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Adverse Sedation Events in Pediatrics: Analysis of Medications Used for Sedation

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ABSTRACT. *Objectives.* **To perform a systematic investigation of medications associated with adverse sedation events in pediatric patients using critical incident analysis of case reports.**

Methods. **One hundred eighteen case reports from the adverse drug reporting system of the Food and Drug Administration, the US Pharmacopoeia, and the results of a survey of pediatric specialists were used. Outcome measures were death, permanent neurologic injury, prolonged hospitalization without injury, and no harm. The overall results of the critical incident analysis are reported elsewhere. The current investigation specifically examined the relationship between outcome and medications: individual and classes of drugs, routes of administration, drug combinations and interactions, medication errors and overdoses, patterns of drug use, practitioners, and venues of sedation.**

Results. **Ninety-five incidents fulfilled study criteria and all 4 reviewers agreed on causation; 60 resulted in death or permanent neurologic injury. Review of adverse sedation events indicated that there was no relationship between outcome and drug class (opioids; benzodiazepines; barbiturates; sedatives; antihistamines; and local, intravenous, or inhalation anesthetics) or route of administration (oral, rectal, nasal, intramuscular, intravenous, local infiltration, and inhalation). Negative outcomes (death and permanent neurologic injury) were often associated with drug overdose ($n = 28$). Some drug overdoses were attributable to prescription/transcription errors, although none of 39 overdoses in 34 patients seemed to be a decimal point error. Negative outcomes were also associated with drug combinations and interactions. The use of 3 or more sedating medications compared with 1 or 2 medications was strongly associated with adverse outcomes (18/20 vs 7/70). Nitrous oxide in combination with any other class of sedating medication was frequently associated with adverse outcomes (9/10). Dental specialists had the greatest frequency of negative outcomes associated with the use of 3 or more sedating medications. Adverse events occurred despite drugs being administered within acceptable dosing limits. Negative outcomes were also associated with drugs administered by nonmedically trained personnel and drugs administered at home. Some injuries occurred on the way to a facility after administration of sedatives at home; some took place in automobiles or at home after discharge from medical supervision. Deaths and injuries after discharge from medical supervision were associated with the use of medications with long half-lives (chloral hydrate, pentobarbital, promazine, promethazine, and chlorpromazine).**

Conclusions. **Adverse sedation events were frequently associated with drug overdoses and drug interactions, particularly when 3 or more drugs were used. Adverse outcome was associated with all routes of drug administration and all classes of medication, even those (such as chloral hydrate) thought to have minimal effect on respiration. Patients receiving medications with long plasma half-lives may benefit from a prolonged period of postsedation observation. Adverse events occurred when sedative medications were administered outside the safety net of medical supervision. Uniform monitoring and training standards should be instituted regardless of the subspecialty or venue of practice. Standards of care, scope of practice, resource management, and reimbursement for sedation should be based on the depth of sedation achieved (ie, the degree of vigilance and resuscitation skills required) rather than on the drug class, route of drug administration, practitioner, or venue.** *Pediatrics* **2000;106:633–644;** ***sedation, adverse events, critical incident, medication errors, monitoring, guidelines, procedures, systems errors, drug overdose, drug–drug interactions, critical incident analysis.***

ABBREVIATIONS. AAP, American Academy of Pediatrics; IV, intravenous; INH, inhalation; NS, not significant; PO, oral; IM, intramuscular; SM, submucosal; PR, rectal; IN, intranasal; SC, subcutaneous; DPT, Demerol, Phenergan, and Thorazine; ASA, American Society of Anesthesiologists; AAPD, American Academy of Pediatric Dentists.

Adverse sedation-related events occur in children for a variety of reasons. Using critical incident techniques, we reviewed 118 adverse sedation-related incidents in pediatric patients of which 95 provided sufficient information to examine systems issues that contributed to the adverse outcomes.[1] We found that death and permanent neurologic injury were more likely to occur in children sedated in nonhospital-based venues, compared with hospital-based venues, although these children

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were older and healthier. Nearly 80% of the events presented initially as respiratory compromise. We interpreted most of the subsequent unacceptable outcomes as the result of failure to rescue the patients.[2,3] Inadequate resuscitation contributed to adverse outcomes more frequently in nonhospital-based venues.

The purpose of the current analysis is to examine the relationship between medication-related factors and the adverse events reported above. Specifically, we examined particular drugs and drug classes, routes of administration, medication errors and overdoses, drug combinations and interactions, the number of medications administered, venues of drug administration and of the adverse event, practitioners, and patterns of drug use.

METHODS

Case reports were obtained from a variety of sources including: the Food and Drug Administration adverse drug reporting system via the Freedom of Information Act, the US Pharmacopoeia, and a survey of pediatric anesthesiologists, pediatric intensivists, and pediatric emergency medicine specialists who were all fellows of the American Academy of Pediatrics (AAP).[1] To focus specifically on medication-related issues, we recorded: patient weight, age, the doses of all sedative medications administered, their routes of administration, the class of practitioner administering the medication, venue of its administration, the venue of the adverse event, and outcome (death, permanent neurologic injury, prolonged hospitalization without injury, or no harm). All cases were independently examined by each of 4 investigators (C.J.C., H.W.K., D.A.N., and J.A.W.) to attribute the probable causes of the adverse events.[1,4,5] Subsequently, all 4 investigators reached consensus on the contributory cause(s). Data were analyzed for each drug, then further examined by combining them into classes of drugs, eg, opioids, benzodiazepines, barbiturates, sedatives, intravenous (IV) anesthetics, local anesthetics, and inhalation (INH) anesthetics. Maximum recommended doses for each medication were derived from the US Pharmacopoeia Dispensing Information book,[6] the *Physician's Desk Reference*,[7] or the *Children's Formulary Handbook*.[8] An overdose was defined as ≥1.25 times the maximum recommended dose. For chloral hydrate, the maximum dose was 100 mg/kg up to 2 g (see "Appendix"). Nitrous oxide and/or halothane were considered sedating drugs if administered at the time of the event; local anesthetics were not considered sedating medications.

Statistical Analysis

Descriptive analyses were conducted for patient demographics, outcomes, medical provider data, and venue. Statistical comparisons consisted of standard t tests or nonparametric group comparisons (eg, χ^2 with correction for small numbers or Mann-Whitney U test). Each report was analyzed independently by 2 pediatric anesthesiologists, 1 pediatric intensivist, and 1 pediatric emergency medicine physician to attribute the probable drug related contributory causes of each adverse event. This removed any bias that might have occurred with discussion among reviewers. Coded responses were sent to a statistical analyst who assessed level of agreement among the 4 reviewers using a 4-rater chance-corrected value (Sav; Sav is an index of agreement of nominal data among a group of raters).[1,9–12] After independent review, the 4 evaluating physicians rereviewed these documents and debated each report. Only cases in which consensus agreement was reached on probable drug-related contributory causes were accepted.[4,5] Disagreements were resolved on a case-by-case basis, and cases unrelated to procedural sedation, those relating to drugs no longer available, and those containing inadequate information for consensus agreement were eliminated from the database.

RESULTS

Four reviewers (C.J.C., H.W.K., D.A.N., and J.A.W.) independently examined 118 pediatric adverse sedation events. There were moderate levels of agreement among the reviewers, indicating that agreement was not by chance. There was also moderate κ-agreement for 2-rater combinations, demonstrating that medical specialty was not a notable influence on reviews. Twenty-three reports were excluded during the group review process because inadequate data were available for adequate evaluation ($n = 1$) or agreement could not be reached ($n = 1$); the case did not involve sedation for a procedure (eg, pain medication after a procedure; $n = 8$); alphaprodine was used for sedation (a drug no longer marketed; $n = 9$); or because the adverse event was unrelated to the sedation process ($n = 4$). The age distribution of the excluded cases was not different from the entire cohort. Ninety-five cases were accepted into the final database and were the basis for this analysis.

The children in the final cohort ranged in age from .08 to 20.0 years (mean ± standard deviation: 5.7 ± 5.5) and weight 2.5 to 75.0 kg (mean ± standard deviation: 21.9 ± 17.3 kg). Thirty-five children (37%) were not harmed by the adverse event or required some additional time in the hospital for treatment of an injury that did not result in permanent neurologic injury. The other 60 children (63%) had adverse outcomes defined as death ($n = 51$) or permanent neurologic injury ($n = 9$). Medication-related adverse events were allocated to the following categories: drug interaction ($n = 44$); drug overdose ($n = 39$ in 34 patients); premature discharge ($n = 11$); prescription/transcription error ($n = 9$); inadequate understanding of administered medications (pharmacokinetics or pharmacodynamics; $n = 8$); administration by unsupervised technician ($n = 4$); and prescriptions administered by a parent ($n = 2$). Some patients had more than 1 drug-related cause for the adverse event, eg, drug overdose and drug administered by a technician.

Patients were sedated with a wide variety of medications, most commonly opioids and benzodiazepines (Table 1). Some children received more than 1 drug from each class of drugs; for some patients the doses or routes of administration were not recorded. There was no relationship between negative outcomes and the general category of drug administered, ie, death and permanent neurologic injury were associated with all drug classes (P = not significant [NS]). Medications were administered by a number of routes: IV, oral (PO), intramuscular (IM), INH, submucosal (SM), rectal (PR), intranasal (IN), and subcutaneous (SC; Table 1). There was also no relationship between negative outcomes and the route of drug administration (P = NS).

Approximately one half of the patients were sedated by more than 1 medication, and often these were given by more than 1 route, eg, IM and INH, PO and IV, PO and INH, or IM and IV. There was an association between adverse outcome and the administration of 3 or more sedating medications (18/20 vs 07/70; $P = .006$, χ^2). In 5 patients, all of whom died, the number of medications administered is not known (Table 2).

Thirty-nine of 170 drug administrations where the

TABLE 1. Route of Drug Administration and Outcome*

Route	IV		PO		IM		PR		SC		IN		INH		SM		Unknown Dose or Route		Total	
Drug	D/I	T	D/I	T	D/I	T	D/I	T	D/I	T	D/I	T	D/I	T	D/I	T	D/I	T	D/I	T
Opioid	9	22	4	4	8	10			1	1							1	1	23	38
Benzodiazepine	9	23	4	4	1	1					4	4					3	4	22	37
Sedative/hypnotic	3	3	17	24	13	16	1	2											34	45
Barbiturate	10	10	2	2	1	1	6	7									1	1	20	21
Ketamine	0	2	0	3	1	3											1	1	2	9
Inhalation anesthetics													12	13					12	13
Local anesthetics									2	2					9	10			11	14
Totals	31	60	27	37	24	31	7	9	3	3	4	4	12	13	9	12	7	8		
Percent adverse outcome	52		73		77		78		100		100		92							

T indicates total for that class of drug and route of administration; D, death; I, permanent neurologic injury.
* One half of the children received >1 medication; in some patients the route of administration could not be determined.

dose was documented were given in ≥1.25 times the maximum recommended dose in 34 patients (23%). Twenty-four of the 34 patients (71%) who received an overdose died or had permanent neurologic injury; all 4 patients who received 2 drugs at an overdose died (2 dental, 1 radiology, and 1 emergency department venue). Table 3 shows the number of administrations, medications, and range of drug overdoses; none of the 39 overdoses (3 local anesthetic and 36 sedating medications) in 34 patients seemed to be a simple decimal place error, ie, there were no 10-fold overdoses.

Table 4 presents the range of drug doses as a fraction of the maximum recommended dose when administration of a single drug was associated with death or permanent neurologic injury. Single doses of chloral hydrate, methohexital, pentobarbital, thiopental, ketamine, and midazolam were administered by a variety of routes. Several of these deaths/injuries occurred despite the fact that the reported doses were within the recommended limits: methohexital (2), chloral hydrate (1), and midazolam (1).

Table 5 describes the use of drugs in hospital-based and nonhospital-based venues. The only suggested pattern of drug use with venue of sedation was that all administrations of nitrous oxide took place in a nonhospital-based venue ($P < .01$) and 8 of 9 ketamine administrations were in a hospital-based facility (one was in an unknown environment; P = NS).

Twelve patients, all <6 years of age, suffered the adverse event either at home ($n = 8$) or in an automobile ($n = 4$); 11 of these had an adverse outcome. Five had undergone or were scheduled for a dental procedure, 5 for radiologic procedures, 1 for audiologic testing, and 1 for circumcision in a pediatrician's office. Ten occurred after discharge and 2 occurred at home before the scheduled procedure. Seven of these 12 children had received 1 medication, 2 received 2 medications, 2 received 3 medications, and 1 received 4 medications. Chloral hydrate was the drug most frequently associated with an adverse event occurring at home or in an automobile ($n = 7$); in 5 cases it was the only drug administered. One of the 7 chloral hydrate associated events occurred at home before arriving at a radiology facility and was caused by a prescription error. In another case, the drug was administered at home but the death was discovered on the child's arrival at the health care facility. Three patients who received chloral hydrate died or suffered permanent neurologic injury after discharge from a nonhospital-based venue. The other fatal event before arrival at a medical facility was associated with administration of midazolam (0.5 mg/kg, PO) at home; this child was found dead in a car seat when the family arrived at the nonhospital-based venue. Other drug combinations associated with an accident after discharge from either a hospital or a nonhospital-based facility all involved IM administration of medications with long half-lives: meperidine, promethazine, and chlorpromazine (Demerol, Phenergan, and Thorazine [DPT]; $n = 1$); pentobarbital (8 mg/kg; $n = 1$); and meperidine and promethazine (DP; $n = 1$).

Children sedated for dental procedures accounted for 32 events resulting in 29 patients suffering death or permanent neurologic injury (11 practitioners were oral surgeons, 17 were dentists with unknown training, 3 were pedodontists, and 1 was a nurse anesthetist supervised by a dentist). The only apparent difference in the pattern of drug class selection by dental practitioners compared with those performing other procedures was the use of nitrous oxide and the use of multiple sedating medications. Eight dental patients received 1 drug, 8 received 2, 10 patients received 3, 1 patient was given 4 drugs, 1 patient was given 5 medications, and in 4 the number of medi-

TABLE 2. Association Between the Use of Multiple Sedative Medications and Outcome*

Number of Medications	n	Death or Neurologic Injury	Prolonged Hospitalization /No Harm
1	45	24	21
2	25	13	12
3	15	13	2
4	4	4	0
5	1	1	0
Unknown	5	5	0
Total	95	60	35

* Note that 50% of children received >1 sedating medication.

TABLE 3. Overdoses* Compared With Number of Administrations*

Drug	Total Administrations	Total Overdoses	Death or Permanent Neurologic Injury Associated With Overdose	Range of Overdoses as a Fraction of Maximal Recommended Dose†
Opioids	37	10	7	1.3–4
Benzodiazepines	33	4	3	1.5–4.62
Sedative/hypnotics	45	11	8	1.25–3.0
Barbiturates	20	7	6	1.32–6.0
Ketamine	8	4	1	1.54–4.14
Local anesthetics	14	3	3	2.06–3.5
Totals	157	39	28	

* Some patients received >1 drug in an overdose.[6,7,94]
† Overdose was defined as ≥1.25 the maximal recommended dose.

cations was unknown. A higher proportion of patients undergoing dental care received 3 or more sedating medications at the time of the severe adverse event (death/permanent neurologic injury), compared with all other specialties combined (11/28 vs 8/62). All 10 patients who received nitrous oxide were dental patients and 9 of these suffered a negative outcome. Drugs coadministered with nitrous oxide and associated with negative outcomes were thiopental (PR, $n = 1$), promethazine (PO, $n = 1$), meperidine (PO, $n = 2$ and IM, $n = 1$), diazepam (PO, $n = 1$ and IV, $n = 2$), chloral hydrate (PO, $n = 2$), and pentobarbital (PO, $n = 1$).

Specific Medications

Opioids

Thirty-eight patients received opioids; opioids were associated with death or permanent neurologic injury in 23 patients, while 5 had prolonged hospitalization without injury and 10 had no harm. Opioids were administered as the only medication in 4 patients, combined with another medication in 16 patients, 2 other medications in 13 patients, 3 other medications in 3 patients, and with 4 medications in 1 patient. Twenty-one patients received meperidine, 10 received fentanyl, 4 morphine, 1 pentazocine, 1 oxymorphone, and 1 nalbuphine.

Benzodiazepines

Thirty-seven patients received benzodiazepines; benzodiazepines were associated with death or permanent neurologic injury in 22 patients, while 8 had prolonged hospitalization without injury and 6 had no harm. Twenty-six patients received midazolam by a variety of routes (Table 1). Midazolam was administered as a single sedative in 7 patients, combined with another medication in 12 patients, combined with 2 sedating medications in 5 patients, and with 3 or 4 sedating medications in 2 patients. Twelve children who received midazolam suffered death or permanent neurologic injury. Four of these 12 patients received midazolam as the only sedative. In 2 of these 4 cases, infants received IV overdoses, while in one third the IV dose was not described. The fourth case was associated with midazolam (PO) and is described above. Ten patients received diazepam: 5 with 1 other medication, 3 with 2 other medications, and 1 each with 3 or 4 other medications. Nine of these patients suffered death or neurologic injury and 1 had prolonged hospitalization. One patient received lorazepam (IM) combined with rectal methohexital, each administered as an overdose. This patient suffered a respiratory arrest during the recovery period and subsequently died.

TABLE 4. Single Drug Administrations Associated With Death or Permanent Neurologic Injury

Drug	Route	*n*	Range of Dose (Percent of Maximum)
Chloral hydrate	PO	7	0.6–3.0
	PR	1	
Methohexital	IV	5	0.73–2.7
	PR	1	
Thiopental	PR	2	1.3–3.5
Pentobarbital	IM	1	1.3
Ketamine	IM	1	1.75
Midazolam	IV	2	0.64–2.7
	PO	1	
	IN	1	

Chloral Hydrate

Fifteen of the 20 patients who received chloral hydrate were undergoing dental or radiologic procedures. Thirteen of the chloral hydrate sedated patients died or sustained a permanent neurologic injury; 5 were dental patients, 5 undergoing radiologic procedures, 2 cardiology procedures, and 1 an audiology procedure. Chloral hydrate was the only medication administered in 7 patients, and in 6 it was combined with other medications. Of the 7 cases in which chloral hydrate was the only drug administered, 4 patients received an overdose; 2 received an unknown amount of drug (1 at home and the other in a hospital venue); and the seventh received a standard dose (60 mg/kg). In the 6 cases in which chloral hydrate was combined with other sedating medications, all doses were within recommended limits. Four of these patients were sedated for dental care: 2 events occurred in a nonhospital-based facility and 2 at home after the procedure. The other 2 were sedated for radiologic procedures: 1 event occurred in the automobile after the procedure and in the other the venue was unknown. One of the patients was known to have an unstable cervical spine. Other preexisting medical problems in the 13 patients who received chloral hydrate and suffered an adverse

TABLE 5. Distribution of Drug Use by Category and Venue*

Drug	*n*	Hospital-Based Venue (*n* = 43)	Nonhospital-Based Venue (*n* = 28)	Unknown Venue (*n* = 24)
Opioids	38	19	9	7
Benzodiazepines	37	18	9	9
Sedative/hypnotic	45	18	16	11
Barbiturates	21	4	8	9
Intravenous anesthetic (ketamine)	9	8†	1	0
Inhalation anesthetics	13	0	11‡	2
Local anesthetics	14	2	8	4

* Note that some patients received >1 medication making the totals greater than the number of patients. The route of administration was not available for all drugs.
† *P* = NS compared with nonhospital-based vneue.
‡ *P* = <.01 compared with hospital-based venue.

outcome (*n* = 1 for each) included: tracheomalacia, tracheostomy, congenital heart disease, Möbius' syndrome, pulmonary artery hypertension, neonatal apnea, and cerebral palsy with seizures. An additional child with undefined congenital heart disease died after receiving an unknown amount of chloral hydrate.

Barbiturates

Twenty patients received barbiturate sedation. Nineteen died or had a permanent neurologic injury. In 10 the barbiturate was the only medication administered, 4 received 2 sedating medications, 1 received 3 sedating medications, 4 received 4 sedating medications, and 1 received 5 sedating medications. One received both methohexital and pentobarbital. The venue of the accident was not described in 8, a hospital-based venue in 3, a nonhospital-based venue in 8, and 1 patient died at home after pentobarbital (8 mg/kg, IM). Eight patients were undergoing dental procedures, 7 radiologic procedures, 3 gynecologic procedures (therapeutic abortions), and 1 an interventional cardiology procedure. Underlying medical problems in these patients included: histiocytosis (1), craniosynostosis (3), asthma (2), and developmental delay (1). The 1 survivor suffered a respiratory arrest after an overdose of rectal thiopental.

Local Anesthetics

Four children received overdoses of local anesthetics. Three were undergoing dental care and received 2 to 3.5 times the maximal recommended doses of either mepivacaine (*n* = 2) or lidocaine (*n* = 1). The other patient was treated in an emergency department and received an accidental IV injection of local anesthetic that was within the maximum recommended dosing limits. Two children initially developed seizures and 2 respiratory depression. Three progressed to cardiac arrest; all 4 children died.

DISCUSSION

Our study demonstrates that children suffered drug-related adverse outcomes after administration of a wide variety of medications. The data suggest a relatively even distribution of adverse sedation events in children across the major drug classes (opioids, benzodiazepines, barbiturates, and sedative/hypnotics). The observation that negative outcomes were associated with all classes of drugs and all routes of administration is clinically important because it points out that these negative outcomes occur not because of the drugs themselves but rather because of drug administration practices (drug combinations, errors, and monitoring standards). These practices likely reflect the skills (or lack of skills) and knowledge (or a lack of knowledge) of the individuals who administered the drugs for procedural sedation. Many events related to medication errors have been well-characterized. Lack of knowledge of the drug, lack of patient information, failure to follow procedures, transcription errors, faulty dose dispensing, inadequate monitoring, and a variety of other causes have all been described and many of these were evident in out database.[13–18] Children in particular seen to be vulnerable; methods for prevention of medication errors in this group have also been described.[19] The recent report from the Institute of Medicine has highlighted a number of initiatives that could be used to reduce medication errors.[20] Clearly the training, the understanding of the pharmacokinetics and pharmacodynamics of the drugs administered, and systems issues (such as drug limits, double-checking drug doses, computer checks of drug doses, improved patient informatics, the direct involvement of pharmacists, and limiting the medications used for certain types of procedures) are potentially important mechanisms for reducing medication errors.[20–32]

Our observations are consistent with these and other reports concerning adverse drug events and medication errors. However, a number of adverse outcomes were related to systems issues, such as inadequate monitoring, lack of skills in cardiopulmonary resuscitation, inadequate recovery procedures, and others causes unrelated to the drugs administered. In addition, nearly one half of the adverse outcomes occurred in nonhospital-based facilities, where the usual hospital-based safety net of state-mandated regulations does not generally apply. Unfortunately there is no way of knowing the actual incidence of these sedation/medication-related events because these were voluntary reports and the data were collected retrospectively. However, it is very likely that the cases that we collected represent a gross underreporting especially because such reports are often used as a tool for measuring hospital/

physician/organizational performance.[33–40] We agree with the Institute of Medicine report which suggests the need for a national mandatory reporting system that would be "afforded legal protections from data discoverability... devoted to analyzing and understanding the causes of errors to make improvements."[20] Other proposed initiatives include voluntary reporting systems such as the Joint Commission on Accreditation of Health care Organization's sentinel event program, the Food and Drug Administration's MedWatch program.[41,42] Such initiatives would help to focus on both drug-related and systems-related issues.

Our study found that there was no clear relationship between the route of administration and negative outcomes. The IV route was used most frequently and was the least associated with negative outcomes; however, compared with other routes of drug administration, the difference did not reach statistical significance. Several adverse events were successfully treated because of timely recognition and antagonism of drug effects. Although the data are somewhat soft, it suggests a possible advantage to the use of drugs that can be reversed if an adverse event should take place. Thus the use of an opioid or benzodiazepine alone or in combination with each other or combined with other sedating medications may be safer because at least one of the drugs has a specific antagonist that can reverse respiratory depression should it occur. The tendency toward a lower complication rate may also be related to the immediate availability of IV access for administration of resuscitative agents. Furthermore, we hypothesize that the tendency toward fewer adverse outcomes when medications are given intravenously may in part be related to the ability of titrate drugs to affect afforded by this route. Single large doses are commonly used when drugs are administered by other routes and there is no titration of drug. Another possibility is that these patients were monitored more closely. These hypotheses should be investigated further in future studies.

In many states, dental office practice certificates are based in part on the route of drug administration. Because our data clearly demonstrate that the route of drug administration is unrelated to outcome, certification of office practice based on route of drug administration does not adequately protect patients. Instead, certification should be based on practitioners' training in the use of these medications and on their sedation assessment, airway management, and resuscitation skills. In addition, the 2 Current Procedure Terminology codes recently established for sedation reimburse practitioners according to the route of drug administration (sedation administered by the IV, IM, and INH routes is reimbursed at 1 rate; medications delivered by the PO, PR, and IN routes are reimbursed at another rate).[8] Many procedures are performed by physicians who are not trained to sedate children or who are uncomfortable sedating children. The new Current Procedure Terminology sedation codes only apply if the physician is performing the procedure himself or herself; this creates a disincentive for independent experienced physicians to participate in the sedation of children for other physicians. The cost to the practitioner or a medical facility to provide safe patient care during sedation for a procedure is related in part to the intensity and duration of the monitoring required. The routine use of an additional person whose only responsibility is to observe the patient certainly is an important factor in this cost. Reimbursement based on route of drug administration is fallacious and should be abandoned.

Many serious adverse events occurred when multiple drugs were administered despite the fact that each was administered in less than the maximum recommended dose. This suggests drug–drug interactions, the category most often associated with an adverse sedation event ($n = 44$) and a phenomenon that has been well-described in clinical studies.[43,44] Adverse outcome has been correlated with the number of drugs used to sedate children having computer-axial tomography scans.[45] Our study found a high association with death or permanent neurologic injury when 3 or more sedating medications were administered. Several children in our cohort suffered an adverse outcome even when appropriate doses of individual medications were administered in combination. This underscores the need for education regarding the potential for a greater than desired depth of sedation when combining sedating medications, even when each is administered within the recommended dosing limits. When administration of multiple drugs is planned, initial doses (mg/kg) should be lower than those for each drug given alone. Also, insertion of an IV line, perhaps after an initial nonparenteral dose of a drug, could facilitate titration of further sedative/analgesics.

Drug overdose was the second most common category of causes attributed to adverse sedation events (39 episodes in 34 patients). None of these involved a 10-fold overdose; this fact suggests that the errors were not simple multiplication/decimal point errors, but rather were caused by a lack of knowledge about drug dosing in children.[19] The 3 local anesthetic overdoses, an issue previously described in dental accidents, underscore the importance of double-checking all drug doses and of setting maximum mg/kg dose limits.[46,47] Perhaps some of these adverse events resulted from the lack of pediatric labeling for nearly every medication used for sedation, analgesia, and amnesia in children.[48–52]

Some children died or suffered permanent neurologic injury even when a single drug was administered in less than maximum recommended doses ($n = 4$). One of these was undergoing an echocardiogram and was sedated with chloral hydrate (60 mg/kg) by a technician; 1 was a 2-year-old sedated for a computer-axial tomography scan with methohexital (20 mg/kg, PR); another was a 3-year-old sedated by a parent with midazolam (.5 mg/kg, PO) who died in the car on the way to the dental office; and the fourth was a 19-year-old undergoing a therapeutic abortion in a clinic who received methohexital (<2 mg/kg, IV). Two of these 4 patients were not protected by the safety net of trained medical personnel. These cases illustrate the essential reason for

having sedation guidelines that admonish against administration of sedating/anxiolytic medications at home or by those not qualified to provide skilled observation and rescue should an adverse event occur. Sedation guidelines allowing preprocedural drug administration at home should be modified to eliminate such practices.

Adverse events occurred in both hospital-based and nonhospital-based venues because of prescription or transcription errors. In 1 case, the pharmacy filled a chloral hydrate prescription for tablespoons instead of teaspoons and at twice the concentration, resulting in a dose 6 times higher than that intended by the prescriber. These types of events illustrate the need to have the same standard of care and vigilance regardless of the route of drug administration, drug class, or the venue in which the drug is administered. Because medication errors may occur at any time and at the hands of very skilled practitioners, sedation areas and delivery systems should be designed to prevent the occurrence of any errors.[20,53,54] For example, procedure policies could require that orders and prescriptions clearly indicate the child's weight, mg/kg, and the total dose to be administered. Further titration of medications should be specified. Because practitioners use a small number of medications for their particular procedures, precalculated drug dosage cards like those commonly used in emergency and critical care settings would be relatively easy to create. Further engineering of injury proof delivery systems should be encouraged.

We were particularly surprised by the number of children who suffered a negative outcome after the administration of chloral hydrate. This drug is widely used for infants and toddlers and has a long-standing reputation as a very safe medication with minimal effects on respiration.[55–58] Chloral hydrate is often used as a single sedating agent or in combination with other sedatives, particularly for dental and radiologic procedures.[59–63] Thirteen of 60 cases resulting in death or permanent neurologic injury involved the use of chloral hydrate alone ($n = 7$) or in combination with other medications ($n = 6$). Adverse events after chloral hydrate included a number of medication-related factors: overdose, administration outside of the safety net of a medical venue (drug given at home), administration by nonmedically trained personnel (technician), and premature discharge from medical observation. One of the children who died after receiving an unintended chloral hydrate overdose was noted by the mother to have a rapid heart beat; this may have been a sign of chloral hydrate toxicity.[64–67] A technician rather than a medically trained individual supervised this child, and the potential clinical implications of the rapid heart rate were ignored. We do not know whether this child would have survived if a nurse or physician had intervened at that point. We suspect that the 2 children with congenital heart disease were vulnerable to the development of cardiac dysrhythmias. It is known that tonsillar and adenoidal hypertrophy and Leigh's encephalopathy are associated with airway obstruction in patients sedated with chloral hydrate.[68–70] Airway obstruction has also been associated with chloral hydrate administration to American Society of Anesthesiologists (ASA) physical status 3 children.[71] We do not know whether any of our cases had similar airway-related problems, but it was most disturbing to find that 1 child who died had received only 60 mg/kg of chloral hydrate, which is well within recommended dose limits. Our study clearly points out that chloral hydrate is no exception to the rule that medications capable of causing depressed levels of consciousness should never be administered by nonmedical personnel in a nonsupervised medical environment.[72]

Some children were injured in car seats on their way home after a procedure. A possible mechanism for the injury was the infant falling asleep with the rhythmic motion of the automobile and the head falling forward, thereby obstructing the upper airway. In the presence of residual drug effect, the child could be unable to arouse or unable to spontaneously reposition the head to relieve the airway obstruction. This sequence of airway obstruction and desaturation has been demonstrated in unsedated full-term neonates placed in car seats.[73] All 9 children who experienced an adverse event (8 of whom died or suffered permanent neurologic injury) at home or in an automobile after a procedure, received drugs known to have a long half-life in infants and children (chloral hydrate, promazine, promethazine, chlorpromazine, or phenobarbital [IM]; see "Appendix"). The active metabolite of chloral hydrate is trichloroethanol. In newborns the half-life of trichloroethanol is 27.8 ± 21.3 hours, whereas in toddlers it is 9.7 ± 1.7 hours.[74] Thus, although at the end of a procedure an infant or toddler may seem to have recovered from the sedative effects of chloral hydrate, residual drug, and active metabolite are still circulating and there is the potential for resedation once the child is no longer stimulated. Two other children who died or suffered permanent neurologic injury after discharge were sedated with the classic combination of DPT or chlorpromazine plus promazine. A pharmacodynamic study of DPT administered to pediatric patients in the emergency department has shown that it took a mean of 19 ± 15 hours for children who received this drug combination to return to normal behavior.[75] The half-life of a single dose of chlorpromazine in adults is 31 hours.[76] A half-life of 3.19 days has been demonstrated in newborns.[77] Children seem to have a shorter elimination half-life compared with adults (7.74 ± .65 hours) but this study was for IV not IM administration[78]; the pharmacokinetics are likely different after IM administration attributable to delayed absorption and depot effect. Promazine and promethazine have a half-lives of 12.65 ± 4.7 hours[79] and 10 to 14 hours in adults, respectively.[80] Promethazine also has age-related differences in pharmacokinetics. The half-life is shorter in children (7.1 ± 2.3 hours) after oral administration, compared with adults (20 ± 4.1 hours).[81,82] The pharmacokinetics of promethazine may also be different after IM administration because of delayed absorption and depot effects. Another drug associated with death after discharge was pentobarbital (8 mg/kg, IM). The

half-life of pentobarbital in children when administered intravenously is 25.5 ± 16 hours.[83] In many of these cases the known pharmacokinetic profile of these agents was apparently ignored because patients were discharged without complete recovery from sedation.

Our discovery of several patients with negative outcomes who received sedation with these medications is particularly relevant considering the widespread and long-time use of these medications for outpatient sedation for procedures, particularly for infants. There are minimal data regarding the pharmacodynamics of any of these drugs in children, especially how age, maturation of hepatic or renal function, route of administration, or enzyme inhibition might alter drug elimination. These cases clearly point out the need for very rigorous recovery procedures and discharge criteria. Our data suggest that children should rest/recover in a quiet monitored area after the end of the procedure, even if they seem to be awake immediately after it is completed. A step-down unit for further observation after discharge from a standard recovery area may be of value in children who have received sedative medications with long half-lives. Patient discharge must only be made by qualified personnel (nurse, physician, and dentist) and not by a technician. We would make the further suggestion that because of the very unfavorable pharmacokinetics and the known drug–drug interactions,[84–86] the combination of DPT should be abandoned, particularly for outpatient procedures and those performed in infants. Although DPT was useful in its time, many other better options are now available to practitioners.

Eight events, of which 5 resulted in death or neurologic injury, occurred in situations with clear evidence that the practitioners did not understand the pharmacology of the drugs that they had administered. Examples of this included several patients who developed chest wall and glottic rigidity after opioid administration, could not be ventilated or oxygenated, and died or sustained severe neurologic injury. Administration of naloxone may have been life saving. Another example was an attempt to reverse a chloral hydrate associated event with naloxone because the practitioner thought that chloral hydrate was an opioid. A third example was local anesthetic toxicity that resulted in seizures and arrhythmias that were then treated with additional lidocaine (IV). These cases clearly underscore the importance of intimate knowledge of the pharmacology and the pharmacodynamics of the medications used for sedation/analgesia. If a physician/dentist is going to administer any medication, they must understand the basic pharmacology of that drug and how to effectively manage expected drug-related complications.

We do not know the reason why dental specialists were disproportionately represented. In fact, we excluded 10 dental cases who died because 9 had received alphaprodine which is no longer manufactured and 1 received a drug (a transdermal fentanyl patch) for postdental surgery pain. Despite these exclusions this specialty had the highest representation with 29/32 suffering death or permanent neurologic injury. There was a very strong relationship of adverse outcomes with nonhospital-based facilities and with dental practitioners ($n = 23$). In some states, the category of sedation called Anxiolysis in the Dental Office Setting permits the prescription or administration of pharmacologic anxiolytics with concomitant use of nitrous oxide, without requirements for a special dental office anesthesia permit, advanced training, or pulse oximetry monitoring.[87] Seven patients who died or sustained permanent neurologic injury were given promethazine, diazepam, or chloral hydrate combined with nitrous oxide administered by nonanesthesiologists for dental procedures. Continuous monitoring of level of consciousness is particularly important, because many dental procedures in themselves compromise the airway: abnormal head and tongue positions; foreign materials (cotton and rubber dams); and the presence of blood, increased secretions, and exogenous water. Negative outcomes were also associated with the patient receiving 3 or more sedating medications. Dental practitioners accounted for the majority of patients who received 3 or more sedating medications and all the patients who received nitrous oxide. Nitrous oxide is generally considered to have minimal effects on respiration and consciousness. However when nitrous oxide is combined with any other depressing medication, even when the sedating medication is administered in standard doses, a state of deep sedation and/or general anesthesia may occur.[46,88–91] It is possible that drug–drug interactions, particularly with nitrous oxide, contributed to the adverse outcomes in the dental setting. The category of Anxiolysis in the Dental Setting, which allows anxiolytics to be combined with nitrous oxide without a requirement for monitoring, should be abandoned; this level of sedation requires the same training in airway management and monitoring as that required for deep sedation/general anesthesia.[72] In addition, the 1998 revision of the American Academy of Pediatric Dentistry (AAPD) sedation guidelines[92] deviates substantially from guidelines published by the AAP[72] and ASA.[93] The AAPD has divided the category of conscious sedation (equivalent to sedation/analgesia for the ASA guideline) into 3 categories. Conscious sedation level 3 is defined as a state of consciousness in which "repeated trapezius pinching or needle insertion in oral tissues elicits reflex withdrawal and appropriate verbalization (complaint, moan, crying)." The ASA document clearly states (and the AAP document will soon state) that reflex withdrawal is not considered to be a state of conscious sedation/ or sedation/analgesia but rather is consistent with a state of deep sedation/general anesthesia. These disparate definitions and approach to sedation monitoring and training need to be made consistent for all patients regardless of practice. We encourage all dental specialists to examine their practices and urge them to develop monitoring guidelines and training requirements similar to those adopted by the AAP and ASA.

CONCLUSION

Children have suffered adverse sedation-related outcomes with a variety of medications; adverse outcome does not seem to be related to drug category or route of drug administration. Even chloral hydrate administered well within the recommended maximal dose limits can cause serious morbidity and mortality. Monitoring of patients who receive this medication should be no less rigorous than that used for patients sedated with other sedative medications. Chloral hydrate should be considered a long-acting drug, capable of severe respiratory depression and/or airway obstruction. Medications with long plasma half-lives (chloral hydrate, promazine, promethazine, chlorpromazine, and pentobarbital) accounted for most of the deaths/injuries that occurred in automobiles or at home after a procedure. DPT should be abandoned for outpatients; a step-down unit for extended observation of outpatients treated with long-acting sedatives may be useful, especially for younger patients. This practice might be even more important for long-acting medications administered IM because a depot effect may occur that would prolong recovery even further. Prescription and transcription errors occur with sufficient frequency as to underscore the importance of a systematic approach to all patients who receive sedative medications, eg, setting mg/kg dose limits, using standardized dosing regimens, and double-checking all doses before their administration. Even standard and acceptable doses of drugs can cause significant morbidity and mortality if the patient is not properly observed. No child should be sedated without the safety net of skilled medical observation; the practice of administering sedating medications at home before a procedure is reckless, associated with the potential for disaster, and should be prohibited. A uniform standard of monitoring should be applied after administration of sedation medication, before, during, and after procedures. There must be no difference in the degree of vigilance related to the sedation or procedure venue or to the practitioner. Uniform monitoring guidelines should be applied by all practitioners and in all venues, where sedation is administered because the effects on the patient are the same regardless of who administers the medication or where it is administered. Office practice certificates should be based on training and expertise in pediatric resuscitation and with advanced airway management skills and not on route of drug administration. The category Anxiolysis in the Dental Setting should require advanced airway management skills, training in both pediatric basic and advanced life support, and appropriate patient physiologic monitoring. The definitions for the various levels of sedation should be unified among specialists. Standards of care, scope of practice, resource requirements, and reimbursement for sedation services should be based on the intensity of the monitoring required and of the duration of the procedure through recovery, not on the route of drug administration. Public agencies such as the Agency for Health Care Quality and Research, National Institutes of Health, National Patient Safety Foundation Research Program, and others should support further investigations into safe yet effective medications, combinations of medications, sedation techniques, training, and improved monitoring modalities.

APPENDIX. Drugs Used for Sedation—Range Recommended and Maximum (Underlined) Recommended Doses Used for This Analysis[6,7,94]

Drug	Route	Half-Life (T½ Hours)* Mean ± SD (Range)	Maximum Recommended Dose (mg/kg)
Fentanyl	IV	1.5 to 3[95–97]	0.00025–0.003
Morphine	IV	2.6 ± 1.7[98]	0.025–0.1
	IM	4.5 ± 0.3[99]	0.5–0.1
Meperidine	PO	6.98 ± 1.9[100]	0.5–2.0
	IV	3.0 ± 0.5[101]	0.5–2.0
	IM	4.5 ± 1.3[102]	0.5–2.0
Oxymorphone	SQ	3.4 (2.6–5.1)[103]	0.02–0.04
Pentazocine	IV	2.33[104]	0.1–0.5
Nalbuphine	IV	2.4 ± 0.4[105]	0.05–0.15
Diazepam	PO	44.5 ± 16.5[106]	0.1–0.4
	IV	20–66[107,108]	0.05–0.25
Midazolam	PO	1.7[109]	0.25–0.75
	IN	~2[110]	0.1–0.3
	IV	1.4–4[109,111,112]	0.025–0.2
Lorazepam		10.5 ± 2.9[113]	0.025–0.05
Chlorpromazine	IM	~31[76]	0.05–1.0
Promethazine	PO	7–14[80,81]	0.1–1.0
	IM		0.1–1.0
Promazine	IM	12.6 ± 4.7[79]	1.0–3.0
Hydroxyzine	PO	7.1 ± 2.3[82]	0.5–1.0
Diphenhydramine	IM	5.4 ± 1.8[114]	0.5–1.25
Chloral hydrate	PO	9.7 ± 1.7[74]	25–100
	PR		(or 2 g total) 25–100 (or 2 g total)
Thiopental	IV	6.1 ± 3.3[115]	0.5–5
	PR		15–30
Methohexital	IV	2.23 ± 0.78[116]	0.25–2.0
	PR	3.21 ± 1.25[116]	15–30
Pentobarbital	PO		2–6.0
	IM		2–6.0
Ketamine	PO		2–10
	IV	3.1 ± 1.6[117]	0.25–1.0
	IM		1–4.0
Mepivacaine	SC		6.0
Lidocaine	SC—with epinephrine		7.0
	SC—without epinephrine		5.0
Prilocaine	SC		7.0

The range of recommended doses is presented with the upper limits underlined. It should be noted that recommendations vary according to the needs of the specialist and patient.

* Note that these half-lives are for older children or adults when pediatric data are absent; the half-lives are likely to be considerably longer in neonates and infants. It should also be noted that the effective half-life (ie, the effect on the central nervous system) may last considerably longer than several serum half-lives. Children with impaired renal or hepatic function, those on vasoactive medications, and those receiving inhibitors of the cytochrome oxidase system (eg, erythromycin, calcium channel blockers, or protease inhibitors) may also have markedly prolonged elimination half-lives.[118–122]

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Writing is hard . . . authors often get stuck in an awkward passage or find a muddle on their screens, and then blame themselves. What should be easy and flowing looks tangled . . . what's wrong with me, each one thinks. Why can't I get this right?

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Submitted by Student

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