Ketofol: Risky or Revolutionary

Abstract

A significant number of articles are published on the use of ketofol for procedural sedation and analgesia (PSA) in both adults and children. The combination of ketamine and propofol has received interest as a PSA regimen that allows for the provision of PSA using drug doses lower than typically required for each agent alone. 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.

The CPD articles will address important questions we have as to the safety and efficacy of ketofol for PSA. Is there evidence that combining two drugs in a single syringe is better or safer than independent dosing of the two drugs. Do the two drugs compliment the actions of each other to make it worthwhile to combine them. To answer this we also need to look at the two individual drugs. A review of the literature will give us important answers to all the questions regarding ketofol.

Introduction

Newer developments in patient care e.g. develpoment of more sophisticated equipment have made surgical procedures quicker and less invasive, to the point where all procedures do not require anaesthesia anymore[12]. Management of fear and anxiety however remains a crucial part of any treatment.

Healthcare professionals are more aware of the need for patient satisfaction. Gone are the days where the doctor made all the decisions regarding a patient's care. Nowadays it is a

shared process, often taking into account personal preferences, financial implications and the patient's opinion and expectations.

As healthcare professionals we are in the position today where we can offer patients a choice as to treatment options, and an alternative to general anaesthesia for certain procedures. Procedural sedation and analgesia (PSA) gives us the opportunity to offer interventions normally reserved for in-hospital, as outpatient procedures. Awareness of the importance of PSA and the need for sedation for procedures outside the operating theater is on the increase e.g. in physician offices, dental surgeries, imaging facilities and emergency departments. PSA is probably the fastest growing area in anaesthesia care.

Whilst PSA can solve a lot of problems, it can also create a lot of problems. The success of any sedation technique largely lies in our hands as sedation practitioners and depends on the decisions we make. Our choice of patients, equipment, premises, and drugs often determines the outcome of the sedation.

Although drugs are just one part of sedation, the selection of drugs for a specific patient is an important factor in the success of the sedation. One of the many challenges facing sedation practitioners is to determine how to apply the guidelines to our individual patients to get the best possible results.[2,17]

Ultimately, the goals of sedation include to provide an adequate level of sedation to make the patient comfortable, minimizing pain and anxiety, maximising amnesia, minimising the potential for adverse drug-related events, controlling behaviour and maintaining a stable respiratory and cardiovascular status.[18] The ideal agent will accomplish all of the above, have a quick onset and offset, be safe in all age groups, be inexpensive and be equally efficacious with multiple routes of administration. Although many drugs have been tried, no single drug fits this profile of an ideal agent.

That does not mean that we must stop searching for the ideal agent. We often have to use different drugs or combinations of drugs to come as near as possible to the ideal agent. We find a similar situation in theatre where anaesthetic drugs are often combined to enhance

their therapeutic effect whilst minimizing possible adverse events. It must however be remembered that combining drugs may change their pharmacokinetic profiles and may increase risk. Three or more sedation drugs administered together do increase the risk of adverse events in procedural sedation[18].

In theory then, in searching for the ideal agent, propofol and ketamine (ketofol) in the same syringe or as independent dosing, should complement one another quite well if we look at the characteristics of the individual drugs. Ketamine mitigates propofol-induced hypotension whilst propofol mitigates ketamine-induced nausea and vomiting and recovery agitation[24]. The combination displays synergic and possibly smoother sedation with the benefit of decreasing the propofol dose. The cardiovascular effects of these two drugs are also opposing in nature and should balance each other out. Add to that the analgesic properties of ketamine, and it might explain the popularity ketofol has had as a PSA drug choice in recent years. An interesting question is, by mixing two different drugs in one syringe, are we purely just combining their different pharmacokinetic and pharmacodynamics effects, or are we actually creating a new drug with its own properties?

To try and answer the question whether ketofol may be near to the ideal drug for PSA we need first to look at the individual characteristics of ketamine and propofol.

Ketamine

Ketamine has withstood the test of time. It is however not the ideal drug for single drug administration for PSA. It is a phencyclidine derived anaesthetic drug that was approved for clinical use in 1970. Ketamine is a N-Methyl-D-Aspartate (NMDA) receptor antagonist with a chemical name of 2-O-chlorophenyl-2-methylamino-cyclohexanone hydrochloride[49]. The antagonism of the NMDA receptor by ketamine is for us as sedation practitioners of enormous importance. 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. As sedation practitioners we see many patients on psychotropic drugs. With the above-mentioned mechanism of action of ketamine we are confident that ketamine can be safely used for PSA in patients on antidepressant drugs. The World Health Organization predicts that by 2020 depression will be the second biggest cause of disability.

Ketamine is a white crystalline powder with a characteristic smell readily soluble in water with a pH of 3,5 - 5,5. The drug is lipid-soluble, and can be administered via various routes[6]. The pKa of ketamine is 7,5, with a protein-binding capacity of 20-25%. Ketamine undergoes hepatic biotransformation, although 90% is excreted via the kidneys.

Ketamine is a racemic mixture of two enantiomers, R(-) ketamine and S(+) ketamine. S(+) ketamine is believed to be more potent and a single enantiomer preparation (ketanest®) is now available in some countries. Lower doses are used due to its higher potency. It is believed that fewer side effects and shorter recovery times are seen. It is a very expensive drug with some doubt whether it has more benefits than the racemic mixture. The R(-) enantiomer has a greater effect on smooth muscle relaxation and the racemic mixture might be more suited for patients with bronchospasm[6].

Ketamine causes dissociative sedation characterized by intense analgesia, sedation and amnesia. Non-competitive NMDA receptor antagonism is associated with the analgesic effects. There is today renewed interest in the analgesic effects of ketamine. Dysphoric reactions and sympathomimetic properties may result from enhanced central and peripheral mono-aminergic transmission. Ketamine blocks dopamine uptake and therefore elevates synaptic dopamine levels. Inhibition of central and peripheral cholinergic transmission could contribute to induction of the anaesthetic state and hallucinations.

The underlying pharmacology of ketamine is fundamentally different from that of other PSA agents. This drug exerts its effect by "disconnecting" the thalamo-cortical and limbic systems, effectively dissociating the central nervous system from outside stimuli (e.g. pain, sight, sound)[22,49]. The resulting trancelike cataleptic state of sensory isolation is characterised by

potent analgesia, sedation and amnesia while maintaining cardiovascular stability and preserving spontaneous respirations and airway reflexes.[22]

Ketamine exerts sympathomimetic activity by inhibiting reuptake of catecholamines.[1] It may increase the heart rate and lead to hypertension, especially in the uncontrolled hypertensive patient. It is a rapid-acting agent that can produce profound anaesthesia, normal pharyngo-laryngeal reflexes, and normal or slightly enhanced skeletal muscle tone.

Of particular importance in sedation, it produces cardiovascular and respiratory stimulation, although a transient and minimal respiratory depression with rapid intravenous administration is also possible. Apnoea and laryngospasm have also been reported but are rare with smaller doses of ketamine[6,44].

Ketamine acts as a bronchodilator probably by two different mechanisms - a central effect inducing catecholamine release, and stimulation of beta-2 adrenergic receptors, and secondly by inhibition of vagal pathways to produce an anti-cholinergic effect acting directly on bronchial smooth muscle[6].

Side effects

Side effects that may be troublesome are nausea and vomiting and emergence reactions. This includes vivid and often unpleasant dreams, feelings of being suspended in space, out-of-body experiences, hallucinations and irrational behaviour[44]. These seem to have a higher incidence in females, in adults, with large doses and with rapid intravenous administration. There is little evidence that giving lower doses reduce the incidence or severity of emergence reactions. Indeed, there is anecdotal evidence that emergence may be more frequent with lower dosages. Emergence reactions have an overall incidence of 10-20% in adults[37] and hallucinations are reportedly lowest in children. It can be reduced by giving a benzodiazepine e.g. midazolam for pre-medication. It is believed that small doses of propofol can be used to attenuate hallucinations[23].

Other side effects include diplopia, nystagmus and hypersalivation. Ketamine may be responsible for muscular hypertonicity, clonus and random purposeless movements. It is believed that patients that require “motionless sedation” will not benefit from ketamine alone[18.] Hiccupping and a short-lived non-allergic rash of the face and neck have also been reported.

Conclusion

It is clear from this introductory CPD article that ketamine is a significant drug in the armementarium of the sedation practitioner. More CPD articles will follow with more important information on the status of ketofol and use in PSA.

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