Clinical and Practical **Psychopharmacology**

Intranasal Drug Delivery in Neuropsychiatry: Focus on Intranasal Ketamine for Refractory Depression

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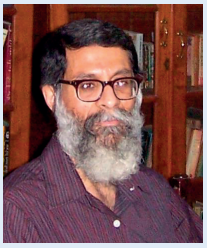

Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

Intranasal drug delivery (INDD) systems offer a route to the brain that bypasses problems related to gastrointestinal absorption, first-pass metabolism, and the blood-brain barrier; onset of therapeutic action is rapid, and the inconvenience and discomfort of parenteral administration are avoided. INDD has found several applications in neuropsychiatry, such as to treat migraine, acute and chronic pain, Parkinson disease, disorders of cognition, autism, schizophrenia, social phobia, and depression. INDD has also been used to test experimental drugs, such as peptides, for neuropsychiatric indications; these drugs cannot easily be administered by other routes. This article examines the advantages and applications of INDD in neuropsychiatry; provides examples of test, experimental, and approved INDD treatments; and focuses especially on the potential of intranasal ketamine for the acute and maintenance therapy of refractory depression.

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Clinical Question

Intravenous ketamine infusion has been found safe[1] and effective[2,3] as a treatment for medication-refractory depression; suicidal symptoms also attenuate.[4] The benefits, however, are transient and seldom persist beyond 1–2 weeks.[5] Some data suggest that repeated infusions, such as on alternate days, prolong the duration of response.[6] However, frequently repeated intravenous ketamine infusion is not a practical treatment strategy for maintenance therapy in patients who relapse after response to ketamine and subsequent maintenance with conventional antidepressant medication. So, how may ketamine responders be treated in the long term to prolong the treatment response?

Introduction

Medications in neuropsychiatric practice are most commonly administered either orally or parenterally. Intranasal drug delivery (INDD) systems, however, have been available for decades; there is a large body of animal literature on the subject, this route of drug administration has long been used in several medical fields, and, more recently, INDD has gained importance even in neuropsychiatry. This article will examine INDD in neuropsychiatry with particular focus on the use of intranasal ketamine in the treatment of refractory depression.

Why Deliver Drugs Intranasally?

INDD systems cater to different situations and needs that are not necessarily mutually exclusive (Table 1). These are briefly discussed below.

Local action. In otorhinolaryngologic practice, medications have for long been administered intranasally (as drops or sprays) for local action. In neuropsychiatry, a patient may require a nasal decongestant if a stuffy nose results from the use of sildenafil or a tricyclic antidepressant drug.[7,8]

Rapid onset of action. INDD is associated with a fast onset of action. This is because there is quick drug absorption from the rich, intranasal vascular bed. Peak blood levels are rapidly attained.[9] As examples, sumatriptan nasal spray[10] and intranasal lidocaine[11] both afford rapid relief from acute migraine. Nicotine nasal spray affords rapid relief from craving in nicotine-dependent individuals.[12]

Bypassing the blood-brain barrier. INDD can deliver drugs directly to the central nervous system, bypassing the blood-brain barrier. Absorption occurs through the olfactory epithelium, and transport through the cribriform plate, via the olfactory pathways, into the brain.[9] An example is the use of insulin spray as an experimental treatment for cognitive decline and Alzheimer's disease.[13] INDD can also be used to study brain functioning. For example, a peptide that interferes with the interaction between D_1 and D_2 receptors was shown to have antidepressant action in the forced swim test in rodents for up to 2 hours after intranasal administration. Inhibition of D_1-D_2 receptor interaction was demonstrated in the prefrontal cortex.[14]

Clinical Points

- Intranasal drug delivery (INDD) systems allow for improved bioavailability, avoidance of the inconvenience and discomfort of parenteral administration, rapid onset of therapeutic action, and bypassing of the blood-brain barrier.
- INDD has been used for test, experimental, and approved indications to treat conditions such as migraine, acute and chronic pain, Parkinson disease, disorders of cognition, schizophrenia, social phobia, autism, and refractory depression.
- Intranasal ketamine is emerging as a potential alternative to intravenous ketamine infusions for patients with refractory depression; at present, however, the data are limited, and so the treatment remains emphatically experimental.

Improvement of bioavailability. INDD can improve bioavailability of drugs such as peptides that may be digested rather than absorbed after oral administration. Examples of approved and experimental treatments include desmopressin for pediatric[15] and geriatric[16] enuresis, insulin for disorders of cognition,[13] and oxytocin for a variety of experimental indications (see below).

Avoidance of parenteral administration. INDD can improve the convenience of drug administration, as with intranasally administered ketamine[17] in place of intravenously infused ketamine for patients with refractory depression.

Table 2 lists a few examples of INDD applications in neuropsychiatry; in this regard, ketamine and oxytocin are perhaps the best-studied agents. Aqueous (4%) lidocaine nasal drops have demonstrated rapid efficacy in episodes of acute migraine.[11] Intranasal ropinirole[18] and other intranasal treatments are being studied for Parkinson disease, and intranasal insulin and other treatments are being studied for mild cognitive impairment and early Alzheimer's disease.[13,19] A neurosteroid, PH94B, was successfully trialled for social anxiety in women.[20] INDD is also being studied for brain neoplasms.[21] This list is not exhaustive.

Intranasal Oxytocin

Intranasal oxytocin may influence social relationships and has been much studied in this regard; notwithstanding the media hype over this so-called love hormone, research has not resulted in straightforward conclusions.[22,23]

There has been much investigation of the possible benefits of intranasal oxytocin for schizophrenia,[24] with improvements recorded in domains such as clinical symptom ratings[25] and social cognition.[26] Intranasal oxytocin has also been studied for autism. For example, 15 children and adolescents with autism spectrum disorder showed improvement during 12 weeks of treatment in the domains of social functioning, repetitive behaviors, and anxiety; some improvements persisted as long as 3 months later.[27] A randomized controlled trial, however, failed to demonstrate efficacy.[28] Some benefits with intranasal oxytocin have also been recorded in social anxiety.[29] Intranasal oxytocin is also being studied for the prevention of posttraumatic stress disorder in persons who experience trauma.[30]

Table 1. Reasons to Consider Intranasal Drug Delivery Systems

Intranasal drug delivery is used in different situations and to cater to different needs that are not mutually exclusive:

1. For local action
2. For faster onset of action
3. To bypass the blood-brain barrier
4. For better bioavailability
5. To avoid parenteral administration

Table 2. Examples of Experimental Intranasal Drug Delivery Applications in Neuropsychiatry

Lidocaine nasal drops for acute migraine
Intranasal ketamine for acute and chronic pain, autism, depression, and other conditions
Intranasal oxytocin for schizophrenia, autism, and other conditions
Intranasal neurosteroids for social anxiety
Intranasal insulin and other treatments for mild cognitive impairment and early Alzheimer's disease
Intranasal ropinirole for Parkinson disease
Intranasal treatments for brain tumors

Intranasal Ketamine

Intranasal ketamine attenuates pain in the emergency room in children[31] and adults.[32] Intranasal ketamine also reduces the severity of pain in migraine.[33] Wink et al[34] reported a 29-year-old woman with autism who was treated with intranasal ketamine (20–60 mg) on 12 dosing occasions across 6 weeks. She showed improvements in mood, social interactions, flexibility, tolerance of changes in routine, motivation, and concentration. Adverse events were mostly mild; the most prominent was headache, which lasted for up to 10 hours after a treatment. A case report also showed benefits with intranasal ketamine in depression.[35]

In a randomized, double-blind, saline-controlled, crossover trial conducted in 20 patients with major depression, Lapidus et al[17] found that a single intranasal dose of ketamine (50 mg) outperformed saline by 7.6 points on the Montgomery-Asberg Depression Rating Scale as assessed 24 hours after dosing; the response rate was 44% vs 6%, respectively. Anxiety ratings also decreased significantly more with ketamine. However, there was no significant separation between ketamine and saline at 3 and 7 days posttreatment. In this study, intranasal ketamine was well tolerated, with few, mild, and very transient adverse effects such as feelings of unreality. There was also a small and transient increase in systolic blood pressure (by 7.6 mm Hg at 40 minutes).

Maintenance treatment with intravenous ketamine infusion maintains treatment gains.[6] Because the antidepressant benefits of intranasal ketamine wear off within 3 days,[17] might maintenance treatment with intranasal ketamine be a viable treatment strategy to extend treatment gains? Regrettably, this has not been investigated in the context of depression. However, in a retrospective chart review of 12 treatment-refractory bipolar youth (10 male; age, 6–19 years) with fear of harm phenotype, Papolos et al[36] reported that

maintenance therapy with intranasal ketamine (30–120 mg) resulted in improvements in anxiety, aggression, fear of harm, cognition, behavior, sleep, and other symptoms. Interestingly, hypomanic symptoms also attenuated with intranasal ketamine. Adverse events were mostly dissociative in nature, and all remitted within an hour, without medical intervention. Intranasal ketamine dosing had to be repeated every 3–7 days to maintain the experienced benefits. In many patients, other medications could be tapered or discontinued. No patient dropped out of treatment, and, at the time of writing, 1 patient had been receiving maintenance intranasal ketamine for over 4 years.

This author (Andrade, unpublished data) has personal experience with using intranasal ketamine in the dose of 50–80 mg per treatment occasion, once in 2–3 days, as maintenance therapy for a 25-year-old, medication- and electroconvulsive therapy–refractory, functionally impaired man with severe depression. The treatment has been ongoing for the past 26 months and keeps depression at bay only when punctually administered. It has been the only intervention to have helped the patient during a 10-year span of life-crippling depressive illness.

One hopes that there will soon be parallel-group, randomized controlled trials examining the safety and efficacy of repeated dosing with intranasal ketamine, followed by trials of its safety and efficacy during maintenance therapy in treatment-refractory depressed patients. Until data from such trials become available, intranasal ketamine will remain an experimental treatment.

Parting Notes

1. The oral bioavailability of ketamine is only 8%–17% because of extensive first-pass metabolism[37,38]; bioavailability is slightly higher, at 29%, when the drug is administered sublingually.[39] Interestingly, both oral and sublingual ketamine have been trialled in depression. In a 4-week, proof-of-concept study, Irwin et al[40] administered oral ketamine (0.5 mg/kg/d) to 14 mildly anxious and depressed patients in hospice care. Four patients dropped out because of nonresponse, and 2, for reasons unrelated to ketamine. All 8 treatment completers showed improvements in anxiety and depression, the former occurring earlier than the latter. Lara et al[41] administered very low dose (10 mg) sublingual ketamine every 2–3 days or weekly to 26 outpatients with refractory unipolar or bipolar depression. Rapid and sustained improvement occurred in mood, cognition, and sleep in 20 patients (77%). The treatment was very well tolerated, with mild, transient light-headedness as the only common adverse effect. Other reports have also been published.[42–44] Oral ketamine has also been used to treat chronic pain.[45,46]
2. Inhalational drug delivery systems, such as those that deliver bronchodilators or steroids to the lungs, have long been used in medicine. These have found recent application in psychiatry, as well. Inhaled loxapine is approved in the United States and the European Union for acute agitation in schizophrenia and bipolar disorder. It is administered using a hand-held, single-dose, single-use device. The drug enters pulmonary alveoli and is quickly absorbed into the systemic circulation. Peak blood levels are attained in 2 minutes, and clinical benefits are evident as early as 10 minutes after drug administration. Inhalational loxapine is contraindicated in the presence of acute respiratory disease and in patients at risk of bronchospasm.[47]
3. Djupesland et al[48] provided an extensive review on anatomic, physiologic, and delivery technology issues related to INDD systems.

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