Something new about ketamine for pediatric anesthesia?

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Purpose of review

This review discusses the place of the old anesthetic ketamine in pediatric anesthesia.

Recent findings

Despite the availability of modern alternatives, ketamine remains a frequently used drug particularly for anesthesia in high-risk children and for procedures outside the operating room. In adult patients undergoing surgery, a renewed interest in this drug is noted. It is the consequence of recent demonstrations of the following effects. First, ketamine is highly effective against surgery and opiate-induced hyperalgesia. Second, it has original antiproinflammatory properties. In other words, it promotes self-limitation of the inflammatory response that follows surgery. In the pediatric population, these benefits wait to be confirmed. Finally, questions arise about the safety of ketamine anesthesia. Ketamine is a potent proapoptotic drug. In rodents treated during the critical period for central nervous system development, long-term behavioral deficits were noted after an anesthetic dose of ketamine. The exact consequences of these proapoptotic properties on human brain tissue development have to be exactly determined and are still debatable.

Summary

Ketamine has not yet revealed all its interactions in humans. Recent discoveries indicate interesting properties on the one hand and potentially deleterious effects on the other.

Keywords

apoptosis, hyperalgesia, inflammatory reaction, ketamine, pediatric anesthesia

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Introduction

This review discusses the place of ketamine in pediatric anesthesia. For this purpose, the mechanism of action of this old anesthetic will be briefly summarized. Its use for pediatric anesthesia will be reviewed in the light of recent literature. Particularly, we will focus on its two properties recently reported in adults (antihyperalgesia and antiproinflammation). Are these beneficial effects specifically reported in the pediatric population? Finally, we will question the potential dangers of using ketamine during periods of central nervous system development.

Mechanism of action

Ketamine is a phenylpiperidine derivative (PCP or 'angel dust') synthesized by Parke–Davis (Calvin Stevens) in the early 1960s. It was designed to become the 'ideal anesthetic' at a time when other anesthetics, either intravenous or volatile, were particularly toxic or, at least, not really easy to use. Its popularity was established in the mid 1970s during the Vietnam war. This was because of two quite different reasons. First, ketamine was revealed to be an exceptional 'battle field' anesthetic. Second, it has potent psychoactive properties. It is still one of the most popular 'recreational drugs' (best known under the name: vitamin *K* or special *K*).

The anesthesia produced by ketamine is qualified as 'dissociative' for two reasons. First, the state of unconsciousness produced is quite different from the other anesthetics. The patient appears 'dissociated' from his environment not simply nonreactive. The second reason is given by the encephalographic recordings. Under ketamine anesthesia, the electrical activity of the thalamus is no longer synchronized with or 'dissociated' from the limbic system. Moreover, there are several other properties that make ketamine a particularly original anesthetic. Under ketamine anesthesia, blood pressure is well maintained even in the case of hypovolemia. Spontaneous breathing and laryngeal reflexes are preserved. This makes ketamine the 'first choice' anesthetic for prehospital anesthesia/analgesia. Another famous characteristic of this drug is its potent ability to induce psychodysphoric symptoms. These symptoms include simple cognitive or memory impairments escalating to

major schizophrenic psychosis in strictly normal patients. This effect is the major limitation to the widespread use of ketamine. The pediatric population was initially thought to be free from this side effect. It was, however, not confirmed.

Pharmacologically speaking, ketamine is a lipophilic drug poorly bound to the plasma proteins (10–30%). Consequently, it has a large volume of distribution (2.5–3.5 l/kg). It is rapidly active (distribution half-life 7–11 min) and its elimination half-life is short (1–2 h). Ketamine is metabolized by the liver and accumulated in the body fat during prolonged use. It is active by several routes (intravenous, intramuscular, sublingual, intrarectal, etc.), a property that makes ketamine a drug particularly attractive for pediatric use. Ketamine is a racemic mixture. The *S*(+) isomer is three times more active than the *R*(−). The pure *S*(+) form has been commercially available for several years (Ketanest R). Except for easier titration, it has no significant advantage when compared with the racemic mixture. Particularly, it is not devoid of any psychodysphoric effect [1].

The mechanism of action of this anesthetic is particularly complex. It is able to interact with numerous receptor or subreceptor systems. For this reason, it was once called 'the nightmare of the pharmacologist'. The different mechanisms are summarized in Table 1 [2–8]. The gamma-aminobutyric acid (GABA) receptor system is a quasi one, the only receptor system not directly affected by ketamine administration.

Use of ketamine for pediatric anesthesia/analgesia

As already mentioned, ketamine remains the first-choice anesthetic for prehospital situations.

Concerning its pediatric use, we have to agree with Lin and Durieux [9] that, despite the availability of modern alternatives, this old anesthetic remains the first choice agent in several clinical situations. For example, ketamine is highly recommended for the induction and maintenance of general anesthesia in children with cyanogenic cardiopathy. In contrast to more recent anesthetic agents, the ketamine-induced increase in vascular resistance and cardiac output does not increase the right/left shunt. For maintenance of anesthesia, the use of ketamine infusion is more accurate than the classic fentanyl/isoflurane mixture [10]. Ketamine anesthesia is mandatory for children presenting with neuromuscular diseases associated with malignant hyperthermia triggered by volatile agents or neuromuscular blocking drugs [11].

Ketamine is frequently used in combination for anesthesia in high-risk children undergoing major surgical procedures [12–14]. Moreover, in normal-risk children, the association of low-dose ketamine (0.25 mg/kg) is effective in preventing emergence agitation, a common side effect observed with the recent volatile agent sevoflurane [15•].

Ketamine is an anesthetic agent particularly suited for diagnostic or therapeutic procedures in children outside the operating theater. The underlying reasons are evident. Ketamine confers sedation and analgesia with no respiratory depression even at deep levels of anesthesia (tracheal intubation is not mandatory) or cardiovascular depression [16•]. It is user-friendly, active by different routes and characterized by a highly predictable duration of action [17,18•,19–21].

Recently, the pharmacokinetic characteristics of ketamine in children undergoing painful procedures in an emergency department were studied by Herd and coworkers [*22*••,*23*•]. These authors reported that an intravenous dose of 1 mg/kg provides a satisfactory sedative serum concentration for painful procedures of less than 5 min duration and produces concentrations associated

Table 1 Reported interactions of ketamine with receptor systems (nonexhaustive list)

System	Effect	Concentration	Clinical effect	Duration	Reference
Excitatory neurotransmission (NMDA receptor)	Antagonist	+++	Anesthesia (unconsciousness, analgesia)	min	[2,3]
		++/+	Psychodysphoric	min	
		+	antihyperalgesia	hours-days	
Monoamine	Inhibition of reuptake	+++	Hemodynamic/analgesia	min	[4,5]
Norepinephrine/epinephrine dopamine serotonine			Addiction potency?		
Cholinergic	Agonist	++	Motor effects, sialorrhea, laryngeal reflexes	min	
Muscarinic nicotinic		++	Analgesia/anesthesia	min	[6]
Purinergic neurotransmission	Agonist				[7]
Adenosine receptors		+	Antiproinflammatory effects	days	
μ,δ,κ opiate receptors	Agonist	++++	Analgesia	min	[8]

NMDA, *N*-methyl-D-aspartic acid.

with an analgesic effect for more than 10 min. Clearance increases with decreasing age.

This particularly favorable profile makes ketamine the object of recurrent discussions and polemics leading to the question of whether ketamine anesthesia is to be administered exclusively by certified anesthesiologists or by other healthcare providers [24]? This obviously indicates that ketamine remains a very popular anesthetic for pediatric anesthesia.

New indications for ketamine in adults: what about the pediatric population?

In contrast with pediatric anesthesia, the use of ketamine in adult patients was, until recently, restricted to prehospital procedures. This situation has changed because of the demonstration of two properties pertinent to the improvement of a patient's outcome: ketamine is active against perioperative hyperalgesia (antihyperalgesia) and it interacts with the inflammatory response to surgery (anti proinflammatory properties).

We will now question the reality of these beneficial effects in the pediatric population.

Antihyperalgesia

Postoperative pain is no more considered as a simple, uncomfortable symptom that spontaneously disappears with surgical wound healing. Adequate treatment of this symptom is mandatory for the following reasons. First, patients with postoperative pain are more prone to present with early cardiovascular or pulmonary complications. Second, they are at a higher risk of developing chronic (residual) postoperative pain. It is recognized that acute postoperative pain leads to chronic (residual) pain in 8 – 11% of patients scheduled for surgery [25]. Inadequate postoperative pain treatment is recognized as a favoring factor for acute pain becoming chronic. At present, important efforts are being made to improve postoperative pain management (patient-controlled analgesia, loco regional techniques, multimodal analgesia, etc.), but, paradoxically, large patient surveys still report unsatisfactory results [26]. One of the explanations underlying this could be that conventional treatments are not active against all the components of this phenomenon. Acute postoperative pain is characterized by two types of symptoms: acute spontaneous pain (primary hyperalgesia) and provoked pain (pain at movement) or secondary hyperalgesia. The two types of symptoms respond to different pathophysiology and consequently deserve different therapeutic approaches. For example, primary hyperalgesia is far more sensitive to opiates than secondary hyperalgesia [27,28]. What is secondary hyperalgesia? It is characterized by the extension of pain sensation at a distance from the surgical wound (non-noxious stimuli become painful in this area). Secondary hyperalgesia is the sign of central nervous system plasticity facilitating pain perception. It normally disappears with wound healing. In several surgical patients, however, secondary hyperalgesia persists despite wound healing and becomes the so-called postoperative residual pain syndrome. Central excitatory neurotransmission (excitatory amino acid glutamate) is involved in this particular nociceptive transmission [29–32]. Moreover, in the perioperative period, there is a drug-induced hyperalgesia. Opiates induce short-lasting analgesia and long-lasting hyperalgesia. This opiate-induced hyperalgesia is also under the influence of excitatory neurotransmission [33,34]. Ketamine is an antagonist of excitatory neurotransmission (*N*-methyl-D-aspartic acid receptor). Numerous experimental and clinical studies conducted in adult patients demonstrate its efficacy to alleviate both tissue destruction and opiate-induced hyperalgesia [35–37]. Ketamine reduces the incidence of postoperative residual pain [36]. For this reason, this old anesthetic is now considered to be an important element of the balanced analgesic techniques in adult patients.

What about secondary hyperalgesia, residual pain and ketamine in pediatric patients? In contrast with adult patients, very few data can be found in the literature. As discussed by Peters *et al.* [38], neonatal surgery probably leads to increased pain sensitivity in later childhood and residual pain. There are, however, no large epidemiologic studies in this population. Ketamine produces some kind of analgesia in children [39,40•]. There is, however, no study designed to evaluate the development of secondary hyperalgesia and the efficacy of ketamine in this population [41]. In particular no study considers the postoperative evolution of the area of hyperalgesia and its reduction after low-dose ketamine administration. Only two case reports give indirect signs (early rehabilitation–prevention of acute opiate tolerance) of ketamine antihyperalgesia, one in an adolescent after spinal instrumentation for the correction of scoliosis and the other in a severely burnt (42%) 9-year-old boy [42•,43•].

As reported in adults, ketamine is active in specific pain syndromes such as neuropathic pain following tumor invasion and fulminating ulcerative colitis [44•,45].

Anti-proinflammatory effect

Ketamine interacts with the inflammatory reaction in a specific way. After trauma or surgery, numerous reactions involving, among others, innate or specific immunity take place. This constitutes the inflammatory reaction. It is intended to restore homeostasis and promote wound healing. These reactions are particularly potent. A defect in their endogenous regulation leads to death by excessive inflammation or, as recently suspected, to long-term inflammatory illnesses such as rheumatoid arthritis or Crohn's disease (excessive proinflammatory reaction).

On the other hand, excessive repression leads to death or superinfection by immune paralysis (excessive anti-inflammatory reaction). An adequate inflammatory reaction results from the equilibrium between proinflammatory and anti-inflammatory influences. Ketamine, administrated in a stress situation favors this equilibrium. This is based on clinical data published several years ago. The survival rate in intensive care unit of patients with septic shock was improved when they received ketamine as a sedative. This was confirmed by several experimental data [46]. The mechanism underlying this effect may be summarized as follows: ketamine specifically reduces the production of proinflammatory cytokines (the 'hormones' of the inflammatory reaction) by interacting with their nuclear transcription precursor the NFκβ. This is achieved by either a specific action of ketamine on the prurinergic receptors (adenosine 2A) and/or a reinforcement of the anti-inflammatory cholinergic reflex [7–14,47].

Nevertheless, at present, the studies conducted in a pediatric population failed to report any beneficial effect of ketamine on the postoperative inflammatory reaction [48–50].

Is ketamine a dangerous drug for pediatric anesthesia?

This question is directly related to the proapoptotic properties of ketamine. Apoptosis or programmed cellular suicide is a natural property of all tissues. This phenomenon is a key player in eliminating elderly cells or unnecessary cells during organogenesis. Recently, pathological apoptosis has been described in infants born to mothers with chronic ethanol exposure (alcohol-related neurodevelopmental disorder) [51]. This toxin interferes with the organogenesis of the central nervous system by promoting excessive cellular suicide in the neuronal tissues. The consequences of this pathological apoptosis become manifest during the first years of life (craniofacial dysmorphogenesis, reduced brain mass, neurobehavioral disturbances, mental retardation).

Using rodent animal models, it was demonstrated that ketamine, along with ethanol, benzodiazepines and volatile anesthetics, determines important neuronal apoptosis during central nervous system organogenesis. It is associated with learning deficiencies. It is important to note that the dose used is the same as that currently used for anesthesia [52].

In humans, chronic (years) recreational use (uncontrolled and significant intake) is associated with severe clinical–behavioral disturbances [53].

This apoptotic effect of ketamine (and the other anesthetics) deserves attention in the field of pediatric anesthesia. In humans, the organogenesis of the central nervous system extends from the sixth month *in utero* untill several years after birth. Consequently, the question is: are the anesthetic drugs safe during childhood? There is no definitive answer at present. It is, however, interesting to point out that no long-term learning or behavioral disturbance was ever noted in children after ketamine or other anesthetic was administered for anesthesia and surgery.

Moreover, when considering the experimental model, the consequences of anesthetic-induced neuronal apoptosis seems species specific. In rodents, pathological apoptosis affects critical regions for learning. This is not the case in mammals in which cortical redundant cells are most exclusively affected [54•]. Nevertheless, studies on primates are undertaken to determine the exact influence of the anesthetics on central nervous system development.

Paradoxically, when going back to the rodent model, ketamine, despite its apoptotic potency, protects against ischemia-induced neuronal destruction [55].

Conclusion

Ketamine remains a particularly useful drug for pediatric anesthesia. Nevertheless, the two properties that initiated the new interest in this old anesthetic in adults (antihyperalgesia and antiproinflammatory) wait to be confirmed in the pediatric population. Finally, the exact consequences of the proapoptotic properties of ketamine on human brain tissue development have to be exactly determined in order to assess the safety of this drug in the pediatric population.

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- •• of outstanding interest

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