Ketamine: old dogs, new tricks

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Keywords: ketamine

Abstract

Ketamine is one of the oldest intravenous anaesthetic agents that is still in clinical use. Its unique mechanism of action and interaction with a variety of different receptors has sparked renewed interest in its use in a host of alternative clinical settings. This review briefly discusses the pharmacology of ketamine and ketamine's potential use in major depressive illness, opioid-induced acute tolerance and as a potential neuroprotective agent.

South Afr J Anaesth Analg 2013;19(1):24-26

Introduction

Ketamine is an old intravenous anaesthetic agent, first described in 1965 and approved for clinical usage in 1970. Ketamine gained widespread acceptance, with the hope that it would function as a sole anaesthetic agent. However, its use declined because of the unpleasant side-effects of the drug and the development of new anaesthetic agents. Regardless, ketamine proved invaluable in certain circumstances and has been widely used to provide anaesthesia or sedation to uncooperative children, as well as for battlefield emergencies and veterinary medicine.

Over the past decade, an explosion of interest has resurfaced in ketamine. The list of its potential uses has expanded to include:

- Treatment of major depressive illness.
- Potentiation of opioid analgesia.
- Sedation and anaesthesia in traumatic brain injury.
- Prevention of opioid-induced acute tolerance.
- Anti-inflammatory actions and anti-tumour actions.

Pharmacology of ketamine

The mechanism of action of ketamine is mainly considered to be noncompetitive antagonism at the N-methyl-D-aspartic (NMDA) receptor. Ketamine is also thought to interact with opioid, monoamine, cholinergic, purinergic and adenosine receptor systems, as well as to have local anaesthetic effects. It has been shown to inhibit tumour necrosis factor-alpha and interleukin-6 gene expressions in lipopolysaccharide-activated macrophages.[1]

Ketamine is water- and lipid-soluble, which renders it absorbable by intravenous, intramuscular, subcutaneous, epidural, oral, rectal and transnasal administration routes. Peak effect is achieved within 1-5 minutes after intravenous administration. After oral administration, bioavailability approximates 16% because of extensive first-pass metabolism. The elimination half-life is short at 2-3 hours. Ketamine is metabolised extensively by the hepatic cytochrome P450 system, by N-demethylation. Its primary metabolite, norketamine, is only one third to one fifth as potent as the original compound. Following oral administration, norketamine plasma levels are three times higher that of intravenous. The metabolites of norketamine undergo renal excretion and the β-elimination half-life of norketamine is approximately 12 hours.[1]

The ketamine molecule contains a chiral carbon atom that marks a chiral centre. Ketamine can exist in two enantiomers: S-ketamine and R-ketamine. S-ketamine has approximately three- to fourfold the potency of the R-ketamine and two times more potency than the racaemic mixture. Nevertheless, equipotent doses of the S-ketatime and the racaemic mixture appear to have similar effects on physiological parameters. Furthermore, the S-ketamine is cleared more rapidly, resulting in a shorter duration of action which allows it to be easily titrated during infusions.

Ketamine in major depressive illness

There are limits to the therapeutic efficacy of current antidepressant agents that enhance serotonin, noradrenaline or dopamine neural functioning in the treatment of depression.

The observation of a rapid antidepressant effect by ketamine has focused attention on glutamate pathway dysfunction as a novel pathophysiology of depression. Berman et al were the first to report a rapid antidepressant response to ketamine in nine clinically depressed patients in a randomised, saline-controlled crossover design. Ketamine-related mood improvement was robust and peaked within 72 hours following a single, low-dose infusion (0.5 mg/kg over 40 minutes). Other randomised controlled studies have subsequently replicated Berman's findings.[2] The antidepressant effect of ketamine, and possible synergistic effects when given with electroconvulsive therapy (ECT), has renewed interest in its use during ECT. However, ketamine may offer additional benefits during ECT. Intense seizure activity at this time may result in cognitive deficits and the mechanism that underlies this is thought to be because of NMDA-mediated excitotoxic neuronal damage. Ketamine is thought to exhibit a degree of neuroprotection via effects on the NMDA receptor. Preliminary evidence from clinical reports of ketamine anaesthesia for ECT seems to confirm this.[3] It has also been suggested that ketamine administered during ECT may prevent excessive long-term potentiation induction and preserve memory function during ECT.[4] There are numerous theoretical reasons, as well as preliminary results, to suggest that the use of ketamine in ECT anaesthesia may be advantageous in terms of cognitive and antidepressant outcomes. Its role as an anaesthetic agent in ECT certainly deserves more study.

Ketamine in neuroprotection

Early reports suggested that ketamine anaesthesia resulted in increases in cerebral oxygen consumption, cerebral blood flow and intracranial pressure. Ketamine was subsequently considered to be contraindicated in patients with raised intracranial pressure, as well as those with traumatic brain injury.[5,6] However, advances in the knowledge of ketamine's pharmacology warrant a re-evaluation of this verdict. The cerebral haemodynamic and metabolic effects of ketamine depend on study setting, the use of controlled ventilation, and other drugs and anaesthetic agents that are used. Ketamine has been used safely under appropriate conditions in patients with intracranial pathology.[7] Ketamine's interaction with regional cerebral haemodynamics and metabolism is complex. Mayberg et al showed that when ketamine was administered as a 1 mg/kg bolus to neurosurgical patients during isoflurane anaesthesia, it reduced intracranial pressure and middle cerebral artery flow velocity, but did not affect mean arterial blood pressure.[8]

Albanese et al demonstrated that administration of ketamine and propofol to head-injured patients with increased intracranial pressure reduced intracranial pressure, but had no effect on cerebral artery flow velocity or mean arterial blood pressure. There is also evidence to show that ketamine has the ability to preserve cerebral vascular autoregulation.[9] Ketamine's stimulation of the cardiovascular system may prevent hypotension and thus maintain the cerebral perfusion pressure, which together with its other advantages over opiate-based sedation, could make the drug a first choice in sedative regimens for patients with brain insults.[7] Renewed interest in ketamine as a neuroprotectant has been supported by animal studies that have reported neuroprotective effects. When used before, during, or after, induction of various brain insults, ketamine protected against hypoxic, ischaemic, mechanical and chemical neuronal damage.[10] When used at low doses in post-injury cultured neurons, neuroprotective effects were found and the observed decrease in necrosis related to a reduction in glutamate neurotoxicity caused by NMDA-receptor blockade by ketamine.[11] Unfortunately, virtually no clinical trial data are available and it is impossible to extrapolate the available animal data to human brain injury.

However, other evidence suggests that NMDA-receptor antagonists produce neurotoxicity under certain conditions. Complete inhibition of normal NMDA-receptor activity reduces brain cell survival and worsens the physiological outcome in rats as NMDA-mediated signal transduction is required to express neurotrophins and other survival-promoting brain proteins.[12] It is also known that large doses of NMDA-receptor antagonists cause apoptosis and cognitive impairment in the developing rat brain. Furthermore, ketamine produces acute vacuolar changes in adult rat brain cells. The co-administration of ketamine and the NMDA antagonist, nitrous oxide, further enhanced vacuole formation, whereas pretreatment with a γ-aminobutyric acid (GABA) agonist prevented these adverse effects.[13] In vitro studies showed cell death in neurons cultured from the rat forebrain after prolonged exposure to ketamine at high concentrations, but apoptosis did not occur at lower concentrations (such as those used clinically). This suggests that neurotoxicity produced by NMDA antagonists is dose-related. Whether the NMDA antagonist that induced the neurodegeneration observed in rats also occurs in humans is unknown. The doses and duration of the administration of ketamine-implicated neurotoxicity in experimental animals do not correlate with, and frequently greatly exceed, those used to produce sedation or anaesthesia in patients. Thus, the potential clinical relevance of the data obtained with regard to rats remains to be clarified.[13]

Ketamine to prevent opioid-induced acute tolerance

Opioid-induced hyperalgesia is defined as a state of nociceptive sensitisation that is caused by exposure to opioids. Receptor desensitisation, comprising loss of receptor function and internalisation, appears to be involved and noxious stimuli such as surgery may enhance opioid-receptor dysfunction via NMDA-receptor-mediated opioid release.[14]

Pretreatment with NMDA-receptor antagonists significantly inhibited mu-opioid receptor dysfunction in neurones and ketamine pretreatment in human and animal studies has been shown to prevent opioid-induced hyperalgesia and acute tolerance.[15,16]

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