Ketamine and Neurotoxicity: Clinical Perspectives and Implications for Emergency Medicine

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Rodent and monkey research has shown that ketamine can induce accelerated programmed nerve cell death (apoptosis) when administered in high doses, for prolonged periods, or both. Concern about similar neurotoxicity with human therapeutic use has prompted ongoing investigations by the Food and Drug Administration and National Institutes of Health. If the results of these inquiries are unfavorable to ketamine, such action could ultimately lead to restricted availability of this drug or even its discontinuation from the market. This article discusses the limitations of the published animal research, the challenges in extrapolating such data to humans, the need for further animal and human investigations, and the potential adverse effect on current clinical practice that might result, should the use of ketamine be restricted or the drug removed from the market. [Ann Emerg Med. 2009;54:181-190.]

INTRODUCTION

Ketamine is the most common agent used in US emergency departments (EDs) to provide sedation/analgesia to children for painful procedures.1-7 This dissociative drug is highly effective and has a strong safety record, as documented in 42 ED series totaling almost 10,000 children (Table).8-48 To a lesser extent, it is also used in ED adults.7

Rodent research has shown that many commonly used drugs including ketamine can induce neuronal cell death (“neuroapoptosis”), typically in newborn animals receiving high doses during prolonged periods.49-62 Nearly all drugs used for sedation and anesthesia in children have been similarly demonstrated to be associated with neuroapoptosis in various animal models.50,62 These include potent inhalation anesthetics used in the operating room, nitrous oxide commonly used in dentistry and elsewhere, barbiturates widely used for radiologic procedures, and benzodiazepines and propofol frequently used for sedation in multiple settings. A preliminary primate study corroborates this effect with ketamine, but only with high, prolonged doses. In this study, short-term exposure, as would be more typical of clinical use, was not associated with apoptosis.63 Thus far, there is no evidence of any such effect in humans at any dose, and the relevance of the animal research, even the primate study, to clinical medicine remains unclear.

Ketamine is the agent most studied thus far on this issue. The clinical implications are important, however, for if ketamine as currently administered does indeed produce accelerated programmed neuronal death, then children may be experiencing unrecognized central nervous system damage and perhaps cognitive sequela.49,64-66 Therefore, research needs to focus on establishing whether these observations occur in the human neonate and infant with the drug doses and concentrations generally used to care for this age group. If it is verified that apoptosis does occur in the clinical setting, then safe means for blocking this effect (eg, 7-nitroindazole, L-carnitine) must be investigated and developed for human application or alternate methods for providing adequate sedation and analgesia safely must be developed.67,68

The systematic removal of ketamine and other implicated drugs from our clinical armamentarium would make it virtually impossible for us to care for children in the ED, the operating room, and any other location where sedation, analgesia, and anxiolysis are indicated. Therefore, there is need for great caution in how the animal studies are placed into clinical perspective, particularly extrapolation of dose, developmental age, and duration of exposure.

The Food and Drug Administration (FDA) recently held a public hearing on the potential neurotoxic effects on the developing brain of ketamine and other implicated drugs.69 The committee concluded that the existing animal research cannot be reliably extrapolated to humans but that the potential threat was sufficient to represent a public health concern. Accordingly, the FDA and the National Institutes of Health (NIH) are investigating the clinical use of ketamine. If the results of these inquiries are unfavorable, such action could lead to restricted availability of this drug or even removal from the market.

This article discusses the limitations of the underlying animal research on which the FDA and NIH investigations are based, the
challenges in extrapolating such data to humans, the need for further animal and human investigations, and the potential adverse effect on clinical practice that might result should the use of ketamine be restricted or the drug removed from the market.

WHAT IS NEUROAPOPTOSIS?

Neuroapoptosis is a natural process of neuronal cell death believed integral to normal mammalian brain development. During standard fetal and neonatal central nervous system development, an excess of neurons is produced and as many as 50% to 70% later undergo internal signals to “commit suicide.”

In animal models, exogenous substances can accelerate this process of programmed cell death by blockade of N-methyl-D-aspartate receptors or stimulation of γ-aminobutyrate A receptors. The resulting central nervous system damage is evident on neuropathologic examination and measures of memory on test animals. The most commonly implicated and

Table. All existing unique series of ketamine in emergency medicine.

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most researched precipitant is ketamine; however, neuroapoptosis has also been associated with ethanol, nitrous oxide, isoflurane, halothane, propofol, benzodiazepines, barbiturates, and anticonvulsants.50

An unanswered question is whether ketamine and other apoptotic drugs actually kill viable neurons and adversely affect development, whether instead they simply accelerate death in cells already destined for termination and leave no permanent sequelae, or whether a child’s normal brain plasticity overcomes such effects.62

KETAMINE NEUROAPOPTOSIS RESEARCH IN RODENTS

Researchers have used in vitro models to investigate ketamine-associated neuroapoptosis. Vutskits et al51 introduced ketamine into newborn rat neuron cultures and found evidence of toxicity with both short-term high-dose exposures and chronic low-dose exposures. However, they found no such toxicity with short-term, low-dose exposure. Wang et al52 exposed newborn rat neuron cultures to a range of ketamine concentrations for 48 hours and observed apoptosis only with the higher concentrations. They then administered an apoptotic concentration during a range of periods and found apoptosis only with exposures of 6 hours or more. Three reports found neurotoxicity with repeated ketamine dosing in vivo: the first with 25 mg/kg (intraperitoneally) administered at 90-minute intervals during 9 hours in 7-day-old rats, and the second with 5 sequential doses of 5 mg/kg intraperitoneally in adult mice.53,70 In the third, neurotoxicity was observed with 7 repeated 20 mg/kg intraperitoneal doses of ketamine in 7-day-old rats, but not with 7 repeated lower intraperitoneal doses (10 mg/kg).54

To better simulate actual clinical use, several investigators have studied single ketamine doses in rodents. Fredriksson et al55 observed apoptosis with single doses of both 50 mg/kg subcutaneously and 25 mg/kg intraperitoneally in 10-day-old mice. In 7-day-old rats, Young et al57 found modest increases in neurotoxicity at doses of 30 mg/kg subcutaneously or less; however, a threshold of 40 mg/kg was required for a substantial increase in neurotoxicity. In 3 different studies, Jevtovic-Todorovic et al58,59 and Jevtovic-Todorovic and Carter60 administered a range of single doses to adult or “aging” rats (subcutaneously or intraperitoneally) and found nerve damage only at doses of 50 mg/kg intraperitoneally or higher. Rudin et al61 administered a range of single ketamine doses (subcutaneously) to 7-day-old mice and found apoptosis with doses of 5 mg/kg or higher but not with doses below this.

In conflict with these reports, 2 investigators have failed to observe neurotoxicity with single high ketamine doses (intraperitoneally) in 7-day-old rats, the first using 25, 50, or 75 mg/kg53 and the second using 20 mg/kg (intraperitoneally).54

NEUROAPOPTOSIS RESEARCH IN MONKEYS

Thus far, there are only 2 studies evaluating ketamine-associated neuroapoptosis in nonrodents. Wang et al71 exposed newborn rhesus monkey neuron cultures to ketamine for a variety of periods; they found no neurotoxicity after 2 hours of exposure but progressive neurotoxicity from exposure times between 6 and 24 hours. Slikker et al63 administered ketamine 20 mg/kg intramuscular followed by high-dose 24-hour infusions (20 to 50 mg/kg/hour) to rhesus monkeys at 3 age groups (in utero at 122 days of gestation, 5 days old, and 35 days old) and found neurotoxicity in the 2 younger groups but not the 35-day-old group. They also administered a 3-hour ketamine infusion to 5-day-old monkeys and found no neurotoxicity. They observed that their ketamine plasma levels were 5 to 10 times higher than those typically used in humans.

EXTRAPOLATION OF ANIMAL RESEARCH TO HUMANS

The animal researchers cited above have been generally guarded about extrapolation of their findings to humans. Olney et al57,64,65 have made qualifying statements such as, “Before engaging in speculation, it must be acknowledged that rodent data provide an imprecise basis at best, and an irrelevant basis at worst, for evaluating human risk.” Arguments against the relevance of these data to humans include age, treatment duration, dose, and the general difficulty of translating animal results to humans.

One criticism centers on the applicability of age-based studies of neonatal animals to humans. It is assumed that developing mammals are at greatest apoptotic risk during the most rapid period of their central nervous system growth. Dobbing and Sands72 have compared the relative periods of these “brain spurts” between species (Figure),3 and it can be seen from this schematic that the velocity of brain growth peaks at approximately 1 month after birth for humans and at about 8 days after birth for rats. Accordingly, although most of the rodent research has been done at the presumed period of peak vulnerability, it is extremely uncommon for children treated in
the ED to receive ketamine during this corresponding period of development. Emergency physicians widely view ketamine as absolutely and relatively contraindicated in infants younger than 3 months and younger than 12 months, respectively; the median ages treated in the largest 2 ED series have been 4 and 6 years, respectively.\textsuperscript{73,74} Although some have postulated that the central nervous system growth phase extends up to the third year after human birth,\textsuperscript{50,57} it is evident from the Figure that the human brain spurt is essentially over at 1 or 2 years of age.\textsuperscript{72} Accordingly, the majority of children currently receiving ketamine in the ED are no longer in a period of rapid central nervous system growth.

The supposition that human children receiving ketamine are well beyond the equivalent neurodevelopmental period of the animals developing apoptosis is even better supported by the comparative neurobiological approach of Clancy et al.\textsuperscript{75} These researchers developed an algorithm, accessible on the Internet (http://www.translatingtime.net), that compares neuroanatomic milestones across species. According to their calculations, the 7-day-old rats (the equivalent of 28.5 days postconception) widely used in neuroapoptosis research correspond to humans at 16 and 22 weeks’ gestation for limbic and cortical regions, respectively. The 122-day postconception monkeys used by Slikker et al\textsuperscript{63} correspond to humans at 20 and 28 weeks’ gestation for limbic and cortical regions, respectively. Thus, according to the calculations of Clancy et al,\textsuperscript{75} the animals experiencing ketamine-induced apoptosis are neurodevelopmentally equivalent to the human midterm fetus or extremely premature neonate, well before the age typical of clinical use.

A second age-related criticism is that several of the animal studies observed neurotoxicity in adult or even elderly rodents, a time of limited central nervous system growth.\textsuperscript{72} This argues against the concept of enhanced vulnerability during a “brain spurt” and that perhaps apoptotic vulnerability is not so much a developmental issue, but rather a characteristic of rodents as a mammalian order.

The criticism based on treatment duration focuses on the use of prolonged ketamine exposure in some studies, something wholly inconsistent with the typical 1 or 2 doses used clinically and the comparison of time exposure in relation to growth between species. Berde and Cairns\textsuperscript{76} assert that “nine hours in an infant rat spans a period of neuronal development corresponding to roughly 8-40 days for infant humans.” Anand and Soriano\textsuperscript{77} describe such research as “...the equivalent to producing general anesthesia for several weeks in the human neonate.” Accordingly, such research can only exaggerate—perhaps substantially—any corresponding human toxicity. The primate studies by Slikker et al\textsuperscript{63} suggest that even in animal models there is likely a time/dose/area under the curve of exposure factor that requires much further research because most ketamine and inhalation anesthetic exposures are for fewer than 3 to 6 hours. In humans, for example, a single ketamine dose of 2 mg/kg intravenously (adults) produces a therapeutic plasma concentration of 0.7 to 2.2 μg/mL that lasts for approximately 10 minutes, with awakening occurring when the plasma level decreases below 0.5 μg/mL.\textsuperscript{78,79} Children may in fact require 0.8 to 4.0 μg/mL to maintain the dissociative state.\textsuperscript{80,81}

Dosing is a third area of concern. Multiple animal studies have shown that approximately 40 mg/kg is the threshold at which neurotoxicity becomes marked relative to baseline.\textsuperscript{56-61} It is typical for ED children to receive far less—most commonly between 1 and 2 mg/kg intravenously—and thus if the toxic thresholds (mg/kg or plasma concentration μg/mL) are similar between species, then clinical doses should represent little or no risk. However, it has been speculated, but not proven, that humans might experience neurotoxicity at a lower threshold than rats because they are sedated at lower doses. Humans require 8 to 16 times less ketamine than rats (on a mg/kg basis) to achieve adequate sedation,\textsuperscript{57,80-82} and thus if one assumes that equipotent doses might predict similar toxicity, then doses of 2.5 to 5 mg/kg could present human risk. The counterargument to this reasoning is that if efficacy differs so markedly between humans and rats, then is it not compelling evidence that ketamine-specific characteristics are not reasonably comparable between these 2 vastly different species? Further, it is unknown whether it is the actual blood level achieved or the comparable pharmacodynamic response achieved that determines potential toxicity.

Finally, the general applicability of animal studies to the human experience has been debated at length.\textsuperscript{83,84} Although animal research is vital to the advancement of medicine, it essentially never has direct clinical applicability. Instead, animal research is used for preliminary hypothesis testing and as a prelude to guide later human studies. Most practicing clinicians wait to see whether the ongoing results from animal investigations ultimately lead to clinically relevant findings in human volunteers or in patients. A simple example is that acetaminophen, one of the safest medications in use by humans today, is highly toxic to cats and a single dose can be fatal.\textsuperscript{85} In summary, the extrapolation of animal neuroapoptosis to humans can be readily criticized. As stated by Anand and Soriano\textsuperscript{77}: “The experimental findings... are certainly sound but it may be premature to apply them to clinical settings at this time.” Todd\textsuperscript{66} echoes this: “It would also be entirely inappropriate for anyone to suggest that anesthesiologists should change their practice based on such work, both because we don’t know if the findings apply to humans and because we have no idea what kind of change would be appropriate.” Soriano et al\textsuperscript{86} and Soriano and Anand\textsuperscript{87} regard any clinical extrapolation of these findings as “premature and inappropriate.” Berde and Cairns\textsuperscript{76} conclude that “[r]esearchers and clinicians should be cautious in changing clinical practice based on preliminary infant animal experiments in the absence of corroborating human data, but these infant animal experiments should cause them to question their practices and to pursue the corresponding human studies.”
IS KETAMINE NEUROPROTECTIVE?
To further complicate thinking about the central nervous system effect of ketamine, other animal research has paradoxically found ketamine to be neuroprotective, presumably through its antagonism of N-methyl-D-aspartate receptors.88-93 Indeed, one group of researchers speculates that because of these properties ketamine might ultimately be a treatment for acute brain injury.94,95 As a result of such research, ketamine was used as a key part of a neuroprotective drug combination used in the only known case of survival from rabies.96

RELEVANT HUMAN RESEARCH
Ketamine was originally synthesized in 1962 and first used in humans in 1965.95 Since its commercial release 38 years ago, ketamine has been widely and continuously used throughout the world. Its wide safety margin and low cost have resulted in high use in the developing world, where trained anesthesiologists are scarce and resources limited.96 The cumulative exposure of adults and children is likely to be scores of millions of total administrations. Despite this, no hint of a suggested association between ketamine and brain damage or learning delay, the presumed sequela of neuroapoptosis, has been reported. Although such lack of notice does not exclude a causal relationship, one could hypothesize that if the clinical effect were more than minimal, then the association would have been recognized long ago. Currently, there is no compelling evidence in the literature of any ketamine-specific brain injury or cognitive loss resulting from the clinical application of this dissociative agent.

This above logic is even more striking when one recalls that during the 1970s and 1980s, it was typical for clinicians to administer ketamine at doses far higher than those generally recommended today. In a review of 97 ketamine series before 1990 totaling 11,589 pediatric administrations, the bulk of doses was typically between 8 and 15 mg/kg, with some up to 17 mg/kg.97 If higher doses truly potentiate neuroapoptosis in humans, then the clinical manifestations should have been substantially more pronounced during these 2 decades than today. Despite this, no problem is apparent.

The existing 42 ED series totaling almost 10,000 children (Table)3-48,73 report no adverse neurologic sequela from ketamine, although admittedly they had limited or no follow-up. Long-term neurodevelopmental studies of children who have received ketamine have not been conducted and would appear to be the only way to definitively resolve this controversy.49

CLINICAL IMPLICATIONS OF THE POTENTIAL RESTRICTION OR DISCONTINUATION OF KETAMINE
Ketamine was FDA approved in 1970 and almost immediately found a preferred application in children for both minor procedures and major surgery.3,97,98 The later availability of alternative agents with shorter and smoother recoveries has substantially diminished the subsequent role for ketamine in modern anesthesia practice. In the 1990s, however, this drug gained widespread popularity in the ED setting, where emergency physicians found that it could reliably and effectively facilitate the treatment of common painful and anxiety-inducing procedures in children such as fracture reduction, laceration repair, and abscess drainage.3,7 An important pharmacodynamic attribute of this dissociative agent is marked cardiovascular stability and minimal effect on respirations in the majority of children. These characteristics no doubt form the basis for the wide margin of safety observed with ketamine.97

An adverse FDA decision could alter ketamine use and availability in several ways. First, the FDA could choose to remove the drug from the market altogether. Second, they could add a “black box” or other warning label that would potently discourage its use and that would likely lead hospital pharmacy and therapeutics committees to restrict its use or remove it from their formularies. Finally, fear of litigation might lead some or all of the remaining manufacturers to abandon production of ketamine altogether, particularly because the drug is inexpensive and thus not a major source of revenue.

Of equal importance is what drug or drug combination could be substituted that has an equal safety and efficacy profile that is also free of causing apoptosis. One cannot remove one drug from the market without a substitute or the FDA will repeat the error made initially with the black box warning placed on succinylcholine in the 1990s. In that instance, the FDA initially stated that “[e]xcept when used for emergency tracheal intubation or in instances where immediate securing of the airway is necessary, succinylcholine is contraindicated in children and adolescent patients.”99 There was no substitute for achieving safe and rapid control of the airway, for the relief of laryngospasm, or intramuscular for children with difficult venous access. This resulted in a huge outcry from the pediatric anesthesia community about the safety of pediatric airway management; another FDA public hearing resulted in more moderate language that was then acceptable to the pediatric anesthesia community that satisfied the concerns for safety while balancing our need to safely care for children.100 Therefore, a word of caution is advised before considering a black box warning or a restriction on the use of ketamine without adequate well-controlled trials that demonstrate that the animal data are applicable to humans and in particular to human neonates and infants.99,101-106

Effect on emergency medicine
The restriction or market withdrawal of ketamine would have a dramatic effect on sedation practice in US EDs because there are no clear alternatives to replace it. Before the widespread implementation of this dissociative agent, most EDs relied on forcible immobilization with papoose boards or by nursing personnel to subdue uncooperative children during procedures. Pharmacologic restraint with ketamine or other sedative/analgesic is now the standard of care throughout the
United States. Any suggestion of a return to the old practice would now be considered ethically unacceptable.

Emergency physicians are adept at inducing moderate sedation with titrated benzodiazepines and opioids; however, younger children typically require deep sedation to humanely complete their procedures, and these combined agents are difficult to titrate to this higher endpoint without substantially greater risk of oversedation or respiratory depression. Because midazolam has also been linked to animal models of apoptosis, this alternative also seems limited. Nitrous oxide, pentobarbital, and chloral hydrate each have a focused role in ED anxiolysis and sedation but lack the complete analgesia optimal for extremely painful procedures, and nitrous oxide and barbiturates have been linked to animal models of neuroapoptosis. Because neither pentobarbital nor chloral hydrate possesses analgesic properties, they have less efficacy for painful procedures unless combined with opioids.

Propofol would be the most promising replacement, should ketamine become less available, and indeed many EDs are now successfully using this deep sedative for fracture reduction and abscess drainage in both children and adults. However, the application of propofol outside of the operating room setting has provoked substantially more controversy from the anesthesia community than has ketamine, and it is still common for emergency physicians to not be permitted access to this agent. Unlike ketamine, propofol can depress protective airway reflexes and is likely to present a higher aspiration risk to ED children, many of whom require urgent procedures despite the lack of standard periods of fasting. Additionally, propofol can be administered by the intravenously, in contrast to ketamine, which can also be administered by the intramuscular or oral routes. Propofol does not possess analgesic properties, necessitating the addition of opioids for painful procedures, and it also has been linked to neuroapoptosis in animal models.

A final alternative to ketamine would be referring these ED children to the operating room for general anesthesia. However, most operating rooms are already at or near capacity and lack the resources to effectively shoulder this additional burden, and once again all the potent inhalation agents (isoflurane>sevoflurane) and nitrous oxide have also been linked to neuroapoptosis in animal models.

Effect on anesthesiology

Anesthesiologists have alternatives for the minority of children for whom they currently select ketamine. Nevertheless, ketamine remains the induction/sedative agent of choice for many anesthesiologists in specific patient populations such as those with cyanotic congenital heart disease, hypovolemia, and hemodynamic instability. Should this drug be restricted or withdrawn, anesthesiologists would need to deal with the resultant surge in referrals from the ED.

Effect in the developing world

Although its current use in the United States is primarily in emergency medicine, ketamine continues to be widely relied on throughout the developing world as a simpler and more economical alternative to inhalational anesthesia for major surgery. Indeed, one foreign anesthesiologist has said that “[w]orldwide, it is likely that more ketamine anaesthetics are given than any other form of anaesthesia.” Any restriction or loss of this agent in these settings would have severe and perhaps catastrophic effect because many such settings lack the equipment or expertise to convert these additional cases to inhalational anesthesia.

SUMMARY AND FUTURE RESEARCH

Although it is beyond dispute that ketamine can induce neuronal death in rodents and other animals, there is thus far no evidence that such an effect occurs in humans. Indeed, such a premise is at complete odds with the wealth of human experience with this agent. However, now that this question has been raised, we are obligated to carefully investigate. A first approach might be the effect of ketamine on biomarkers of neurologic injury such as protein S-100B and neuron-specific enolase. Ultimately, however, it appears that this question can be resolved only through long-term epidemiologic study of children receiving ketamine that also excludes exposure to all other medications that have a similar association in animal models. Such a study should be funded and conducted, but there will be enormous problems with developing adequate controls and sufficient case numbers to arrive at a secure resolution. Until the results of such studies are available, there is insufficient evidence to alter current clinical practice. The ample benefits of ketamine sedation in children substantially outweigh its theoretical risks. Should it ultimately be demonstrated that neuroapoptosis does occur with ketamine or other implicated drugs at clinically relevant doses, then it will be imperative to develop either alternative safer agents or effective mechanisms for blocking the neurotoxic effect.

The authors would like to thank Sulpicio Soriano, MD, and Andreas W. Loepke, MD, PhD, for their kind review of the article and many helpful suggestions.

Supervising editors: Michael W. Shannon, MD; Donald M. Yealy, MD

Dr. Shannon and Dr. Yealy were the supervising editors on this article. Dr. Green did not participate in the editorial review or decision to publish this article.

Funding and support: By Annals policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article that might create any potential conflict of interest. The authors have stated that no such relationships exist. See the Manuscript Submission Agreement in this issue for examples of specific conflicts covered by this statement.
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Publication dates: Received for publication September 9, 2008. Revision received September 23, 2008. Accepted for publication October 1, 2008. Available online November 6, 2008.


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