Transdermal Ketamine: A Rising Star in Pain and Inflammation

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Abstract

Ketamine is a powerful dissociative anesthetic with a rich history in medicine due to its remarkably complex, dose-dependent pharmacology. Originally synthesized in 1962 as a safer and more effective alternative to phencyclidine (PCP), ketamine has expanded its clinical applications to include analgesia and immunomodulation. Approximately 11–40% of adults in the United States report suffering from chronic pain, affecting more people than diabetes, heart disease, and cancer combined. Current therapies such as opioid agonists, non-steroidal anti-inflammatory drugs (NSAIDs), gabapentinoids, antidepressants, and topical anesthetic agents are first-line treatments for various pain conditions. However, prolonged use of such medications can lead to debilitating side effects ranging from tolerance or dependence (physical and psychological) to exacerbation of other chronic health conditions, making it essential to explore alternative interventions. This approach creates clinical opportunities for ketamine's use as a monotherapy and multimodal agent due to its unique qualities. From its origins as a potent anesthetic and analgesic agent to its current exploration as a novel treatment in psychosomatic disorders, ketamine's pharmacology continues to be an area of active research and development

Mechanisms at the Receptor Level [3-5]

There are numerous mechanisms for ketamine's analgesic, anesthetic, and immunomodulatory effects. Its most important pharmacological properties are derived from dose-dependent, non-competitive antagonism of the N-methyl-D-aspartate (NMDA) receptor. Commonly activated by glutamate, an excitatory amino acid, NMDA receptors are involved in neurotransmission of nociception and found centrally (brain and dorsal horn of spinal cord) and peripherally, which serve as the target for transdermal application. It's important to note that there are multiple binding sites on and within the receptor, which account for ketamine's myriad actions. One such example is allosteric antagonism of the NR2B subunit, known to be involved in the phenomena of emotional perception and memory of pain. Other analgesic and anesthetic mechanisms include interaction with opioid receptors (mu, kappa, and delta), muscarinic receptors, Na/K ion channels, and MOA transporters (serotonin and dopamine). Immunomodulation is achieved by direct inhibition of nitric oxide-synthase and activity on toll-like receptors such as AMPA receptors, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid, which lead to down regulation of pro-inflammatory responses and gene expression. Ketamine's peripheral pharmacological actions are dose-dependent with a range of affinity for receptors and specific binding sites.

Plasma concentrations associated with analgesia and inhibition of inflammatory mediators are in the low to intermediate micromolar ranges (0.3-1μM and 10-100 μM) and (≥ 100μM), respectively. When administered transdermally, higher local tissue concentrations may occur, ultimately benefiting the patient with different mechanisms working synergistically.

Additionally, NMDA intrachannel binding shortens the opening time, which decreases the amplification of the response to a repeated stimulus, also known as "wind up". This phenomenon is considered as an elementary form of CNS sensitization and antagonism is more important if the NMDA channel has been previously opened by glutamate. This "use dependence" concept explains why ketamine analgesic properties are efficient if the pain is chronic and/or due to inflammation. Interactions between opioid and NMDA receptors explain the antihyperalgesic properties of ketamine, although the connections are still unclear. Opioids favor phenomena of acute and chronic tolerance, termed opioid-induced hyperalgesia. These effects are dose-dependent, resulting from the involvement of NMDA receptors in the CNS, leading to signaling between surface receptors of the same cells. Following the activation of opioid receptors and protein kinase C (pkC), a cascade of events (pkC activation, prostaglandin and nitric oxide systems, and transcriptional changes) leads to a down-regulation (underlying tolerance) and a blunted response of opioid receptors (underlying hyperalgesia). The antagonism of NMDA receptors allows ketamine to exert a preventive action on these phenomena.

Safety in the Periphery [5-7]

Considering the limitations of existing administration routes, transdermal ketamine appears to be a promising alternative with an excellent side effect profile. This approach utilizes the skin as a reservoir, providing dilution and a sustained release into the circulatory system, bypassing the gastrointestinal (GI) tract and hepatic first-pass metabolism. Maintaining a slow and sustained release is critical for ketamine, whose rapid sedative, dissociative, and cardiovascular effects tend to disappear quickly at lower doses. As a moderately lipophilic molecule, ketamine is capable of penetrating the skin via transdermal application and has been dosed from 0.5% to 10% in creams, ointments, and patch systems. Pharmacokinetic analyses in both animal and human trials continue to assuage ketamine's safety concerns. A proof-of-concept study by Akan et al investigated the effects of transdermal ketamine in rodent behavioral models with a 5% ointment applied to the dorsal horn twice daily for two days and then analyzed the serum concentrations of ketamine, and its primary metabolite norketamine.

The data revealed detectable levels (10-20 ng/mL) over 24 hours without any sedative or hemodynamic effects. A double-blind placebo-controlled crossover trial by Finch et al displayed that 10% topical ketamine lacks any detectable systemic absorption and appears safe in adults with the most common adverse effects being mainly dermatologic (skin irritation, pruritic plaque, and allergic reaction). A pilot study by Morley-Forster et al assessed the safety and systemic absorption of external ketamine in patients with neuropathic pain. In this trial, 9 participants applied 10% gel 3 times a day with serum levels checked at days 0, 3, and 7. All levels were below 10 ng/mL and the only reported side effects were itching, mild burning, and nausea. Overall, external ketamine is well-tolerated in adults with only local adverse effects and deserves more comprehensive studies to bolster its use in clinical practice.

Therapeutic Roles: Multimodal Analgesia and Monotherapy [4,5,7,8]

The majority of efficacy data is derived by case reports, case studies, pilot trials, and retrospective studies investigating both nociceptive and neuropathic pain (+/- inflammation). While this approach may be inherently limited, the evidence in favor of exploring ketamine's optimum vehicle, doses, frequencies, and patient populations continues to grow and the need for more robust research remains warranted.

Neuropathic pain results from injury to the somatosensory system (lesion, disease) and can involve peripheral and central sites; manifestations include spontaneous (paresthesia, pain), negative (hypoesthesia, hypoalgesia), and positive (allodynia, hyperalgesia) sensory symptoms. Positive symptoms may include peripheral sensitization, central sensitization in the spinal cord, and central changes. Sensitization, or pain 'wind-up', perpetuates chronic neuropathic pain even when ongoing peripheral sensory input is absent. "Wind-up" is thought to cause allodynia, hyperalgesia, and hyperpathia. Several classes of analgesics exhibit partial efficacy (antidepressants, anticonvulsants, and opioids) with most limited by negative systemic effects. Recent improvements in our understanding of the underlying pathophysiology of neuropathic pain have led to prioritization of clinical efficiency and efficacy of treatments and yielded the idea of a "multimodal analgesia". This approach is defined by utilizing mechanistically-diverse analgesics to effectively manage pain and mitigating both reliance on a single therapy and adverse effects. With NMDA receptors present throughout the CNS and periphery (nerves and tendons) and interaction with various other receptors, channels, and transporters, transdermal ketamine has a role in refractory neuropathic, inflammatory, and nociceptive pain as evidenced by its limited but increasing use in monotherapy and multimodal approaches.

Complex Regional Pain Syndrome [5,7,10]

Complex Regional Pain Syndrome (CRPS) is a form of chronic pain affecting the legs or arms, which can be triggered by injury (fracture, trauma, surgery), illness, or nerve damage (lesions or inflammation). Its two forms are divided by the absence (CRPS-1) and presence (CRPS-2) of nerve damage. This malady presents an interesting opportunity to showcase the range of ketamine's pharmacological properties in both nociceptive and neuropathic pain (+/- inflammation) as monotherapy and in combination with other analgesics. A double-blind placebo-controlled crossover trial by Finch et al examined topical ketamine gel (0.5 mL of 10%, 50 mg) in twenty patients with CRPS and reported reduction in allodynia and punctate responses on the symptomatic limb 30 minutes after application; this was due to a local action because application to the healthy limb had no such effect. A case report by Kessel Hesselink et al described topical ketamine 10% cream applied thrice daily reduced pain more than 50% after one month in a wheelchair-bound patient with CRPS type 1 as well as swelling and skin discoloration in both lower extremities. A stepwise multimodal approach utilizing ketamine 10%, amitriptyline 5%, and dimethylsulfoxide (DMSO) 50% was attempted in a case report by Kopsky et al. Amitriptyline was applied initially for 1 month, followed by ketamine, and then DMSO. The patient reported an additional 10-20% decrease in pain level following amitriptyline.

Acute Pain: Venipuncture [11]

Emergency medicine provides another opportunity to compare ketamine to other agents when treating acute, nociceptive pain, which arises from many medical procedures such as establishing intravenous (IV) access for blood sampling and fluid administration. A prospective, double-blind randomized controlled trial by Heydari et al evaluated the efficacy of ketamine 10% cream against EMLA cream (lidocaine/prilocaine 2.5%/2.5%) in 300 patients who required venipuncture during their care within a health system. The primary and secondary endpoints were reduction of reported pain severity score and onset of local anesthesia and side effects, respectively. The results showed no statistically significant difference in efficacy between ketamine and EMLA. On the other hand, the rate of complications and adverse events was significantly higher in the EMLA group. This study design reinforces ketamine's growing potential by combining a larger, more robust data set with another clinical use for external ketamine, acute vs chronic pain.

Conclusion

The history of development and diverse clinical uses are a testament to ketamine's almost unparalleled pharmacological versatility and potential across medical fields.

From its origins as a potent anesthetic and analgesic agent to current exploration as a novel treatment in psychosomatic disorders, ketamine's pharmacology continues to be an area of active research and development. With NMDA receptors present throughout the CNS and periphery (nerves and tendons), transdermal administration has a role in neuropathic, inflammatory, and nociceptive pain. It is increasingly used for pain management and palliative care as both monotherapy and adjunct to standard of care. Low to intermediate doses (5-10%) produce a potent analgesic effect, making it a suitable alternative for individual cases of refractory pain after opioids and other adjuvants have been exhausted. While the evidence regarding efficacy for chronic pain management is limited, it should be concluded that ketamine may provide short-term benefits in chronic pain. Given the rise in compounding, it is imperative that physicians become familiar with the mechanisms, appropriate doses, and adverse effects to treat patients experiencing opioid tolerance, inflammatory pain, neuropathy, nociceptive pain or a combination of these factors.

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