Inadvertent Ketamine Overdose in Children: Clinical Manifestations and Outcome

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Study objective: We sought to characterize the clinical manifestations, outcome, and etiology of inadvertent ketamine overdose in the emergency department.

Methods: We investigated cases of inadvertent ketamine overdose in children seen in the ED solicited through electronic mail subscription lists or reported to the Institute for Safe Medication Practices. The clinical manifestations, outcome, and reported cause for each case are described.

Results: We identified 9 cases of inadvertent ketamine overdose in children treated in the ED. Patients received either 5 (n=3), 10 (n=5), or 100 (n=1) times the intended dose, either by the intramuscular (n=5) or intravenous (n=4) route. All 9 experienced prolonged sedation (3 to 24 hours). Four experienced brief respiratory depression shortly after administration, and assisted ventilation was performed in 2. Two children without respiratory difficulty or hypoxemia were intubated by their physicians as a precaution. In 5 children, the dosing error was not discovered until late in the sedation, often when the child was not waking at the expected time. No adverse outcomes were noted, and all children were normal neurologically on discharge and longer-term follow-up if available.

Conclusion: No adverse outcomes were noted in 9 healthy children treated in the ED who inadvertently received 5 to 100 times the intended dose of ketamine. Toxicity manifested as prolonged sedation in all 9 and brief respiratory depression in 4. The margin of safety in ketamine overdose may be wide, although less common and more serious outcomes cannot be excluded by this small, self-reported sample.

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INTRODUCTION

Ketamine is an increasingly popular drug choice for emergency department procedural sedation in children. Sedation with this dissociative agent demonstrates a wide margin of safety when specific patient exclusion and monitoring guidelines are followed.[1,2]

Little is known about supratherapeutic doses of ketamine, including the minimal toxic or lethal dose in humans.[3,4] There are 9 cases in the literature of patients inadvertently receiving large doses of ketamine (range, 22 to 56 mg/kg IM and 13 to 15 mg/kg IV) over the past 30 years, typically from dosing miscalculations (Table 1).[5-8] Respiratory depression was noted in all patients, and 8 were normal on recovery and experienced no sequelae. The ninth child, a critically ill infant, died.[5]

We assembled a case series of inadvertent ketamine overdoses in the ED to better characterize the clinical manifestations, outcome, and etiology of such events.

MATERIALS AND METHODS

After learning of 2 occurrences of inadvertent ketamine overdose, we actively solicited additional cases by using electronic mail subscription lists of general emergency physicians, pediatric emergency physicians, emergency medicine residency directors, and emergency medicine researchers in July 1998. Additional cases were obtained through incidents reported to the

Table 1.
Previously reported occurrences of inadvertent ketamine overdose.

Case No.	Reference	Sex	Age	Indication	Intended Dose	Administered Dose	Complications	Sedation Duration	Outcome
1	Litovitz[5]	Female	2 mo	Intubation	Unknown	10 times the intended dose administered intravenously	Cardiopulmonary arrest leading to death during ICU intubation in infant after heart surgery	Death	Death
2	Jensen[6]	Female	2 y	Hip relocation	~10 mg/kg IM	50 mg/kg IM	Respiratory depression with "slight" cyanosis, assisted ventilation × 20 min	10 h	Normal on recovery
3	Corssen[7]	Unknown	24 d	Facial surgery	~10 mg/kg IM	22 mg/kg IM	Respiratory depression; anesthesiologist elected to intubate for remainder of surgery	Unknown	Normal on recovery
4	Corssen[7]	Unknown	3 mo	Facial surgery	~10 mg/kg IM	56.1 mg/kg IM	Respiratory depression; anesthesiologist elected to intubate for remainder of surgery	Unknown	Normal on recovery
5	Corssen[8]	Male	20 mo	Pneumoencephalography	2.2 mg/kg IV	13.2 mg/kg IV	Transient respiratory depression resolving without assisted ventilation	Unknown	Normal on recovery
6	Corssen[8]	Male	5 y	Pneumoencephalography	2.2 mg/kg IV	15.4 mg/kg IV	Transient respiratory depression resolving without assisted ventilation	Unknown	Normal on recovery
7, 8, 9	Corssen[8]	Unknown	"<1 y"	Pneumoencephalography	11 mg/kg IM	24.2–30.8 mg/kg IM	Respiratory depression resolving within 2–5 min without assisted ventilation	Unknown	Normal on recovery

Institute for Safe Medication Practices (Warminster, PA), a nonprofit advocacy group.

We interviewed medical personnel directly involved in these cases in person, by telephone or electronic mail, or a

Table 2.
Currently reported occurrences of ketamine overdose.

Magnitude of Overdose	Case No.	Sex	Age	Indication	Intended Dose	Administered Dose	Reason for Error	Complications	Sedation Duration	Outcome
5 times intended dose	1	Female	14 m	Laceration	5 mg/kg IM	25 mg/kg IM	Unknown	Just after injection, transient respiratory depression was noted (lowest oxygen saturation 85%), which promptly resolved without assisted ventilation	24 h total, with overnight pediatric ICU observation	Normal on recovery and at 72 h
	2	Female	4 y	Laceration	4 mg/kg IM	20 mg/kg IM	Misread 100-mg/mL vial as 100 mg/vial	Five min after injection, transient respiratory depression was noted (lowest oxygen saturation 92%), which promptly resolved without assisted ventilation	4 h in ED	Normal at discharge; longer-term follow-up unavailable
	3	Male	4 y	Laceration	4 mg/kg IM	20 mg/kg IM	Misread 100-mg/mL vial as 100-mg/vial	None	17 h total, overnight pediatric ICU observation	Normal at discharge; longer-term follow-up unavailable
10 times intended dose	4	Male	4 y	Fracture reduction	1 mg/kg IV	10 mg/kg IV	Inadvertently used 100-mg/mL bottle instead of 10-mg/mL	Two min after administration, the child experienced respiratory depression with progressive desaturation (lowest 65%). Ventilation was assisted for 9 min followed by normal spontaneous respirations.	3 h and 15 min in ED	Normal at discharge and 7-mo follow-up
	5	Female	5 y	Laceration	2 mg/kg IV	20 mg/kg IV	Inadvertently used 100-mg/mL bottle instead of 10 mg/mL	Minutes after administration, the child experienced respiratory depression (lowest oxygen saturation 85%). Ventilations were assisted for 2 minutes followed by normal spontaneous respiration.	3 h in ED	Normal on discharge and at recheck the next day
	6	Male	7 y	Fracture reduction	1.0 mg/kg IV	10 mg/kg IV	Math error with 50-mg/mL vial	None	3 h in ED	Normal on recovery and 5-mo follow-up
	7	Male	3 y	Lumbar puncture	3 mg/kg IM	30 mg/kg IM	Unknown	None	Overnight pediatric ICU observation	Unavailable
	8	Male	5 y	Laceration	5 mg/kg IM	50 mg/kg IM	Math error	Prophylactic intubation (see text for details); no respiratory depression	5 h in ED	Normal on recovery and at 30 d
100 times intended dose	9	Male	3 y	Fracture reduction	0.5 mg/kg IV	50 mg/kg IV	Mistook 100-mg/mL vial as 1 mg/mL	Prophylactic intubation (see text for details); no respiratory depression	9 h total; overnight pediatric ICU observation	Normal on recovery and at 1- and 3-d telephone

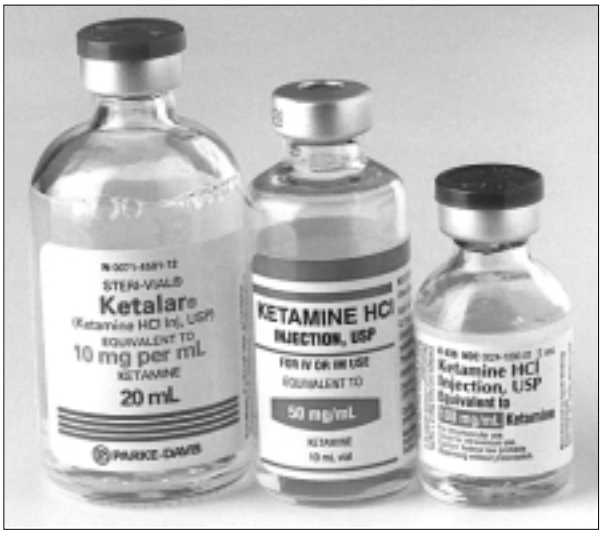
combination of these methods, and recorded standardized clinical information about each case. Routine questions were patient age, sex, indication, intended dose and route, administered dose, reason for error (if known), airway complications, hypoxemia (defined as oxygen saturation <90%), other complications, duration of sedation, and status at long-term follow-up. We excluded cases if these data were unavailable.

This study was exempt from institutional review board review.

RESULTS

We identified 11 total cases of inadvertent ketamine overdose, 6 through electronic mail solicitation and 5 through the Institute for Safe Medication Practices. We excluded a critically ill adult who died shortly after receiving a 10-fold ketamine overdose during intubation. A second excluded case was a child who experienced prolonged sedation but no other adverse effect after ketamine overdose; however, the reporting physician was unable to recall further details or locate the chart.

Figure.
Representative ketamine formulations and labeling available at the time of this report, including the 3 manufacturers (left to right): Parke-Davis, Bedford Laboratories, and Sanofi-Winthrop Pharmaceuticals; and the 3 available concentrations (left to right) 10 mg/mL, 50 mg/mL, and 100 mg/mL. Note that in the middle and right bottles, the total volume of the vial is in small type.



The remaining 9 patients are described in Table 2. All were from separate hospitals, and each contact interviewed was previously unaware of the other occurrences. In 8 cases the treating physicians were interviewed, and in 1 the information was obtained from the hospital pharmacist investigating the overdose. Overdoses were either 5 (n=3), 10 (n=5), or 100 (n=1) times the intended dose. One episode each occurred in 1996 and 1997, with the remaining events all occurring in 1998. In 5 of the children, the dosing error was not discovered until late in the sedation course, often when the child was not waking at the expected time.

Prolonged sedation (3 to 24 hours) was reported in all patients. Four children experienced brief respiratory depression, and assisted ventilation was performed in 2. Two children without respiratory depression or hypoxemia were electively intubated by their treating physicians as a precaution. Contacts did not report any other complications. Ketamine overdoses associated with intubation are described in greater detail as follows.

In case 8, a 10-fold dosing error was recognized within minutes after administration in a 5-year-old boy. The treating physician elected to intubate the child as a precaution 10 minutes later; however, there was no respiratory depression, hypoxemia, or hemodynamic compromise either before or after intubation. The child maintained spontaneous respirations with blow-by oxygenation without mechanical ventilation for 4 hours and then was extubated as he awakened. He was discharged from the ED awake and alert 5 hours after injection.

In case 9, a 3-year-old boy in whom 8 mg (0.5 mg/kg) of intravenous ketamine was ordered inadvertently received 800 mg. His nurse mistakenly assumed that a 100-mg/mL vial instead contained 1 mg/mL. The child experienced normal onset of sedation without respiratory depression and was maintaining oxygen saturation of 100% on room air when the error was discovered 15 minutes later. Forty minutes after administration, the physician noted “erratic respirations” despite continued 100% oxygen saturation and elected to intubate the child as a precaution. The patient was admitted to the pediatric ICU for observation and was extubated 9 hours later as he awakened. Seventeen hours after administration, he was discharged awake, alert, and normal. There was no hypoxemia or hemodynamic compromise at any point during his ED or pediatric ICU stay.

DISCUSSION

Little is known about larger than therapeutic doses of ketamine, including the minimal toxic or lethal dose in human subjects.[3,4] We herein report the largest case series of ketamine overdose ever reported. Importantly, we noted 2 primary forms of toxicity at 5 to 100 times the intended dose: transient respiratory depression and prolonged sedation. No adverse outcomes were noted in this self-reported sample, and the margin of safety in ketamine overdose may be wide.

Table 1 describes the 9 cases of inadvertent ketamine overdose previously reported in the literature. None occurred in the ED setting. Administered doses ranged from 2.2 to 10 times the intended dose. Excluding the critically ill infant who died, toxicity in the remaining 8 cases manifested as brief respiratory depression. All of these 8 patients were normal on recovery, and no adverse outcomes were reported. Sedation duration was specified in only one occurrence, and this child required 10 hours to recover. The 2 categories of toxicity noted in these reports, respiratory depression and prolonged sedation, mirror our newly reported cases.

Respiratory depression is uncommon with ketamine but has been reported when ketamine is pushed by rapid intravenous bolus; when central nervous system (CNS) injuries, masses, or abnormalities are present; or when the drug is administered to ill neonates.[2,3] In all of these reports and situations, respiratory depression invariably occurs at the time of peak concentrations of drug in the CNS: 1 to 2 minutes after intravenous administration and 4 to 6 minutes after intramuscular injection. Accordingly, available data suggest that ketamine-associated respiratory depression is likely a direct result of unusually high CNS concentrations. It is recommended that intravenous doses be given over at least 1 to 2 minutes to blunt the peak CNS concentrations.[2,3] Respiratory depression with intramuscular ketamine is rare,[1] presumably because the slower absorption by this route prevents excessively high CNS concentrations.

The duration of ketamine sedation is dependent on CNS concentrations. Resolution of clinical dissociation occurs through drug redistribution into the peripheral tissues, with an ultimate elimination half-life of 1 to 3 hours.[3] When administered intramuscularly, the unique dissociative state begins within 5 minutes and persists for 15 to 30 minutes. When administered intravenously, dissociation begins within 1 minute and persists for 10 to 15 minutes.[3] Extended sedation would be expected with higher doses, in that the redistribution phase would be prolonged. We noted recoveries lasting 3 to 9 hours with intravenous administration and 4 to 24 hours with intramuscular administration.

Assuming appropriate supportive airway management, our data and the cases previously reported suggest that ketamine overdoses of 5 to 10 times the intended dose appear unlikely to be life-threatening or associated with adverse outcomes in healthy children. The intraperitoneal dose at which ketamine is lethal for 50% of mice is 224 mg/kg,[4] which is 150 times the typical human therapeutic intravenous doses.

Ketamine use is ubiquitous in contemporary veterinary practice and is noted to demonstrate a wide margin of safety for animal surgery.[9,10] Arnbjerg[10] performed intentional overdoses in 20 cats with 50 to 100 mg/kg intramuscular ketamine to determine the signs of toxicity. Recovery was prolonged, but respiratory status and vital signs remained stable in all animals. He concluded that "there were no clinical signs of acute toxicity" and "even severe misjudgments of the body weight should not lead to fatal results."

One dosing error noted in our series (n=2) was assuming that the 100-mg/mL (5-mL) vial contained 100 total mg rather than the actual 500 mg, resulting in 5 times the intended dose being administered. The Figure shows the labels of the most common brands of these formulations. On all labels, the concentration is prominently displayed; however, the total volume of the vial is clearly shown by only 1 of the 3 manufacturers. Although human error cannot be excused on the basis of this factor alone, it seems plausible that more prominent display of the total milligrams in the vial might have prevented some of the currently reported overdoses.

A second error observed in this series (n=2) was confusing the 100-mg/mL vial with the 10-mg/mL vial, resulting in administration of 10 times the intended dose. Although human error cannot be excused on the basis of this confusion alone, it highlights the potential for error when 2 different formulations of the same drug are concurrently used in the same ED. The remaining causes of dosing errors were a math error (n=2), unknown (n=2), and mistaking a 100-mg/mL vial as 1-mg/mL (n=1).

We recommend that emergency physicians take action to lower the likelihood of such ketamine overdoses in their departments. In EDs in which ketamine administration is new or infrequent, we suggest that actual drug administration be restricted to physicians and nurses specifically trained in its use. To minimize confusion, only 1 of the 3 available ketamine formulations should be stocked. EDs that use primarily the intramuscular route

should stock only the 100-mg/mL concentration to minimize volume-related injection discomfort. This formulation is not advisable for direct intravenous administration through standard syringes, however, because it is difficult to maintain dosing accuracy and spread the injection over at least 1 minute. Instead, the 100-mg/mL concentration can be administered intravenously by using a tuberculin syringe or alternatively by diluting 1:10 with saline solution and then administering with a standard syringe. EDs that use only the intravenous route might consider stocking just the diluted 10-mg/mL formulation. Some EDs that use primarily the intravenous route but occasionally administer ketamine intramuscularly might consider the 50-mg/mL concentration as suitable for both purposes.

This study is subject to the limitations typical of a convenience sample, including uncertainty whether the occurrences we obtained through our sources are representative of all inadvertent ketamine overdose situations. It is reasonable to assume that overdoses with no adverse outcome would be more likely to be reported through our electronic mail solicitation and that physicians involved with more serious complications or death might be either unwilling to share such experiences or in fact be prohibited from such contact by hospital risk managers. In contrast, however, it is reasonable to assume that more serious overdoses would tend to be reported to the Institute for Safe Medication Practices. Hospital pharmacists regularly report serious drug errors to this high-profile advocacy organization, which uses this protected information to lobby pharmaceutical manufacturers for improvements in product packaging and labeling.

The clustering of the majority of our cases in 1998 likely reflects the growing popularity of ketamine sedation in the ED. We believe that emergency physicians must be prepared to encounter situations similar to those described. Given the toxicities noted in this sample, the first attention of the physician should be directed at airway maintenance and assessment of oxygen saturation, especially in the first 5 to 10 minutes after administration, when the risk may be greatest. Physicians should be prepared to closely monitor the child during an extended recovery period, either in the ED or the pediatric ICU.

To date, reported inadvertent overdose with ketamine has been uncommon, but may be expected to increase with the growing popularity of this drug. Our self-reported series suggests that overdoses in healthy children are associated with prolonged sedation and sometimes brief respiratory depression, although rarer more serious outcomes cannot be excluded.

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REFERENCES

1. Green SM, Rothrock SG, Lynch EL, et al: Intramuscular ketamine for pediatric sedation in the emergency department: Safety profile with 1,022 cases. *Ann Emerg Med* 1998;31:688-697.

2. Green SM, Rothrock SG, Harris T, et al: Intravenous ketamine for pediatric sedation in the emergency department: Safety and efficacy with 156 cases. *Acad Emerg Med* 1998;5:971-976.

3. Green SM, Johnson NE: Ketamine sedation for pediatric procedures. Part 2: Review and implications. *Ann Emerg Med* 1990;19:1033-1046.

4. Micromedex, Inc: Ketamine HCl, in *Poisindex*. Denver, CO: Micromedex, Inc; 1998.

5. Litovitz TL, Smilkstein M, Felberg L, et al: 1996 Annual Report of the American Association of Poison Control Centers toxic exposure surveillance system. *Am J Emerg Med* 1997;15:497-500.

6. Jensen AMH: 200 Anaesthesias with ketamine, in *Proceedings of the Third European Congress of Anaesthesiology*. Prague: Avicenum-Czechoslovak Medical Press, 1972:602-603.

7. Corssen G, Bjarnesen W: Recent advances in intravenous anesthesia. *J Am A Nurse Anesth* 1966;34:416-427.

8. Corssen G, Groves EH, Gomez S, et al: Ketamine: Its place in anesthesia for neurosurgical diagnostic procedures. *Anesth Analg* 1969;48:181-188.

9. Warren RG: *Small Animal Anesthesia*. St Louis: CV Mosby, 1983.

10. Arnbjerg J: Clinical manifestations of overdose of ketamine-xylazine in the cat. *Nord Vet Med* 1979;31:155-161.