

Ketofol 11: Risky or Revolutionary

Abstract

We are busy with a series of CPD articles on ketofol, a combination of ketamine and propofol, that is increasingly used for procedural sedation and analgesia for various surgical procedures. In the last article we looked at ketamine. This article will provide more information about ketamine. The use of a combination of ketamine and propofol (ketofol) for PSA shows promise as a “drug” that minimizes adverse effects of ketamine or propofol as single drugs. Ketofol could be used as a single syringe combination of ketamine and propofol, or administered through independent dosing of the two drugs. The combination of propofol and low-dose ketamine is potentially a viable anaesthetic alternative, capable of providing effective analgesia, high-quality sedation, good operating conditions, and a recovery profile that is perhaps similar to that of propofol and remifentanyl¹.

Introduction

Ketamine

Ketamine inhibits catecholamine uptake, which exerts a sympathomimetic effect. This effect leads to an increase in blood pressure, stroke volume and heart rate whilst maintaining systemic vascular resistance¹¹. These effects usually reach a maximum about two minutes after injection and settle over 15-20 minutes and do not appear to be dose-related⁴⁹. For PSA ketamine is used in such low doses that hypertension is more or less never an issue, even in the controlled hypertensive patient. If a patient develops hypertension during sedation where ketamine is used other causes of hypertension must be excluded.

There can however be a wide variation in individual response with higher doses of ketamine, and occasionally there can be a large increase in blood pressure, unrelated to a pre-

operative history of hypertension. It is thought that these adrenergic responses are centrally mediated and that benzodiazepines can blunt these effects. It also means that ketamine will be the right drug for a shocked patient, but less ideal for the patient with chronic ischaemic heart disease ⁶.

While ketamine does not prevent obstruction and airway compromise in an unconscious patient, airway reflexes tend to be better preserved than with other induction/hypnotic agents. It is now suggested that ketamine in fact protects against hypoventilation with deep sedation. It is postulated that less airway manoeuvres will be necessary with ketamine use to keep the oxygen saturation levels above 95%. This is of significant importance for the sedation practitioner as patients may slip inadvertently into deeper levels of sedation.

The inclination for ketamine to retain laryngeal protective reflexes therefore “permits” laryngospasm to occur in deeply sedated, dissociated or unconscious patients ²². The preservation of skeletal muscle tone during ketamine anaesthesia prevents atelectasis, and changes in ventilation-perfusion, and functional residual capacity ⁴⁹.

Risk factors that may be associated with ketamine-associated airway and respiratory adverse events are high intravenous doses of ketamine and the concomitant use of anti-cholinergics¹¹. The use of glycopyrrolate during ketamine sedation seems to increase the likelihood of respiratory events by up to four times. Children under the age of 2 or older than 13 years are likely to be more at risk ²⁹. It is now believed that if a sedation practitioner needs an anti-cholinergic drug during ketamine sedation, atropine should be the drug of choice as airway adverse events, emergence phenomena, and nausea and vomiting are much less with atropine.

A potential disadvantage of benzodiazepines when administered with ketamine is the competition for the hepatic degradation enzymes, delaying ketamine metabolism as much as two times ⁴⁴. This is probably not significant with the low doses of ketamine we use for PSA.

Ketamine causes dissociative sedation and does not display the dose-response continuum observed with other PSA agents like propofol. This dissociation is seen at a dosing threshold of 1.0-1.5 mg/kg when administered intravenously^{22,36}. Once this threshold is reached, additional doses of ketamine do not enhance or deepen sedation, as would be the case with the administration of non-dissociative drugs. It has a narrow transition zone, suggesting that adequate sedation is either present or not at a given dose. This unique mechanism of action has led to the belief that ketamine does not operate on the sedation continuum²². Some clinicians believe a specific sedation level must still be established on the traditional sedation continuum for ketamine.

There is a lot of interest in the use of ketamine for analgesia during and after PSA. Ketamine is known as an analgesic in sub-dissociative doses (0.1 – 0.5 mg/kg) and when used as an infusion in doses of 0.2 – 0.3 mg/kg/hour. The two main metabolites, norketamine and hydroxynorketamine, are both active and contribute to analgesia even after the operation. The ketamine metabolites are excreted via the kidneys with an elimination half-life of 2-3 hours in adults^{6,49}.

Ketamine is a NMDA receptor antagonist and reduces postoperative pain by blocking “pain wind-up” (central sensitization) in the spinal dorsal horn and trigeminal nucleus caudalis^{7,49}. Low-dose ketamine has been shown to be effective when used in place of opioids to achieve analgesia during procedures¹. In addition to blocking NMDA receptors, it also induces an analgesic effect by nitric oxide synthase inhibition. Frequent repeat sedation with ketamine, as often seen in burn victims, can lead to tolerance with the need for increased doses. This tolerance generally lasts three days⁶.

An interesting development in the evolution of ketamine is its antidepressant effect due to its action on the glutamatergic system. Ketamine reduces the pre-synaptic release of glutamate, an excitatory neurotransmitter. This is an extremely important point as those patients with depression have excessive levels of glutamate.

Because the mechanism of action of ketamine is mainly considered to be non-competitive antagonism at the NMDA receptor it is important to give a reasonable initial dose of ketamine to attain ideal procedural conditions. Using ketamine alone, Ramaswamy et al found that a dose of 1.5 mg/kg administered intravenously, reliably achieved dissociative sedation levels, whereas half of the patients receiving lower doses required supplemental dosing ^{41,10}. Some clinicians will disagree with the above dose as ketamine is not usually administered as a single drug sedation agent, but combined with other drugs for PSA.

The pharmacokinetics of ketamine is consistent with a two-compartment model and peak plasma concentrations are reached within 60 – 90 seconds with intravenous administration. This gives us valuable information as to the time that the operator should wait to start a painful procedure after administration of ketamine. It must be remembered that rapid intravenous administration of ketamine may lead to respiratory depression.

Ketamine can also be administered orally, per rectum, nasally, sublingually or by the intramuscular route. The intravenous bolus sedation dose of ketamine is between 0,25 - 1mg/kg, with a time to peak effect of 60 – 90 seconds, and a duration of action of 5 - 10 minutes. The sedative dose when given intramuscularly is 2 – 4mg/kg. The bioavailability with intravenous administration is 90% but with oral and rectal administration it is only 16%. The short duration of action, the analgesic properties and the favourable safety profile make this a very popular drug for PSA ³². Ketamine is a very safe drug in the hands of the trained practitioner, a fact even acknowledged by the FDA.

The level of consciousness (LOC) is extremely important for sedation practitioners as we do not want our patients to become unconscious outside the operating theatre. One way of objective monitoring the LOC is to use the bispectral index (BIS). BIS monitoring in ICU settings and during anaesthesia help practitioners to assess the depth of anaesthesia (LOC) by using data from the electroencephalogram. It is believed to be accurate for single agents such as midazolam, propofol, and volatile agents, but there is some doubt about the validity for ketamine and the opiates. Smischney et al concluded that the BIS values during anaesthesia were higher when ketofol was compared to propofol, and this may lead to

relative anaesthetic overdose during general anaesthesia⁴⁰. As sedation practitioners we believe that the BIS has an important role to play to assess the LOC. It is not always easy to assess the LOC with the subjective sedation scales we use. The trend of the BIS over time during sedation is extremely important even if “controversial” agents like ketamine and ketofol are used. The use of the BIS should be supported when ketofol is used as a bolus administration especially in young children.

The ability of ketamine to produce dissociative sedation without significant respiratory depression will offer an advantage over techniques using only opioid drugs. Fabbri et al propose the routine use of a continuous infusion of sub-anaesthetic doses of ketamine for PSA¹⁴. The combination of ketamine with low doses of remifentanyl and a propofol infusion has been showed to be a safe and effective technique to achieve moderate sedation and analgesia, whilst avoiding deep sedation. With the low doses of ketamine used (5mcg/kg/min) no emergence reactions were reported¹⁴.

Ketamine is very effective when administered as a single bolus dose. It can however be combined with other drugs. A large meta-analysis report that there are no dose-related adverse events across the standard dosing range, only with unusually high intravenous doses of e.g. >2,5mg/kg or total >5,0 mg/kg²⁹.

It is believed that the minimum dose at which the dissociative state can reliably be achieved in children is 1,5 mg/kg³⁶. Not everybody agrees with this. It is not possible to predict a minimum dose to achieve dissociation. As a general rule it is probably better to start at a lower dose and “top-up” the initial dose. It is rare that we administer more than 1 mg/kg of ketamine as a dissociative dose. To “top up” the dissociative dose of 1 mg/kg a dose of 0.2 mg/kg of ketamine can be administered intravenously.

Ketamine can cause side effects and every sedation practitioner must take note of this. It is known that ketamine can produce nausea and vomiting. The incidence is probably dose dependent but more significant with intramuscular administration. Psychotropic (psychedelic) effects or “emergence phenomena” are reported with ketamine. This is usually

not troublesome after PSA. There are reports of a higher incidence of laryngospasm when ketamine is used in patients undergoing procedures that stimulate the posterior pharynx e.g. endoscopy and in patients with upper respiratory tract infections or recent infections ²⁹. Some researchers believe that an increase in secretions when ketamine is used may contribute to a higher incidence of laryngospasm.

Absolute contraindications for the use of ketamine are infants less than three months old and patients with a history of psychosis, alcohol abuse, drug abuse or schizophrenia ²². With the latest information as to the effect of ketamine on depression we are more comfortable to use small doses of ketamine in patients on psychotropic drugs.

Caution should also be exercised in patients with suspected cardiovascular disease, uncontrolled hypertension, porphyria and patients with thyroid disorders or on thyroid medication.⁶ The theoretical risk of a raised intra-ocular and intracranial pressure makes central nervous system masses, hydrocephalus, glaucoma and open eye injuries relative contra-indications ²². It is believed that S+ ketamine (ketanest®) is a better choice as a sedative/analgesic agent for PSA in patients with increased intracranial pressure. Latest studies show that racemic ketamine does not increase intracranial pressure.

Dosing scheme for ketamine

Route	Dose	Onset	Time to peak effect	Duration of action
Oral	4 – 6 mg/kg, combined with other sedatives 2 mg/kg	> 5 min	20 min	4 – 6 hours

Intravenous	0.2 – 1 mg/kg	1 – 2 min	2 – 3 min	10 – 15 min
Intramuscular	2 – 4 mg/kg	2 – 5 min	10 – 15 min	30 – 90 min
Rectal	4 – 6 mg/kg	10 min	30 min	30 – 90 min

Conclusion

It is clear that ketamine is a significant drug in the armamentarium of the sedation practitioner. The drug has many of the characteristics of an ideal sedative/analgesic agent, and we discover more are more about this drug. A problem with significant drugs is that you may find people that may use it for other purposes.

One of the biggest problems facing us at the moment regarding ketamine centers round the recreational use of the drug. Chronic intake of ketamine has been shown to produce significant adverse effects e.g. ketamine cystitis.

More CPD articles will follow with more important information on the status of ketofol and its use in PSA.

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