Ketamine: New Indications for an Old Drug

Maria Giuseppina Annetta*, Domenico Iemma, Cristiana Garisto, Chiara Tafani, Rodolfo Proietti

Institute of Anaesthesia and Intensive Care, Catholic University of the Sacred Heart, Rome, Italy

Abstract: Ketamine is a non-competitive antagonist to the phencyclidine site of N-methyl-d-aspartate (NMDA) receptor for glutamate, though its effects are mediated by interaction with many other receptors. It has been introduced in clinical use since 1960’s but today it is not largely employed as a general anaesthetic for its undesired psychic effects (emergence reactions) occurring in approximately 12% of patients. In the last decade, there has been a renewed interest in the use of subanaesthetic doses of ketamine for the treatment of acute and chronic pain. In the late 1990’s, multiple prospective, randomised, controlled study has shown the efficacy of low dose of ketamine for postoperative pain relief, for analgesia during regional or local anaesthesia, and for opioid-sparing effect. At present, non-definitive conclusion can be drawn. More data are needed to define the possible long term effects and the clinical goal of ketamine use.

Key Words: Ketamine, Analgesia, Opioids.

INTRODUCTION

Ketamine is a neuroleptic anaesthetic agent in clinical use since the 1960’s. Chemically designed as a dl2-(o-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride, it’s a phencyclidine derivative (known as the street drug “angel dust”), which acts primarily as a non-competitive NMDA receptor antagonist, by binding to the phencyclidine binding (PCP) site. When it was first introduced in the clinical use, it was regarded as an ideal and complete anaesthetic drug, since it provides all the required components of surgical anaesthesia: pain relief, immobility, amnesia and loss of consciousness. In fact, ketamine – unlike most other anaesthetic induction agents - produces an anaesthetic state characterised by profound analgesia, unaltered response to carbon dioxide (CO₂), normal pharyngeal-laryngeal reflexes, bronchodilation, normal or slightly enhanced skeletal muscle tone, and cardiovascular stimulation. However, like other phencyclidines, it possesses some adverse effects which occur during awakening from anaesthesia and are termed “emergence reactions”.

PHARMACOLOGY

Ketamine exists as a racemic compound containing equimolar amounts of the enantiomers. S(+) ketamine has a fourfold greater affinity for NMDA receptors than does R(-) ketamine. This difference results in a clinical anaesthetic potency of S(+) ketamine approximately two times greater than that of racemic and four times greater of than that of R(-) ketamine, whereas S(+) ketamine has a shorter duration of action [1].

Following intravenous administration, ketamine concentration has an initial slope (alpha phase) lasting about 45 minutes with a half-life of 10-15 minutes. This phase corresponds clinically to the anaesthetic effect of the drug.

The anaesthetic action is terminated by combination of redistribution from the CNS to peripheral tissues and by hepatic biotransformation by the cytochrome P-450 system. Urine excretion is minimal. Metabolites are pharmacologically active and norketamine (metabolite I), which is the better known metabolite, is 1/3 as active as ketamine in reducing halothane requirement (MAC). The later half-life of ketamine (beta-phase) is 2.5-3.0 hours. The mean total body clearance (1.4 L/min) is approximately equal to liver blood flow, which means that changes in liver blood flow affect clearance (i.e. use of halothane, which reduces hepatic blood flow, reduces ketamine clearance).

The pharmacodynamic of ketamine has been found to be dose dependent. In subanaesthetic dose it was found to exhibit analgesic properties. At concentration between 0.9-2.5 µmol/L it exerts its affinity to PCP binding site, whereas levels above 28 µmol/L would result in an interaction with µ-opioid receptors, while concentrations above 50 µmol/L will suppress sodium channels. Levels between 50-100 µmol/L will display local anaesthetic properties, whereas above 100 µmol/L ketamine will also affect the voltage operated membrane channels. Inhibition of various characteristics of pain is reported to be obtained by serum concentration below 1 µmol/L; i.e. 1/10 to 1/5 of an anaesthetic dose, which is reported to be above 4-5 µmol/L of racemic ketamine [2]. The S enantiomer - because of its higher anaesthetic power and its 10 percent faster hepatic biotransformation - enables quicker recovery than the racemic mixture.

Ketamine is a potent non-competitive antagonist to the phencyclidine site of N-methyl-d-aspartate (NMDA) receptor for the neurotransmitter glutamate, though it interacts with more than one type of pharmacological receptor to produce its effects. The analgesia appears to be at least partially mediated by opioid receptors at the brain, spinal cord and peripheral sites. Ketamine binds to mu and kappa opioid receptors rather than to delta and to sigma receptors which may mediate the dysphoria that can be induced by ketamine. Other receptors involved with the ketamine action are the non-NMDA glutamate, nicotinic and muscarinic cholinergic, glutamatergic.
monoaminergic, as well as sodium and calcium channels. The primary anaesthetic effect is probably via the NMDA mechanisms [3, 4].

NMDA receptors (NMDARs) are ionotropic receptors (ligand-gated ion channels) which control a cation channel that is highly permeable to monovalent ions and calcium. The channel activation is unique in that requires simultaneous binding of glutamate with glycine as an obligatory coagonist. At resting membrane potential the NMDAR channels are blocked by extracellular magnesium and open only on simultaneous depolarization and agonist binding [5]. When stimulated, the cell is depolarised, the magnesium block is relieved and calcium enters into the cell setting off a cascade of events. This seems to be the predominant site of action ketamine in producing anaesthesia [3]. The evidence suggests a use-dependent blockade; the anaesthetic molecule enters the open channel, binds and then is trapped as the channel closes. Studies have shown that ketamine inhibits NMDA receptor-mediated neurotransmitter release (i.e. regional effects involving acetylcholine, dopamine, GABA, norepinephrine), as well as sodium influx and intracellular calcium levels [3].

NMDA receptors mediate neuronal signalling and regulate neuronal gene expression. Excessive stimulation of these receptors can induce neurodegeneration in the central nervous system and death. There is considerable evidence that pain associated with peripheral tissue or nerve injury involves NMDAR activation [5]. Consistent with this, NMDAR antagonists have been shown to effectively alleviate pain-related behaviour in animal models as well as in clinical situations [6]. However, NMDARs are important for a normal CNS function, and the use of NMDARs antagonists can often be limited by serious side effects, such as memory impairment, psychotomimetic effects, ataxia and motor incoordination.

The importance of these receptors in anaesthesia is related to their involvement in pain processing, neuronal plasticity, induction and maintenance of central sensitization ("wind-up" phenomenon) after noxious stimuli. However, NMDA receptors mediate also peripheral sensitisation and visceral pain [5, 7]. These events appear to be relevant not only in chronic pain but also to determine, in part, duration and intensity of postoperative pain.

Therefore, blocking these processes by inhibiting NMDA receptor signalling might be useful in preventing development of prolonged pain states. NMDA antagonists can prevent the induction of central sensitisation. No selective NMDA receptor antagonists are available for clinical use; however, several compounds approved for use in humans for other indications have significant NMDA receptor-blocking properties. Of these, ketamine and Mg$^{2+}$ are of particular interest. In experimental studies, ketamine inhibits functioning NMDA receptors activated by glutamate/glycine. Compared with the isomers, racemic ketamine showed a two-fold inhibitory potency than did R(-)-ketamine and a significant nearly four-fold less potency than S(+)-ketamine. Mg$^{2+}$ and ketamine interact in an additive manner at NMDA receptor level. Thus the combination of the compounds may give additional benefits for the patient without an increase in side effects. This issue may be relevant not only to the analgesic effects of NMDA receptor blockade, but also to its neuroprotective actions [8]. Therefore, the analgesic effects of ketamine and Mg$^{2+}$ are enhanced in the presence of volatile anaesthetics, the cerebral protective effects of the compounds may be potentiated in a similar manner [9].

### Neurological Effects

The anaesthetic state produced by ketamine has been termed "dissociative anaesthesia" in that, rather than general electroencephalographic (EEG) depression, there is EEG evidence of dissociation between the thalamocortical and limbic system. In this state, the thalamus and neocortex exhibit synchronous delta bursts while the ventral hippocampus and amygdala exhibit theta waves characteristic of arousal. There is also evidence that ketamine depresses transmission of impulses in the medial medullary reticular formation, which is important to transmission of the affective-emotional components of nociception from the spinal cord to higher brain centres. The anaesthetic state produced, rather than an unresponsive sleep state, is a cataleptic-like state of unresponsiveness with occasional coordinated but seemingly purposeless movements of arms, legs, trunk and head. The ketamine-anaesthetised patient has profound analgesia but keeps his eyes open and maintain many reflexes such as corneal, cough and swallow, although they should be not assumed to be protective. There may be lacrimation and salivation but not recall of surgery or anaesthesia.

Emergence reactions have occurred in approximately 12% of patients. The psychological manifestations may vary in severity between pleasant dream-like states, hallucinations and vivid bad dreams, extracorporeal experiences (sense of floating out of body) and illusions. In some cases these states have been accompanied by confusion, excitement and irrational behaviour. They usually occur in the first hour of emergence and disappear within 1 to several hours. No residual psychological effects are known to result from use of ketamine. It has been postulated that the psychic emergence reactions occur because of ketamine-induced depression of auditory and visual relay nuclei, leading to misinterpretation and misperception of auditory and visual stimuli. Their incidence is least in the younger patients (below 15 years old) and in the elderly (over 65 years of age). Other factors that affect the incidence of emergence reactions are dose, gender (more frequent in women compared with men), psychologic susceptibility and concurrent use of drugs. Larger doses and rapid administration seem to be associated with a higher incidence of adverse reactions. Although certain personalities types seem to be more prone to the development of emergence reactions, in a recent work Kudoh [10] showed that in schizophrenic patients ketamine was not associated with exacerbation of psychosis during the first postoperative month. Benzodiazepines seem to be effective in attenuating and treating ketamine emergence reactions.

At the central nervous system level (CNS), ketamine has rather unusual effects, since it increases cerebral blood flow (CBF) with little or no effect on overall cerebral metabolic rate (CMR). The most relevant increase occurs in the anterior cingulate, in the thalamus, in the putamen and in the frontal cortex, which are the brain structures related to pain processing. Consequently, the oxygen extraction fraction is
Ketamine has a neuroprotective effect in animals with cerebral damage [13], may be because of NMDA receptor antagonism. However, since ketamine increases cerebral blood flow (CBF) even in sedative or analgesic doses, its use in patients with increased intracranial pressure or decreased intracranial compliance was not recommended. However, in healthy humans, the cerebral blood volume (CBV) was slightly increased only in the frontal cortex [11]. Probably, since ketamine increases mean arterial pressure (MAP), a slight additional vasodilation is sufficient to cause an increase of CBF. The increase of CBF may be also due to ketamine-induced release of vasoactive neurotransmitters, i.e. acetylcholine and norepinephrine.

The effect of ketamine on intracranial pressure (ICP) is not a major clinical dilemma. An increase in CBV is usually associated with increased ICP. According to the work of Långsjö [11], subanaesthetic doses of ketamine produce only a small increase of CBV in healthy human brain and thus, only minor increases of ICP would be expected. Though, in a compromised brain with increased ICP, even marginal increases of intracranial volume could have harmful effects, because of a further exponential increase of ICP. Recent reports suggest that ketamine-associated rises of ICP in neurosurgical patients are apparently due to inadequate ventilation, since they can be prevented by mechanical ventilation [3]. The association ketamine-midazolam – if compared to midazolam-sufentanil – has similar efficacy in maintaining intracranial pressure and cerebral perfusion pressure in severe head injury patients under mechanical ventilation [14, 15]. In ketamine-sedated patients, electroencephalographic activity of the cortex is decreased (i.e., EEG depression and burst suppression are noted). The more potent S(+)-isomer of ketamine produces a progressive decrease in EEG amplitude and frequency, while larger doses of R(-)-ketamine are unable to produce the same degree of EEG suppression. The ketamine anticonvulsant activity is attributed to the inhibition of NMDA receptors [15, 16, 17].

In brain trauma patients, ketamine has several clinical advantages, such as maintenance of hemodynamic status, maintenance of cerebral perfusion pressure (CPP), absence of withdrawal symptoms and better tolerance to enteral nutrition [14]. The neuroprotective effects of ketamine have been shown in several experimental and clinical works [13, 18, 19], and seem to be secondary to NMDA receptors block and to inhibition of transmembrane calcium influx. Initiation of the cascade of inflammatory response and release of neurotoxic mediators (such as nitric oxide NO, prostaglandins, leukotrienes, free radicals, tumor necrosis factor TNF, interleukins, etc) may cause neuronal apoptosis and consequent cerebral damage [20]. Ketamine may influence apoptosis through changes in apoptosis-regulating proteins and interfering with the inflammatory response. After cardiac surgery, ketamine has been shown to attenuate the release of interleukins, TNF, NO, and to reduce postischaemic adherence of neutrophils in the coronary vascular system [21, 22].

CARDIOVASCULAR EFFECTS

Unlike other anaesthetic drugs, ketamine is not a depressor of the cardiovascular system and is usually associated with increase in blood pressure, heart rate and cardiac output. Elevation of blood pressure begins shortly after administration, reaches a maximum within few minutes and usually returns to preanaesthetic values within 15 minutes. The cardiovascualr stimulation is associated with increase in cardiac work and myocardial oxygen consumption. In patients with coronary artery disease (CAD) and hypertension, ketamine should be avoided because tachycardia and increased blood pressure may cause myocardial ischaemia.

The haemodynamic changes are not dose-related. The mechanisms by which ketamine stimulates the cardiocirculatory system remains unknown, although studies suggest that an intact central nervous system and arterial baroreceptors are required [23]. The stimulating effect of ketamine seems to be central because it inhibits postsynaptic NMDA receptors and presynaptic afferent processes in medial nucleus tractus solitarius. There seems to be also a peripheral action, through the inhibition the intraneuronal uptake of catecholamines (cocaine-like effect). The rise in noradrena-line levels is detectable in the blood after ketamine administration and the pressure response is blocked by α- and β-adrenoceptor antagonists and by sympathetic ganglion blockade.

Because of the cardiovascular profile, ketamine has been advocated as the drug of choice for intravenous induction of hemodynamically unstable patients; nonetheless, it should be used with caution in critically ill patients with depleted catecholamine stores and exhaustion of sympathetic nervous system (SNS). Pulmonary vascular resistance also tends to rise; pulmonary shunting may increase, if a cardiac septal defect is present.

The immunomodulatory action of ketamine deserves a special comment: it may be important in the induction of anaesthesia in septic patients. In experimental septic shock, ketamine preserves the cardiovascular function and have the least deleterious effect on hypoxic tissues if compared to other anaesthetics (halothane, isoflurane, alfentanil) [24]. The protective effect of ketamine in septic patients may be secondary to its suppression of excessive production of proinflammatory cytokines [25, 26]; this might also explains why ketamine reduces the need for inotropic support in these patients [27]. In infected parturients, ketamine should be considered anaesthetic of choice for induction and maintenance of anaesthesia because of maternal hemodynamic stability and maintenance of uteroplacental blood flow [28].

PULMONARY EFFECTS

Ketamine does not produce significant ventilatory depression. The response to carbon dioxide is unaltered, unless a large dose is administered rapidly or an other respiratory depressant drug (e.g. an opioid) is given. In spontaneous breathing patients, the minute ventilation is maintained at the
same level as in the awake state although a transient [1 to 3 minutes] decrease in respiratory rate can occur after ketamine bolus administration of an induction dose (2 mg/kg
neurodegenerative diseases such as Parkinson’s disease. In fact, analgesic doses of ketamine (0.2-0.5 mg/kg) administered during labour do not depress the newborn, and ketamine has been safely used in patients with myopathies and susceptibility to malignant hyperthermia.

b) Analgesia During Regional or Local Anaesthesia

Typically, ketamine has been used in the ICU to facilitate the performance of brief but painful procedures, such as changing burn dressings. Subanesthetic doses (0.2-0.5 mg/kg intravenously or 1.5-2.0 mg/kg intramuscularly) can produce a rapid onset and offset of intense analgesia and amnesia. Tolerance to ketamine develops quickly requiring progressively increased doses. [40].

Several clinical studies are available on this indication, and they are discussed in a recent review [36]. The possibility of ketamine-induced neurotoxicity after peridural or caudal anaesthesia is still a matter of debate.

c) Pain Therapy with Ketamine in Post-Anaesthesia Care

When ketamine is combined with an opioid, it provides a significant opioid sparing effect, with longer analgesia than when either analgesic is used alone [41]. This synergism probably results from the different site of action of opioids (acting presynaptically) whereas the NMDA receptor is located postsynaptically. Many papers are available on this matter, mostly showing positive results, which advocate the use of ketamine [36]. A recent systematic review [38] has concluded that small dose ketamine is a safe and useful adjuvant to standard practice opioid-anaesthesia.

In particular, ketamine should be considered when postoperative pain requires large doses of opioids (such as after abdominal and thoracic surgery) and in “difficult to manage” patients (such as cancer patients with opioids tolerance or patients with chronic postoperative neuropathic pain) [36, 37, 38].

A very interesting field of investigation is the use of ketamine in patient control analgesia (PCA), though much uncertainty still exists about the actual incidence of psychic adverse effects [38]. Generally speaking, the risk of hallucination is a major concern for the physician: the risk appears to be minimum when ketamine is administered during anaesthesia, but it is not irrelevant when the drug is given to the conscious patient; the association with benzodiazepine is not effective in reducing the risk; the actual clinical impact of other psychic non-hallucinatory effects (dreams, etc.) is still unclear.

Most likely, a better definition of the protocol of administration, with regards both to total dosage and timing, will help in minimizing the risk of such undesired side effects.

Finally, if sub-anesthetic dose intravenous treatment with ketamine proves to be an effective and safe therapeutic modality it will have implications that transcend the field of pain medicine. In fact, the NMDA receptor is the major excitatory receptor protein and it is implicated in a variety of neurodegenerative diseases such as Parkinson’s disease, Alzheimer’s disease, amyotrophic lateral sclerosis and even epilepsy, stroke, head trauma and schizophrenic disorders [2].

REFERENCES