Journal of Clinical Anesthesia and Intensive Care

Commentary

Drug delivery via the upper nasal space: A novel route for anesthesiologists, intensivists and emergency department physicians?

Stephen Shrewsbury*, Jasna Hocevar-Trnka, John Hoekman

Impel NeuroPharma Inc., Seattle, WA, USA

*Author for correspondence:
Email: sshrewsbury@impelnp.com

Received date: December 11, 2020
Accepted date: February 19, 2021

Citation: Shrewsbury S, Hocevar-Trnka J, Hoekman J. Drug delivery via the upper nasal space: A novel route for anesthesiologists, intensivists and emergency department physicians? J Clin Anesth Intensive Care. 2021; 2(1): 8-14.

Keywords: Upper nasal delivery; Olanzapine; Precision Olfactory Delivery; Agitation; Psychiatric boarding; Autism; Schizophrenia; Bipolar disorder; Psychosis

Many drugs are effective systemically, but slow onset of non-intravenous routes of administration may limit their clinical utility. While anesthesiologists usually have intravenous (IV) access for drug delivery, other healthcare professionals in less controlled situations such as acute crises in the emergency room, critical care settings, or urgent needs in the community, may need non-invasive drug delivery [1].

One such situation is acute agitation. Limited approved options for the management of this difficult situation can lead to many hours of "boarding", where initial administration of strong sedatives can lead to heavily sedated patients lying on a gurney for several hours in the Emergency Department (ED). In turn this can delay diagnosis, appropriate triage and initiation of definitive treatment. Boarding increases the cost of observation and blocks ER access for other patients. There are even fewer options for treating acute agitation in the community creating a large unmet need. Delivery of a second generation antipsychotic, olanzapine, to the upper nasal space resulting in rapid blood levels to match those after intramuscular injection may address that need. This commentary refers to the recent phase 1 safety, pharmacokinetic (PK), and pharmacodynamic (PD) study in healthy adult volunteers, SNAP 101, which compared the results from the Precision Olfactory Delivery (or POD®) device, to intramuscular (IM) injection, and to oral disintegrating tablet (ODT) [2] and may suggest a future suitable option.

The Clinical Problem

Many clinical situations call for rapid systemic blood levels of drugs – both in the hospital and the community. Life-threatening emergencies span indications across many medical disciplines: seizures, coronary ischemia, diabetic ketoacidosis, trauma management. Other emergencies, often disabling, requiring rapid drug delivery are no less urgent and include acute agitation, migraine, off episodes in Parkinson's disease and febrile seizures. Furthermore, there are pathologies that require the rapid and effective delivery of life-saving drugs in the absence of a healthcare practitioner, such as anaphylactic shock or status epilepticus.

Recent advances in delivery technology have aimed at providing adequate systemic levels of required medication by consistent, reproducible delivery either to absorptive mucosal surfaces such as buccal mucosa [3], nasal mucosa [4], pulmonary epithelium [5-7], or by bypassing existing barriers such as with transdermal delivery systems [8,9]. Each of these options have their advantages and disadvantages – and none can be said to be perfect. The patient's individual needs and issues, the required medication, as well as the circumstances under which the medication can be delivered will determine the most appropriate option(s) for drug delivery. The advantages and disadvantages of non-injected routes of administration are summarized in Table 1.

For the anesthesiologist, IV access will likely always be required however not necessarily always easily achieved. While IV therapy is the gold-standard for sedation in case of major procedures, establishing an IV access may be challenging in a pediatric population due to the stress provoked

Route of delivery	Advantages	Disadvantages
Buccal	• Low risk of pain • Avoids first pass metabolism improving bioavailability over oral and rectal administration • May allow spitting out of product once effect achieved • Easy to administer • Can be self or caregiver administered	• Product development may be complex and take longer • Taste masking may be required • Dissolving drug may be swallowed • Not suitable for uncooperative patients • Patients can spit out the medication when unobserved • Slower onset (than IV)
Nasal	• Low risk of pain • Potentially reduce systemic side effects (for some preparations) • Direct delivery to site of action for nasal disease • Avoids first pass metabolism improving bioavailability over oral and rectal administration • Easy and fast delivery that increases patient's compliance • May allow rapid absorption and rapid onset of action • No sterile technique required • Immediately and readily available for all patients. • May allow future direct delivery to the cerebrospinal fluid and/or brain may be possible ("direct nose-to-brain") - upper nasal space only [25] • Useful for drugs that are active in low doses • Suitable for self-medication or caregiver administration • Can be used in nauseous patients	• Bad taste (may require some taste masking) • May drip from the nose • Mucosal health impacts absorption • Concentrated formulation may be required • Nasal formulations may be complex and costly • Nasal delivery device adds to cost of product • Availability of suitable and affordable delivery devices • Patient preference (may be culturally influenced) • Variable response may reduce confidence
Inhaled	• Drugs are delivered directly to their site of action in the lung for a localized effect (in lung diseases) • Lower doses for pulmonary disease are needed than when given systemically (oral or IV) • Rapid response compared to systemic delivery • Reduce systemic side effects (to drugs being administered for pulmonary disease) • Breath actuated dry powder systems may overcome manufacturing issues (stability of drug in HFA propellants) • Control of particle size dictates what airway level drug reaches • Can be used in nauseous patients	• Irritant effects on airways and mucosal surfaces • Delivery systems can be cumbersome and time consuming • Incorrect use of inhaler decreases therapeutic effect • Manufacturing of effective devices may be costly • Manufacturing and stability of formulation (if suspended in HFA propellant) may be complex

Transdermal	• Convenient • Low risk of pain • Self-administration by patients • Reduction of gastrointestinal side effects (compared to oral) • Eliminates frequent dosing • Stable plasma levels due to a constant drug concentration • Drug with a short half-life can be delivered easily • Ease of use enhances patient compliance • Generally inexpensive • Can be used in nauseous patients	• Limited range of drugs that can be delivered • Skin irritation and local or even systemic allergic reactions • Complex development pathway • Consistent drug delivery over time may be challenging (for depot patches)
Oral	• Minimal pain • Ease of use • Many medications available • Extended-release options allow reduced dosing frequency • Disintegrating tablets avoid "cheeking" and may speed absorption • Drug shelf-life stability high	• Slow onset of action • May have low bioavailability • Subject to variable absorption due to: » Recent food » Type of food » Gastro-Intestinal comorbidity or dysmotility • Reluctance to take if nauseated, or history of dysphagia • Subject to first pass metabolism
Rectal	• Minimal pain • No shot needed • Can be used in nauseous patients • May be less expensively formulated	• Variable first pass metabolism/bioavailability • Somewhat slow onset of action • Socially unacceptable for many patients (certainly in public) • Limited medications that can be delivered in this fashion

Table 1: Advantages and disadvantages of non-injected drug delivery.

by interaction with medical staff, separation anxiety, psychomotor restlessness caused by pain the child might be experiencing in trauma situations, and violent behavior disorders exacerbated under stress.

The usual practice for pediatric sedation is use of either oral or rectal sedation, [10] but these delivery routes require a considerable amount of time to take effect leading to delays in care and interrupted patient flow. Instead, use of nasally delivered anxiolytics such as midazolam, widely used for management of seizures [11], might be a preferred method of delivery. Pain relief is another important aspect of a pediatrician's clinical practice. The child's pain perception is affected by many factors and children are often anxious about any medical procedures, even minor ones. It has been shown that the nasal administration of a sedative with a quick onset is an effective and safe method to reduce anxiety and should be considered the first choice for procedural sedation in children [11].

The intensivist is faced with even greater challenges as Intensive Care Unit (ICU) patients may present with a unique set of problems that may jeopardize IV access. One of those situations is accidental catheter removal (ACR) in critically ill patients experiencing severe agitation. It is reported that 71% of critically ill patients experience psychomotor agitation driven by anxiety and delirium during their stay in the ICU [12]. ACR in critically ill patients can be associated with potentially life-threatening complications due to interruption of vital drug therapy such as inotropes/vasopressors or anti-epileptic

medications [13]. Establishing new IV access in such patients is an emergency procedure and may require sedation for IV access to be reestablished. This can be challenging as it often requires physical restraint and IM injection that carries the risk of accidental needle stick injury to health care personnel. Nasal delivery can be a safer option in this setting. Successful and rapid sedation of agitated patients in the ICU with nasal midazolam followed by definitive IV access has been reported [13]. The pharmacological treatment of agitation in the ICU is not well studied, but the present standard practice is to first ensure adequate pain control followed by addition of an anxiolytic and a neuroleptic if delirium is present [12,14]. While use of haloperidol in ICU settings is not well studied, it remains widely used because of its rapid onset of action, lowered risk of seizure, and a possible favorable effect on delirium [12]. However, side effects such as cardiac arrythmias, extrapyramidal symptoms and anticholinergic effects have been reported. Therefore, the use of new atypical antipsychotic drugs in ICU patients might be beneficial in case of contraindication or side-effects with haloperidol. To date, olanzapine is the only novel antipsychotic shown to be a safe and efficient alternative to haloperidol, and only in one study [15]. In the SNAP 101 study [2] the reported maximum plasma levels (C_{max}) of olanzapine following delivery of a novel powder formulation to the upper nasal space exceeded those following the corresponding IM dose, in the same healthy volunteers, but with faster time to maximum concentration (T_{max}). The median T_{max} after IM olanzapine 5 mg was 20 minutes versus 15 minutes for INP105 5 mg and at the 10 mg doses the corresponding times were 15 and 10 minutes respectively [2] (see below and Figure 1). This data may be of interest to anesthesiologists and intensivists.

Caregivers in EDs are often faced with patients experiencing life threatening seizures, acutely agitated or combative patients, and trauma patients. In most of those situations, use of oral therapies may not be feasible due to various clinical factors (e.g., level of consciousness, intolerance, obstructions, trauma, pending general anesthesia) [16]. Severely agitated, traumatized or hemodynamically compromised patients present a challenge for establishing IV access in settings where staff with required technical skills may not be readily available and a danger of injury to caregivers during IM administration of medications to agitated patients is high. The practice of nasal administration of sedatives, hypnotics, analgesics, and even antipsychotics has been reported as a growing trend for an alternative route of administration by caregivers in EDs, prehospital and outpatient settings, situations where IV access can be challenging [17].

History of Nasal Drug Delivery

Nasal delivery of drugs has been around for many years dating back even to ancient Ayurvedic medicine [18], possibly 6,000 years BCE. Ancient Egyptians, Greeks and Romans certainly used perfumes, may have burnt herbs for sniffing, and at least the Romans used smelling salts. More recently tobacco (as snuff from the 16th century), and a wide range of hallucinogens have been self-administered nasally. Although the use of peyote dates back to 3000 years BCE, it was only recently [19] that the technique of atomizing perfumes was further developed to deliver liquid sprays inside the nose.

Recently, attempts have been made to understand and improve options for the nasal route of delivery [20], but this has generally been by altering the formulations delivered, by the addition of absorption enhancers and mucoadhesives to try to prevent gravitational loss, or slow mucociliary clearance, while still being delivered to the anterior nose and lower nasal space [21]. Nasal delivery may offer

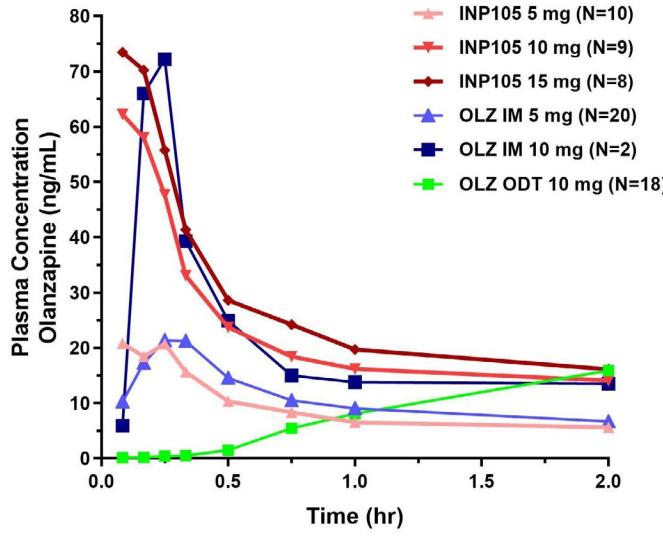

Figure 1: Mean plasma olanzapine concentrations from 0 to 2 hours (SNAP 101 data [2]). IM: Intramuscular; INP105: Investigational Product (OLZ delivered by POD (Precision Olfactory Delivery) device; ODT: Oral Disintegrating Tablet; OLZ: Olanzapine.

an alternative route of administration for not only small molecules, but also for large molecules such as peptides and proteins and even for vaccines, e.g., FluMist®, and perhaps in the future, whole cells, for which oral administration is unfeasible [22].

Nasal administration, until recently, consisted of the presentation of a cloud of droplets delivered by a simple atomizer to deposit in the vestibule or lower nasal space, anterior to the nasal valve. Liquid formulations, delivered as large droplets, coalesce and with a patient seated or standing, may run out of the front of the nose onto the upper lip or down the back of the nasopharynx to be swallowed. In either case, the delivered drug is then not available for absorption across the multilayered respiratory mucosa in the front and lower parts of the nose. Delivery to the lower nasal space, or nasal vestibule, was most used for treatment of local allergic disease, or symptomatic management of congestion and blockage secondary to local infections of the nose or sinuses. Most nasal delivery programs for systemically acting drugs have focused on trying to increase absorption through the mucosa of the lower nasal space rather than to target a different part of the nose where absorption can occur more readily. For local diseases of the nose, systemic drug absorption may not be desirable with either chronic repetitive administration (e.g., with nasal corticosteroids), or with acute symptomatic treatment (e.g., the decongestant pseudoephedrine which may act as a systemic stimulant). More recently the OptiNose® technology was developed that uses a patient's breath for propulsion of a powder drug formulation into the nose [23,24]. Compared with traditional spray pump delivery, the OptiNose® provided significantly larger drug depositions above the nasal valve in the upper posterior segment of the nasal passage and reduced anterior deposition [25,26].

Slow, or incomplete, absorption of a known drug from an oral dose may be ineffective – especially in an urgent situation. Upper nasal space delivery might be a favorable alternative route for systemic drug delivery in those cases providing rapid, efficient and non-invasive methods for targeted drug delivery. The upper nasal space provides a large surface area which is highly vascularized, allowing for a high permeability to drugs, only now being specifically targeted.

To target the upper nasal space, Impel NeuroPharma (Impel) has been developing the POD device, that precisely and reproducibly delivers drugs (both liquid and powder versions are in clinical development) [18] to the highly vascular mucosa of the upper nasal space. Proper design of drug delivery devices plays an important role in ensuring that the entire drug dose is delivered to the target site in the nasal cavity. The POD device is a novel, self- (or caregiver-) actuated, propellant-powered system, tailored to each individual drug formulation currently being developed. The propellant pushes the drug past the nasal valve and into the olfactory epithelium lined upper nasal space. Here the approximately 9 cm^2 [*27]* highly vascular, ciliated epithelium is less prone to edema and swelling. This epithelium is thin and regular and covered in less mucus which may allow the deposited drug to be absorbed quickly and efficiently into the systemic circulation. The administration of a single 5 mg dose (of INP105) takes one actuation (one squeeze of the device) and is complete within ~0.3 seconds.

Impel has published data with three different drug-device combination products all designed to provide rapid blood levels. The lead POD clinical program is with dihydroergotamine mesylate (DHE) – a still popular treatment at headache centers for acute migraine even after 70 years since it was first approved and 25 years since a nasal formulation, Migranal®, was approved [19]. The STOP 101 study compared 2 mg DHE delivered by the traditional nasal spray (Migranal), to 1.45 mg DHE delivered by the POD system to the upper nasal space (and a third treatment, IV DHE often used in headache centers) [27]. Faster and 4-fold higher absorption as seen by the C_{max} reached was observed with 1.45 mg of DHE delivered by POD compared to Migranal. POD delivery of DHE approached the same blood level as IV DHE 1.0 mg injection by 20 minutes, and matched it from T_{max} (30 minutes) all the way to 48 hours, while the C_{max} reached $1/10^{th}$ of the level of IV administration [27].

Olanzapine (OLZ) has been approved for use as an IM injection of 10 mg for patients with acute agitation on a background of schizophrenia or bipolar disorder. The SNAP 101 data showed that delivery of a novel spray dried formulation of OLZ (at doses of 5 mg, 10 mg or 15 mg) by the POD device resulted in similar levels of, but faster time to reach the C_{max} of OLZ compared to IM injection of the same dose in healthy adult volunteers. Absorption was also much faster than the less extensively absorbed 10 mg ODT [2]. These doses were self-administered by conscious cooperative adults, but the POD delivery technology has the potential to be delivered by caregivers (for example to patients with early morning off episodes in Parkinson's disease), before resorting to injection, thus avoiding the risk of needle stick injury to either patient or caregiver (such as in cases of acute agitation). IM injection especially to a restrained patient may lead to a breakdown of trust and lack of even minimal cooperation. The POD device can potentially even be used in an unconscious patient lying on the floor. This may allow administration of a range of medications where rapid and consistent blood levels are needed while sparing the requirement for syringe, needle and IV (or IM) access. The POD system is propellant-powered so is independent of a patient's breathing cycle or ability to sniff, and potentially less affected by the position of the patient's head. It also allows administration of drugs that otherwise might be affected by gastrointestinal dysmotility, nausea, or where absorption may be hampered by recently ingested food, or where first pass metabolism in the liver of a well absorbed drug leads to inadequate blood levels.

The Clinical Data

The clinical data published from the phase 1 SNAP 101 trial of OLZ in healthy adult volunteers illustrates the opportunities that this technology may provide [2]. The study compared the effects (safety, PK and PD) in a two period, cross over study with a 2-week washout between periods. In the first period, 40 adults randomly received one of either OLZ IM 5 mg (20 subjects), OLZ IM 10 mg (2 subjects, before this dose was discontinued) or OLZ ODT 10 mg (18 subjects). In the second period, in 3 staggered cohorts, 37 subjects received INP105 5 mg (n=10), 10 mg (n=9), 15 mg (n=8), or placebo (n=10) (in a 3:1 active:placebo double blind assignment in each cohort). The speed of initial absorption measured as the C_{max} and extent of absorption, measured as the area under the curve (AUC), of plasma concentration versus time was similar to the equivalent dose when injected IM (Figure 1). In the healthy volunteers studied the 3 doses of POD-OLZ (known as INP105 in this program) of 5 mg, 10 mg, and 15 mg, delivered as 1, 2 or 3 actuations respectively, were well tolerated with fewer adverse events reported than with the IM injection of OLZ 5 mg, 10 mg, or with ODT 10 mg. Most TEAEs were reported once only. Those reported more than once in any one group (Table 2) were: dizziness (4 subjects with OLZ IM 5

	Number (%) of Subjects						
	OLZ IM 5 mg (n=20)	OLZ IM 10 mg (n=2)	OLZ ODT 10 mg (n=18)	INP105 5 mg (n=10)	INP105 10 mg (n=9)	INP105 15 mg (n=8)	Placebo (n=10)
Any adverse event	18 (90.0)	2 (100)	15 (83.3)	8 (80.0)	6 (66.7)	6 (75.0)	1 (10.0)
Dizziness	4 (20.0)	1 (50.0)	0	1 (10.0)	2 (22.2)	0	0
Dizziness postural	6 (30.0)	1 (50.0)	8 (44.4)	2 (20.0)	1 (11.1)	1 (12.5)	0
Fatigue	0	0	0	2 (20.0)	0	0	0
Headache	2 (10.0)	0	6 (33.3)	1 (10.0)	0	1 (12.5)	0
Hypotension	1 (5.0)	2 (100)	2 (11.1)	0	2 (22.2)	0	0
Nasal congestion	0	0	0	0	1 (11.1)	2 (25.0)	0
Nausea	0	0	2 (11.1)	0	1 (11.1)	0	0
Orthostatic hypotension	3 (15.0)	0	0	1 (10.0)	0	2 (25.0)	0
Orthostatic tachycardia	2 (10.0)	0	0	1 (10.0)	0	0	0
Restlessness	0	0	2 (11.1)	0	1 (11.1)	1 (12.5)	0

Table 2: Incidence of treatment-emergent adverse events (with at least 2 events in any one group) (Safety Population) (SNAP 101 data [2]). IM: Intramuscular; INP105: Investigational Product (OLZ delivered by POD (Precision Olfactory Delivery) device; ODT: Oral Disintegrating Tablet; OLZ: Olanzapine.

mg, 2 subjects with INP105 10 mg), postural dizziness (6 subjects with OLZ IM 5 mg, 8 with OLZ ODT 10 mg, 2 with INP105 5 mg), fatigue (2 with INP105 5 mg), headache (2 with OLZ IM 5 mg, 6 with OLZ ODT 10 mg), hypotension (2 with OLZ IM 10 mg, 2 with OLZ ODT 10mg, 2 with INP105 15 mg), nasal congestion (2 with INP105 15 mg), orthostatic hypotension (3 with OLZ IM 5 mg, 2 with INP105 15 mg), orthostatic tachycardia (2 with OLZ IM 5 mg), and restlessness (2 with OLZ ODT 10 mg). Of note this powder formulation of OLZ was well tolerated, even at the maximum 15 mg dose tested (requiring 3 actuations), with fewer reported adverse events than for the corresponding doses delivered by IM injection or given orally (OLZ ODT).

In addition to focusing on safety of the novel formulation when delivered to the upper nasal space and comparing the PK with the approved OLZ IM 5 mg and OLZ ODT 10 mg doses, PD data was collected from these healthy volunteers using a Visual Analog Scale (VAS), Agitation/Calmness Evaluation Scale (ACES), and Digit Symbol Substitution Test (DSST). These assessments showed dose related CNS effects with INP105 versus double blind placebo – starting as early as 15 minutes after dosing. OLZ ODT 10 mg by comparison had few effects until 2 hours post administration. In addition, as it was anticipated that hypotension, and/or orthostatic hypotension would be seen with OLZ, blood pressure was carefully monitored in both periods. Reassuringly, there was little change seen post dosing with INP105 [2].

What Does This Data Mean for Physicians and Patients?

As medicines become more and more sophisticated, their ability to affect rapid therapeutic response may be limited not by the effectiveness of the molecule itself but the speed with which an effective plasma concentration can be reached and the drug delivered to the site of action. In recent decades this has resulted in more interest in how and where the drug is delivered to the body. In particular, can it be done without resorting to an injection either into a vein, muscle, or below the skin? IV injection remains the "gold standard" for getting maximum drug levels almost as rapidly as it is injected or infused but remains impractical for many clinical situations. IV injection is practical in situations where IV access is otherwise required, such as with anesthesia, and it will likely always remain so – but requires a healthcare practitioner to administer.

Anesthesiologists and other intensivists may welcome access to products that deliver, without a needle, effective drugs as part of their premedication regimen. This may be especially true in a pediatric population, or urgent situations in agitated patients in the ICU. To induce relaxation in an agitated patient, facilitating easier subsequent intravenous access without causing excessive sedation, may improve the ability to triage and initiate definitive treatment sooner. ED physicians (and psychiatrists) and their staff coping with patients suffering acute agitation with a background of either mental illness, such as schizophrenia or bipolar disorder or neurodevelopmental

disorders such as autism, are also likely to appreciate the opportunity to administer an effective therapy to a compliant patient without a needle. This will also be appreciated by the patients themselves. The results from the SNAP 101 study suggest that this is a potentially realizable objective [2].

There are advantages and disadvantages for all the non-injected delivery systems (Table 1), and each will have their advocates and detractors. No one option may suit every patient, or every occasion, but as more medicines become available and the opportunity to treat many previously untreatable conditions becomes realizable, the delivery of the medicine to the systemic circulation rapidly and consistently may be crucial for the success of the product, and certainly more popular with patients than reaching for the syringe and needle when a rapidly delivered and effective dose of medicine is needed. Of the non-injection options, delivery to the upper nasal space may be a viable, reliable, and effective route of administration.

References

1. Park C, Meghani NM, Amin HH, Nguyen VH, Lee BJ. Patient-centered drug delivery and its potential applications for unmet medical needs. Therapeutic Delivery. 2017 Aug;8(9):775-90.
2. Shrewsbury SB, Hocevar-Trnka J, Satterly KH, Craig KL, Lickliter JD, Hoekman J. The SNAP 101 Double-Blind, Placebo/Active-Controlled, Safety, Pharmacokinetic, and Pharmacodynamic Study of INP105 (Nasal Olanzapine) in Healthy Adults. The Journal of Clinical Psychiatry. 2020 Jun 30;81(4):0-.
3. Shojaei AH. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharm Sci. 1998 Jan 1;1(1):15-30.
4. Illum L. Nasal drug delivery—Recent developments and future prospects. Journal of Controlled Release. 2012 Jul 20;161(2):254-63.
5. Rau JL. The inhalation of drugs: advantages and problems. Respiratory Care. 2005 Mar 1;50(3):367-82.
6. Dhand R. Inhaled drug therapy 2016: the year in review. Respiratory Care. 2017 Jul 1;62(7):978-96.
7. Newman SP. Drug delivery to the lungs: challenges and opportunities. Therapeutic Delivery. 2017 Jul;8(8):647-61.
8. Paudel KS, Milewski M, Swadley CL, Brogden NK, Ghosh P, Stinchcomb AL. Challenges and opportunities in dermal/transdermal delivery. Therapeutic Delivery. 2010 Jul;1(1):109-31.
9. Guy RH. Transdermal drug delivery. Drug delivery. 2010:399-410.
10. Coté CJ, Wilson S. Guidelines for monitoring and management of pediatric patients before, during, and after sedation for diagnostic and therapeutic procedures: update 2016. Pediatric Dentistry. 2016 Jul 15;38(4):13E-39E.
11. Tazeroualti N, De Groote F, De Hert S, De Ville A, Dierick A, Van der Linden P. Oral clonidine vs midazolam in the prevention of sevoflurane-induced agitation in children. A prospective, randomized, controlled trial. British Journal of Anaesthesia. 2007 May 1;98(5):667-71.
12. Chevrolet JC, Jolliet P. Clinical review: agitation and delirium in the critically ill–significance and management. Critical Care. 2007 Jun;11(3):1-5.
13. Shrestha GS, Joshi P, Bhattarai K, Chhetri S, Acharya SP. Intranasal midazolam for rapid sedation of an agitated patient. Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine. 2015 Jun;19(6):356.
14. Tsuruta R, Fujita M. Comparison of clinical practice guidelines for the management of pain, agitation, and delirium in critically ill adult patients. Acute Medicine & Surgery. 2018 Jul;5(3):207-12.
15. Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. Intensive Care Medicine. 2004 Mar;30(3):444-9.
16. Corrigan M, Wilson SS, Hampton J. Safety and efficacy of intranasally administered medications in the emergency department and prehospital settings. American Journal of Health-System Pharmacy. 2015 Sep 15;72(18):1544-54.
17. Bailey AM, Baum RA, Horn K, Lewis T, Morizio K, Schultz A, et al. Review of intranasally administered medications for use in the emergency department. The Journal of Emergency Medicine. 2017 Jul 1;53(1):38-48.
18. Putheti RR, Patil MC, Obire O. Nasal Drug delivery in Pharmaceutical and biotechnology: present and future. E-Journal of Science & Technology. 2009 Sep 1;4(3).
19. Illum L. Nasal drug delivery—Recent developments and future prospects. Journal of Controlled Release. 2012 Jul 20;161(2):254-63.
20. Djupesland PG. Nasal drug delivery devices: characteristics and performance in a clinical perspective—a review. Drug Delivery and Translational Research. 2013 Feb;3(1):42-62.
21. Ugwoke MI, Agu RU, Verbeke N, Kinget R. Nasal mucoadhesive drug delivery: background, applications, trends and future perspectives. Advanced Drug Delivery Reviews. 2005 Nov 3;57(11):1640-65.
22. Van Velthoven CT, Kavelaars A, Van Bel F, Heijnen CJ. Nasal administration of stem cells: a promising novel route to treat neonatal ischemic brain damage. Pediatric Research. 2010 Nov;68(5):419-22.
23. Djupesland PG, Skretting A, Winderen M, Holand T. Breath actuated device improves delivery to target sites beyond the nasal valve. The Laryngoscope. 2006 Mar;116(3):466-72.
24. Djupesland PG, Skretting A. Nasal deposition and clearance in man: comparison of a bidirectional powder device and a traditional liquid spray pump. Journal of Aerosol Medicine and Pulmonary Drug Delivery. 2012 Oct 1;25(5):280-9.
25. Hoekman J, Ray S, Aurora SK, Shrewsbury SB. The Upper Nasal Space – a novel delivery route ideal for central nervous system drugs. US Neurology 2020; 16(1):25-31.
26. Moran DT, Rowley JC, Jafek BW, Lovell MA. The fine structure of the olfactory mucosa in man. Journal of Neurocytology. 1982 Oct 1;11(5):721-46.
27. Shrewsbury SB, Jeleva M, Satterly KH, Lickliter J, Hoekman J. STOP 101: A phase 1, randomized, open-label, comparative bioavailability study of INP104, dihydroergotamine mesylate (DHE) administered intranasally by a I123 Precision Olfactory Delivery (POD®) device, in healthy adult subjects. Headache: The Journal of Head and Face Pain. 2019 Mar;59(3):394-409.