a pediatric critical care physician. The providers evaluated and recorded pertinent medical history, American Academy of Anesthesiologists (ASA) physical status classification (Table 2),⁸ and a focused medical examination. Parental consent for the study was not obtained as the database did not include any patient identifiers. Parents were notified by the clinic nurses at the time of initial assessment about the database and had the option to opt out. Although some parents elected to opt out of the study, this number was not tracked. Upon completion of the procedure, the sedation data recorded included: start and end times of the procedure, medication(s) used and administration time(s), patient demographics, achieved level of sedation according to UMSS, complications, successful completion of the procedure, and patient disposition. The retrospectively collected data used the same data collection sheet and evaluated the same metrics, using electronic medical records. The data were then recorded by study personnel with subsequent storage in a password-protected, secure University of Missouri internal electronic database. The study design was approved by the institutional review board at our institution.

Subjects with the following criteria were included: elective sedation performed in our pediatric outpatient procedure suite, age 2 months to 3 years, complete

Table 2. ASA Physical Status Classification System

ASA Classification	Definition
I	Normal, healthy patient
II	Patient with mild systemic disease
III	Patient with severe systemic disease
IV	Patient with severe systemic disease that is a constant threat to life
V	Moribund patient who is not expected to survive without the operation
VI	Patient declared brain-dead and whose organs are being removed for donor purposes

ASA, American Academy of Anesthesiologists

Table 3. Demographics (N = 534)*

	Chloral Hydrate (n = 368)	Pentobarbital (n = 166)
Age		
< 1 yr	128 (34.8)	102 (61.4)
1–3 yr	240 (65.2)	64 (38.6)
Sex, male	219 (59.5)	94 (56.6)
Sedation level		
Deep	235 (63.9)	69 (41.6)
Moderate	133 (36.1)	97 (58.4)

* Data presented as n (%).

procedural record documented for subjects who were reviewed retrospectively, and ASA status classification I to II (healthy subjects and subjects with mild systemic disease). Exclusion criteria included subjects with an ASA status classification of III or higher owing to the increased risk of complications, subjects older than 3 years of age, sedation for esophagogastroduodenoscopy or EEG, urgent or inpatient procedure, and subjects who did not meet fasting criteria prior to the initiation of the procedure.

Dosing of pentobarbital 4 to 6 mg/kg with a maximum dose of 50 mg. The first dose was 4 mg/kg, followed by 2 mg/kg after 15 to 20 minutes if the desired level of sedation was not achieved. Dosing of chloral hydrate was a single dose of 25 to 50 mg/kg with a maximum dose of 1000 mg. Both pentobarbital and chloral hydrate in our study were unflavored. Sedation medications were administered by a sedation credentialed pediatric critical care physician and monitoring started following the first dose of medication. Sedation nurses documented vital signs, level of sedation using UMSS, and procedure progress every 3 to 5 minutes. To ensure better sedation results, subjects were placed in a private, dark, and quiet room. Subjects were observed for at least 1 hour after the last medication administration and until back to baseline mentation.

For the prospective group, the complications were tracked and recorded by sedation nurses with predetermined definitions agreed upon by both the nurses and physicians prior to the initiation of the study. Documented complications included the following: 1) hypotension defined as blood pressure less than fifth percentile for age or 20% below baseline; 2) the need to use intravenous fluid for any complication including, but not limited to, hypotension, hypoglycemia, or vomiting; 3) airway complications including: a) desaturation, defined as <90% SpO₂ for greater than 10 seconds with or without need for airway intervention, b) minor airway rescue maneuvers, including repositioning, suctioning, supplemental oxygen, oral or nasal airway placement; 4) major airway complications: a) apnea, defined as cessation or pause of spontaneous ventila-

Table 4. Rescue Medications

	Chloral Hydrate (n = 130)	Pentobarbital (n = 30)
Ketamine IV	2	2
Ketamine IM	0	5
Propofol bolus	40	15
Propofol infusion	29	6
Dexmedetomidine infusion	14	0
Dexmedetomidine PO	0	2
Dexmedetomidine IN	0	0
Midazolam IV	38	0
Midazolam PO	5	0
Fentanyl IV	2	0
Morphine IV	0	0

IM, Intramuscular; IN, Intranasal; IV, Intravenous; PO, oral

tion for greater than 20 seconds with or without need for intervention, b) other airway rescue maneuvers (e.g., bag mask ventilation, tracheal intubation); 5) emesis; 6) prolonged sleep time, defined as sleeping for more than 1 hour after the end of the procedure; and 7) prolonged crying and irritability for more than 30 minutes after awakening. The same complications were documented by examining the medical records of the chloral hydrate group. The medical records were examined by the same physicians who provided sedation in our institution.

Owing to the higher rate of pentobarbital use in younger children (<1 year of age), we elected to further stratify the groups according to age. For that reason, we created 2 subgroups: <1 year of age and 1 to 3 years of age. To achieve a power of at least 90%, we calculated the need to evaluate the sedation of 90 subjects from the chloral hydrate group and 140 from the pentobarbital group. In order to cover any possible variability in practice, we elected to expand the chloral hydrate group to include all subjects sedated with chloral hydrate for at least 3 years.

We used Pearson χ^2 and binary logistic regression tests in SPSS Version 17.0 (SPSS Inc, Chicago, IL). A $p < 0.05$ was considered statistically significant.

Results

There were 2779 patient encounters included in the prospective database. Of those, 166 received oral pentobarbital (6%) as their primary sedative agent. The retrospective data of 368 subjects who received chloral hydrate and met the inclusion criteria were used for this study. A total of 534 subjects were included in the analysis. The demographics of both groups are shown

Table 5. Medication Complications by Patient Age

Complications	Chloral Hydrate (n = 368)	Pentobarbital (n = 166)	p value
Hypotension			
<1 yr	1/128	0/102	1.000
1–3 yr	6/240	0/64	0.349
Intravenous fluids			
<1 yr	1/128	0/102	1.000
1–3 yr	6/240	0/64	0.349
Minor airway complications			
<1 yr	11/128	2/102	0.030
1–3 yr	13/240	1/64	0.315
Major airway complications			
<1 yr	1/128	0/102	1.000
1–3 yr	1/240	1/64	0.377
Emesis			
<1 yr	0/128	1/102	0.443
1–3 yr	5/240	0/64	0.588
Prolonged sleeping time			
<1 yr	0/128	16/102	<0.001
1–3 yr	0/240	12/64	<0.001
Crying			
<1 yr	3/128	0/102	0.256
1–3 yr	1/240	0/64	1.000

in (Table 3). One hundred thirty-six subjects (82%) of the pentobarbital group and 238 (65%) of the chloral hydrate group were successfully sedated using only the primary medication without the need for a rescue medication ($p < 0.001$), and we used a wide range of rescue medications, the most common being propofol (Table 4).

Subjects less than 1 year of age who received chloral hydrate had a statistically significant higher rate of airway complications (8.6% chloral hydrate, 2% pentobarbital, $p = 0.03$), whereas subjects of all studied ages who received pentobarbital had a statistically significant longer sleeping time (>1 hour after the end of the procedure) (16.7% pentobarbital, 0% chloral hydrate, $p < 0.001$). There was no significant difference noted in hypotension, need for intravenous fluids, apnea, nausea, emesis, and crying for all age groups (Table 5).

Discussion

Since the discontinuation of chloral hydrate, pediatric procedural sedation providers have been seeking an effective and safe oral alternative. Most of that effort had concentrated on intranasal dexmedetomidine as the most logical alternative.^{3,9–11} In a recent study evalu-

ating the variation in pediatric procedural sedations across children's hospital emergency departments in the United States, the authors documented a significant decrease in the use of chloral hydrate and a mild decrease in the use of pentobarbital. But documented a significant increase in the use of dexmedetomidine and other intravenously administered sedation medications (i.e., propofol, ketamine, and fentanyl).¹² Although dexmedetomidine may be an effective and safe alternative to chloral hydrate, the practical use of the medication is limited owing to the longer time to achieve the desired effect (20–40 minutes), which makes it less desirable in a busy clinical environment.^{3,9–11,13,14}

In this study, we defined sedation success as the ability to complete the desired study without the need for an unplanned second (rescue) medication. The efficacy of chloral hydrate as a sedation medication has been widely variable in the literature.^{3,4,11,15} From those studies we recognize the wide spectrum of procedures performed using chloral hydrate, which may have contributed to the variability of the success rate between studies. Highly stimulating procedures (e.g., EEG, magnetic resonance imaging, auditory brainstem response) and less stimulating procedures (e.g., computed tomography scan, echocardiogram, and

physical exam) would not all be expected to have the same success rate when using an orally administered sedation medication.^{16,17} In addition, chloral hydrate is well known for its poor taste and it requires a large volume for sedation (500 mg/5 mL or 250 mg/5 mL), thus causing difficulty in dose administration. Variable gastric absorption also results in unpredictable onset of action and difficulty in ensuring adequate sedation.

Pentobarbital, on the other hand, has been used extensively as a sedation medication for procedural sedation, although it has been studied more often by the intravenous route rather than the oral route. Pentobarbital has been reported in many studies to be associated with a higher risk of complications, including hypotension, respiratory depression, and prolonged recovery time.^{5,15,18–21} When the intravenous form of pentobarbital (50 mg/mL) is used orally, the volume needed to achieve the desired sedation effect is small allowing for ease in administration.

Our study demonstrates that orally administered pentobarbital was associated with a higher rate of successful sedation as a primary sedation medication when compared to chloral hydrate. We also found that it was associated with a lower risk of airway complications, but longer sleeping time, which is similar to what has been reported in the literature.⁴

Our study is limited owing to a few factors. There was no chloral hydrate available at the time of the study to obtain prospective observational data, so we had to rely on a retrospective review of the medical records for the study subjects. Our study was limited to sedation outside of the operating room and outside of the critical care unit, so we did not include any hospitalized subjects in the analysis and all data were obtained for a single institution. Also, the age of the subjects in this study was limited to young children below the age of 3 years. Our practice had avoided the use of pentobarbital for older age groups owing to the perceived lack of efficacy in older children, which may have limited the generalizability of our finding.

In future studies, we plan to assess the role of the environment on the achieved level of sedation and the rate of success using oral pentobarbital as a primary sedation medication. This will allow us to truly evaluate the feasibility of using this method of sedation in busy and loud sedation services.

We conclude that for pediatric patients younger than 3 years of age undergoing sedation for imaging studies, pentobarbital was associated with a higher rate of successful sedation and fewer airway complications when compared to chloral hydrate, but it was associated with longer recovery time than chloral hydrate. Oral pentobarbital may be an acceptable and practical alternative for chloral hydrate. We still recommend using the medication in a quiet environment with minimal stimulation until the child reaches an acceptable level of sedation for the procedure.

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REFERENCES

1. Hassanzadeh Rad A, Aminzadeh V. The comparison between effect of chloral hydrate and diphenhydramine on sedating for electroencephalography. *Iran J Child Neurol*. 2016;10(4):25–29.
2. Chan AM, Tan GK, Loh HP, et al. Safety and efficacy of chloral hydrate sedation in paediatric sedation for ophthalmic procedures. *Ann Acad Med Singapore*. 2017;46(4):138–144.
3. Zhang W, Wang Z, Song X, et al. Comparison of rescue techniques for failed chloral hydrate sedation for magnetic resonance imaging scans—additional chloral hydrate vs intranasal dexmedetomidine. *Paediatr Anaesth*. 2016;26(3):273–279.
4. Mason KP, Sanborn P, Zurakowski D, et al. Superiority of pentobarbital versus chloral hydrate for sedation in infants during imaging. *Radiology*. 2004;230(2):537–542.
5. Strain JD, Harvey LA, Foley LC, et al. Intravenously administered pentobarbital sodium for sedation in pediatric CT. *Radiology*. 1986;161(1):105–108.
6. Ziegler MA, Fricke BL, Donnelly LF. Is administration of enteric contrast material safe before abdominal CT in children who require sedation? Experience with chloral hydrate and pentobarbital. *AJR Am J Roentgenol*. 2003;180(1):13–15.
7. Malviya S, Voepel-Lewis T, Tait AR, et al. Depth of sedation in children undergoing computed tomography: validity and reliability of the University of Michigan Sedation Scale (UMSS). *Br J Anaesthesia*. 2002;88(2):241–245.
8. Dripps RD. New classification of physical status. *Anesthesiol*. 1963;24:111.

9. Cao Q, Lin Y, Xie Z, et al. Comparison of sedation by intranasal dexmedetomidine and oral chloral hydrate for pediatric ophthalmic examination. *Paediatr Anaesth*. 2017;27(6):629–636.
10. Behrle N, Birisci E, Anderson J, et al. Intranasal dexmedetomidine as a sedative for pediatric procedural sedation. *J Pediatr Pharmacol Ther*. 2017;22(1):4–8.
11. Reynolds J, Rogers A, Medellin E, et al. A prospective, randomized, double-blind trial of intranasal dexmedetomidine and oral chloral hydrate for sedated auditory brainstem response (ABR) testing. *Paediatr Anaesth*. 2016;26(3):286–293.
12. Miller AF, Monuteaux MC, Bourgeois FT, et al. Variation in pediatric procedural sedations across children's hospital emergency departments. *Hosp Pediatr*. 2018;8(1):36–43.
13. Sulton C, Kamat P, Mallory M, et al. The use of intranasal dexmedetomidine and midazolam for sedated magnetic resonance imaging in children: a report from the pediatric sedation research consortium. *Pediatr Emerg Care*. 2017. Epub ahead of print]
14. Yu Q, Liu Y, Sun M, et al. Median effective dose of intranasal dexmedetomidine sedation for transthoracic echocardiography in pediatric patients with noncyanotic congenital heart disease: an up-and-down sequential allocation trial. *Paediatr Anaesth*. 2017;27(11):1108–1114.
15. Malviya S, Voepel-Lewis T, Tait AR, et al. Pentobarbital vs chloral hydrate for sedation of children undergoing MRI: efficacy and recovery characteristics. *Paediatr Anaesth*. 2004;14(7):589–595.
16. Mataftsi A, Malamaki P, Prousalis E, et al. Safety and efficacy of chloral hydrate for procedural sedation in paediatric ophthalmology: a systematic review and meta-analysis. *Br J Ophthalmol*. 2017;101(10):1423–1430.
17. Needleman HL, Joshi A, Griffith DG. Conscious sedation of pediatric dental patients using chloral hydrate, hydroxyzine, and nitrous oxide—a retrospective study of 382 sedations. *Pediatr Dent*. 1995;17(7):424–431.
18. DiFrancesco MW, Robertson SA, Karunanayaka P, et al. BOLD fMRI in infants under sedation: comparing the impact of pentobarbital and propofol on auditory and language activation. *J Magn Reson Imaging*. 2013;38(5):1184–1195.
19. Teshome G, Belani K, Braun JL, et al. Comparison of dexmedetomidine with pentobarbital for pediatric MRI sedation. *Hosp Pediatr*. 2014;4(6):360–365.
20. Mallory MD, Baxter AL, Kost SI; Pediatric Sedation Research Consortium. Propofol vs pentobarbital for sedation of children undergoing magnetic resonance imaging: results from the pediatric sedation research consortium. *Paediatr Anaesth*. 2009;19(6):601–611.
21. Warden CN, Bernard PK, Kimball TR. The efficacy and safety of oral pentobarbital sedation in pediatric echocardiography. *J Am Soc Echocardiogr*. 2010;23(1):33–37.