Supportive Care in Cancer (2019) 27:3639–3645
https://doi.org/10.1007/s00520-019-04854-6

REVIEW ARTICLE

Intranasal therapy with opioids for children and adolescents with cancer: results from clinical studies

Silvia Triarico[1] · Michele Antonio Capozza[1] · Stefano Mastrangelo[1] · Giorgio Attinà[1] · Palma Maurizi[1] · Antonio Ruggiero[1]

Received: 21 May 2018 / Accepted: 9 May 2019 / Published online: 1 June 2019

Abstract

Opioids are essential for the treatment of pain, which is a serious symptom for children and adolescents affected by cancer. Intranasal opioids may be very useful for the treatment of breakthrough pain in children and adolescents with cancer, for their little invasiveness, ease of administration, rapid onset of action, and high bioavailability. Intranasal drug delivery may be influenced by anatomical and physiological factors (nasal mucosa absorption area, mucociliary clearance, enzymatic activity, anatomical anomalies, chronic or inflammatory alterations of nasal mucosa), drug-related factors (molecular weight, solubility), and delivery device. Fentanyl is a lipophilic opioid commonly proposed for intranasal use among pediatric patients, but no studies have been conducted yet about intranasal use of other available opioids for management of pediatric cancer pain. In this review, we analyze several elements which may influence absorption of intranasal opioids in children and adolescents, with a focus on pharmacokinetics and therapeutic aspects of each opioid currently available for intranasal use.

Keywords Intranasal · Opioids · Cancer pain · Pediatric patients · Fentanyl

Introduction

Pain is one of the most concerning symptoms for children and adolescents affected by cancer from the moment of diagnosis through disease treatment or progression. Cancer-related pain can be caused directly by the tumor itself, from nerve infiltration, external nerve compression, or inflammation of organs. Moreover, pain may occur because of procedures, radiation or chemotherapy treatments, or during mucositis. Demanding challenges in pediatric oncology include finding a prompt pain control regimen and improving the quality of life (QoL) of pediatric patients and their families [1].

A multimodal analgesic regimen may provide better pain management in children, but the use of opioids remains the foundation of therapy for cancer-associated pain. Codeine, fentanyl, hydromorphone, methadone, morphine, buprenorphine, oxycodone, and tramadol are currently available opioids [2].

✉ Silvia Triarico
silviatriarico@libero.it

[1] Pediatric Oncology Unit, Foundation "A. Gemelli", Catholic University of Sacred Hearth, Largo A. Gemelli, 8, 00168 Rome, Italy

Opioids may be administered through oral, intravenous, intramuscular, subcutaneously, transdermal, and intranasal (INas) route. INas drug delivery is gaining consensus especially among pediatric patients, because of ease of administration, the rapid onset of action, the high bioavailability of many drugs, and the non-invasiveness to the pediatric patients. In fact, oral medication intake may be difficult for children with mucositis or nausea and vomiting. Furthermore, children may not have yet learned to swallow oral medication or sometimes they may be not able to swallow solid oral dosage forms for the presence of nausea, vomit, or oral mucositis. In pediatric oncology care settings, patients typically have a central venous catheter (CVC) placed. Prior to CVC placement, obtaining intravenous (IV) access may be another painful experience [3].

Other than for the delivery of opioids for analgesia, a wide variety of medications are delivered through INas route in pediatric patients, such as the live influenza vaccine, desmopressin for diabetes insipidus, fluticasone for rhinosinusitis, midazolam or lorazepam for seizures and anxiolysis, ketamine or midazolam for sedation, and naloxone for oversedation or overdose [4].

Clinicians need to be aware of the limitations of INas use which include small nasal absorption area, rapid mucociliary

clearance, the presence of enzymatic activity on the nasal mucosa, poor permeability for hydrophilic or heavy molecules, and the possibility of anatomical anomalies or chronic alterations of nasal mucosa [5].

This review analyzes the main aspects of INas opioids used in pediatric patients with cancer, with a description of anatomical, physiological, drug-related factors and delivery devices which may enhance or diminish the absorption and bioavailability of INas-administered drug. Furthermore, we provide a focus on pharmacokinetics and therapeutic characteristics of the opioids currently available for INas use in children and adolescents.

Mechanism involved in INas drug delivery

INas drug delivery depends on anatomical, physiological, and drug-related factors, which may enhance or reduce drug absorption and consequently its bioavailability and efficacy. Table 1 describes the foremost factors that may improve INas drug absorption.

Anatomical and physiological factors

The nose is separated by the nasal septum into two airways; each one is composed of the atrium, the vestibule, and the turbinates. The atrium is located in the anterior part of the nasal cavity, covered by squamous and transitional epithelium. The vestibulum is comprised of a respiratory epithelium with ciliated columnar cells, covering a wide surface area which impacts on drug absorption. Nasal epithelial cells are inter-connected on the apical side by a series of junctional complexes, including tight junctions (TJs), which form a dynamic and semi-permeable diffusion barrier between the epithelial cells. There are three turbinates for each nasal cavity (superior, middle, and inferior turbinate). Around the inferior turbinate is the respiratory zone, which is the foremost site of INas drug absorption due to the presence of a very large surface area and an affluent blood source. Partial obstruction of the nasal cavity by a septal deviation or a turbinate hypertrophy (usually observed in children suffering from rhinosinusitis) may interfere with drug deposition on the respiratory zone, influencing the absorption of INas-delivered drugs. Conditions such as epistaxis, chronic rhinitis, or nasal polyposis may reduce the available nasal surface area for INas drug absorption. About the 3–5% of surface area in the nasal cavity is covered by the olfactory epithelium, located on the septum, and lateral wall in the superior part of nasal airways is not very easy to reach. The olfactory zone is not involved much in the systemic absorption of the drug, but it is able to offer direct access to the central nervous system (CNS), bypassing the blood-brain barrier. However, only few studies have demonstrated in humans that CNS drugs can be absorbed directly by the olfactory zones [6].

Table 1 Anatomical, drug-, and delivery device-related factors that improve INas drug absorption

Top factors for INas drug absorption
No anatomical anomalies or alterations of nasal mucosa
0.2–0.3 mL of drug volume per nostril
Drug diameter not inferior to 10 μm
Lipophilicity
MW below 300 Da
Addition of hydrophobic groups (cyclodestrin)
Mucoadesive and non mucoadesive formulations
Peptides and protein drugs inhibitors
Atomized spray delivery device

The arterial blood flow is dense mainly in the respiratory zone and it derives from terminal branches of the external carotid (across the sphenopalatine and facial arteries) and the internal carotid (across the ophthalmic artery). Thus, the venous drainage involves the facial, the retromandibular, and the internal jugular vein, which drains directly through the superior vena cava into the right heart chambers and finally into systemic circulation, avoiding the hepatic first-pass effect. This provides direct systemic absorption, bypassing pass liver metabolism which often limits the biovailability of oral drugs [6]. Moreover, the absorption of INas-administered drugs depends on factors which reduce or enhance nasal blood flow. Infectious nasal conditions and drugs which stimulated muscarinic or peptidergic receptors (such as tachykinins) may induce vasodilatation, enhancing INas drug absorption. Conversely, vasoconstriction negatively impact on INas drug bioavailability as seen with alpha-1 adrenergic receptor agonists (such as phenylephrine, oxymetazoline) [7].

INas drug absorption may be also limited by mucociliary clearance. It has been demonstrated that 30 min after INas administration, about the 50% of the dose may be eliminated by the ciliated cells of the respiratory zone. Consequently, the time that a drug is in direct contact with the nasal mucosa impacts its finally absorption. Mucociliary clearance may be diminished after endoscopic sinus surgery for pediatric patients with chronic sinusitis, in children affected by cystic fibrosis, in those who have undergone cranial radiotherapy, or in those on therapies which reduce cilia beat frequency (such as cholinergic antagonist, beta adrenergic receptor antagonists, general anesthetics) [8].

Drug-related factors

The small surface area of nasal mucosa limits the volume of the administered INas drug to 0.2–0.3 mL per nostril. Volumes greater than 1 mL per nostril are not really absorbed from nasal mucosa and overflow from the nasal cavity. Furthermore, the administration of a volume (for

example 0.2 mL) in one administration seems to be better deposited on the surface area and thus better absorbed than the same volume dispensed in two administrations (for example in 2 unit of 0.1 mL). The administration of INas drugs to both nostrils would be preferred for enhancing surface area of absorption [9].

High lipophilicity enhances the absorption of INas-administered drugs. Lipophilic molecules are absorbed directly and freely via the transcellular route through the epithelial cells by passive diffusion or via active receptor- or transporter-mediated processes. Hydrophilic molecules can take the transcellular or the paracellular route (which involves the tight junction between the epithelial cells). For hydrophilic drugs transported via the paracellular route, molecular weight (MW) is the chief determinant of the rate and degree of transport. In fact, there is a linear correlation between the log (%drug absorbed) and the log (MW) [10].

The tight junction (TJ) diffusional barrier allows the interchange of small ions, whereas the transport of larger molecules is limited. For drugs with a MW below 300 Da, nasal absorption is very quickly and complete, whereas for molecules with a MW above 1 kDa, absorption is too slow to be effective, with a limited biodisponibility (below 5%). Liposolubility seems to be a determinant condition for optimal nasal absorption for drugs with a MW between 300 Da and 1 KDa. Moreover, the degree of ionization impacts positively on INas drug absorption because a molecule charged at physiological pH and with a high MW may not freely diffuse through epithelial cells (trancellular route), but requires alternative pathways through transporter or paracellular diffusion [11].

The addition of hydrophobic groups may increase the liposolubity of a drug, enhancing its capacity to freely diffuse across nasal epithelium. Cyclodestrins are cyclic excipients with an external hydrophilic surface and lipophilic internal cavity used for increasing the solubility of lipophilic drugs. It has been demonstrated that their addition to INas drugs considerably enhance the lipophilicity of the drug [9, 12].

Another way for improving the biovailability of INas drug is the adoption of mucoadesive formulations (spheres, gels, or powders) that enable increased contact duration of drug with nasal mucosa, adhering to the mucus layer and decelerating mucociliar clearance. Dextrans, chitosan, and alginates have been used to create mucoadhesive formulation. Also non-mucohadesive compounds (such as polyethylen-glycols, calcium carbonate, and polyacrylate gels) may be adopted for improving INas absorption; nevertheless, no studies have been conducted for their use in children [13].

Mucociliar clearance plays a main role in the local degradation of INas drugs, but also a large group of enzymes involved in degradation of molecules (such as endopeptidases or caboxypeptidases) or in drug metabolism (such as P450 cytocrome) or in biotransformation (such as dehydrogenase, esterases, gluthatione S-transferase, and UDP-glucuronosyltransferase) take part in drug metabolism. Peptides and protein drugs inhibitors (such as bacitracin, amastatin, camostat, and puromycin) have been employed for limiting enzymatic degradation by epithelial cells, but they produce only a modest increase in the bioavailability of INas compounds [14].

INas delivery devices

Clinicians have to consider the child's compliance for the adoption of the more advantageous INas delivery route. INas opioids may be delivered as drops, nebulization, spray bottle, and atomized spray. Drops are a simple route for INas delivery, but they require a compliant child to be in supine position. Nebulization is widely adopted for aerosol-therapy and well tolerated in children because it avoids nasal irritation; still, it dispenses the drug not only to nasal mucosa but also to the mouth, pharynx, and lungs with a minor plasma concentration than systemic administration [6, 15].

Spray bottles seem to be well endured by pediatric patients, with a good profile of efficacy more for local (such as fluticasone for rhinitis) than systemic use. The use of mucosal atomizing devices (MADs) allows the administration of minute and well-absorbed particles, with less drug overflow in the oropharynx, with improved clinical efficacy than drops and significantly less opponent behavior in smaller children. The plume angle (which is the effective angle of the droplets deposited) and administration angle are critical factors in determining deposition efficiency of atomized spray. Deposition efficacies of about 90% can be achieved with 30° administration angles and plume angles of 30° Furthermore, the diameter of the particles emitted by the spray must not be smaller than 10 μm, for preventing a leaking in the lower airways during the respiratory flow [16].

INas use of opioids

Cancer-related pain can be divided into a chronic and an acute component. "Breakthrough pain" is a type of acute pain, defined as an episode of severe pain of any duration that occurs in patients that receive a stable analgesic regimen, with a baseline pain that it is stable and mild to moderate in intensity. Surveys repeatedly demonstrated that most "breakthrough pain" episodes have a peak in intensity within a few minutes and persist for 30 to 60 min. These episodes commonly require a treatment with analgesics with rapid onset of action and a duration equivalent to the episode's time course. INas route can be effective for breakthrough pain for its very short onset of action. Furthermore, the duration of action of INas administration match the time course of breakthrough pain episodes [17].

Table 2 summarizes the different pharmacokinetic characteristics of most commonly used INas opioids.

Table 2 Main characteristics of INas opioids: lipophilicity Log (C_{oct}/C_{water}), MW, pKa, and relative analgesic potency (modified by Stanislas Grassin-Delyle et al.)

Drug	Log (C_{oct}/C_{water})	MW (Da)	pKa	Relative analgesic potency
Morphine	0.76	285	7.9	1
Oxycodone	0.82	315	8.3	2
Remifentanil	1.76	376	8.1	50–200
Hydromophone	1.84	285	8.5	5
Naloxone*	2.09	327	7.9	
Sufentanil	3.95	386	8.0	500–1000
Fentanyl	4.05	336	8.4	50–100
Buprenorphine**	4.98	468	8.4	40

*Pure antagonist

**Partial μ receptor agonist

The several opioids have same physicochemical characteristics in terms of MW and pKa (acid-base dissociation constant). They may be easily absorbed via the INas route because of their MW (between 285 and 425 Da), but the lipophilicity varies greatly from the morphine (that is the least lipophilic) to the fentanyl and buprenorphine (that are the most lipophilic).

Morphine

Morphine is the most hydrophilic opioid [Log (Coct/Cwater):0.76] usually available for oral administration. When orally administered, its bioavailability is between 20 and 32%, because of significant gastrointestinal metabolism and hepatic first-pass effect [18].

Because of its low lipophilicity, INas morphine is mainly ingested and absorbed in the small intestine, with a small bioavailability (about 10% compared with IV administration). Moreover, the bioavailability of INas morphine may be extended with a five- to sixfold increase by adding chitosan microspheres to its formulations. In fact, when this compound was tested in 12 healthy volunteers, its bioavailability was 60% with a T_{max} (time to have maximum plasma concentration) of 15 min or less [19].

Pavis et al. investigated the tolerability and efficacy of an INas chitosan-containing morphine solution for the management of breakthrough pain in cancer patients with long-term oral morphine treatment. The formulation was acceptable, generally well tolerated (excluding an unpleasant taste in the mouth and a slight nasal irritation), with quickly onset of action (about 5 min) [20].

Stoker et al. in their study in 187 patients, post-bunionectomy confirmed the foremost efficacy and duration of action of INas morphine in solution with chitosan (Rylomine®) when compared with the IV route. When combined with oleic acid (which is an absorption promoter), INas morphine shows a bioavailability of 22%, with onset of action after 9 min and a T_{max} from 10 to 30 min [21].

The results of these studies conducted in adult patients demonstrate that the bioavailability of INas morphine may be improved by formulations with microspheres and/or of absorption promoters; however, no data are yet available for INas morphine administration in pediatric patients.

Oxycodone

Oxycodone is a relatively hydrophilic compound [Log (Coct/Cwater):0.82] and its oral bioavailability is between 50 and 90% [15].

Takala et al. administered INas oxycodone hydrochloride (0.1 mg/kg) in ten healthy volunteers, obtaining a bioavailability lower than IV administration, ranging widely from 25 to 67%. The Tmax of INas oxycodone was 25 min, considerably shorter than IV administration [22].

Lofwall et al. compared the pharmacokinetics of INas crushed OxyContin (the extended-release form of oxycodone) tablets with IV immediate-release oxycodone solution in height healthy adult volunteers, showing that crushed OxyContin tablets were rapidly absorbed by the INas route. They had high intranasal bioavailability, from 75 to 78%. T_{max} occurred after 52 or 65 min, depending on the dose. Crushing and snorting OxyContin tablets was a highly efficient drug delivery method that clearly bypasses the extended-release Acrocontin (Purdue Pharma) drug delivery matrix [23].

Nevertheless, these studies have been conducted in adult populations and no data are available for INas oxycodone administration in children.

Hydromorphone

Hydromorphone is an opioid analgesic eight times more potent and less hydrophilic [Log (Coct/Cwater): 1.84] than morphine.

Coda et al. in 24 healthy volunteers found a mean bioavailability of 52.4% and 57.5% after 1 mg and 2 mg of INas single doses of IV hydromorphone hydrochloride, with T_{max} of 20

and 25 min, respectively. INas hydromorphone seems to achieve greater plasma levels (fourfold higher) and a more rapid absorption when compared with oral tablets and rectal suppositories. Most frequent adverse events include somnolence and dizziness with all routes of administration and a bad taste after INas doses [24].

A pilot dose-ranging study of INas hydromorphone in patients with trauma-related pain demonstrated that initial pain relief occur within 10–15 min, with a 30% reduction in pain intensity within 30 min and a 50% reduction in pain intensity within an hour after INas hydromorphone administration [25].

Although INas hydromorphone seems to be appropriate in adult patients requiring multimodal pain control or unresponsive to oral medications, further studies are required to investigate its role in pediatric patients with cancer pain.

Buprenorphine

Buprenorphine can be used both as analgesic or substitute in opioid dependence. Despite its very high lipophilicity [Log (Coct/Cwater): 4.98], only one study has analyzed its pharmacokinetics properties, demonstrating a mean intranasal bioavailability of 48.2% with T_{max} of 31 min [2]. No studies are available about INas buprenorphine in children and adolescents.

Fentanyl

INas fentanyl seems to have the best INas absorption among opioids, because it has a very high lipophilicity [Log (Coct/Cwater): 4.05] and low MW (336 DA). Its analgesic activity is 100-fold higher than morphine. INas fentanyl shows a bioavailability of 89% and a T_{max} of 13 min (versus 6 min for the IV route) [26].

Two double-blind, placebo-controlled and randomized studies, about the efficacy of INas fentanyl spray and oral transmucosal fentanyl in the management of breakthrough cancer pain, confirmed that the time to onset of action of INas route is about 10 min. Kress at al. found a duration of action of about 60 min after INas fentanyl administration in breakthrough pain in patients with cancer [27].

Moreover, in their study about INas fentanyl administrated in adults undergoing third-molar extraction, Christrup et al. demonstrated a dose-dependent increase of the analgesic effect. They showed an extension of the duration of action from 120 min with a dose of 75 mcg to 240 min with a dose of 200 mcg [28].

INas fentanyl have been authorized for marketing in three formulations: an aqueous solution (Instanyl®) and two pectin-based mucoadhesive formulations (PecFent®, Lazanda®).

Recently, mucoadhesive formulations of INas fentanyl have been achieved adding into spray formulation additives (such as pectin, chitosan, chitosan–poloxamer 188) which form a thin gel over the mucosa that improves nasal penetration and decreases local irritation. Pectin is a vegetal polysaccharide that became a gel when become in contact with cells calcium.

Chitosan and chitosan–poloxamer 188 is a compound used to increase viscosity of INas solution [29]. High viscose pectin gel or chitosan formulations have a lower bioavailability than aqueous formulations because of their longer absorption phase and T_{max}, with lower C_{max} (maximum plasma concentration). This different pharmacokinetic is consequent to a slower diffusion of active principle within the gel and to a rapid elimination of insoluble particles by mucociliary clearance before the absorption though nasal mucosa [30].

Viral or allergic rhinitis seems to not influence the absorption of INas fentanyl aqueous solution. Conversely, INas fentanyl is not indicated during a treatment with local vasoconstrictor, which may reduce its absorption of about 20%. Pectin-based formulations need to be further investigated in patients with allergic rhinitis and viral infections that may alter local environment, modifying calcium concentration and influencing gelling process of pectin [31].

Possible adverse effects caused by INas fentanyl are epistaxis, nasal wall ulcers, rhinorrhea, throat irritation, and dysgeusia (attributed to posterior flow). INas fentanyl is contraindicated if there are recurrent episodes of epistaxis or previous radiotherapy of the head [27].

INas fentanyl is approved for breakthrough cancer pain in adults, but it is commonly used in pediatric emergency rooms. When IV fentanyl is drawn up into a syringe and administered INas by using a mucosal atomization device, its analgesic and pharmacokinetic profile appears similar to IV administration in children, with a bioavailability of 70–80% [32].

A 2014 Cochrane Review on the use of INas fentanyl via syringe and nasal atomizer showed that it may be an effective analgesic for the treatment of patients with acute moderate to severe pain, with minimal distress to children [3].

Mudd et al. demonstrated that INas fentanyl is effective in analgesia in children, producing a lower time to analgesic medication administration [33].

In pediatric patients, INas fentanyl produces an equivalent pain control, when compared to IV and oral morphine or ketamine with a low side-effect profile [34].

Whereas, the lack of pediatric randomized controlled trials for any commercially available INas fentanyl delivery system, INas fentanyl should strongly be considered for patients presenting with moderate-to-severe pain without the possibility of IV access (such as in acute traumatic injuries) and for breakthrough pain management in children with oncologic diagnoses.

Remifentanil

Remifentanil hydrochloride is an ultra-short-acting opioid that undergoes rapid metabolism by tissue and plasma esterases. INas remifentanil has been administered using a blunt plastic cannula in 17 young children (aged from 1 to 7 years), with a rapid absorption and T_{max} of 3.47 min. Nevertheless, no additional data on bioavailability are accessible [35].

Sufentanil

Sufentanil is rapidly and effectively absorbed from the human nasal mucosa, because it is two times more lipid soluble than fentanyl [Log (Coct/Cwater):3.95], with a bioavailability of 78% and T_{max} of 10 min. INas sufentanil application was described also as a safe and effective method for premedication to anesthesia in children and for postoperative analgesia in adults [36, 37].

However, higher doses may be associated with a higher incidence of postoperative nausea and vomiting. Compared with midazolam, INas sufentanil shows advantages with less respiratory depression and postoperative nausea/vomiting and decreased time to discharge. In pediatric patients, after INas sufentanil single dose (2 mcg/kg) a T_{max} of 15–30 min may be obtained [38].

A more recent study conducted by Nielsen at al. showed a T_{max} of 13.8 min and a bioavailability of 24.6% [39].

Although INas sufentanil administration was widely approved as a safe premedication of anesthesia in children, no studies have been conducted for breakthrough pain management in pediatric patients.

Naloxone

Naloxone is a competitive antagonist of the μ opioid receptor, which has been used clinically for many years to reverse the effects of opioids. Several clinical studies suggest its efficacy when INas administered [40].

INas naloxone shows lesser bioavailability (totally not superior to 50%) than intramuscular route (4% versus 36%, respectively), with a shorter duration of action (usually less than an hour) [41].

The use of INas naloxone has been part of the clinical routine for a decade for reversing the effects of sufentanil and other commonly used opioids in children. The effect of INas naloxone in reversing the effect of sufentanil has been impressive in most patients, with a faster recovery and a higher patient safety [42].

Conclusions

INas route may considerably improve drug delivery among pediatric patients, because it is quick, simple to use, and less invasive than intravenous, intramuscular ,or subcutaneously routes. Because of their short onset of action, INas opioids can give a very rapid resolution of breakthrough pain in children and adolescents with cancer, that are already under treatment with chronic treatment of opioids.

Lipophilicity differs widely between opioids, greatly affecting their INas absorption. Fentanyl is a lipophilic opioid, broadly proposed and examined for INas use in pediatric patients with pain. But, no studies exist about the adoption of other INas opioids in pediatric patients. Thus, studies about the pediatric INas use of other opioid are required in order to progress data about their potential use for analgesia in children and adolescents with cancer.

Funding information This work was supported by Fondazione per l'Oncologia Pediatrica.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Mercadante S (2004) Cancer pain management in children. Palliat Med 18:654–662
2. Ruggiero A, Coccia P, Arena R, Maurizi P, Battista A, Ridola V, Attinà G, Riccardi R (2013) Efficacy and safety of transdermal buprenorphine in the management of children with cancer-related pain. Pediatr Blood Cancer 60:433–437
3. Murphy A, O'Sullivan R, Wakai A et al (2014) Intranasal fentanyl for the management of acute pain in children. Cochrane Database Syst Rev 10(10):CD009942. https://doi.org/10.1002/14651858.CD009942.pub2
4. Del Pizzo J, Callahan JM (2014) Intranasal medications in pediatric emergency medicine. Pediatr Emerg Care 30(7):496–501; quiz 502–4. https://doi.org/10.1097/PEC.0000000000000171
5. Morrison EE, Costanzo RM (1990) Morphology of the human olfactory epithelium. J Comp Neurol 297(1):1–13
6. Salib RJ, Harries PG, Nair SB, Howarth PH (2008) Mechanisms and mediators of nasal symptoms in non-allergic rhinitis. Clin Exp Allergy 38(3):393–404
7. Newman SP, Morén F, Clarke SW (1987) Deposition pattern from a nasal pump spray. Rhinology 25(2):77–82
8. Wolfe TR, Braude DA (2010) Intranasal medication delivery for children: a brief review and update. Pediatrics 126(3):532–537
9. Costantino HR, Illum L, Brandt G, Johnson PH, Quay SC (2007) Intranasal delivery: physicochemical and therapeutic aspects. Int J Pharm 337(1–2):1–24
10. Arora P, Sharma S, Garg S (2002) Permeability issues in nasal drug delivery. Drug Discov Today 7(18):967–975
11. Kurkov SV, Loftsson T (2013) Cyclodextrins. Int J Pharm 453(1):167–180

12. Jiang L, Gao L, Wang X, Tang L, Ma J (2010) The application of mucoadhesive polymers in nasal drug delivery. Drug Dev Ind Pharm 36(3):323–336
13. Zhang X, Zhang QY, Liu D et al (2005) Expression of cytochrome p450 and other biotransformation genes in fetal and adult human nasal mucosa. Drug Metab Dispos 33:1423–1428
14. Pandey RK, Bahetwar SK, Saksena AK, Chandra G (2011) A comparative evaluation of drops versus atomized administration of intranasal ketamine for the procedural sedation of young uncooperative pediatric dental patients: a prospective crossover trial. J Clin Pediatr Dent Fall 36(1):79–84
15. Leow KP, Smith MT, Watt JA, Williams BE, Cramond T (1992) Comparative oxycodone pharmacokinetics in humans after intravenous, oral, and rectal administration. Ther Drug Monit 14:479–484
16. Tong X, Dong J, Shang Y, Inthavong K, Tu J (2016) Effects of nasal drug delivery device and its orientation on sprayed particle deposition in a realistic human nasal cavity. Comput Biol Med 1(77):40–48
17. Mercadante S, Portenoy RK (2016) Breakthrough cancer pain: twenty-five years of study. Pain 157(12):2657–2663
18. Westerling D, Persson C, Hoglund P (1995) Plasma concentrations of morphine, morphine-3-glucuronide, and morphine-6-glucuronide after intravenous and oral administration to healthy volunteers: relationship to nonanalgesic actions. Ther Drug Monit 17:287–301
19. Illum L, Watts P, Fisher AN et al (2002) Intranasal delivery of morphine. J Pharmacol Exp Ther 301:391–400
20. Pavis H, Wilcock A, Edgecombe J, Carr D, Manderson C, Church A, Fisher A (2002) Pilot study of nasal morphine–chitosan for the relief of breakthrough pain in patients with cancer. J Pain Symptom Manag 24:598–602
21. Stoker DG, Reber KR, Waltzman LS, Ernst C, Hamilton D, Gawarecki D, Mermelstein F, McNicol E, Wright C, Carr DB (2008) Analgesic efficacy and safety of morphine–chitosan nasal solution in patients with moderate to severe pain following orthopedic surgery. Pain Med 9:3–12
22. Takala A, Kaasalainen V, Seppala T, Kalso E, Olkkola KT (1997) Pharmacokinetic comparison of intravenous and intranasal administration of oxycodone. Acta Anaesthesiol Scand 41:309–312
23. Lofwall MR, Moody DE, Fang WB, Nuzzo PA, Walsh SL (2012) Pharmacokinetics of intranasal crushed OxyContin and intravenous oxycodone in nondependent prescription opioid abusers. J Clin Pharmacol 52:600–606
24. Coda BA, Rudy AC, Archer SM, Wermeling DP (2003) Pharmacokinetics and bioavailability of single-dose intranasal hydromorphone hydrochloride in healthy volunteers. Anesth Analg 97:117–123
25. Wermeling DP, Clinch T, Rudy AC, Dreitlein D, Suner S, Lacouture PG (2010) A multicenter, open-label, exploratory doseranging trial of intranasal hydromorphone for managing acute pain from traumatic injury. J Pain 11:24–31
26. Kaasa S, Moksnes K, Nolte T et al (2010) Pharmacokinetics of intranasal fentanyl spray in patients with cancer and breakthrough pain. J Opioid Manag 6:17–26
27. Kress HG, Oronska A, Kaczmarek Z et al (2009) Efficacy and tolerability of intranasal fentanyl spray 50 to 200 microg for breakthrough pain in patients with cancer: a phase III, multinational, randomized, doubleblind, placebo-controlled, crossover trial with a 10-month, open-label extension treatment period. Clin Ther 31: 1177–1191
28. Christrup LL, Foster D, Popper L, Troen T, Upton R (2008) Pharmacokinetics, efficacy, and tolerability of fentanyl following intranasal versus intravenous administration in adults undergoing third-molar extraction: a randomized, double-blind, double-dummy, two-way, cross-over study. Clin Ther 30:469–481
29. Fisher A, Watling M, Smith A, Knight A (2010) Pharmacokinetics and relative bioavailability of fentanyl pectin nasal spray 100–800 mcg in healthy volunteers. Int J Clin Pharmacol Ther 48:860–867
30. Fisher A, Watling M, Smith A, Knight A (2010) Pharmacokinetic comparisons of three nasal fentanyl formulations; pectin, chitosan and chitosan–poloxamer 188. Int J Clin Pharmacol Ther 48:138–145
31. Nave R, Sides EH, Colberg T et al. (2009) Pharmacokinetics of intranasal fentanyl spray (INFS) in subjects with common cold. 6th congress of the European federation of IASP chapters, Lisbon
32. Borland ML, Bergesio R, Pascoe EM, Turner S, Woodger S (2005) Intranasal fentanyl is an equivalent analgesic to oral morphine in paediatric burns patients for dressing changes: a randomised double blind crossover study. Burns 31:831–837
33. Mudd S (2011) Intranasal fentanyl for pain management in children: a systematic review of the literature. J Pediatr Healthcare 25: 316–322
34. Hansen MS, Mathiesen O, Trautner S et al (2012) Intranasal fentanyl in the treatment of acute pain: a systematic review. Acta Anaesthesiol Scand 56:407–419
35. Verghese ST, Hannallah RS, Brennan M, Yarvitz JL, Hummer KA, Patel KM, He J, McCarter R (2008) The effect of intranasal administration of remifentanil on intubating conditions and airway response after sevoflurane induction of anesthesia in children. Anesth Analg 107:1176–1118
36. Lundeberg S, Roelofse JA (2011) Aspects of pharmacokinetics and pharmacodynamics of sufentanil in pediatric practice. Paediatr Anaesth 21(3):274–279
37. Karl HW, Keifer AT, Rosenberge JL et al (1992) Comparison of the safety and efficacy of intranasal midazolam or sufentanil for preinduction of anesthesia in pediatric patients. Anesthesiology 76(2): 209–215
38. Zedie N, Amory DW, Wagner BK, O'Hara DA (1996) Comparison of intranasal midazolam and sufentanil premedication in pediatric outpatients. Clin Pharmacol Ther 59(3):341–348
39. Nielsen BN, Friis SM, Romsing J et al (2014) Intranasal sufentanil/ketamine analgesia inchildren. Paediatr Anaesth 24(2):170–180
40. Barton ED, Colwell CB, Wolfe T, Fosnocht D, Gravitz C, Bryan T, Dunn W, Benson J, Bailey J (2005) Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. J Emerg Med 29:265–271
41. Dowling J, Isbister GK, Kirkpatrick CM, Naidoo D, Graudins A (2008) Population pharmacokinetics of intravenous, intramuscular, and intranasal naloxone in human volunteers. Ther Drug Monit 30: 490–496
42. Vanky E, Hellmundt L, Bondesson U, Eksborg S, Lundeberg S (2017) Pharmacokinetics after a single dose of naloxone administered as a nasal spray in healthy volunteers. Acta Anaesthesiol Scand 61(6):636–640