Intravenous Methohexital for Brief Sedation of Pediatric Oncology Outpatients: Physiologic and Behavioral Responses

David R. Freyer, DO*; Allison E. Schwanda, MD‡; Dominic J. Sanfilippo, MD§;
Richard M. Hackbarth, MD§; Nabil E. Hassan, MD§; John S. Kopec, MD§; and Maria Teresa Neirotti, MD‖

ABSTRACT. *Objective.* **In this successor to a preliminary retrospective study, we sought to confirm the apparent safety and efficacy of intravenous methohexital (MHX) for brief, unconscious sedation of pediatric hematology/oncology outpatients undergoing painful, invasive procedures.**

Methods. **This prospective study was conducted in a children's hospital-based hematology/oncology clinic. Following published monitoring guidelines for deep pediatric sedation, MHX (1.0 mg/kg) was administered immediately before each procedure, 1% xylocaine was given locally, and additional MHX was titrated to maintain minimal response to pain during the procedure. For each patient, the procedural and physiologic response data reported below were recorded from the onset of sedation through recovery. Behavioral distress responses were measured using a standardized pediatric observational tool (Procedure Behavioral Checklist).**

Results. **Two hundred and thirty-three procedures were carried out in 76 patients ranging .1 to 19.6 years of age. The mean cumulative MHX dose/procedure was 4.6 ± 2.9 mg/kg. The mean lengths of time from initiation of sedation until completion of the invasive procedure, attainment of patient arousability, discontinuation of monitoring, and attainment of patient alertness were 8 ± 5, 19 ± 8, 19 ± 9, and 22 ± 9 minutes, respectively. Relative to presedation values, mean arterial pressure (MAP), heart rate, and respiratory rate showed maximum mean percent changes of −16.6, +17.8, and +13.4, respectively (all clinically insignificant). Complications among procedures were transient and included hiccoughs and myoclonus (each 10%); oropharyngeal secretions (6%); and pain at the injection site, emergence phenomena, and mild stridor (each 3%). Of two procedures (.9%) affected by transient upper airway obstruction associated with emesis or secretions, only one briefly needed mask ventilation. No procedures required intubation or early termination. In 49 additional procedures assessed for patient distress, observed pain responses were absent to mild in 45 (92%) and moderate in 4.**

Conclusion. **MHX appropriately administered provides sedation which is effective, safe, well tolerated, and of short duration, making MHX attractive for use in pediatric oncology outpatients and other populations with similar sedation needs.** *Pediatrics* **1997;99(5). URL: http://www.pediatrics.org/cgi/content/full/99/5/e8;** ***methohexital, pain, procedures, quality of life, sedation.***

ABBREVIATIONS. MHX, methohexital; MAP, mean arterial pressure.

Invasive diagnostic or therapeutic procedures, such as lumbar punctures and bone marrow aspirations and biopsies, are required for the management of most children with cancer and serious hematologic disorders. The physical and emotional distress caused by these procedures are notable and have been well documented in behavioral studies of children with cancer.[1–3] Because procedure-related discomfort has been identified by children as the most negative aspect of their cancer treatment, efforts to improve their quality of life have included minimizing the acute distress associated with the procedures.[4] One such approach has been the use of brief sedation or anesthesia to reduce the anticipation and actual experience of pain during the invasive procedures.

The selection of a sedation agent appropriate for that purpose is dependent upon several factors. These include the procedures, which vary in type, combination, duration, invasiveness, and frequency; the patients, who have variable coping capabilities; and the treatment setting, which is typically a busy outpatient clinic. Accordingly, desirable characteristics in a sedation agent for this patient population include rapid onset, predictable efficacy, controllable duration, and short recovery time, as well as convenient administration, manageable side effects, and feasibility relative to institutional resources.

With the above in mind, since 1991 we have operated a joint sedation program staffed by our Divisions of Hematology/Oncology and Critical Care Medicine, in which children are routinely offered brief, unconscious sedation while undergoing their invasive outpatient procedures. In our institution, the agent used almost exclusively for this purpose has been methohexital sodium for intravenous use (MHX; Brevital, Lilly). MHX is an ultrashort-acting barbiturate which results in rapid induction of sleep with fewer cumulative effects and more rapid recovery than with other barbiturates.[5] MHX was selected for use in our program because its properties appeared consistent with those of a desirable sedation agent described above, as suggested by the prior

From the Divisions of *‖Hematology/Oncology and §Critical Care Medicine, DeVos Children's Hospital, Grand Rapids, Michigan; and *‡§Department of Pediatrics, Michigan State University College of Human Medicine, East Lansing, Michigan.

Presented in part at the annual meeting of the American Society of Clinical Oncology, Los Angeles, CA, May 20–23, 1995.
Received for publication Feb 27, 1996; accepted Jun 19, 1996.

Reprint requests to (D.R.F.) Division of Pediatric Hematology/Oncology, DeVos Children's Hospital, 100 Michigan NE, Grand Rapids, MI 49503.

experience of our pediatric intensivists using MHX for invasive procedures in critically ill children. Our preliminary experience using MHX for the sedation of pediatric oncology outpatients was recently reported in a retrospective study.[6]

Because of limitations related to its retrospective design, however, we undertook this larger, prospective study in which we sought to confirm the apparent safety and efficacy of MHX for pediatric oncology outpatients undergoing invasive procedures. The specific aims of this study were: 1) to characterize in greater detail the physiologic responses of children receiving MHX sedation while undergoing invasive procedures; 2) to determine more accurately the types and incidences of adverse reactions in children receiving MHX sedation; and 3) to measure the levels of behavioral distress exhibited by children undergoing invasive procedures while receiving MHX sedation.

MATERIALS AND METHODS

During the time period encompassed by this study, all children with cancer or hematologic disorders requiring invasive procedures were offered MHX sedation unless there were medical contraindications to its use, including demonstrated hypersensitivity or intolerance of MHX or other barbiturates; significant congenital or acquired upper airway obstruction; and oral intake within 6 hours before the procedure. Patients electing to receive MHX sedation as standardly administered at our institution constituted the subjects of this study. Informed consent was obtained from the responsible adult before each sedation procedure. Sedation procedures were conducted by a board-certified pediatric intensive care specialist (responsible solely for MHX administration, patient monitoring, and management of associated complications); a pediatric hematology/oncology physician or nurse practitioner (responsible solely for performing the invasive procedure); and a pediatric hematology/oncology procedure nurse. Sedation was provided in accordance with current American Academy of Pediatrics guidelines for elective use of deep sedation in children.[7] All procedures were performed within the pediatric hematology/oncology clinic in a dedicated sedation procedure room equipped with wall suction, wall oxygen with appropriate administration devices, and monitoring equipment described below. Complete pediatric resuscitation equipment was immediately available at all times. The study was approved by our Institutional Review Board before collection of physiologic and behavioral response data reported here.

Sedation Procedure

Sedation procedures were performed as we have described previously.[6] In brief, venous access was secured before sedation using tunneled central venous catheters when present, or peripheral angiocatheters if not. Upon entry of each child into the sedation procedure room, vital signs and transcutaneous capillary oxygen saturation (SaO_2) were measured as monitors were applied. Before drug administration, the sedation procedure was reviewed with the child and parents. MHX (1.0 mg/kg) was then given by slow intravenous push as supplemental oxygen by nasal cannula was started at the discretion of the intensivist. Parents remained at bedside until their child was unconscious, at which time the child was positioned, 1% xylocaine (buffered with $NaHCO_3$) was administered locally, and the invasive procedure(s) was performed. Additional MHX was titrated as needed to achieve and maintain a level of sedation where patient movement required only minimal restraint. Monitoring of vital signs and SaO_2 were carried out as described below. Upon completion of the invasive procedure(s), parents returned to bedside as their child awakened.

Physiologic Response Assessments

To measure the physiologic responses of children undergoing MHX sedation, the following medical instrumentation was used: Hewlett Packard Cardiorespiratory Monitor/Terminal, Model 78534B (heart and respiratory rates); Dinamap Vital Signs Monitor, Model 1846 SX (blood pressure); and Nellcor Pulse Oximeter, Model N-100 (SaO_2). Physiologic response measurements were begun with initiation of sedation and recorded at 3 minute intervals until patients became arousable following recovery from sedation, as defined below. Data capture forms were completed prospectively by the procedure nurse to record the following information for each procedure: 1) date; underlying diagnosis; current weight; relevant interval history; type of invasive procedure(s); and route of venous access; 2) heart and respiratory rates, blood pressure, and SaO_2 at 3-minute intervals; 3) cumulative MHX dose administered; 4) rate of oxygen flow, if utilized; 5) lengths of time from initiation of sedation to completion of the invasive procedure(s), attainment of arousability (defined as the recovery of appropriate and purposeful responses to verbal and tactile stimuli), discontinuation of monitoring, and attainment of alertness (defined as the recovery of presedation levels of cognitive interaction with the environment); 6) the occurrence and severity of several defined adverse reactions, including pain at the injection site, hiccoughs, myoclonus, oropharyngeal secretions, stridor, laryngospasm, clinically significant vital sign changes, and emergence phenomena; and 7) any other clinical information deemed relevant by either attending physician.

Behavioral Distress Assessments

Separate informed consent was obtained for participation in this portion of the study. Behavioral responses of children undergoing MHX sedation for painful procedures were measured utilizing the Procedure Behavioral Checklist, a standardized observational distress scale developed by LeBaron and Zeltzer.[8] For each sedation event, one of two dedicated observers involved with the study (M.T.N. or a trained registered nurse) evaluated eight defined distress behaviors exhibited by the child, categorized as verbal (crying, screaming, and verbalized stalling, anxiety, and pain) or muscular (muscle tension, physical movement, and need for restraint). For each behavior, the maximal response was recorded as absent, very mild, mild, moderate, intense, or extremely intense. Distress responses were recorded prospectively at four time points: preprocedure (child entering treatment room); intraprocedure (during the painful procedure itself); postprocedure (during recovery from sedation); and at end of monitoring (child leaving treatment room).

RESULTS

Patients and Procedures: Characteristics

The gender, ages, and diagnoses of the 76 study patients are displayed in Table 1. As indicated in Table 2, 233 consecutive outpatient procedures performed with patients receiving MHX sedation comprised the physiologic response component of this study (an additional 49 procedures were performed for behavioral distress assessments). Of the 233 procedures, 159 (68.2%) were isolated diagnostic or therapeutic lumbar punctures (for intrathecal administration of cancer chemotherapeutic agents). Bone

TABLE 1. Patient Characteristics

Gender	Patients
Male	32
Female	44
Age	**Years**
Median	5.9
Range	0.1–19.6
Diagnosis	**Patients**
Acute leukemia	52
Lymphoma	5
Solid tumor	2
Brain tumor	2
Hematologic disorder	15

TABLE 2. Outpatient Procedures Performed

Procedure	Number
Therapeutic lumbar puncture	154
Bone marrow aspiration and biopsy	28
Therapeutic lumbar puncture and bone marrow aspiration	17
Bone marrow aspiration	11
Diagnostic lumbar puncture and bone marrow aspiration	6
Diagnostic lumbar puncture	5
Therapeutic lumbar puncture and bone marrow aspiration and biopsy	4
Diagnostic lumbar puncture and bone marrow aspiration and biopsy	4
Other	4
Total	233

marrow aspirations with or without biopsies constituted 70 (30.0%) of the procedures, 31 of which were followed by lumbar puncture. Four miscellaneous procedures were brainstem audio-evoked response measurements (two), echocardiography (one), and removal of a tunneled central venous catheter (one), all in combination with lumbar puncture or in children refractory to standard forms of sedation. For the 233 procedures, venous access for MHX administration was by existing tunneled central venous catheters in 173 (74.2%) and temporary peripheral angiocatheter in 60 (25.8%).

Procedural Data

As indicated in Table 3, patients in this study underwent an average of 3 ± 2 procedures (range, 1 to 11). The mean cumulative MHX dose per procedure, representing the initial loading dose plus quantities given subsequently to maintain the desired level of sedation, was 4.6 ± 2.9 mg/kg (range, 1.1 to 9.5). The average duration of the invasive procedure itself was 8 ± 5 minutes (range, 2 to 29). As defined in Materials and Methods, the average time from onset of sedation to the achievement of arousability was 19 ± 8 minutes; to the discontinuation of all monitoring was 19 ± 9 minutes; and to the achievement of alertness was 22 ± 9 minutes; as determined from the 94 procedures in which all three values were recorded. Most procedures were performed with low-flow supplemental oxygen being administered at the discretion of the attending pediatric intensivist.

Physiologic Responses

Figure 1 displays the mean percent changes in vital signs during MHX sedation, compared with baseline values, shown at 3-minute intervals from initiation of sedation through 30 minutes (only 10 of the 233 procedures extended beyond this time). Transient

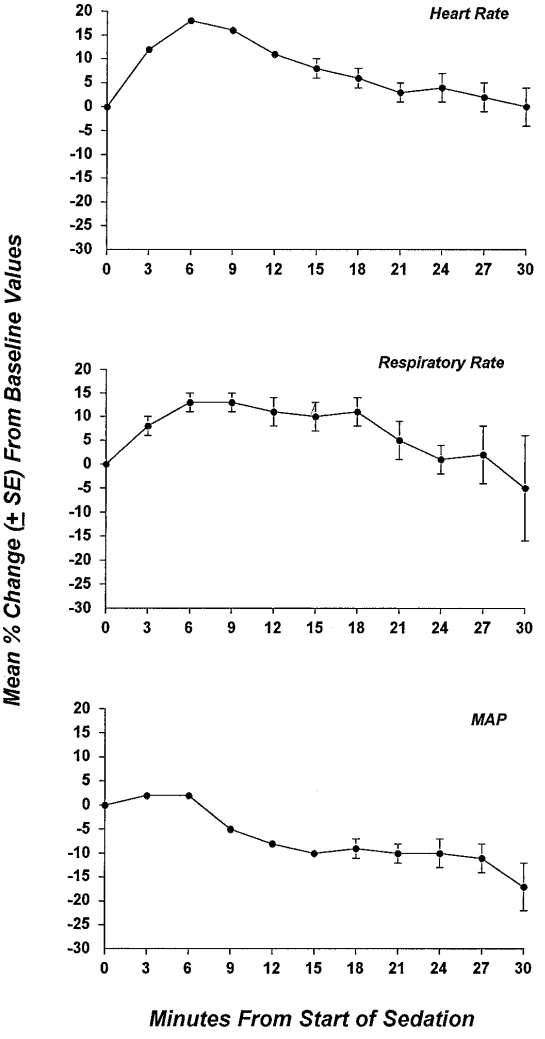

Fig 1. Mean percent changes in heart rate (top), respiratory rate (middle), and mean arterial pressure (bottom) during methohexital sedation, as compared with baseline values. For each procedure, heart rate, respiratory rate, and blood pressure were recorded at 3-minute intervals from onset of sedation through recovery of arousability. Systolic and diastolic blood pressure measurements were later converted to mean arterial pressue values. The percent change in each vital sign, compared with the baseline (presedation) value, was calculated for each time point of each procedure. Mean values for these percent changes at each time point were then determined by combining data from all procedures. The standard error is shown when the value exceeds 1. Data are derived from those procedures in progress at each time point through 30 minutes from onset of sedation.

increases of all vital signs were noted within the first 9 minutes of monitoring, coinciding with the painful procedure. For both the heart and respiratory rates, maximal percent increases of 17.8 and 13.4, respec-

TABLE 3. Summary of Procedural Data From 233 Outpatient Procedures

Parameters	Mean ± SD	Range	Comment
Number of sedations per patient	3 ± 2	1–11	
Cumulative MHX dose per procedure (mg/kg)	4.6 ± 2.9	1.1–29.5	
Duration of invasive procedure (minutes)*	8 ± 5	2–29	n = 86
Time to arousability (minutes)*	19 ± 8	6–54	n = 94
Time monitored (minutes)*	19 ± 9	6–54	n = 94
Time to alertness (minutes)*	22 ± 9	6–59	n = 94

* As measured from onset of sedation. See "Methods" for definitions of terms.

tively, were noted at 6 minutes, before gradually returning toward baseline with further time. While the MAP also increased initially, it decreased with further time to below baseline values, with the maximal percent decrease of 16.6 being observed in the relatively small number of patients still being monitored at 30 minutes. Substantial variation between patients in the magnitude of their vital sign changes was noted at every time point. None of the measured vital sign changes was noted to be clinically significant.

Also for each procedure, SaO_2 was measured continuously and recorded at 3-minute intervals. Of the 233 procedures, seven (3.0%) were associated with measured but clinically insignificant decreases of SaO_2 below 94%, which responded to the simple addition or increase of low-flow supplemental oxygen.

Adverse Reactions

Based on our previous experience, patients were monitored for several potential adverse reactions during MHX sedation (see Materials and Methods). If noted, these, their severity, and any other reactions were recorded on the data capture forms. All adverse reactions encountered in the 233 procedures are summarized in Table 4. As indicated, the vast majority of reactions were mild, transient, and required minimal or no intervention for management. The most common reactions were transient hiccoughs or peripheral myoclonus, affecting 24 and 23 procedures, respectively. Fifteen (6.4%) procedures were associated with mild-moderate oropharyngeal secretions which were easily managed by simple suctioning at the discretion of the attending pediatric intensivist. In eight (3.4%) procedures with peripheral venous access, patients briefly complained of a burning sensation proximal to the infusion of the initial MHX loading dose. During patient recovery from sedation, seven (3.0%) procedures were associated with transient behavioral phenomena such as tearfulness or restlessness, which completely resolved with reassurance and a low-stimulation environment. Mild to moderate stridor was noted in six (2.6%) procedures, all managed with simple airway positioning (and increased supplemental oxygen in one). Interestingly, only five of the patients with oropharyngeal secretions, and none of those with stridor, had an interval history of upper respiratory symptoms before sedation.

Two (0.9%) procedures were associated with transient airway obstruction: one in a 14.6-year-old child with acute myelogenous leukemia who vomited thick gastric secretions but responded promptly to suctioning, airway positioning, and increasing supplemental oxygen; the other in a 3.7-year-old child with acute lymphoblastic leukemia who had copious oropharyngeal secretions and possible incomplete laryngospasm, and responded rapidly to suctioning and brief (<30 seconds) positive-pressure assistance with a bag-mask device. None of the 233 procedures was associated with apnea, intubation, or early termination for any reason. All invasive procedures were completed with a satisfactory level of sedation.

Behavioral Distress Responses

To confirm the efficacy of MHX sedation, formal behavioral distress assessments were performed during 49 additional, consecutive, evaluable, invasive procedures. The clinical characteristics of patients, types of invasive procedures, and sedation methods used were comparable to those in the 233 procedures described above. Using the Procedure Behavioral Checklist, the severity of eight defined verbal and muscular distress responses was rated at the preprocedure, intraprocedure, postprocedure, and end of monitoring phases of sedation. As indicated in Table 5, verbal distress responses were "absent" or "very mild" in virtually all phases of sedation in all 49 procedures. Muscular distress responses consisted chiefly of transient, unconscious withdrawing movement upon initiation of the procedure itself (intraprocedure phase of sedation), where a rating of "moderate" was noted in four procedures (ratings of "absent," "very mild," or "mild" were noted in the remainder). As indicated in Table 5, minimal to no muscular or verbal distress was noted following cessation of the painful stimuli (during the postprocedure and end of monitoring phases).

DISCUSSION

The purpose of this study was to confirm and extend our encouraging initial experience using intravenous MHX for brief, unconscious sedation of pediatric oncology outpatients undergoing invasive procedures.[6] In this present study, we have prospectively evaluated a larger number of patients for more detailed physiologic response data, as well as for behavioral response data using a standardized observational tool. The results reported here indicate that MHX does indeed induce brief sedation which is effective, safe, well tolerated, and possesses favorable characteristics for use in the pediatric oncology outpatient clinic setting. Our study population was

TABLE 4. Number of Adverse Reactions Among 233 Outpatient Procedures

Type of Reaction	Grade			Total (%)	Intervention
	Mild	Moderate	Severe		
Hiccoughs	22	2		24 (10.3)	
Myoclonus	19	3	1	23 (9.9)	
Oropharyngeal secretions	14	1		15 (6.4)	Suctioning
Pain at injection site	7	1		8 (3.4)	
Emergence phenomenon	6	1		7 (3.0)	Reassurance
Stridor	4	2		6 (2.6)	Repositioning
Transient airway obstruction		2		2 (0.9)	Brief bagging (1 procedure)
Shivering	1			1 (0.4)	

TABLE 5. Number of Invasive Procedures Associated With Behavioral Distress During MHX Sedation (n = 49)*

Phase of Sedation	Distress Responses‡§	Grade of Distress					
		None	Very Mild	Mild	Moderate	Intense	Extremely Intense
Preprocedure	Verbal	46	2	1	···	···	···
	Muscular	38	5	5	1	···	···
Intraprocedure	Verbal	48	1	···	···	···	···
	Muscular	26	12	7	4	···	···
Postprocedure	Verbal	49	···	···	···	···	···
	Muscular	45	2	1	1	···	···
End of monitoring	Verbal	46	2	1	···	···	···
	Muscular	47	···	1	1	···	···

* Forty-nine invasive procedures were performed in 35 children sedated with MHX and assessed for behavioral distress using the Procedure Behavioral Checklist (LeBaron and Zeltzer, 1982).
‡ Defined verbal responses: verbalized anxiety, pain, and stalling; crying; screaming.
§ Defined muscular responses: muscle tension; physical movement; use of restraint.

both large (relative to other published pediatric oncology sedation studies) and typical for patient characteristics and invasiveness of procedures performed in such patients.

Methohexital is an ultrashort-acting oxybarbiturate available as a monosodium salt for intravenous administration.[5] The drug is highly lipid soluble and, after infusion, undergoes rapid uptake by gray matter in the central nervous system.[9] Accordingly, the onset of its sedative effect is nearly immediate (within 30 seconds).[5] The drug then undergoes redistribution into less vascular areas of the brain and other tissues with a distribution half-life of approximately 6 minutes.[10] It is believed that this rapid redistribution phase of MHX is primarily responsible for its short duration of sedative effect. However, MHX is also extensively extracted and metabolized by the liver and subsequently excreted by the kidney with an elimination half-life of 3.5 hours.[10,11] Therefore, it tends not to accumulate in body tissues as extensively as other highly fat soluble barbiturates, such as thiopental.[5]

Introduced for clinical use in the early 1960s, MHX has continued to be used primarily for preoperative induction of anesthesia in children via the rectal[12–14] or intravenous[11,15] routes. Before the initiation of our MHX sedation program in 1991, published applications of single-agent MHX for brief pediatric sedation were limited to diagnostic or therapeutic radiology (by the intramuscular route)[16,17] and dentistry (by the rectal route).[18] Given its nearly immediate onset and short duration of effect, MHX given intravenously offered the possibility of rapidly achieving an adequate level of sedation which could then be maintained in highly individualized fashion through the frequent titration of additional small amounts of MHX. Such dosing flexibility seemed well suited for pediatric oncology outpatients, where consistent sedation efficacy and short recovery times are desirable despite varying duration and invasiveness of procedures.

The results of our study appear to confirm these characteristics. As measured from the onset of sedation, the mean time to patient alertness was only 22 minutes, which included performance of the invasive procedures themselves (Table 3). This time is shorter than the 30 minutes to patient alertness noted in our previous study, a difference probably accounted for by the 20% reduction in the cumulative MHX dose used in this study. Because the patient populations, invasive procedures, and loading MHX dose were comparable between our two studies, this reduction in cumulative dose may reflect further refinement of our dose titration technique. Despite the lower MHX dose, the level of sedation provided continues to be effective, as suggested by the favorable behavioral response data discussed below. Few pediatric oncology sedation studies report the time required for either sedation onset or recovery. Defined differently between studies, recovery from sedation appears to have ranged between approximately 1 and 4 hours as reported for oral midazolam,[19] oral ketamine,[20] and a combination of intravenous midazolam/ketamine or etomidate/fentanyl.[21] Relative to these studies, the total time per patient required for completion of procedures and sedation appear to be substantially less with intravenous MHX. This characteristic is not only beneficial for patients, but also promotes efficiency for our pediatric intensivists, by allowing five to seven sedations to be performed sequentially on each of two clinic days per week.

Two specific aims of this prospective study were to characterize in further detail the physiologic responses and adverse reactions to MHX sedation in this patient population. Both the heart and respiratory rates increased transiently by approximately 10 to 20% during the time coinciding with the painful stimulus. In contrast, for the MAP there was a gradual 10 to 15% decrease below baseline during sedation, a change which could represent the normal response of a sleeping child, possibly magnified by mild preprocedure anxiety elevating the baseline measurement. As with our previous experience, these measured physiologic responses to sedation, including the decreased MAP, were clinically insignificant and needed no intervention.

Adverse reactions encountered in this study were similar to our previous experience in type, overall lack of severity, and minimal need for intervention. Because of their importance, respiratory complications were monitored carefully. The most frequent of these was increased oropharyngeal secretions easily managed with simple suctioning. While this may well be considered an expected occurrence in deep pediatric sedation, we elected to track oral secretions to provide a more complete description of typical

management required for safe sedation using MHX. Isolated, nonobstructive stridor of mild to moderate severity was noted in 2.6% of procedures and was managed with simple airway repositioning. Rare, but of importance, were two episodes of transient upper airway obstruction, as described in Results. Neither of these patients had any interval history of upper respiratory symptoms before sedation. Both patients had received previous MHX without difficulty, and MHX was given subsequently to the first child without complication. Combining our two studies of MHX sedation involving 365 procedures in 109 children, there have been four (1.1%) episodes of transient upper airway obstruction. No patients have required intubation, experienced apnea, or needed premature termination of their procedure for any reason. These data suggest the incidence of these complications is very low under the conditions utilized here, though the need for expert airway management during deep sedation remains.[7] Other sedation agents utilized in the pediatric oncology population have been associated with varied side effects including decreased blood pressure,[19,22,23] hypoxemia,[19,21–24] behavioral reactions,[18,25,26] laryngospasm,[25] emesis,[21,22,24] pruritis,[22,24] cough,[25] arrhythmias,[27] and respiratory arrest.[28] Thus, the adverse reactions with MHX encountered here appear less serious than many reported for similar types of pediatric sedation. Overall, our procedural experience compares favorably with published applications of MHX in other patient populations, which we have summarized elsewhere.[6]

Another specific aim of this study, unable to be addressed in our retrospective study, was confirmation of the efficacy of MHX sedation through formal behavioral distress assessments. In all but a few procedures, observed distress was rated mild, very mild, or absent altogether (Table 5). The maximal distress response noted across all procedural phases consisted of transient muscular withdrawal movements during the invasive procedure itself. We regard this as evidence that MHX sedation is effective in reducing procedure-related behavioral distress, inasmuch as the endpoint for dose titration was not the elimination of all pain responses but their reduction to mild levels, as an indication of adequate, but not excessive, sedation. It is difficult to exclude any possibility of bias inherent in observational assessments of behavioral distress. In this study, we attempted to maximize their reliability by utilizing in prospective fashion an established, standardized, relatively simple checklist of clearly defined behavioral items appropriate for detecting anxiety in children.[8] Further, we limited our study's behavioral observers to two: a research project physician with pediatric anesthesiology training and experience (M.T.N.), and an experienced pediatric hematology registered nurse, both of whom observed several sedation procedures and were familiar with the Procedure Behavioral Checklist before performing assessments for this study. Although for ethical reasons this study did not evaluate a comparable control group of unsedated children undergoing painful procedures, we believe the observed levels of distress were far below those expected without MHX sedation, based upon our own historical observations of children before its regular use, as well as behavioral studies documenting the extreme anxiety and physical discomfort caused by these invasive procedures for children with cancer.[1–4] This study did not specifically evaluate whether children had any substantial, unpleasant, immediate or remote recall of the invasive procedures performed while they were sedated with MHX. However, the minimal levels of any distress measured preprocedure and at end of monitoring suggest they did not.

This study indicates the several characteristics of MHX sedation which are advantageous for pediatric oncology outpatients. Our success with this approach has led us to extend its use to children needing similar sedation for other procedures, eg, radiation therapy treatment for infants and toddlers, tunneled central venous catheter placement, and gastrointestinal endoscopy. However, it is also appropriate to recognize conditions required for its safe administration which may influence patient convenience, costs of sedation, and institutional feasibility. Regarding patient convenience, MHX and similar intravenous agents require restriction of oral intake for several hours before procedures, as well as procurement of venous access. To minimize the time in which oral intake must be actively restricted, we limit procedures to morning hours and schedule the youngest children first. This study suggests that venous access via an existing central venous catheter will be available in approximately 75% of patients. In the remainder, insertion of a peripheral venous angiocatheter must be accomplished. We consider the transient distress associated with that maneuver to be justified by the excellent quality of pain prevention during the more invasive procedures(s) subsequently performed during sedation. The use of oral sedatives will not eliminate this source of discomfort for all patients, because many need peripheral venous access for other reasons. Moreover, many oral agents pose their own inconveniences and limitations compared with MHX, including typically slower onset of effect, variable absorption, inability to be titrated rapidly and precisely according to individual need, prolonged somnolence, and patient refusal to ingest the medication. Our study did not include a longer term assessment of patient or parent satisfaction with various aspects of their experience with MHX sedation. As further sedation alternatives continue to become available, such information could aid in selecting from among them and should be sought in future studies.

The cost of deep sedation with MHX or similar agents is influenced by the need for appropriate personnel and equipment to ensure safety of the child at all times. Because much of the same equipment, facilities, and ancillary staff must also be available for safe conscious sedation, an important cost difference for deep sedation relates to the need for a "competent individual" whose sole responsibility is monitoring and managing the deeply sedated child, as recommended in current guidelines published by the American Academy of Pediatrics.[7] In our approach,

this individual is a pediatric intensivist who typically charges the standard fee for a comprehensive consultation for each sedation event. This consultation encompasses patient evaluation before sedation, direct management of the sedation itself, and patient supervision through recovery from sedation. Although not specifically measured in this study, reimbursement for this consultative service appears to be comparable to other pediatric intensive care procedures at our institution and varies somewhat with the specific third party payor. In other institutions, specific figures can be expected to vary according to geographic region, institutional billing practices, and prevailing reimbursement systems.

Finally, the requirements for safe conduct of deep pediatric sedation may also affect its feasibility relative to resources available within specific institutions. Sedation of pediatric oncology outpatients using MHX is a realistic option for institutions capable of adhering to current American Academy of Pediatrics guidelines for elective use of deep sedation.[7] Most operational sedation programs, including ours, represent adaptations to circumstances and opportunities unique to their particular institutions. Because the safety of sedated children must remain paramount, one of several alternatives for conscious sedation may be substituted where the use of MHX is deemed impractical.

Reduction of pain during invasive procedures has been identified by the American Academy of Pediatrics as an important goal for children with cancer.[29] To achieve this, it is necessary to acknowledge that all approaches to pain management, even those which are exclusively behavioral, engender some degree of patient inconvenience, added expense, and institutional burden when compared with the historical practice of providing none whatsoever. In our experience reported here, we have determined that the considerable benefits of MHX sedation outweigh its few, relative disadvantages described above. With the recent development of this and other successful regimens, it may be important for future pediatric sedation studies to include well-designed, prospective comparisons of the cost and convenience, as well as safety and efficacy, of different agents and approaches.

ACKNOWLEDGMENTS

This project was supported in part by American Cancer Society grant ACSIRG-188 in conjunction with the Comprehensive Cancer Center of Michigan State University College of Human Medicine (AES; DRF and DJS, sponsors).

The authors acknowledge the contributions of Michael J. Bouthillier, PharmD, Alan Davis, PhD, and Sandra Hardy, RN, BSN. Expert secretarial assistance was provided by Ms Arlene Sprengelmeyer.

REFERENCES

1. Jay SM, Ozolius M, Elliot CH, Caldwell S. Assessment of children's distress during painful medical procedures. *Health Psychol.* 1983;2:133–147
2. Katz ER, Kellerman J, Siegel SE. Behavioral distress in children with cancer undergoing medical procedures: developmental considerations. *J Consult Clin Psychol.* 1980;48:356–365
3. Zeltzer L, LeBaron S. Hypnosis and non-hypnotic techniques for reduction of pain and anxiety during painful procedures in children and adolescents with cancer. *J Pediatr.* 1982;101:1032–1035
4. Schechter N. Pain in children with cancer. In: Foley KM, ed. *Advances in Pain Research and Therapy*. New York, NY: Raven Press, Ltd; 1990:57–71
5. McEvoy GK, ed. *American Hospital Formulary Service Drug Information*. Bethesda, MD: American Society of Hospital Pharmacists; 1992:1324–1325
6. Schwanda AE, Freyer DR, Sanfilippo DJ, et al. Brief unconscious sedation for painful pediatric oncology procedures: intravenous methohexital with appropriate monitoring is safe and effective. *Am J Pediatr Hematol Oncol.* 1993;15:370–376
7. American Academy of Pediatrics, Committee on Drugs and Section on Anesthesiology. Guidelines for the elective use of conscious sedation, deep sedation, and general anesthetic in pediatric patients. *Pediatrics.* 1992;89:1110–1115
8. LeBaron S, Zeltzer L. Assessment of acute pain and anxiety in children and adolescents by self-reports, observer reports, and a behavior checklist. *J Consult Clin Psychol.* 1984;52:729–738
9. Harvey SC. Hypnotics and sedatives. In: Goodman LS, Gilman A, eds. *The Pharmacological Basis of Therapeutics*. 6th ed. New York, NY: Macmillan; 1980:339–375
10. Hudson RJ, Stanski DR, Burch PG. Pharmacokinetics of methohexital and thiopental in surgical patients. *Anesthesiology.* 1983;59:215–219
11. Bjorkman S, Gabrielson J, Quaynor H, et al. Pharmacokinetics of intravenous and rectal methohexitone in children. *Br J Anaesth.* 1987;59:1541–1547
12. Christensen PA, Balslev T, Hasselstrom L. Comparison of methohexital and pentobarbital for premedication in children. *Acta Anaesthesiol Scand.* 1990;34:478–481
13. Karhunen U. Sleep effect of rectal methohexitone (10 mg/kg) in children premedicated for anaesthesia. *Dev Pharmacol Ther.* 1988;11:92–95
14. Forbes R, Vandewalker G. Comparison of two and ten percent rectal methohexitone for induction of anaesthesia in children. *Can J Anaesth.* 1988;35:345–349
15. Westrin P. Methohexital dissolved in lipid emulsion for intravenous induction of anesthesia in infants and children. *Anesthesiology.* 1992;76:917–921
16. Schoch JP, Robert R, Ramboatiana R, et al. Intramuscular MHX: a single and reliable means of sedation for cerebral computed tomography in children. *Aggressologie.* 1990;31:45–48
17. Jeffries G. Radiotherapy and children: anesthesia. *Anesthesia.* 1988;43:416–417. Letter
18. Hunter MJ, Griswold JD, Rosenberg M. Administration of methohexital for pediatric outpatient dentistry. *Anesth Prog.* 1990;37:248–251
19. Sievers TD, Yee JD, Foley ME, Blanding PJ, Berde CB. Midazolam for conscious sedation during pediatric oncology procedures: safety and recovery parameters. *Pediatrics.* 1991;88:1172–1179
20. Tobias JD, Phipps S, Smith B, Mulhern RK. Oral ketamine premedication to alleviate the distress of invasive procedures in pediatric oncology patients. *Pediatrics.* 1992;90:537–541
21. Ferrari L, Barst S, Pratila M, Bedford RF. Anesthesia for diagnostic and therapeutic procedures in pediatric outpatients. *Am J Pediatr Hematol Oncol.* 1990;12:310–313
22. Sandler ES, Weyman C, Conner K, et al. Midazolam versus fentanyl as premedication for painful procedures in children with cancer. *Pediatrics.* 1992;89:631–634
23. Kaikov Y, Chan KW, Pritchard S, et al. Midazolam effect on cardiovascular and respiratory systems in pediatric oncology children. *Proc Am Soc Pediatr Hematol Oncol.* 1992;1:31–32. Abstract
24. Louie RR, Eisenberg L, Herzog PF, et al. Fentanyl for sedation/analgesia during painful procedures. *Proc Am Soc Pediatr Hematol Oncol.* 1992;1:31. Abstract
25. Fisher DM, Robinson S, Brett CM, Perin G, Gregory GA. Comparison of enflurane, halothane, and isoflurane for diagnostic and therapeutic procedures in children with malignancies. *Anesthesiology.* 1985;63:647–650
26. Bennets G, Briones G, Secola R. Ketamine for conscious sedation during pediatric oncology procedures. *Proc Am Soc Pediatr Hematol Oncol.* 1992;1:22. Abstract
27. Saarnivaara L, Hiller A, Oikkonen M. QT interval, heart rate and arterial pressures using propofol, thiopentone or methohexitone for induction of anaesthesia in children. *Acta Anaesthesiol Scand.* 1993;37:419–423
28. Yaster M, Nichols DG, Deshpande JK, Wetzel RC. Midazolam-fentanyl intravenous sedation in children: case report of respiratory arrest. *Pediatrics.* 1990;86:463–467
29. Zeltzer LK, Altman A, Cohen D, et al. Report of the subcommittee on the management of pain associated with procedures in children with cancer. In: Schechter N, Altman AJ, Weisman SJ, eds. Report of the consensus conference on the management of pain in childhood cancer. *Pediatrics.* 1990;86(5 suppl, Pt 2):826–831

Intravenous Methohexital for Brief Sedation of Pediatric Oncology Outpatients: Physiologic and Behavioral Responses

David R. Freyer, Allison E. Schwanda, Dominic J. Sanfilippo, Richard M. Hackbarth, Nabil E. Hassan, John S. Kopec and Maria Teresa Neirotti

Pediatrics 1997;99;e8
DOI: 10.1542/peds.99.5.e8

Intravenous Methohexital for Brief Sedation of Pediatric Oncology Outpatients: Physiologic and Behavioral Responses

David R. Freyer, Allison E. Schwanda, Dominic J. Sanfilippo, Richard M. Hackbarth, Nabil E. Hassan, John S. Kopec and Maria Teresa Neirotti

Pediatrics 1997;99;e8
DOI: 10.1542/peds.99.5.e8