Clinical Resource Guide: Ketamine

INTRODUCTION TO KETAMINE

Ketamine is a rapid-acting general anesthetic drug that, due to new insight into its properties and mechanisms of action, is seeing increased use in many fields including pain management, psychiatry, and palliative care. At sub-anesthetic doses, it has potential to offer quick and lasting relief for patients experiencing severe pain, anxiety, respiratory distress, refractory seizures, and treatment-resistant depression. This article will focus on the role of ketamine in the setting of palliating incurable disease, and specifically, as a co-analgesic in poorly controlled pain, neuropathic pain, and relief of anxiety of depression.

Pharmacist Corner Objectives

1.) Describe the clinical significance and potential mechanisms of action of ketamine

2.) Understand variability in onset and duration of action based on route of administration

3.) Outline clinical pearls and important notes regarding implementing ketamine into your practice

SUGGESTED MECHANISMS

Ketamine has multiple suggested mechanisms. It is known to antagonize NMDA receptors which plays a role in its pain, anti-depressant, and anti-epileptic effects. It is thought to interact with sodium and calcium channels, inhibit noradrenergic and serotonergic reuptake, inhibit the inflammatory cascade, and boost neural plasticity. Specifically, emerging research shows ketamine may promote synaptogenesis, or the formation of synapses (the points of contact where information is transmitted between neurons). This is significant in countering the synapse loss and atrophy associated with chronic depression and stress and may explain its extended duration past detectable drug levels.

PHARMACOLOGICAL USES AND CONSIDERATIONS OF KETAMINE				
Route	**Usual adult dose**	**Onset of action**	**Duration of action**	**Notes**
Oral	10mg TID-QID increasing to a maximum of 100mg QID (use parenteral formulation for oral route)	30min	4-6hr ***Note:** therapeutic benefit may outlast noted duration of action. See clinical pearls.	• Peak plasma concentrations within 30 minutes • Norketamine, an active metabolite is 2-3x higher in PO administration • Administration be discontinued or held for several weeks after desired pain control is reached • Analgesic use should be limited to palliative care/pain specialists
Intranasal SPRAVATO® (esketamine)	56mg-84mg twice per week (induction phase) 56-84mg weekly to every 2 weeks (maintenance phase)	20min	3-12hr ***Note:** therapeutic benefit may outlast noted duration of action. See clinical pearls.	• Only available through REMS (Risk Evaluation and Mitigation Strategy) program due to risks for sedation, dissociation, respiratory depression, and abuse • SPRAVATO® is not for use to prevent or relieve pain
Parenteral	Initiation: 50-100mg/day Titrate in increments of 25-50mg/day up to 300mg/day	0.5min	0.5-2hr ***Note:** therapeutic benefit may outlast noted duration of action. See clinical pearls.	• Careful monitoring of heart rate, blood pressure, and psychotomimetic effects should occur • Consider empirically reducing opioids by 25-50% due to drowsiness
Topical	Various doses. Frequencies of TID-QID have been reported	Variable reports of minutes-hours	Variable	• Well tolerated; reduced risk of side effects compared to other routes of administration • Oral rinse has been used to treat mucositis • Gel may be used to treat neuropathy • Often compounded with other topical analgesics

PHARMACOLOGICAL MANAGEMENT: CLINICAL PEARLS

1. A short-term “burst treatment” of ketamine administered over 2-4 days may provide ongoing therapeutic benefit for several weeks.

2. The analgesic effects of ketamine may be useful for painful dressing changes, mucositis, orthopedic emergencies, neuropathy, and hyperalgesia.

3. Ketamine is not licensed for oral use. To prepare an oral solution, use two 10ml vials of ketamine 50mg/ml for injection and 80ml of purified water. This solution can be refrigerated and stored for 1 week.

4. Ketamine should be reserved for severe, treatment-resistant depression in special situations. An interdisciplinary approach should be taken which includes consulting with a clinician who has specialized expertise.

5. Common side effects include dissociation, dizziness, sedation, nausea, vomiting, hallucinations, cardiovascular changes, and headache. Memory impairment, dysuria, and hepatobiliary toxicity may occur with long term exposure. Side effects can be reduced by using haloperidol or benzodiazepines.

SUMMARY

There is increasing interest in the role of ketamine in palliative care, especially in the management of pain. When used for this purpose, sub-anesthetic dosing is used, either alone or as an adjunct to other medications. Oral and topical ketamine formulations may be especially useful for patients experiencing refractory symptoms who wish to remain home.

REFERENCES:

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