REVIEW PAPER

Ketamine

D. Staroverov

University Teaching Hospital, Lusaka, Zambia
Department of Anaesthesia, P.O Box 500011
E-mail: dmitriystaroverov@yahoo.com.au

INTRODUCTION

Ketamine is still wide-used anesthetic, especially in resource-poor countries. For instance, in Zambia the ketamine anesthesia seems to be used in every second anesthetic management,[1] especially in district hospitals. This anesthetic has very complicated "course of life": from general recognition till burning indignation. Despite of its ketamine takes sturdy stand for performing anesthesia in extremely critical conditions (e.g., hypovolaemic shock).

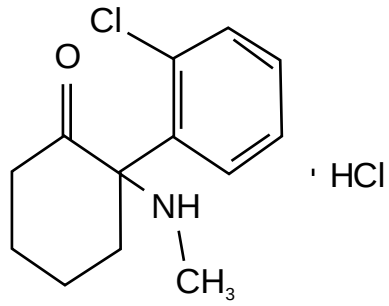
Ketamine – intravenous dissociative anesthetic agent developed by American pharmaceutist Stevens C. in Parke-Davis Lab (1962). In 1965 professor Domino EF described ketamine as a potential psychedelic.[2] *Dissociate anaesthesia* is a trance-like cataleptic state characterized by profound analgesia, sedation, amnesia and immobilization, with retention of protective airway reflexes, spontaneous respirations and cardiopulmonary stability.[3]

PHARMACOLOGY

Ketamine – phencyclidine derivate and is classified as an N-methyl-D-aspartate (NMDA)-receptor antagonist. Ketamine contains a chiral center producing two optical isomers. The S (+)-enantiomer (Ketanest S) would appear to offer some clinical advantages over the racemic mixture – R (-) because it's a more effective anesthetic and analgesic drug with a more rapid recovery and less psychotomimetic side-effects.[4,5,6] However more common commercially available preparation is a racemic mixture.

Systemic name - 2-(2-chlorophenyl)-2-methyamino-cyclohexan-1
Chemical formula – $C_{13}H_{16}ClNO$-HCl
Molecular weight – 274.19
pH (ketamine hydrochloride) is 3.5-5.5 (moderately acidic)
pKa – 7.5

Figure 1: Chemical structure of ketamine



Water solutions of ketamine are stable at a room temperature and available in 1%, 5% and 10% aqueous solutions.

Pharmacokinetics

- negligible protein binding – 12-35 %[7]
- distribution half-life – 11-16 min[8]
- elimination half-life – 2-3 hrs[9]
- distribution volume at steady state – 2.5-3.5 l/kg[9]
- clearance – 12-17 ml/kg/min[9]
- high lipid solubility (quick penetration into the brain and crosses blood-brain barrier easily)

Key words: *Ketamine*

- extensively metabolized by hepatic microsomal cytochrome P-450 enzymes (N-demethylation). Its metabolite, water-soluble, norketamine, has 1/3-1/5 potency and doesn't penetrate into central nervous system (CNS).
- Only 2-3% as unchanged drug is excreted in the urine, approximately 90% is excreted the same way as metabolites. The rest of the drug by feces.

Pharmacodynamics

Ketamine causes dissociation between the thalamocortical pathways and limbic systems (hippocampus).[10,11] Ketamine blocks the open ion channel of the NMDA-receptors and inhibits glutamate activation, thereby reducing the excitatory effects of glutamate on neurons in the CNS.[12] Anesthetic depresses the transmission of nerve impulses in the medial medullary reticular formation, blocking nociception from the spinal cord to brain pathways.[13] As well antagonizes muscarine and nicotinic acetylcholine receptors of the brain.[14] Perhaps it action at the nicotinic receptor is responsible for behavioral adverse effects.[15]

INFLUENCE ON

Central nervous system

During monoanesthesia by ketamine the cortical EEG are characterized by the appearance of β-activity (4-7 Hz). That picture of generalized and hypersynchronized β-rhythm is characterized for the excitation of limbic brain structures (hippocampus). It is known as limbic seizure.[16] If firstly administer benzodiazepines (e.g., diazepam, 0.1-0.2 mg/kg) then ketamine occur diazepam's tranquilization with the development of fast EEG-rhythm (15-25 Hz). Furthermore haemodynamics and respiration remain stable.

Ketamine can activate epileptogenic foci in patients with known seizure disorders.[17]

Ketamine is generally causes the increase in cerebral blood flow (CBF), intracranial pressure (ICP) and cerebral oxygen consumption ($CMRO_2$). In animal study, the ketamine-induced increase in ICP was prevented by hyperventilation and diazepam pre-treatment.[18,19]

Some animal studies have shown that ketamine may produce a marked neuroprotective effect mediated by antagonism of NMDA channels, therefore preventing calcium influx during states of neurocellular ishaemia.[20,21,22] However, the results of some animal experiments are contradictory.[23]

Cardiovascular system

Ketamine stimulates the cardiovascular system due to direct stimulation of the sympathetic nervous system (central baroreflex inhibition).[24] Ketamine causes the sympathoneuronal release of noradrenaline[25] and inhibits extraneuronal noradrenaline uptake.[26] That's all explains the increase in arterial pressure (up to 15-20%), heart rate (up to 20%), pulmonary artery pressure (40-47%) and cardiac output (up to 20%) usually seen on induction of anesthesia with ketamine.[27] These hemodynamic changes are not dose-related. Ketamine has intrinsic myocardial depressant effects which may become apparent only in the seriously ill patients with depleted catecholamine reserves.[28]

Ketamine may compromise the balance between myocardial oxygen supply and demand in patients with coronary ischemic disease.[29] In children with poor right ventricular reserve this drug seems to be safe.[30]

Respiratory system

Ketamine has minimal effect on respiratory system. It is often recommended for induction of anesthesia in patients with asthma because of its ability to produce bronchodilation (effect on the central sympathetic system, direct relaxant affect on airway smooth muscles).[31] Concise apnoe is rarely seen which is associated with rapid or large dose of intravenous administration. Bronchorrhoea may also occur which can produce the laryngospasm in children (an antisialagogue usage is recommended).

Gastrointestinal system

Hypersalivation. Don't affect liver function tests. Incidence of postoperative nausea and vomiting are minimal.

Visual system

Ketamine increases intraocular pressure (IOP) for a short time. In one study, Nagdeve NG et al, showed low-dose ketamine anesthesia (3 mg/kg IM) not altered the IOP compared induction dose (6 mg/kg IM) for pediatric surgery.[32] Nystagmus and eye movements may occur during surgical procedures.

Muscular system
Slightly enhanced skeletal muscle tone and movements are often occur.

Immune system
Ketamine results in a significant reduction in leucocyte's activation during sepsis, while it also suppresses pro-inflammatory cytokine production *in vitro.*

Pregnancy
Ketamine crosses the placenta and concentration in the fetus is proportional to those in the mother. Pregnancy category – B.

Psychoneurological effects
- Experimental antidepressant use: using subanesthetic doses of ketamine – 0.5 mg/kg during 40-60 minutes helps in a treatment-resistant depression.[33,34,35,36] NMDA is receptor for the neurotransmitter glutamate. The glutamate system has been implicated in depression recently, not only serotonin and norepinephrine.
- Treatment of addiction: some studies were dedicated to the treatment for alcohol and heroin addiction.[37,38]
- Pharmacological model of schizophrenia: ketamine and other NMDA-antagonists (PCP, MK-80) are considered to be the best available pharmacological models of schizophrenia to date. Ketamine produce the negative symptoms (alogia, social withdrawal), positive symptoms (delusions, hallucinations) and cognitive deficits of schizophrenia.
- "Club drug": is also known as "special K" (www.clubdrugs.gov). It can be injected, snorted or smoked. In small doses ketamine can cause dream-like states and hallucinations (delusions). In high doses ketamine can cause amnesia, delirium, impaired motor function, high blood pressure and respiratory depression. In 2003, 0.8 percent of young New Zealanders had tried ketamine, with 0.2% having used within the previous year.[39]

INDICATIONS
1. Sedation:
- in some minor surgical procedures: debridement, dressing changes, extraction, removal of tampon, EUA and so on.
- in the emergency department (ED)[15]
2. Anesthesia:
- as induction agent in hypovolaemic and shocked patients (ASA IV class)
- in some specific pathology (see below)
- in the developing countries as a single general intravenous agent
3. Analgesia
- to relief an acute postoperative pain – inhibits nociceptive central hypersensitization[40] and NMDA-receptor-mediated ion currents[41]
- pre-emptive analgesia (subanaesthetic doses)[42,43]
- chronic cancer pain[44]

The usage in some specific conditions

Cardiovascular surgery
Bartoc C. et al. have shown a significant anti-inflammatory effect of low-dose ketamine (0.5 mg/kg during induction of anesthesia) in cardiac surgical patients. It mitigated increases in IL-6 (pro-inflammatory cytokine) and C-reactive protein, as well as increased in IL-10 (anti-inflammatory cytokine). Therefore these changes protect patients to some degree from vasodilatation in postoperative period.[45] It's has been confirmed by other studies.[46,47] Another study has been shown that ketamine is preferable induction drug for pericardiectomy.[48]

Patients with endotoxemia (septic shock)
Ketamine shows benefit effects (inhibited hypotension, metabolic acidosis and cytokines responses) in animal model with injected endotoxins.[49,50]

Patients with asthma
Ketamine is a drug of choice as an induction agent at asthmatic patients.[51,52] This anesthetic relaxes the bronchiolar musculature (due to its sympathomimetic properties) and prevents the bronchoconstriction induced by histamine[53], decreasing the risk of bronchospasm.[54] However, its effectiveness in asthma failed to demonstrate any benefits compared with standard therapy in the ED.[55]

Adjunct to regional anesthesia
There are some studies and case reports that ketamine can be used as an adjunct to neuroaxial

blocks by intrathecal or epidural route. An intrathecal dose of 1 mg ketamine combined with intrathecal morphine obtained effective pain relief in cancer patients. [56] Encouraging finding have been shown S (+)-ketamine strengthened the duration of analgesia. [57,58] But the Food and Drug Administration (FDA) has not approved ketamine for regional anesthesia. The probable cause - ketamine's preservative, chlorobutanol, has been demonstrated neurotoxic effect during subarachnoid anesthesia.[59]

DOSAGE

- *per os* route of administration*:* 3-10 mg/kg. Onset of action in 10-12 min. Average duration of action up to 25-40 min. [60, 61]
- *intramuscular* route of administration: 4-5 mg/kg for adult, 6-8 mg/kg for children. Onset of action in 3-5 min. Average duration of action up to 30 min. Mean recovery time about 90-150 min.
- *intravenous* route of administration*:* 1-2 mg/kg slowly over 1 min (to prevent transient respiratory apnoea and enhanced pressor response). Onset of action in 30-45 sec. Duration is about 7-15 min. Repeating doses of 0.25-0.5 mg/kg can be given every 10 min as required or 30-90 µg/kg/min. Mean recovery time is approximately 60-90 min.
- *pre-emptive analgesia:* 0.15-0.25 mg/kg IV

Adjunctive medications

It still controversial because of controlled clinical studies has not been performed.

Anticholinergic drugs (e.g., atropine) are often administered with ketamine to prevent the hypersalivation (antisialagogue effect) that occurs in some patients. Dose of atropine is 0.02 mg/kg with only needs to be given with the initial dose of ketamine. Benzodiazepines (diazepam, lorazepam, midazolam) are widely used along with ketamine in order to reduce the incidence of the emergence phenomenon, but it increases respiratory depression and prolongs recovery; dose of diazepam: 0.015 mg/kg.

SIDE EFFECTS

- nausea and vomiting
- hypersalivation
- laryngospasm
- increased blood pressure and intracranial pressure
- tachycardia
- nystagmus
- respiratory apnoea
- *emergence phenomenon* (disorientation, sensory and perceptual illusions, vivid dreams, euphoria, excitement and fear). This phenomenon occurs at up to 30% patients. The presumed cause is that R (-)-enantiomer has high affinity for sigma opioids receptor.[62] Risk factors: age over 10 years, female sex, rapid IV administration, prior personality disorders, excessive noise or stimulation during recovery.[63, 64]

CONTRAINDICATIONS

- hypersensitivity
- severe cardiovascular disease: unstable angina pectoris, decompensated heart failure, malignant arterial hypertension
- previous psychotic abnormality
- intra-ocular pathology: glaucoma, acute globe injury
- high predisposition to laryngospasm or apnoea: active pulmonary or upper airway infection; age less 3 months, procedures involving stimulation of posterior pharynx
- cerebral spinal fluid obstructive states: severe head injury, space-occupying lesions in CNS, hydrocephalus
- full meal within 3-4 hours (increased risk of aspiration)

INTERACTIONS

Inhalation anaesthetics: blocks the indirect cardiac stimulating of ketamine

Halothane: decreased hepatic clearance of ketamine, resulting to prolonged recovery

Benzodiazepines: increases sedative effects

Propofol: "ketofol", strengthening of sedative and analgesic properties[65]

Opioids: decreased opioids requirements

Non-depolarizing muscle relaxants: potentiation of neuromuscular blockade.

REFERENCES

1. Jochberger, S., Ismailova, F., Lederer, W. et al. Anesthesia and its allied disciplines in the developing world: a nationwide survey of the Republic of Zambia. *Anesth Analg* 2008;106 (3): 942-948.

2. Domino, E.F., Corssen, G. Dissociative anesthesia: further pharmacological studies and first clinical experience with the phencyclidine derivative CI-581. *Anesth Analg* 1966;45:29-40.
3. Kraus, B., Green, S.M. Sedation and analgesia for procedures in children. *N Engl J Med* 2000; 342: 938-945.
4. Kruger, A.D. Current aspects of using ketamine in childhood. *Anaesthesiologie und Reanimation* 1998; 23 (3): 64-71.
5. White, P.F., Ham, J., Way, W.L. et al. Pharmacology of ketamine isomers in surgical patients. *Anesthesiology* 1980; 52: 231.
6. White, M., de Graaff, P., Renshof, B., ven Kan, E., Drolijic, M. Pharmacokinetics of S (+) ketamine derived from target-controlled infusion. *Brit J Anaesth* 2006; 96 (3): 330-334.
7. Harrison, N.L., Sear, I.W. Chapter 24: Intravenous anesthetics. In: Evers AS, Maze M (eds). *Anesthetic pharmacology: physiologic principles and clinical practice*. Elsevier. Inc, 2004: 407.
8. Reves, J.G., Glass, P.S.A, Lubarsky, D.A., McEvoy, M.D. Chapter 10: Intravenous nonopioid anesthetics. In: Robert D. Miller. *Miller's Anesthesia* (6th edition): Churchill Livingstone, 2005: 346.
9. Clements JA, Nimmo WS. Pharmacokinetics and analgesic effect of ketamine in man. *Br J Anaesth* 1981; 53: 27-30.
10. Miyasaka, M., Domino, E. Neural mechanisms of ketamine-induced anesthesia. *Int J Neuropharmacol* 1968; 7: 557-573.
11. Idvall, J. Ketamine – a review of clinical applications. *Anesth Pharm Rev* 1995; 3: 82-89.
12. Orser, B.A., Pennefather PS, MacDonald JF. Multiple mechanisms of ketamine blockade on N-methyl-D-aspartate receptors. *Anesthesiology* 1997; 86: 903-917.
13. Ohtani, M., kikuchi, H., Kitahata, L.M. et al. Effects of ketamine on nociceptive cells in the medial medullary reticular formation of the cat. *Anesthesiology* 1979; 51: 414-417.
14. Vincent, J.P., Cavey, D., Kamenka, J.M. et al. Interaction of phenylcyclidines with the muscarinic and opiate receptors in the CNS. *Brain Res* 1978; 152: 176.
15. Cromhout, A. Ketamine: its use in the emergency department. *Emerg Med* 2003; 15 (2): 155-156.
16. Schwartz, M.S., Virden, S and Scott, D.F. Effects of ketamine on the electroencephalogram. *Anaesthesia* 1974; 29: 135.
17. Bennett, D.R., Madsen, J.A., Jordan, W.S. et al. Ketamine anesthesia in brain-damaged epileptics: electroencephalographic and clinical observations. *Neurology* 1973; 23: 449.
18. Artru, A., Katz, R.A. Cerebral blood volume and CSF pressure following administration of ketamine in dogs: modification by pre- and post-treatment with hypocapnia or diazepam. *J Neurosurg Anesth* 1989; 1: 8.
19. Thorsen, T., Gran, L. Ketamine/diazepam infusion anesthesia with special attention to the effect on cerebrospinal fluid pressure and arterial blood pressure. *Acta Anaesthesiol Scand* 1980; 24: 1-4.
20. Pfenninger, E. Neuroprotection by ketamine at the cellular level. *Anaesthetist* 1997; 46: S47-54.
21. Marco, F.W., Goodrich, J.E. and Dominick, M.A. Ketamine prevents ischemic neuronal injury. *Brain Res* 1988; 452: 329.
22. Reeker, W., Werner, C., Mollenberg, O. et al. High-dose S (+)-ketamine improves neurological outcome following incomplete cerebral ischemia in rats. *Can J Anaesth* 2000; 47: 572-578.
23. Albin, M.S. et al. Ketamine hydrochloride fails to protect against acute global hypoxia. *Anesth. Rev* 1988; 15: 80.
24. Slogoff, S., Allen, G.W. The role of baroreceptors in the cardiovascular response to ketamine. *Anesth Analg* 1974; 53: 704-707.
25. Zsigmond, E., Kothary, S., Matsuki, A. Diazepam for prevention of the rise in plasma catecholamines caused by ketamine. *Clin Pharmacol Ther* 1974; 15: 223.
26. Salt, P.J., Barnes, P.K., Beswick, F.J. Inhibition of neuronal and extraneuronal uptake of noradrenaline by ketamine in the isolated perfused rat heart. *Br J Anaesth* 1979; 51: 835-838.
27. Johnstone, M. The cardiovascular effects of ketamine in man. *Anaesthesia* 1976; 31: 873.
28. Lippmann, M., Appel, P.L., Mok, M.S. et al. Sequential cardiorespiratory patterns of anesthetic induction with ketamine in critically ill patients. *J Crit Care Med* 1983; 11: 731-734.
29. Folts, J.D., Afonso S, Rowe GG et al. Systemic and coronary hemodynamic effects of ketamine in intact anaesthetized and unanaesthetized dogs. *Br J Anaesth* 1975; 47: 686.

30. Hickey, P.R., Hansen, D.D., Cramolini, G.M. et al. Pulmonary and systemic hemodynamic responses to ketamine in infants with normal and elevated pulmonary vascular resistance. *Anesthesiology* 1985; 62: 287-293.
31. Sato, T. Ketamine relaxes airway smooth muscle contracted by endothelin. *Anesth Analg* 1997; 84: 900-906.
32. Nagdeve, N.G., Yaddanapudi, S., Pandav, S.S. The effect of different doses of ketamine on intraocular pressure in anesthetized children. *J Pediatr Ophthalmol Strabismus* 2006; 43 (4): 219-223.
33. Correll, G.E., Futter, G.E. Two cases studies of patients with major depressive disorder given low-dose (subanesthetic) ketamine infusions. *Pain Med* 2006; 7 (1): 92-95.
34. Khamsi, R. Ketamine relieves depression within hours. *New Scientist* August 08, 2006.
35. Liebrenz, M., Borgeat, A. et al. Intravenous ketamine therapy in patients with a treatment-resistant major depression. *Swiss Med. Wkly* 2007; Apr. 21; 137 (15-16): 234-236.
36. Kudoh, A., Takahira, Y. et al. Small-dose ketamine improves the postoperative state of depressed patients. *Anesth Analg* 2002; 95 (1): 114-118.
37. Krupitsky, E.M., Grinenko, A.Y. Ketamine psychedelic therapy (KPT): a review of the results of ten years of research. *J Psychoactive Drugs* 1997; 29 (2): 165-183.
38. Krupitsky, E.M., Burakov, A.M., Dunaevsky IV et al. Single versus repeated sessions of ketamine-assisted psychotherapy for people with heroin dependence. *J Psychoactive Drugs* 2007; 39 (1): 13-19.
39. http://www.nzdf.org.nz/ketamine
40. Chapman, V., Dickenson, A.H. The combination of NMDA antagonism and morphine produces profound antinociception in the rat dorsal horn. *Brain Res* 1992; 573: 321-323.
41. Kafali, H., Aldemir, B., Kaygusuz, K. et al. Small-dose ketamine decreases postoperative morphine requirements. *Eur J Anaesthesiol* 2004; 21 (11): 916-917.
42. Schmid, R.L., Sandler, A.N., Katz, J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. *Pain* 1999; 82: 111-125.
43. Dahl, J.B., Moiniche, S. Pre-emptive analgesia. *Brit Med Bulletin* 2004; 71: 13-27.
44. Campbell-Fleming JM, Williams A. The use of ketamine as adjuvant therapy to control severe pain. *Clin J Oncol Nurs* 2008; 12 (1): 102-107.
45. Bartoc, C., Frumento, R.J., Jalbout, M. et al. A randomized, double-blind, placebo-controlled study assessing the anti-inflammatory effects of ketamine in cardiac surgical patients. *J Cardiothorac Vasc Anesth* 2006; 20 (2): 217-222.
46. Roytblat, L., Roy-Shapira A, Greemberg SL et al: Preoperative low-dose ketamine reduces serum IL-6 response after abdominal hysterectomy. *Pain Clin* 1996; 9: 327-334.
47. Roytblat, L., Talmor, D., Rachinsky, M. et al: Ketamine attenuates the interleukin-6 response after cardiopulmonary bypass. *Anesth Analg* 1998; 87: 266-271.
48. Kingston, H.G., Bretherton KW, Holloway AM et al. A comparison between ketamine and diazepam as induction agents for pericardiectomy. *Anaesth Intensive Care* 1978; 6: 66-70.
49. Van der Linden, P., Gilbart, E., Engelman, E. et al. Comparison of halothane, isoflurane, alfentanil and ketamine in experimental septic shock. *Anesth Analg* 1990; 70: 608-617.
50. Taniguchi, T., Shibata, K., Yamamoto, K. Ketamine inhibits endotoxin-induced shock in rats. *Anesthesiology* 2001; 95: 928-932.
51. Burburan, S.M., Xisto DG, Rocco PRM. Anaesthetic management in asthma. *Minerva Anesthesiol* 2007; 73: 357-365.
52. Corssen, G., Guitierrez, J., Reves, J.G. et al. Ketamine in the anesthetic management of asthmatic patients. *Anesth Analg* 1972; 51: 588-596.
53. Wanna, H.T., Gergis SD. Procaine, lidocaine, and ketamine inhibit histamine-induced contracture of guinea pig tracheal muscle in vitro. *Anesth Analg* 1978; 57: 25-27.
54. L'Hommedieu, C.S. The use of ketamine for the emergency intubation of patients with status asthmaticus. *Ann Emerg Med* 1987; 16: 568-571.
55. Howton, J.C., Rose, J., Duffy, S., Zoltanski, T., Levitt MA. Randomized, double-blind, placebo-controlled trial of intravenous ketamine in acute asthma. *Ann Emerg Med* 1996; 27:170-175.
56. Yang, C.Y., Wong, C.S., Chang, J.Y. et al. Intrathecal ketamine reduces morphine

requirements in patients with terminal cancer pain. *Can J Anaesth* 1996; 43: 379-383.
57. Unlugenc, H., Ozalevi, M., Gunes, Y. et al. A double-blind comparison of intrathecal S (+)-ketamine and fentanyl combined with bupivacaine 0.5% for Caesarean delivery. *Eur J Anaesthesiol* 2006; 7: 1-7.
58. Weber, F., Wulf, H. Caudal bupivacaine and S (+)-ketamine for postoperative analgesia in children. *Pediatr Anaesth* 2003; 13: 244-248.
59. Malinovsky, J.M., Lepage, J.Y., Cozian, A. et al. Is ketamine or its preservative responsible for neurotoxicity in the rabbit? *Anesthesiology* 1993; 78: 109-115.
60. Gutstein, H.B., Johnson, K.L., Heard MB et al. Oral ketamine preanesthetic medication in children. *Anesthesiology* 1992; 76: 28-33.
61. Tobias, J.D., Phipps S, Smith B et al. Oral ketamine premedication to alleviate the distress of invasive procedures in pediatric oncology patients. *Pediatrics* 1992; 90: 537-541.
62. Harrison, N.L., Sear, I.W. Chapter 24: Intravenous anesthetics. In: Evers AS, Maze M (eds). *Anesthetic pharmacology: physiologic principles and clinical practice*. Elsevier. Inc, 2004: 408.
63. Garfield, J.M., Garfield, F.B., Stone, J.G. et al. A comparison of psychologic responses to ketamine and thiopental-nitrous oxide-halothane anesthesia. *Anesthesiology* 1972; 36: 329-338.
64. Sussman, D.R. A comparative evaluation of ketamine anesthesia in children and adults. *Anesthesiology* 1974; 40: 459-464.
65. Willman, E.V., Andolfatto, G. A prospective evaluation of "ketofol" (ketamine/propofol combination) for procedural sedation and analgesia in the emergency department. *Ann Emerg Med* 2007; 49 (1): 23-30.