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Propofol sedation in children: sleep trumps amnesia[★]

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Abstract

Objective—Detailed assessments of the effects of propofol on memory in children are lacking. We assessed the feasibility of measuring memory during propofol infusion, as commonly performed in sedation for MRI scanning. In addition, we determined the onset of memory loss in relation to the onset of sedation measured by verbal responsiveness.

Materials and methods—Children scheduled for sedation for MRI received a 10-min infusion of propofol (3 mg/kg) as they viewed and named 100 simple line drawings, one shown every five seconds, until they were no longer responsive (encoding). A control group receiving no sedation for MRI underwent similar tasks. Sedation was measured as any verbal response, regardless of correctness. After recovery from sedation, recognition memory was tested, with correct yes/no recognitions matched to sedation responses during encoding (subsequent memory paradigm).

Results—Of the 48 children who received propofol, 30 could complete all study tasks (6.2 ± 1.6 years, 16 males). Individual responses could be modeled in all 30 children. On average, there was

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Author's contribution

R.V. designed and conducted the study and wrote the manuscript. E.K. conducted the study. M.M. conducted data collection and analysis. J.R. designed study tasks and conducted statistical analysis. F.R. conducted the statistical analysis and wrote portions of the manuscript. K.M. helped to design the study and wrote portions of the manuscript.

Conflict of interest

The authors have no potential conflicts of interest.

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a 50% probability of no verbal response 3.1 min after the start of infusion, with 50% memory loss at 2.7 min. Children receiving propofol recognized $65 \pm 16\%$ of the pictures seen, whereas the control group recognized $93 \pm 5\%$.

Conclusion—Measurement of memory and sedation is possible in verbal children receiving propofol by infusion in a clinical setting. Despite propofol being an amnestic agent, there was little or no amnestic effect of propofol while the child was verbally responsive. It is important for sedation providers to realize that propofol sedation does not always produce amnesia while the child is responsive.

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Keywords

Memory; Pediatrics; Sleep; Sedation

1. Introduction

Propofol is the most commonly used anesthetic drug for procedural sedation in pediatric patients, with its use described for both anesthesiologist and nonanesthesiologist administration [1–6]. The detailed effects of propofol on memory function in a clinical setting have not been studied in children as propofol is usually administered as a bolus medication. Rather than using a bolus, if propofol were infused over a 10-min period to achieve adequate sedation for MRI scanning (eg, similar to the use of dexmedetomidine) [7], more detailed measures of memory loss with respect to sedation would be possible along a continuum from awake to verbal unresponsiveness.

The temporal relationship between memory loss and onset of sedation as propofol concentrations increased could identify an amnestic memory effect, which is well described in adults [8–12]. The present study assessed the feasibility of carefully measuring memory and sedation effects in children in a clinical setting. In addition, modeling response probabilities against time for memory and sedation were attempted in each child as propofol infusion produced verbal unresponsiveness. The present paradigm was based on previous adult volunteer studies examining the memory effects of intravenous agents [9,11].

A standardized visual picture-naming task was used to measure memory and sedation during propofol induction for MRI [13]. Responses were quantitated by estimating the time after the start of propofol infusion when 50% probability of no recognition memory occurred and when 50% probability of no verbal responsiveness occurred. We hypothesized that data of sufficient quality could be obtained to allow the modeling of individual memory and sedation responses. Moreover, the amnestic effect of propofol would be evidenced by a large time difference between 50% probability of memory loss and 50% probability of sedation.

2. Materials and methods

2.1. Study design

This study was designed to obtain estimates of sedation and memory effects of propofol during slow bolus infusion in a pediatric population, mirroring the common practice of

dexmedetomidine delivery, or occasionally propofol, for children undergoing sedation for MRI [6,7,14]. No previous data were available to optimize study design nor to conduct a power analysis. Recruitment continued until a sample of 30 children who completed all study tasks was obtained for analysis.

All patients provided assent, and a parent or guardian provided informed consent before participation. The primary end-point was to determine the ability of the recruited patients to successfully name and recognize pictures and determine individual thresholds for sedation and memory.

Between May 2012 and April 2014, children between 4 and 14 years of age, >8 kg in weight, and scheduled to receive propofol sedation for MRI were recruited. Exclusion criteria were patients who were scheduled to undergo short procedures (<15 min), who lacked the capacity to recognize and verbalize pictures, who could not speak English, and who had recently received (<5 half-lives) medication that could affect memory/concentration (eg, diphenhydramine, diazepam). A control group of children was accrued shortly after the start of the study to determine if any of the study pictures were poorly remembered in the absence of propofol.

2.2. Picture naming tasks

Pictures consisted of black and white line drawings obtained from a standardized dataset (International Picture Naming Project, <http://crl.ucsd.edu/experiments/ipnp/> last accessed 2/23/2016), which included pictures from the original Snodgrass and Vander-wart set [13]. Pictures were selected such that children of the age range in the present study would be able to name them without difficulty. Because of the number of pictures required for the study and the total picture pool available to draw from, some “borderline” pictures were included (eg, typewriter). Because of this, there was a possibility of some study pictures being too difficult to name for children of this age group, and therefore, a control group of children not requiring sedation for MRI was accrued.

Children were asked to name the pictures to ensure that the pictures were attended to as subsequent memory is affected by attention and the cognitive processes engaged during encoding. Pictures were shown at three different times throughout the day.

The first picture set was shown after informed consent was obtained, during which the picture naming task was practiced with a set of 20 practice pictures prior to undergoing the encoding task. The child was asked to name the practice pictures, with a new one shown every five seconds. Any verbal response was considered as a confirmation that the picture was observed and registered, eg, “I don’t know” or an incorrect identification of an object was considered a positive response. Those without at least eight positive responses were withdrawn from the study. These practice pictures were not shown again.

Pictures were shown for the second time during the encoding task, where 100 different study pictures were displayed to the child as sedation was induced with propofol or with no medication in the control group. Study pictures were presented to the child every five seconds using a nonferrous-containing flip book to enable the administration of the task in

the MRI room. Half ($n = 50$) of these pictures were also shown during the recognition task, before the patient was discharged to home.

Pictures were shown for the third and final time during the recognition task after procedural sedation had worn off (a similar time interval was allowed to elapse for children in the control group). The last set of 100 pictures consisted of 50 study pictures that were previously shown during the encoding task and 50 pictures that were never shown before (novel “lure” pictures). Thus, recognition memory was tested by a second presentation of half of the study pictures shown during the encoding task.

The order of pictures in each task was the same for each child, and during the recognition task, previously presented study pictures were interspersed among the novel pictures.

2.3. Slow “bolus” propofol infusion and subsequent memory task

A simple paradigm that may allow to differentiate memory effects from sedation is to infuse the drug such that increasing concentrations occur over a period of approximately 10 min, which is similar to previous studies in adult volunteers [9]. During the period when drug concentration and sedation are increasing, pictures are presented, and memory for these are tested at a later time.

Verbal responses to naming these pictures were recorded through the progression of sedation to the end-point, ie, absence of verbal response. Any verbal response to the picture was scored as positive (no sedation, “1”) response.

By definition, memory is a retrospective behavioral measure. In other words, when a stimulus is presented, one cannot determine whether it is remembered or not until the memory for this stimulus is tested at some later time point, a procedure called subsequent recognition. Recognition was tested after sedation had worn off after the MRI scanning session using equal numbers of previously presented and novel (not presented) pictures to test for guessing, which is particularly relevant in this age group. For example, if a child said “yes” to every picture, a 100% hit rate (correct recognition of previously presented pictures) would be obtained. Thus, a false alarm (FA) rate was obtained as an estimate of guessing. The FA rate is a “yes” response to a novel (“lure”) stimulus, and some FAs were expected in each case. In the example of 100% hit rate, the FA rate would be 50%. Normally, FA rates occur in the order of 5–10%. In the present study, a FA rate of >20% was considered to represent a situation where correct recognition (hits) data were unreliable; a number of patients were excluded from analysis for this reason.

The first presentation of a study picture occurred during “encoding” (just before MRI scanning), and testing for the memory of that picture occurred during “recognition” after the sedation had worn off. Using the results of recognition (whether a picture was or was not remembered), one can retrospectively mark whether the picture presentation during encoding was subsequently remembered or not. Using this subsequent memory paradigm, one can investigate changes in conditions during encoding (such as the presence of a drug) to determine their effect on subsequent memory.

The subsequent memory paradigm allowed us to determine the time after the start of infusion at which a 50% probability of memory loss and 50% probability of sedation (no verbal response) occurred. The occurrence of 50% memory effect substantially earlier than 50% sedation effect may imply an amnestic effect of the drug. As the memory effect of amnestic drugs changes rapidly during a 10- to 30-min period following encoding, subsequent recognition memory is best tested beyond this time frame, as done in the present study [9,11].

2.4. Encoding task

The study pictures shown during the induction of sedation were all different from the practice group of pictures. Sedation was administered as a “slow bolus” over 10 min (3 mg/kg propofol) using an intravenous infusion delivery system (MRidium 3850 MRI IV Infusion Pump System, IRadimed, Winter Springs, FL). Sedation was maintained with a continuous infusion of 250 µg/kg/min propofol until the completion of the MRI. During the induction of sedation (or before scanning in the control group), a new picture was shown every five seconds as the child was encouraged to name the item in the picture. Pictures were shown until the child was unresponsive with eyes closed or in the case of the control group, until all the 100 study pictures were viewed. To ensure consistency in timing, the encoding task was simultaneously presented on a laptop computer using E-Prime software (Psychology Software Tools, Sharpsburg, PA). The same order of pictures as given in the flip book was preprogrammed and simultaneously displayed on the laptop at the start of the drug infusion in the group receiving propofol or study picture viewing in the control group. The laptop was positioned such that it was visible to the person with the flip book, with a new picture displayed in the flip book as soon as it appeared on the laptop. Response times were recorded by the E-Prime software as another researcher pressed a key whenever a verbal response was made.

2.5. Recognition memory task

After the completion of the MRI scanning, when the child had met institutionally established discharge criteria, recognition memory was tested using 50 previously presented study pictures intermixed with an equal number of novel (“lure”) pictures that were not shown before. The child was instructed to verbalize either “yes” or “no” to communicate whether the picture was shown during the encoding task just before MRI scanning.

2.6. Statistical analysis

Descriptive statistics were generated to characterize the study samples by using frequencies for categorical variables and means and standard deviations for continuous variables.

2.6.1. Primary endpoint—The main goal of this pilot study was to determine if adequate data could be collected in this clinical setting to allow the estimation of memory responses along the full sedation continuum from awake to verbal unresponsiveness in children who received propofol for procedural sedation. This involved the calculation of a sedation and memory threshold for each child. To achieve sufficient number of responses to allow threshold estimation in each individual, the 10-events-per-parameter rule may be relevant [15]. We chose a balance between adequate number of stimuli to obtain reliable estimates

and number of stimuli that children of this age can process without fatigue. We decided to use the 50% probability threshold as a quantitative measure of response as this would provide the greatest number of responses before and after the threshold to improve the accuracy of modeling (as opposed to using 10% or 90% thresholds). We could model individual responses in all children who could fully complete the memory tasks.

2.6.2. Sedation threshold—During the encoding task, naming the picture within five seconds, either correctly or incorrectly, was a valid response. To assess sedation, the important response measure was whether the child could provide a verbal response to the study picture. As children who received propofol became sedated and gradually sleepier as the infusion continued, he/she was less likely to make a valid response.

2.6.3. Memory threshold—During the recognition task, responses were coded as true positives (correct recognition of a previously presented picture, ie, hits, coded as “1”), false negatives (“no” for pictures that were shown before, coded as “0”), and FAs for pictures nominated as “yes” but not shown before.

Sedation and memory responses were best modeled using a logit link function. Binary responses [verbal response (“1”)/no verbal response (“0”) at encoding, hits (“1”)/false negatives (“0”) at recognition] were modeled using this function to estimate the effect of the drug while treating time as a random effect to estimate child-specific responses, accounting for over-dispersion, and assuming that the correlation between individual responses were unstructured. Statistical interaction terms were included in the models to test for a difference in response over time. All statistics were generated using statistical analysis software (SAS, version 9.3; SAS Institute, Cary NC). Mixed models were estimated using the GLIMMIX procedure, and all statistical tests were two sided with an α of 0.05.

3. Results

Of the 50 children for whom consent was obtained, two were withdrawn upon parental request after the practice task, and thus, 48 children received propofol infusion. Of the 48 children (16 males) who received propofol infusion, four dropped out during the encoding task, and seven were unable to complete the recognition task. Seven additional children were excluded from analysis because of a high FA rate of >20%. Thus, 30 children completed all study tasks, and all 30 individual memory and sedation responses to propofol could be modeled. Twenty control patients received no propofol but underwent the same tasks with similar timelines as those who received propofol. Because the control group consisted of children who could tolerate MRI scanning without sedation, they were somewhat older, weighed more, finished the scan procedure in a shorter time, and were ready for discharge earlier (having received no medications). The final recognition task in the control group was delayed as much as the children and parent’s tolerance would allow so that the time interval between encoding and recognition was as close to the propofol group as feasible. However, the recognition task in the control group occurred approximately 30 min sooner (Table 1). According to our previous experience, memory decay over this time frame of two hours following encoding would be negligible in both groups [8].

3.1. Encoding task responses

Any verbal response was considered a positive (“1”) response, whereas no verbal response while the child had their eyes open or closed (asleep) was considered a negative response (“0”). However, a number of verbal responses were possible, and the breakdown of these is presented in Table 2.

3.2. Recognition task responses

A number of children were excluded because of high FA rates, which in some cases approached 50% (ie, they tended to always say a picture has been seen before, even for novel pictures). We chose a FA rate of 20% as a marker of the child not understanding the nature of the recognition task. The validity of excluding these children is demonstrated by the fact that the FA rate in the analysis group was $5.5 \pm 6.4\%$, which is much closer to a typical FA rate for yes/no recognition task. The control group had a lower FA rate of $1.4 \pm 2.1\%$, which was conforming to almost perfect recognition (hits) of 0.93 (Table 2).

The hit rate for study pictures seen during encoding in the group receiving propofol (0.65 ± 0.16) was substantially lower than that in the control group, indicating some degree of memory loss for pictures seen during this period (the hit rate was calculated only for pictures seen and excluded any study pictures shown after eyes were closed). Interestingly, the hit rate for correctly named pictures was significantly higher than for wrongly named pictures [$t(29) = 4.5$, $p < 0.01$], indicating that correctly naming a picture made it more memorable, possibly on the basis of semantic processing [16]. No such effect was observed in the control group, but this may have represented a ceiling effect as all classes of stimuli had almost perfect hit rates. We conducted additional analyses to quantitate the performance characteristics of children during the recognition task. Children showed good discrimination between previously presented and new items (correct recognition of study pictures and correct rejection of “lures”), with a d' of 2.54 ± 0.64 . Response bias tended to be conservative, with $C = 0.70 \pm 0.34$. In other words, if the child was unsure whether they had seen the picture before, they tended to give a “no” (not seen before) response.

3.3. Memory and sedation responses

Fig. 1 summarizes individual and group average sedation and memory responses. The distribution of individual time differences between the 50% memory and sedation effects is shown in Fig. 1(B). A positive time value indicates that memory loss occurred before sedation onset. Almost all patients, 29/30, lost memory within two minutes of achieving sedation. A number of individuals lost memory after the onset of sedation (negative time values). However, it should be noted that there is some error present in modeling responses, particularly with individual responses. The more reliable group averages demonstrate memory loss shortly before sedation. At this infusion rate (3 mg/kg over 10 min), the group average time to 50% (CI 47.4–53%) probability of no verbal response was 3.1 min (no CI was determined as time was the predictor variable). Similarly, 50% (CI 45.2–53%) probability of recognition memory loss was achieved at 2.7 min. Thus, on average, memory loss occurred 24 s before a similar probability of sedation.

4. Conclusion

To date, it was unknown whether propofol's actions on memory in a common clinical setting included both an amnestic component and a purely sedative effect. As the pharmacodynamics of propofol are different in children than those in adults, the amnestic effects evident in adult volunteers may be different in children [17]. As volunteer studies would be quite difficult to perform in children, a behavioral paradigm that can be utilized in the clinical settings may provide valuable information. The common use of propofol for procedural sedation of children for non-painful diagnostic MRI allowed to examine the relationship of drug-induced sedation to memory function in a clinical setting [5,6,18–20].

The sedative effect of propofol can be measured in real time, eg, by assessing reaction time or the presence of a behavioral response while the drug is being administered (eg, keeping eyes open or performing a simple task such as naming a picture). However, the assessment of memory is by definition retrospective. Events and conditions (such as the presence of a drug) during the encoding of a memory are related to the presence or absence of recognition memory at a later time using a subsequent memory paradigm such as the one in this study. Importantly, the data obtained for both sedation and memory responses were reliable enough to allow the modeling of individual responses for those completing all the memory tasks, demonstrating the feasibility of this approach. Despite the well-known amnestic properties of propofol, in the present study, memory loss in the propofol group as a whole closely corresponded to the onset of sedation. Individually, there was little evidence of early memory loss, for example, more than two minutes before the onset of sedation. It should be noted that the measure of sedation used in the present study, ie, the lack of verbal response, was a crude measure and would take substantial sedation to ablate. However, more sensitive measures of sedation (such as a directly measured reaction time) would likely diminish the difference in time between memory loss and onset of sedation. Because of the MRI environment, specialized equipment to measure reaction times was not available.

Propofol's amnestic effects occur at serum concentrations that produce little sedation [9,11,12]. There are thus two competing effects on memory function, one is the amnestic action of propofol and the other is that of sedation. Sedation interferes with the perception of stimuli, ie, it impairs the processing of material in working memory, a process "upstream" of the mechanisms producing amnesia by loss of encoded information [11]. Thus, rapid induction of sedation would "hide" any amnestic effects of the drug. Consequently, amnestic effects are most evident when drug concentrations are slowly increased or are maintained at a constant while increasing the steps such as in studies using volunteers [8–12,21]. The infusion rate chosen in the present study was rapid enough to mask any period during which amnesia may have been evident. Thus, in essence, sleep (sedation) trumped amnesia.

There are limitations to our study, the main one being the challenges of working with children, particularly when presenting them with recognition tasks that include the identification of 100 images, which may have resulted in fatigue and noncompliance with the tasks. Nevertheless, 30 of 48 children completed all the study tasks.

In conclusion, the present study demonstrated that propofol infusion for procedural sedation in pediatric population does not substantially impair memory when verbal responsiveness is present. Sedation providers should be aware of the potential of recall before the onset of sleep if propofol is administered at a rate similar to that in the present study where sleep was induced a few minutes after starting drug administration. Further studies will be required to evaluate if the well-described amnestic effects of propofol in adults are present in children. The present data are consistent with the previously described amnestic action of propofol, which occurs soon after encoding in adults but is masked by rapid onset of sedation in the present study. In clinical settings, it is important for practitioners to realize that when propofol is used for the induction of sedation in children, memory function is likely present until loss of response to verbal stimulation occurs.

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Fig. 1.

Top graph: Individual probabilities are represented by the faint plots and group averages are shown in bold. Sedation was measured by probability of verbal response. The probabilities of both sedation and subsequent recognition memory are plotted against time (in seconds), which was used as the predictor variable over the period of propofol infusion before scanning started. As the bold lines demonstrate, the probability of recognition memory loss occurred at an earlier time than the same probability of sedation. The lower graph represents the difference in time between 50% probabilities of memory loss and sedation in each individual. The distribution of individual time intervals revealed that most differences were positive (memory loss occurred somewhat before sedation).

Table 1

Demographics of the study groups.

	Statistic	Propofol (n = 30)	Control (n = 20)
Age (years)	mean (std)	6.2 (1.6)	8.8 (2.2)
	median	5.6	9.2
	min–max	4.2–11.0	4.4–12.6
	t-test		4.6 p < 0.01
Weight (kg)	mean (std)	24.0 (9.1)	33.1 (10.8)
	median	22.0	33.8
	min–max	12.7–53.4	17.4–52.2
	t-test		3.1 p < 0.01
Male	n (%)	16 (53.3%)	9 (45.0%)
Cancer-related diagnosis (number of pts)		30	20
Region Scanned (number of pts)	Brain	18	11
	Brain-Spine	2	3
	Spine	2	1
	Head/Neck	5	1
	Abd/Pelvis/Chest	3	4
Length of scan (minutes)	mean (std)	72.2 (25.3)	54.5 (28.6)
	median	66.0	46.5
	min–max	33.0–135.0	25.0–141.0
	t-test		2.3 p = 0.02
Time from scan start to discharge (minutes)	mean (std)	113.4 (39.4)	71.0 (35.0)
	median	98.0	59
	min–max	61.0–214.0	34.0–161.0
	t-test		4.1 p < 0.01
Time from encoding to recognition (minutes)	mean (std)	146.0 (44.5)	117.9 (44.8)
	median	133.0	106.0
	min–max	90.0–221.0	47.0–187.0
	t-test		2.1 p = 0.04

Table 2

Encoding and subsequent memory responses.

Encoding Task (before scanning)	Statistic	Number of pictures PROP (max = 50)	Hit rate ^a PROP	Number of pictures CONTROL (max = 50)	Hit rate ^a
Number of Pictures Seen	mean (std)	20.9 (6.9)	0.65 (0.16)	50	0.93 (0.05)
	median	21.5			
	min-max	9-37			
Correct Naming	mean (std)	12.8 (5.3)	0.71 (0.16)	40.3 (5.4)	0.93 (0.06)
	median	12		43	
	min-max	4-26		26-45	
Incorrect Naming	mean (std)	4.4 (2.7)	0.54 (0.26) ^b	6.7 (3.1)	0.94 (0.1) ^b
	median	3.5		6	
	min-max	0-10		3-16	
"I don't know"	mean (std)	0.8 (1.6)		1.25 (1.7)	
	median	0		0.5	
	min-max	0-6		0-6	
No response with eyes open	mean (std)	2.9 (2.4)		1.7 (3.5)	
	median	3		0	
	min-max	0-10		0-11	
Number of pictures after eyes closed	mean (std)	29.0 (6.9)	0.04 (0.05) ^c	N/A	
	median	28.5			
	min-max	13-41			

^aHit rate is calculated for all stimuli presented with the given encoding response, less overall FA rate, which was $5.5 \pm 6.4\%$ for the group receiving propofol and $1.4 \pm 2.1\%$ for CONTROL (eg, if Correct Naming occurred for 13 of 50 stimuli, with 10 recognized correctly and a FA rate of 6%, the hit rate was therefore $10/13 = 76\% - 6\% = 71\%$).

^bThis hit rate includes all noncorrect responses with eyes open (incorrect naming, "I don't know," and no response).

^cAny hits for stimuli presented after eyes closed are considered false alarms and are included in the false alarm rate.