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Mini review

Developmental neurotoxicity of ketamine in pediatric clinical use

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HIGHLIGHTS

- History and pharmacology of ketamine.
- Ketamine induces neuronal cell death in developing brains.
- Ketamine alters the neurogenesis of early developing brains.
- Current studies on the developmental neurotoxicity of ketamine in pediatric clinical use.

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ABSTRACT

Ketamine is widely used as an anesthetic, analgesic, and sedative in pediatric clinical practice and it is also listed as an illicit drug by most countries. Recent *in vivo* and *in vitro* animal studies have confirmed that ketamine can induce neuronal cell death in the immature brain, resulting from widespread neuronal apoptosis. These effects can disturb normal development further altering the structure and functions of the brain. Our recent studies further indicate that ketamine can alter neurogenesis from neural stem progenitor cells in the developing brain. Taken together, these findings identify a novel complication associated with ketamine use in premature infants, term newborns, and pregnant women. Recent data on the developmental neurotoxicity of ketamine are reviewed with proposed future directions for evaluating the safety of ketamine in these patient populations.

Contents

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1. Ketamine

Ketamine was synthesized as a substitute for phencyclidine (PCP) in 1962, and found to produce excellent anesthesia with rapid onset (Domino, 2010). In 1964, this newly-synthesized drug was introduced into clinical human studies and produced remarkable anesthesia with minimal side effects. Soon thereafter, physicians extended the application of ketamine to many clinical practices: ophthalmic surgery (Harris et al., 1968) pediatric surgery (Del Prete et al., 1968), neurosurgical procedures (Corssen et al., 1969), pediatric cardiac catheterization and other procedures (Ginsberg and Gerber, 1969; Szappanyos et al., 1969; Wilson et al., 1969). A wider usage of ketamine in humans occurred during the Vietnam War with documented safety in resource-poor settings (Mercer, 2009). Ketamine has been widely accepted in clinical settings because of its profound analgesic, sedative, dissociative and amnestic effects, while maintaining protective airway reflexes, spontaneous respirations, and cardiopulmonary stability.

With the increasing popularity of ketamine use in clinics, the psychotropic effects of ketamine attracted more and more people to consume it as a recreational drug, or use it as a date rape drug (Graeme, 2000; Jansen, 2000). Considering the increased abuse of ketamine and criminal offences relating to ketamine, the DEA (Drug Enforcement Administration) listed ketamine as a Schedule III non-narcotic substance under the Controlled Substances Act in 1999. Coincidentally, in the same year, ketamine was found to induce neurodegeneration in the developing brain (Ikonomidou et al., 1999), which led to heated discussions on the neurotoxicity of ketamine use in children. Further studies have indicated that high doses or repeated ketamine doses can induce cell death, especially apoptosis, in many kinds of *in vivo* and *in vitro* models from mice, rats, and monkeys (Amr, 2010; Fredriksson et al., 2004; Scallet et al., 2004; Takadera et al., 2006; Wang et al., 2005, 2006; Zou et al., 2009a, 2009b). Also, ketamine was found to disturb normal neurogenesis of neural stem progenitor cells (NSPCs) in the developing brain (Dong et al., 2012). These findings forced scientists and physicians to reconsider the safety and toxic effects of ketamine in pediatric settings. Developmental neurotoxicity is being explored and clarified as a new complication of ketamine following its clinical use in Pediatrics.

2. Pharmacology

Major pharmacological effects of ketamine are related to the antagonism of NMDA receptors, a tetrameric protein complex that forms a ligand-gated calcium ion channel (Duchen et al., 1985; Harrison and Simmonds, 1985; Honey et al., 1985; Martin and Lodge, 1985; Snell and Johnson, 1985; Thomson and Lodge, 1985; Thomson et al., 1985). Ketamine non-competitively binds to the phencyclidine site inside the NMDA receptor and blocks the influx of calcium (Bolger et al., 1986; Ffrench-Mullen and Rogawski, 1992; O'Shaughnessy and Lodge, 1988). Ketamine-produced blockade of NMDA receptors depends on the opening state of the calcium ion channel in the NMDA receptor. Varying composition of NMDA receptor subunits determines temporal and regional specificity and unique functional properties (Monyer et al., 1992; Paoletti and Neyton, 2007).

Ketamine also acts on other receptors. S(+)-ketamine can reduce opioid consumption after surgery (Lahtinen et al., 2004), and reverse opioid tolerance in pain management (Mercadante et al., 2003) indicating that it may interact with opioid receptors to some extent. Recent publications also indicate ketamine may stimulate dopaminergic receptors (D2) *in vitro* (Seeman and Guan, 2008; Seeman et al., 2005) with even higher affinities than the NMDA receptors (Kapur and Seeman, 2002; Seeman and Guan, 2009; Seeman et al., 2009; Seeman and Lasaga, 2005). Effects of ketamine on dopaminergic receptors may support the theory of glutamatergic contributions to schizophrenia (Gilmour et al., 2012). Ketamine and PCP can directly act on dopaminergic receptors or block NMDA receptors to increase the release of dopamine; and dopamine dysfunction in brains may trigger the underlying mechanisms of schizophrenia (Javitt, 2010). Ketamine hydrochloride is water soluble and lipid permeable. It is readily absorbed *via* intravenous, intramuscular, subcutaneous, epidural, oral, rectal, and transnasal routes of administration, as well as intraperitoneal injection in laboratory animals (Aroni et al., 2009; Flecknell, 1998). Brain uptake and redistribution occur rapidly due to its low binding to plasma proteins. Thus, uptake and distribution of ketamine to children's brains occurs rapidly in pediatric settings or to fetal brains *via* the placental barrier in obstetric settings. Ketamine is metabolized by N-demethylation and oxidation in the hepatic cytochrome P450 system (by CYP2B6 and CYP3A4), and its primary metabolite, norketamine, is one third to one fifth as potent as the original compound (White et al., 1982).

3. Clinical use and complications

Ketamine is widely used for four major clinical indications: anesthesia, analgesia, sedation, and antidepressant effects (Domino, 2010). Ketamine-induced anesthesia is described as a dissociative anesthesia, characterized by profound analgesia and amnesia with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability (Green et al., 2011). Under ketamine anesthesia, blood pressure is well maintained even in the presence of hypovolemia. Spontaneous breathing occurs and laryngeal reflexes are preserved. This makes ketamine the 'first choice' anesthetic for pre-hospital anesthesia/analgesia. Also, ketamine can be used for premedication, sedation, induction and maintenance of general anesthesia. In pediatric practices combinations of ketamine with other anesthetics like propofol or midazolam, are utilized in pediatric plastic surgery (Zook et al., 1971), oral surgery (Birkhan et al., 1971), neurosurgery (Chadduck and Manheim, 1973), cardiac anesthesia (Koruk et al., 2010; Radnay et al., 1976), ophthalmic surgery (Raju, 1980), gastrointestinal procedures (Shemesh et al., 1982), and for diagnostic and interventional cardiac procedures (Singh et al., 2000).

Subanesthetic doses of ketamine can produce analgesic effects as an 'anti-hyperalgesic', 'anti-allodynic' or 'tolerance-protective' agent (Visser and Schug, 2006). Ketamine is also suitable for acute and chronic pain management (Amr, 2010; Blonk et al., 2010; Noppers et al., 2010; Visser and Schug, 2006). Ketamine can induce excellent analgesic effects in patients with chronic cancer pain and chronic neuropathic pain (Bell, 2009; Ben-Ari et al., 2007; Elsewaisy et al., 2010; Holtman et al., 2008; Kalina et al., 2008). Studies on chronic phencyclidine and later ketamine abusers, found that ketamine had antidepressant effects in depressed patients (Berman et al., 2000; Hashimoto, 2010; Kudoh et al., 2002; Valentine et al., 2011). The study of the basic mechanisms of ketamine's antidepressant effects may provide new lead targets to develop better agents to treat psychiatric patients with major depressive disorder and other forms of depression. In children, ketamine produces potent analgesia (Da Conceição et al., 2006; Dal et al., 2007). Although ketamine was under reevaluation because of its neurotoxicity in the developing brain, in pediatric clinical settings, it is being used increasingly to supplement opioids for pain after major surgery (Anderson and Palmer, 2006). In the emergency department (ED), intensive care unit (ICU), and during invasive examination procedures, when conscious sedation is necessary for pediatric patients, ketamine is a popular choice. A large number of clinical studies indicate that combinations of ketamine and midazolam (McGlone,