Chapter 10
Therapeutic Intranasal Delivery for Alzheimer's Disease

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Abstract Alzheimer's disease (AD) is an age-related detrimental neurodegenerative disorder with no effective treatment, which is clinically characterized by progressive memory decline and cognitive dysfunction, altered decision making, apraxia, language disturbances, etc., and often histologically manifested by the deposition of amyloid-beta (Aβ) plaques and the formation of neurofibrillary tangles. AD is a global health crisis, currently, more than 35 million people worldwide were estimated to be afflicted by AD, and the number is expect to increase with the aging of the society. Current therapy is based on neurotransmitter or enzyme replacement/modulation, and recently, stem cells therapy is proposed as a promising strategy for AD. However, effective strategies for AD treatment has not been achieved. One of the major problems is the blood–brain barrier (BBB), which hampers drug delivery into the brain. Intranasal (IN) route will overcome this obstacle by delivering drugs or cells directly to the central nervous system (CNS) through the olfactory and trigeminal neural pathways. Here, we demonstrate how intranasal delivery systems works and its advantages and disadvantages. Moreover, we discuss and summarize some latest findings on IN delivery of drug and cell in AD models, with a focus on the potential efficacy of treatments for AD.

Keywords Intranasal delivery · Therapy · Alzheimer's disease

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10.1 Introduction

Alzheimer's disease (AD) is an age-dependent neurodegenerative disorder that is pathologically characterized by intracellular neurofibrillary tangles and extracellular amyloid beta (Aβ) plaque, neural apoptosis and neuron loss in the brain. Moreover, disturbance of metals homeostasis, extensive oxidative stress, mitochondrial damage and distribution, neuroinflammatory and calcium imbalance also contribute to the pathogenesis [1]. AD is the most common type of dementia and clinically characterized by progressive decline in learning and memory, aphasia, disuse, agnosia, spatial skills and executive dysfunction, as well as personality and behavior change. AD is the fifth cause of death among people over 65 years [2], its threats to life and reducing life quality of the patient and their families brings serious social and economic problems to the world. However, AD is a complex disease, the etiology and pathogenesis of AD is still unclear and effective therapeutic strategies remain unavailable.

Currently, acetylcholinesterase inhibitors (AChEIs), such as tacrine, donepezil, galantamine and rivastigmine are the main drugs for AD treatment. Besides, chelators that selectively bind to transition metals and reduce oxidative stress are also attractive approach to combat AD. In addition, nuclear factor kB (NF-kB), GSK3, peroxisome proliferator-activated receptor-g (PPAR-g) are suggested to regulate Aβ deposition, tau hyperphosphorylation and NFTs formation, oxidation, inflammation, demyelination and excitotoxicity, are potential targets for neuroprotective therapies. Despite major advances in neurotherapeutics, poor brain penetration due to the blood-brain barrier (BBB) pose a big challenge. Intranasal (IN) delivery, therefore, is emerged as a promising way since it bypasses the BBB in a noninvasive way, allowing direct drug delivery to the brain via a large surface area in the olfactory region and respiratory epithelium with less systemic side effects. In this chapter, we review IN delivery of AChEIs, natural anti-oxidants, insulin, nerve growth factor (NGF), peptides and several other molecules and the application to translational and clinical studies for AD treatment.

10.2 IN Delivery

10.2.1 Advantages and Challenges

IN delivery is a promising strategy to deliver drugs directly to the brain. Compared to oral administration, IN delivery of drugs achieves fast effects, avoids first-pass metabolism, reduces the side effects of systemic exposure, enhances practicality and compliance because it is noninvasive. However, the problems with IN delivery are mucociliary clearance of drugs and poor nasal permeability. To overcome this, mucoadhesive formulations or chemical penetration enhancers were explored and summarized in Fig. 10.1 [3]. These formula are generally safe and could enhance

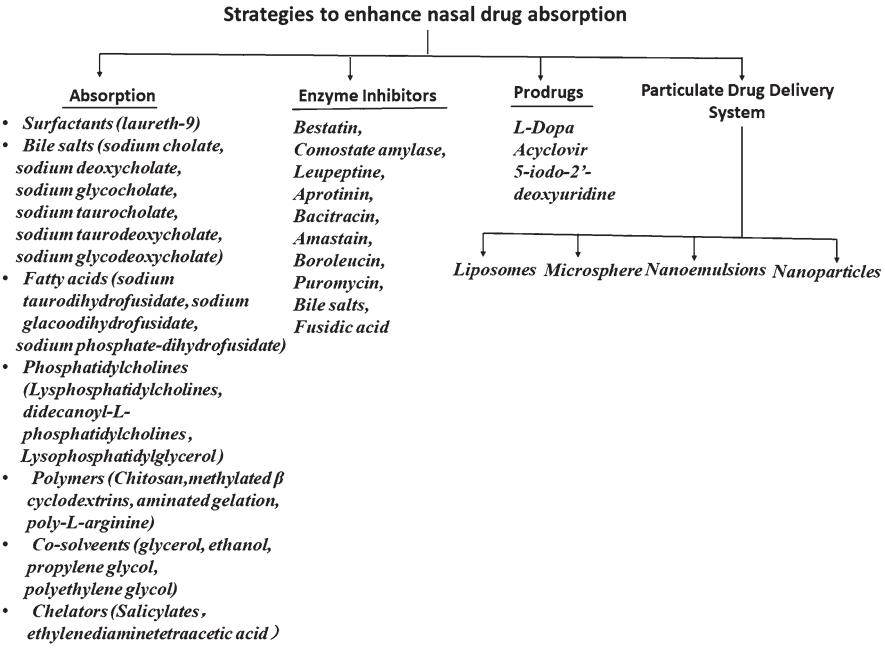

Fig. 10.1 Strategies to enhance nasal drug absorption

the stability of drugs, improve the drug absorption, protect the drugs from enzymes and chemical degradation and/or efflux back into the nasal cavity, prevent drug irritant effects, control drug release and reduce their ciliary clearance. Meanwhile, the molecular weight of polymers, free chain length, cross-link density as well as the hydration, pH, swelling, etc. should be taken into consideration for enhanced mucoadhesion.

10.2.2 Pathways of Transport from Nose to Brain

Major cerebral routes of IN delivery are olfactory pathway, rostral migratory stream pathway, and trigeminal pathway (shown in Fig. 10.2) [4].

Drugs were transported from nose to brain in intracellular or extracellular ways as shown in Fig. 10.3. The first step in intracellular transport across the olfactory and respiratory epithelia includes endocytosis into olfactory sensory neurons and trigeminal ganglion cells, respectively. This is followed by intracellular transport to olfactory bulb and brain stem, including transcytosis or transcellular transport of drug into lamina propria. Transcytosis involves the permeation of lipid soluble molecules across the apical cell membrane, intracellular space and basolateral membrane either by passive diffusion or receptor-mediated endocytosis. In terms of

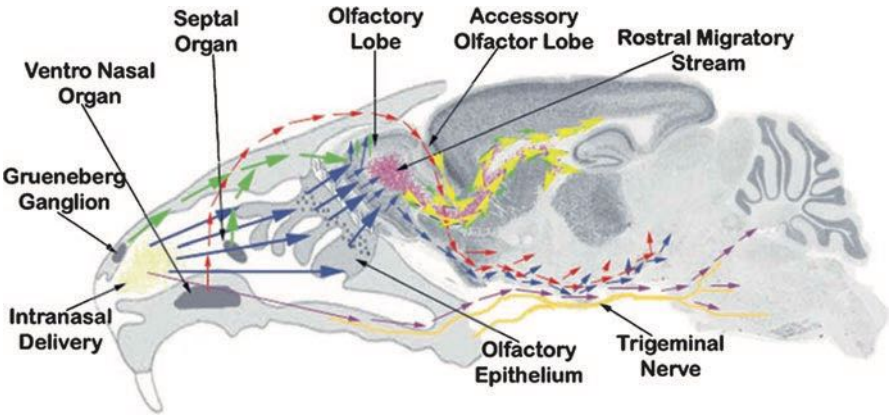

Fig. 10.2 Schema showing major routes of entry utilized after intranasal delivery of therapeutics in mice. Intranasally administered material (yellow deposits) is picked up by sensory neurons of Grueneberg ganglion, septal organ (green arrows), olfactory epithelium (blue arrow), and ventro-nasal organ (red arrow). The sensory neurons of Grueneberg ganglion, septal organ (green arrows), and olfactory epithelium (blue arrow)—all projecting to the granule cells of the olfactory lobe—eventually drain intranasally-administered material into the rostral migratory stream (RMS) (yellow arrowheads) and olfactory track at the base of the mid-brain (blue and red arrows). The material tracked into the RMS reaches the lateral and third ventricle in the close vicinity of hippocampus. The sensory neurons of ventro-nasal organ (red arrows) project to the accessory olfactory lobe, which further combine with the olfactory track at the base of the mid-brain. The material trafficked along the trigeminal nerve also combines with the olfactory track delivering to pons and hind brain, reaching to the fourth ventricle

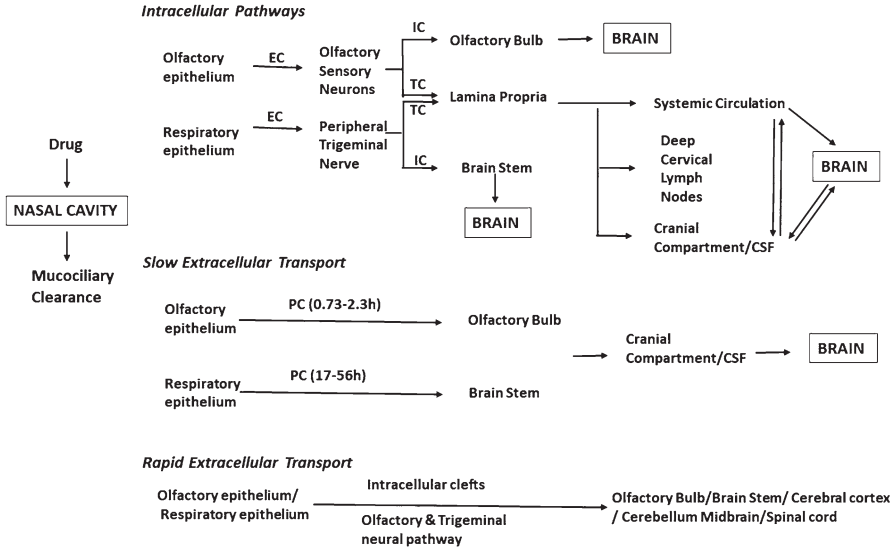

Fig. 10.3 Pathways for IN delivery system to the brain

extracellular transport, it has been estimated to take 0.73–2.3 h to diffuse from olfactory epithelium to olfactory bulb along olfactory associated extracellular pathway and 17–56 h from respiratory epithelium to brain stem along trigeminal associated extracellular pathway. This is an important pathway for the absorption of polar or hydrophilic substances, peptides and proteins. These molecules diffuse slowly from nasal membrane into the blood stream, later into the olfactory mucosa and finally transported into CNS. This pathway is less efficient with respect to transcellular pathway and is strongly dependent on drug molecular weight and size. Moreover, this mechanism is quite fast and responsible for transport of low molecular weight drugs to CNS within minutes of administration. The drugs may also be transported by rapid extracellular delivery through intercellular clefts in the olfactory and respiratory epithelium and extracellular transport along the olfactory and trigeminal neural pathway to reach the brain. Once the drug reaches lamina propria it may transport to systemic circulation; enter deep cervical lymph vessels; enter cranial compartments associated with olfactory nerve bundles.

10.3 IN Delivery Strategies for AD

IN delivery for AD treatment was first proposed by Frey in 1989. And accumulating evidence showed that IN route is a promising approach for delivery of drugs, molecules and cells in AD and is more effective than oral and intravenous (IV) route.

10.3.1 Tacrine

Tacrine (1, 2, 3, 4-tetrahydro-9-aminoacridine) is the first reversible AChEI approved for AD treatment. However, its clinical application has been limited due to low oral bioavailability, extensive hepatic first-pass effect, rapid clearance from the systemic circulation, and hepatotoxicity. To deal with these problems, Jogani et al. [5] investigated the IN delivery of tacrine, and found it could be directly transported into the brain from the nasal cavity and resulted in higher bioavailability with reduced distribution into non-targeted tissues. This selective localization of tacrine in the brain may be helpful in reducing dose, frequency of dosing and dose-dependent side effects, and proved to be an interesting new approach in delivery of the drug to the brain for the treatment of AD. Additionally, IN mucoadhesive microemulsion of tacrine improve brain targeting and fastest retrieval of memory in scopolamine-induced amnesic mice [6]. Luppi et al. reported that albumin nanoparticles carrying native and hydrophilic derivatives β-cyclodextrin derivatives can be employed for the formulation of mucoadhesive nasal formulations to modulate the mucoadhesion and permeation at the administration site [7]. Using these methods, tacrine was promising to be re-introduced for AD treatment.

10.3.2 Galantamine

Galantamine is another AChEI, however, it was discontinued for AD treatment for low aqueous solubility, dose volume limitations, and side effects such as nausea and vomiting. Therefore, researchers investigated addition of co-solvents, cyclodextrins and counter-ion exchange to enhance its solubility. Among which, galantamine-lactate represents a viable candidate for IN delivery [8]. Researchers further reported IN formulations of galantamine containing methylated-β-cyclodextrin as a stabilizer. L-a-phosphatidylcholine didecanoyl, a lipid surfactant and disodium edetate as a chelator [9] resulted in greater permeation without toxic effects to cells. In addition, galantamine hydrobromide combined with cationic chitosan nanoparticles were successfully delivered to different brain regions shortly after intranasal administration, improved pharmacological efficacy and in vivo safety, suggesting a promising way to improve AD management [10].

10.3.3 Rivastigmine

Rivastigmine is also a AChEI for AD treatment. However, the extensive first-pass metabolism and low aqueous solubility lead to poor bioactivity of the drug in vivo. Researchers found that IN administration of rivastigmine showed higher concentration in CNS regions and longer action on inhibiting the activity of AChE than intravenous (IV) administration [11]. What's more, IN administration of rivastigmine could improve distribution and pharmacological effects in CNS, especially in hippocampus, cortex and cerebrum [11]. Moreover, Shah et al. formulated rivastigmine with microemulsion (ME) and mucoadhesive microemulsions (MMEs) and found that MMEs with 0.3% w/w chitosan showed higher diffusion. Also, chitosan-modified ME are free from nasal ciliotoxicity and stable for 3 months [12]. Arumugam et al. [13]. investigated multilamellar liposomes for IN delivery of rivastigmine using soy lecithin and cholesterol by the lipid layer hydration, and showed higher AUC and Cmax compared with oral-treated group and also suggested that liposomal formulations accumulated in nasal mucosa and released the drug slowly. Fazil et al. [14]investigated IN delivery of rivastigmine loaded chitosan (CS) nanoparticles, and found the brain/blood ratio of rivastigmine was highest in the nanoparticles IN group. These results indicated that the intranasal route was a promising strategy for delivering rivastigmine and rivastigmine nanoparticles into brain.

10.3.4 Physostigmine

Physostigmine, an AChEI, is ineffective when administrated orally as it undergoes extensive first-pass metabolism. IN delivery of physostigmine combined with arecoline, a muscarinin agonist, has shown to be efficient to improve cognition. The nasal BA of physostigmine was 100% compared with IV administration and that of arecoline was 85% compared with intramuscular administration [15]. NXX-066, a physostigmine analogue, could be absorbed rapidly and completely into systemic circulation after nasal administration with Tmax of 1.5 min which was lesser than physostigmine [16]. However, the concentration of drug in CSF was very low after IN administration indicating that uptake into CSF was not enhanced by nasal administration. Therefore, the transport of drugs to CNS via IN administration may be better for poorly soluble drugs but insignificant for drugs which are completely and rapidly absorbed into systemic circulation.

10.3.5 Huperizin A

Huperizin A (Hup A), an unsaturated sesquiterpene alkaloid, is a powerful and reversible AChEI. It could easily penetrates the BBB, however, it influences peripheral cholinergic system and leads to side effects. To overcome these limitations, Zhao et al. [17] investigated nasal delivery of Hup A by means of in situ gel of gellan gum, and found that concentration of the drug after 6 h in the cerebrum, hippocampus, cerebellum, left olfactory bulb and right olfactory bulb were 1.5, 1.3, 1.0, 1.2 and 1.0 times of those after IV administration, and 2.7, 2.2, 1.9, 3.1 and 2.6 times of those after oral administration. The results revealed that IN route was a viable option for improving the brain-targeting efficiency of Hup A and also reduced the side effects to peripheral tissues. Moreover, nanoparticles have been found to improve drug transport across the epithelium due to the small particle size and the large total surface area [18].

10.3.6 Tarenflurbil

Tarenflurbil (TFB) is an Aβ42 and γ-secretase modulator. Poor brain penetration of TFB was one of the major reasons for its failure in phase III clinical trials conducted on AD patients. Thus it is urgent to improve drug delivery to brain through intranasally delivered nanocarriers. In vitro release studies proved the sustained release of TFB from nanoparticles loaded TFB (TFB-NPs and TFB-SLNs), indicating prolonged residence times of drug at targeting site. Pharmacokinetics suggested improved circulation behavior of nanoparticles and the absolute bioavailability, as

well as the brain targeting efficiency. These encouraging results proved that therapeutic concentrations of TFB could be transported directly to brain via olfactory pathway after intranasal administration of polymeric and lipidic nanoparticles [19]

10.3.7 Quercetin

Quercetin, an antioxidative agent, could eliminate free radicals and protect the brain from injury. However, its therapeutic efficacy has been hampered by low solubility in the blood, rapid metabolism in the intestine and liver, and limited ability to cross the BBB. Researchers found that IN administration of quercetin liposomes modulate cognitive impairment and inhibit acetylcholinesterase activity in hippocampus of AD. This may be attributed to its antioxidant property as evidenced by decreased lipid peroxidation and increased level of antioxidant enzymes superoxide dismutase and glutathione peroxidase. Moreover, IN administration of quercetin liposomes significantly increased the survival of neurons and cholinergic neurons in hippocampus of the AD model.

10.3.8 Insulin

AD is associated with abnormal metabolism, and IV insulin administration in AD patients has been shown to improve memory recovery [20]. However, high dose is required to achieve sufficient concentration in the brain and this may lead to hypoglycemia. IN administration of insulin is a promising approach to overcome these limitations. IN administration was suggested to be safe and effective for increasing brain insulin levels, and exerts rapid effects on EEG parameters, memory, attention, mood and self-confidence without any systemic side effects [21]. IN insulin also reduced biomarker of neurodegeneration [22] and the CSF Aβ 40/42 ratio [20]. However, sex and ApoE genotype should be considered as suggested in a controlled clinical trial that only ApoE-e4-negative individuals showed significantly improvements in cognitive performance and functional abilities were relatively preserved for women [20]. In addition, glucagon-like peptide-1 (GLP-1) could stimulate insulin secretion, enhance insulin responsiveness, stimulate neuritic growth and protect against glutamate-mediated excitotoxity, oxidative stress, trophic factor withdrawal, and cell death. What's more, GLP-1 can cross BBB, and effectively reduce brain APP-Aβ burden in AD. Therefore, developing synthetic long-lasting analogues (receptor agonists) of GLP-1, e.g. Geniposide or Extendin-4, can help to preserve cholinergic neuron function. Additionally, a future approach could be to genetically mesenchymal or stem cells to provide sustained delivery of neuro-stimulatory and neuro-protective agonists to restore insulin levels and functions in the brain [23].

10.3.9 Deferoxamine

Accumulation of metal leads to oxidative stress, inflammation, and contribute to neurodegenerative such as AD. Deferoxamine (DFO), a natural prototype iron chelator/radical scavenger, has been clinically applied to slow down the progression of the cognitive decline associated with iron-induced AD, however, targeting to the brain remained an issue. Hason reported that intranasal administration of DFO (2.4 mg) in C57 mice resulted in micromolar concentrations at 30 min within brain, and IN administration of 10% DFO (2.4 mg) three times a week for three in 48-week-old APP/PS1 mice significantly reduced the escape latencies in Morris water maze [24]. Guo et al. [25] reported iron-induced abnormal tau phosphorylation in cortical and hippocampal regions was suppressed by IN administration of DFO. In another study they found that IN administration of DFO reduced neuritic plaque formation, inhibited iron-induced amyloidogenic APP processing, rescued synapse loss and reversed behavioural alterations in APP/PS 1 mice [25]. And recently Fine et al. reported that IN deferoxamine affects memory loss, oxidation, and the insulin pathway in streptozotocin induced rat model of Alzheimer's disease [26].

10.3.10 R-Flurbiprofen

R-flurbiprofen was found to offer neuroprotective effects by inhibiting mitochondrial calcium overload induced by β-amyloid peptide toxicity in Alzheimer's disease (AD). However, poor brain penetration after oral administration posed a challenge to its further development for AD treatment. Study suggested that serum albumin-based nanoparticles administered via the nasal route may be a viable approach in delivering R-flurbiprofen to the brain to alleviate mitochondrial dysfunction in AD [27].

10.3.11 Curcumin

Curcumin (diferuloyl methane) has been found to exert beneficial effects on experimental models of AD by inhibiting Aβ aggregation, inflammation, tau phosphorylation in the brain, and improve memory and cognitive deficits in rats [28]. However, the poor aqueous solubility, chemical instability in alkaline medium, rapid metabolism and poor absorption from gastrointestinal tract limited its application. Chen et al. found that IN delivery of curcumin thermosensitive hydrogel resulted in short gelation time, longer mucociliary transport time and prolonged residence in nasal cavity of rats, without significant toxicity and integrity of mucocilia [29]. What's more, distribution of curcumin thermosensitive hydrogel via IN administration in

cerebrum, cerebellum, hippocampus and olfactory bulb were enhanced. Some researched found that curcumin mucoadhesive nanoemulsions had a significantly higher release, higher flux and permeation across sheep nasal mucosa, with no obvious toxicity [30].

10.3.12 Piperine

Piperine (PIP) is a phytopharmaceutical with neuroprotective potential in Alzheimer's disease (AD). Oral PIP delivery is disadvantageous for the hydrophobicity and pre-systemic metabolism. Therefore, researchers developed monodisperse intranasal chitosan nanoparticles (CS-NPs) for brain targeting of PIP and found that PIP-NPs could significantly improve cognitive functions as efficient as standard drug (donpezil injection) with additional advantages of dual mechanism (Ach esterase inhibition and antioxidant effect). Meanwhile, CS-NPs could significantly alleviate PIP nasal irritation with no brain toxicity. Mucoadhesive CS-NPs were successfully tailored for effective, safe, and non-invasive PIP delivery with significant decrease in oral dose [31].

10.3.13 Angiotensin Receptor Blocker

The Renin-angiotensin system in the brain has been implicated in pathogenesis of cognitive decline. Danielyan et al. found that IN administration of losartan, an angiotensin receptor blocker, at sub-antihypertensive dose (10 mg/kg every other day for 2 months) exhibited neuroprotective effect in the APP/PS1 transgenic mouse model. There was a significantly reduction in Aβ plaques, interleukin-12, p40/p70, IL-1β, granulocytemacrophage colony-stimulating factor and increased IL-10 in mice treated with IN losartan compared with the vehicle group. The authors concluded that IN administration of losartan had direct anti-inflammatory and neuroprotective effect in CNS at concentration below than that would cause hypotensive reaction in AD patients [32].

10.3.14 Neurotrophic Factors

Neurotrophic factors plays a critical role in neural growth, regeneration and repair. IN delivery was proposed as a non-invasive technique for application of neurotrophic factors. IN delivery of NGF to the brain was rapid and efficient, and was found to decrease cholinergic deficits, phosphorylated tau and Aβ in AD11 mice [33]. Besides, some researchers found that the intranasal administration was

significantly more effective than the ocular one, in rescuing the neurodegenerative phenotypic hallmarks in AD11 mice [34]. Capsoni et al. also studied the form of NGF mutated at R100 called "painless" hNGFER100 to overcome limitations of NGF due to its potent nociceptive action [35]. The mutant showed neurotrophic and anti-amyloidogenic activity in neuronal culture and a reduced nociceptive activity in vivo. Its IN administration in App X PS1 mice prevented the progress of neurodegeneration and behavioral deficits, indicating that hNGFR100 mutants variants as a new generation of therapeutics for neurodegenerative diseases.

Human acidic fibroblast growth factor (haFGF) plays significant roles in development, differentiation and regeneration of brain neurons. It regulates synaptic plasticity and processes attributed to learning and memory by improving cholinergic nerve functions [36]. However, its transport to brain is limited by BBB barrier. Lou et al. [28] investigated a novel technique of delivering haFGF14-154 to brain by fusing it with transactivator of transcription protein transduction domain, a cell penetrating peptide. And the efficacy of Tat-haFGF14-154 is markedly increased when loaded cationic liposomes for intranasal delivery in APP/PS1 mice as evidenced by ameliorated behavioral deficits, relieved brain Aβ burden, and increased the expression and activity of disintegrin and metal loproteinase domain-containing protein 10 in the brain [37].

Basic fibroblast growth factor (bFGF) promotes the survival and neurite growth of brain neurons, and modulates synaptic transmission in the hippocampus [22]. Intranasal administration of bFGF solution could help to improve the memory impairments of AD model rats, but limitations are the poor stability in nasal cavity and small transport amount. Researchers used nanoparticles conjugated with Solanum tuberosum lectin (STL), which selectively binds to N-acetylglucosamine on the nasal epithelial membrane for its brain delivery. The areas under the concentration-time curve of 125I-bFGF in the olfactory bulb, cerebrum, and cerebellum of rats following nasal application of STL modified nanoparticles (STL-bFGF-NP) were 1.79–5.17 folds of that of rats with intravenous administration, and 0.61–2.21 and 0.19–1.07 folds higher compared with intranasal solution and unmodified nanoparticles, respectively. The spatial learning and memory of AD rats in STL-bFGF-NP group were significantly better. Together with the value of choline acetyltransferase activity of rat hippocampus, the histological observations of rat hippocampal region, their study indicated that STL-NP was a promising drug delivery system for peptide and protein drugs such as bFGF to enter the CNS and play the therapeutic role.

Intranasal administration of plasma rich in growth factor PRGF Endoret to APP/PS1 mice for 4 weeks effectively reduced Aβ accumulation, tau hyperphosphorylation, astroglial activation, synaptic loss, and inflammatory responses, while promoted Aβ degradation, stimulated global improvements in anxiety, learning, and memory behaviors [38], suggesting that IN delivery of PRGF-Endoret may hold promise as an innovative therapy in AD.

10.3.15 Peptide

Vasoactive intestinal peptide (VIP) is a major neuropeptide has been found to be neuroprotective and plays important role in learning and memory. Gozes et al. synthesized a potent lipohilic analogue of VIP [stearyl-norleucinel7] VIP ([St-Nle17] VIP) and found it prevented Aβ-induced cell death in rat cerebral cortical cultures with greater potency than VIP. Daily i.c.v. injections of [St-Nle17]VIP significantly improved performance of animal in Morris water maze test in animals treated with the cholinergic blocker [39]. Another study showed that daily intranasal administration of PEI-conjugated R8-Aβ(25–35) peptide significantly reduced Aβ amyloid accumulation and ameliorated the memory deficits of the transgenic mice [40]. Peptides corresponding to the NF-κB essential modifier (NEMO)-binding domain (NBD) of IκB kinase (IKK) or IκB kinase (IKK) specifically inhibit the induction of NF-κB activation without inhibiting the basal NF-κB activity. After intranasal administration, NBD peptide entered into the hippocampus, reduced hippocampal activation of NF-κB, suppressed hippocampal microglial activation, lowered the burden of Aβ in the hippocampus, attenuated apoptosis of hippocampal neurons, protected plasticity-related molecules, and improved memory and learning in 5XFAD mice [41]. IN delivery of H102 (a novel β-sheet breaker peptide) liposomes could significantly ameliorate spatial memory impairment of AD rats, increase the activities of ChAT and IDE and inhibit plaque deposition, with no toxicity on nasal mucosa [42]. Nasal administration of the β sheet breaker peptide AS 602704 was also suggested as an approach for treatment of Alzheimer's disease [27]. Taken together, these studies suggests that intranasal administration is a feasible route for peptide delivery.

10.3.16 Hormone

Melatonin, an indole amide neurohormone, has been found to protect neurons against Aβ toxicity and inhibit the progressive formation of β-sheets and amyloidfibrils, however, it has been found to have low oral BA, short biological half-life and erratic pharmacokinetic profile. Jayachandra Babu et al. [43] studied IN transport of melatonin using polymeric gel suspensions prepared with carbopol, carboxymethyl cellulose (CMC) and PEG400, and found that the concentration of melatonin in olfactory bulbs after IN administration were higher.

17β-estradiol and its brain-selective 17β-estradiol prodrug were proved to be an effective early-stage intervention in an AD mouse [44]. However, adverse peripheral effects and low estradiol water solubility were the main problems for its application. Water-soluble prodrugs, 3-N, N-dimethylamino butyl ester hydrochloride, 3-N, N-diethylamino propionyl ester hydrochloride and 3-N, N-trimethylamino butyl ester iodide, 17-N, N-dimethylamino butyl ester hydrochloride have been proposed to increase the solubility of 17β-estradiol [45]. In another preclinical study,

estradiol solubility was enhanced by chitosan nanoparticles, which behaves as a bioadhesive material and binds strongly to the negatively charged mucin through electrostatic interactions, thus increasing significantly the half-time of clearance of estradiol. Moreover, the CSF concentration of estradiol following IN administration than that of IN administration [46].

Allopregnanolone (Allo), a neurosteroid, was proved to enhance neurogenesis in the hippocampus and restored learning and memory of AD mouse. However, low solubility pose a challenge for oral administration. Some researcher demonstrated that intranasal Allo increased hippocampal BrdU-labeled nuclei and PCNA protein levels in both aged wild type mice and young 3xTg AD mice [47].

10.3.17 Immunization

Vaccination with Aβ1-42 has been found to prevent Aβ accumulation and clearance of amyloid plaques [48]. Cattepoel et al. [49]. studied immunization of APP transgenic mice with single-chain variable fragment (scFv) derived from full IgG antibody raised against C-terminus of Aβ. scFv was found to enter brain after IN application and bind to amyloid plaques in cortex and hippocampus of APP transgenic mice, and inhibit Aβ fibril formation and neurotoxicity. Chronic IN administration of scFv was found to reduce congophilic amyloid angiopathy and Aβ plaques in cortex of transgenic AD mice. Another investigation confirmed that oligomeric amyloid- antibody (NU4) was able to enter the brain and maintain for 96 h post IN administration, and showed evidence of perikaryal and parenchymal uptake of NU4 in 5XFAD mouse brain, confirming the intranasal route as a non-invasive and efficient way of delivering therapeutics to the brain. In addition, this study demonstrated that intranasal delivery of NU4 antibody lowered cerebral amyloid- and improved spatial learning in 5XFAD mice [4]. Moreover, Wheat germ agglutinin enhanced cerebral uptake of antibody after intranasal administration in 5XFAD mice, resulted in greater reduction of cerebral Aβ compared to the unconjugated anti-Aβ antibody delivered intranasally in Alzheimer's 5XFAD model [50].

10.3.18 Cell-Based Therapy

Cell transplantation is a promising strategy for nervous system (CNS) disorders for the paracrine effect and multi-differential potential. However, the poor migration and homing of cells to the brain after IV delivery are the main barriers for effective treatment, IN provides a more efficient and targeted method for delivering cells to the brain than systemic administration. Moreover, IN delivery of therapeutic cells helps to avoid problems associated with surgical transplantation, such as the low survival rate of transplanted cells, limitations in cell dosage, immunological

response and the impracticality of repeated surgical administration. Danielyan et al. reported that 7 days after IN delivery, MSCs were detected in the olfactory bulb (OB), cortex, amygdala, striatum, hippocampus, cerebellum, and brainstem of (Thy1)-h[A30P] αS transgenic mice. IN delivered macrophages could be detected in the OB, hippocampus, cortex, and cerebellum of 13-month-old APP/PS1 mice [51]. However, additional work is needed to determine the optimal dosage to achieve functional improvement in these mouse models. In another report, repeated intranasal delivery of soluble factors secreted by hMSCs in culture, in the absence of intravenous hMSCs injection, was also sufficient to diminish cerebral amyloidosis and neuroinflammation in the mice, suggesting that these may be used in combination or as a maintenance therapy after IV delivery of hMSCs [52].

10.4 Conclusion and Future Perspectives

AD is a multifactorial disease with complex pathogenesis. Various neuroprotective molecules, growth factors, viral vectors, and even stem cells, or other alternatives ways have been explored to intervene AD, however, the efficacy to deliver these agents to the brain was still low. IN administration bypasses the BBB and delivers a wide range of agents to the brain through olfactory, rostral migratory stream, and trigeminal routes. It provides a more effective approach to deliver drugs or cells. However, despite the progress made in area of IN delivery of drugs to brain, IN delivery for AD is still under preclinical stage for the safety and toxicity concerns. The extended contact of formulations with nasal mucosa may lead to irritation, tissue damage, epithelial/sub epithelial toxicity or ciliotoxicity and may result in environment suitable for microbial growth. In addition, IN drug formulation should be developed not to damage the primary olfactory nerves and the sense of smell. Moreover, long-term studies in animals and humans need to be carried out to confirm the effectiveness and drawbacks.

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Chapter 11
Intranasal Medication Delivery in Children for Brain Disorders

Gang Zhang, Myles R. McCrary, and Ling Wei

Abstract Intranasal administration is an attractive option for the delivery of many therapeutic agents especially for the treatment of central nervous system (CNS). In contrast to drugs that require delivery by peripheral injection, which requires blood brain barrier permeability of the injected drug for CNS delivery and may cause anxiety and infection, the intranasal route allows drugs to bypass the BBB due to its highly specialized nasal anatomy and the olfactory pathway. Due to its non-invasive nature and easy procedure, intranasal drug delivery is particularly suited for use in children and may be performed by medical staff or family members. This article will review the use of intranasal medications with a focus on their utility in children. We will provide an overview of the nasal anatomy and its impact on drug delivery, the side effects of drugs specific to intranasal delivery, and a list of the medications which are currently administered intranasally. The most common drug classes for intranasal delivery in pediatrics include sedatives and analgesia, drugs for seizure control, opioid antagonists, and antimigraine medications. In summary, intranasal delivery is a versatile method for drug application with a wide range of clinical utility, and especially effective in the pediatric population.

Keywords Intranasal · Pediatrics · Non-invasive · Drug delivery · Drug administration

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11.1 Introduction

Traditionally, pediatric medications are delivered via oral, rectal, subcutaneous, intramuscular, intravenous, and, occasionally, intraosseous routes. There are benefits to each application. While most practical, oral medication delivery is slow in onset, difficult when patients are vomiting, and problematic when the patient's oral intake is restricted. In addition, children often refuse to swallow oral medications, potentially limiting their reliability. The rectal route may be used for young children but is less desirable for older children and adolescents. Parenteral delivery causes pain, anxiety, higher resource consumption, and the risk for contaminated needlestick injury. Furthermore, intravenous access in children may be difficult for inexperienced providers. Intraosseous delivery is reserved for rare, serious emergencies. Intranasal delivery has garnered increasingly more attention. Intranasal delivery provides a non-injection route for pediatric clinicians. Importantly, this method is noninvasive, essentially painless, and particularly suited for children [1, 2]. The application may also be performed easily by parents and even patients themselves, so it is becoming a hot topic in pediatric medicine.

The abundant capillaries and lymphocytes on nasal mucosa facilitate drug absorption directly into the systemic circulation [3]. The digestive effect of enzymes on drugs in the nose is far less than that in the gastrointestinal tract, which must first undergo metabolism in the liver [4]. In addition, the olfactory tissue in direct contact with the central nervous system allows nasally administered drugs to be rapidly transported into the brain, which provides an effective route of administration for the central nervous system diseases in children. Nasal administration of vaccines is equally attractive due to its high efficacy and tolerance in children [5].

11.2 History and Development

Modern medical research on intranasal delivery has a history of several decades. An early study by Barash PG in 1980 characterized intranasal delivery of 10% hydrochloric acid cocaine solution, showing that the drug was rapidly absorbed and the plasma concentration peaked after 15–60 min [6]. Following this work, studies on nasal administration became increasingly common. In 1984, a "Seminar for nasal delivery route for systemic administration" was held in the United States. In 1991, the European Academic Conference on "Buccal and nasal administration as an alternative to the intravenous administration" was held in Paris. This route of administration has been further studied for modern pharmacological treatments [7].

11.3 Characteristics of Intranasal Delivery

11.3.1 The Nose: Anatomy and Function

The nasal cavity is a complex organ anatomical structure. The physiological characteristics of the nasal cavity influence processes including drug deposition, drug removal, and drug absorption. The external nose consists of paired nasal bones and upper and lower lateral cartilages. Internally, the nasal septum divides the nasal cavity into a right and left side. The nasal septum is mainly composed of cartilage and skin, so the drug absorption rate in this area is very low [8]. The lateral nasal wall consists of inferior and middle turbinates and occasionally a superior or supreme turbinate bone [9]. The opening of the sinuses is also found under the middle turbinates on the lateral nasal wall. The effective drug absorption area is in the turbinates that are rich in blood vessels. The lacrimal system drains into the nasal cavity below the anterior inferior aspect of the inferior turbinates [10].

11.3.1.1 Nasal Mucosa

The surface area of human nasal mucosa is about 150 cm^2. Epithelial microvilli of the mucosa, which are similar to small intestine villi, increase the effective area for drug absorption. The sub-epithelium of the nasal mucosa contains abundant capillaries and lymphatic capillaries which allow for rapid drug absorption into blood circulation [11]. The nasal mucosa also plays an important role as a first level defense against pathogens and allergens which enter the body via the nose. Mucous secreted by this specialized layer of cells can trap foreign pathogens as they enter the cavity [12, 13]. Under normal conditions, the sinuses produce around 1 quart of mucous per day; however, when inflamed, mucous production can increase more than two-fold [14]. The mucous also contains immune factors such as immunoglobulins including secretory IgA which can prevent bacteria adherence [15].

11.3.1.2 Nasal Mucosal Cilia

Mucociliary transport, which clears trapped foreign bodies, relies on both mucus production and ciliary function. Consequently, the cilia within the nose play a role in the airway defense system and are an important mediators of this first line of defense for the body [16]. Nasal hairs and the sticky mucous blanket of the nasal mucosa continuously help clear foreign bodies and prevent xenobiotics like allergens, pathogens, and foreign particles from reaching the lungs.

There are three distinct functional areas in the nasal cavity: the vestibular, olfactory and respiratory zones [17]. The vestibular zone serves as the first barrier against airborne particles and is sparsely vascularized. The lining in the vestibular zone is comprised of stratified squamous and keratinized epithelial cells with nasal hairs.

The olfactory area enables olfactory perception and is highly vascularized. The respiratory area has a mucous layer produced by highly specialized cells to serve as an efficient air-cleansing system [18]. Due to their rich vascularization, the olfactory and the respiratory zones serve as efficient absorption surfaces for topically applied drugs [19].

11.3.2 The Connection Between the Nasal Cavity and the Central Nervous System (CNS)

The nasal cavity consists of the nasal vestibule, respiratory region, and the olfactory region. Among these, the olfactory region partly overlies the cribriform plate and is located high in the nasal cavity [20]. The cribriform plate is a bony structure containing pores. Due to its close vicinity to the cerebrospinal fluid and direct interface with the nervous system, the olfactory region has been the focus of research interests for possible nose-to-brain delivery. There are three main routes by which drugs can be absorbed into the CNS following nasal administration: via the blood circulation in the respiratory region, through the mucosa in the olfactory region, and directly by the olfactory nerve [1]. Absorption via blood circulation in the respiratory region occurs primarily in the respiratory region. Along this pathway, the drug is absorbed into the systemic circulation from the nasal cavity, distributed to the BBB along with the blood, and passed through the CNS. The metabolism of drugs in this fashion is similar to that of intravenous injection, and the factors affecting targeting *in vivo* are basically the same [21]. In the olfactory region, drug absorption can occur directly through the olfactory mucosa, then transferred to the CSF. Finally, some intranasally delivered drugs can enter the central nervous system directly through the olfactory nerves in the olfactory area of the nasal cavity. Early observations of patients with nasal infections revealed that the meninges can also become infected, suggesting there is a direct route to the CNS from the nasal cavity. Researchers have confirmed that transport does indeed occur between the olfactory nerve and the CNS [8, 22]. This suggests that nasally administered drugs can directly target the CNS and potentially avoid both systemic circulation and the blood brain barrier. The mechanisms of drug transport through the olfactory nerve has not been fully elucidated, but there are some reports detailing viruses and heavy metal particles entering the CNS via the olfactory nerve [23, 24].

11.3.3 Characteristics of Nasal Administration

11.3.3.1 Bioavailability

Compared to oral delivery, nasal administration does not need to pass through the gastrointestinal tract to directly reach the site of action. This avoids degradation in the gastrointestinal fluid and the first-pass metabolism from the liver. Since the route

of delivery to the CNS is more direct, only a small amount of drug (generally ~a tenth of the oral dose) is needed to reach an effective concentration. For example, intranasal salbutamol can relieve dyspnea in children with bronchospasm. However, the dose for intranasal delivery is only 100 μg compared with 2–4 mg by oral administration. Another example is the antiarrhythmic drug propranolol. Propranolol is greatly affected by first-pass metabolism after oral administration and the bioavailability is only 7–19%. Nasal administration can increase the bioavailability to nearly 100%.

11.3.3.2 Convenience, Compliance, and Costs

Intranasal delivery is typically quite simple. Many patients or their parents can administer medication using this method. Unlike some oral preparations, intranasal methods do not require spacing around meal time. The simplicity and convenience of intranasal delivery allows for higher patient compliance [25]. This treatment method is especially easy for children. Formulations are already prepared to treat the common cold, fever, upper respiratory tract infections, and other common ailments [26, 27]. It is also suitable for some patients who cannot take medications orally for various reasons. Intranasal medication delivery is also quite cost-effective, especially when time and resource use as well as patient satisfaction are concerned [28, 29].

11.3.3.3 Kinetics

Drugs given via nasal administration are absorbed and act quickly. The nasal absorption rate of non-peptide drugs is comparable to that of drugs injected intravenously [30]. The rapid action and convenience of intranasal delivery make it a suitable method for drugs used in emergent situations. For example, nitroglycerin is commonly used for the treatment of angina in patients with coronary heart disease and can relieve pain in 2–5 min and may benefit from intranasal administration [31]. Nasal administration of anticonvulsant drugs such as diazepam and clonazepam can be used in epileptic seizures. Studies comparing the average effective time of diazepam indicated intranasal delivery was significantly faster than intramuscular delivery for the treatment of convulsions in children [32–35].

11.4 Adverse Effects

Adverse effects specific to intranasally delivered medications are infrequent [36]. Some drugs may affect the movement of or may be toxic to cilia within the nose. This may play a role in reducing drug tolerance. The molecular size of intranasally delivered drugs may affect ciliary toxicity [37]. Studies have found that macromolecular drugs are relatively less toxic to nasal cilia, however, certain small molecule

synthetic drugs may have a more pronounced effects on nasal ciliary movement [37]. However, drugs with larger molecular weights may not be absorbed as efficiently as drugs with smaller molecular weights [38]. Other drugs may affect the nasal mucosa. The mucosal toxicity of some drugs may limit advances in research and are more appropriately administered by other means. The balance between absorption and mucosal toxicity requires further study.

11.5 Common Uses for Intranasal Medications in Children

Intranasal medications have been used for a variety of purposes including vaccine delivery, rhinosinusitis, seizures, migraines, sedation and analgesia, and delivery of opioid antagonists. In children, the most common use of the intranasal delivery techniques is for sedation and analgesia, anxiolysis, anti-epileptics, and migraine control. A summary of these medications and recommended doses are listed in Table 11.1.

11.5.1 Sedatives and Analgesia

At present, the clinical use of pediatric preoperative medication is usually via intramuscular or intravenous administration. However, the patients are usually awake preoperatively, and fear of injection and the "white coat effect" may cause unwanted changes in blood pressure and heart rate. Amplifying the negative experiences associated with surgery may also have an impact on the patient's psychological development. Intranasal delivery of drugs such as benzodiazepines and opioids might reduce the pre-operative stress.

Midazolam is commonly used for pediatric sedation. The drug can be administered by oral, rectal, intramuscular, intravenous and intranasal routes [54, 55]. Intranasal midazolam is quite useful for procedural sedation. Theroux et al. found that for preschool children requiring laceration repair surgery, 0.4 mg/kg intranasal midazolam could reduce crying and struggle scores compared with intranasal saline placebo or no intervention [56]. Ljungman et al. reported that parents and nurses described less anxiety, discomfort, and procedural problems in children who received intranasal midazolam at 0.2 mg/kg versus placebo. Some of the adverse effects that have been reported for intranasal midazolam include nasal irritation, unpleasant taste, salivation, nausea and vomiting, changes in vision, and gait difficulties [57].

Fentanyl is an ideal intranasal drug because of its high lipophilicity and relatively low molecular weight. Peak plasma concentrations can be reached within 10–15 min after delivery. Borland et al. found that 1.7 mg Hg/kg intranasal fentanyl was equivalent to 0.1 mg/kg intravenous morphine for analgesia in children [39]. Adverse reactions to intranasal fentanyl are rare and include nosebleeds and unpleasant tastes [11, 39]. Other work has also shown that intranasal fentanyl is effective in

Table 11.1 Comparative doses by route for intranasal medications

	Intranasal	Intravenous	Oral	Other	References
Sedation and analgesia					
Fentanyl	Dose: 1–2 ug/kg; onset: 5–10 min; duration: Related to blood level; half-life is longer than intravenous delivery respiratory depression last longer than analgesia. Available concentrations: 50 ug/mL; as metered dose for adult patients:100 ug/spray, 400 ug/spray	Dose: 1–4 ug/kg dose (higher doses may be needed in younger children); onset: Immediate; duration: 30 min to 1 h	Approved for patients >16 years	Buccal: approved for patients aged >18 years	[39–41]
Midazolam	Dose: 0.2–0.3 mg/kg (maximum, 10 mg) (use only in patients >6 month of age); onset: 5 min; duration: 30–60 min; available concentrations: 1 mg/mL, 5 mg/mL	Dose: 0.05–0.1 mg/kg (maximum, 10 mg); onset: 1–5 min; duration: 20–30 min	Dose: 0.25–0.5 mg/kg; onset: 10–20 min; duration: Variable		[42–45]
Ketamine	Optimum dose not determined yet in children (off-label); available concentrations: 10, 50, 100 mg/mL	Dose: 0.5–2 mg/kg; onset: 30 s; duration: 5–10 min (recovery 1–2 h)	Dose: 6–10 mg/kg; onset: 1–5 min; duration: 20–30 min		[43, 46, 47]
Anti-epileptics					
Midazolam	Dose: 0.2 mg/kg (maximum,10 mg) (>1 month of age); onset: 5 min; duration: 30–60 min; available concentrations: See above	Dose: Loading 0.06–0.15 mg/kg; infusion: 1–7 ug/kg per min		Buccal dose: 0.25–0.5 mg/kg (maximum, 10 mg) (>3 month of age); onset: Unclear; duration: Unclear	[43, 48, 49]
Lorazepam	(off-label) dose: 0.1 mg/kg (maximum, 4 mg); onset: Unclear; duration: Unclear; available concentrations: 2 and 4 mg/mL	Dose:0.05–0.1 mg/kg (maximum,4 mg/dose); onset: 5 min; duration: 8–12 h			[50]
Opioid antagonist					
Naloxone	No recommendations in children, in adults (off-label); dose: 2 mg onset: 8–13 min; duration: Unclear; available concentrations: 0.4 and 1 mg/mL	Dose: 0.1 mg/kg (maximum, 2 mg); onset: 2 min; duration: 20–60 min			[51, 52]
Antimigraine					
Sumatriptan	Dose: 5, 10, 20 mg (>5 years of age); onset: 15–30 min; duration: Unclear; available concentrations: 5 and 20 mg per 0.1 mL		Not approved for children	Subcutaneous dose: 3–6 mg; (6–18 years of age) onset: 10 min to 2 h; duration: Unclear	[53]

treating pain associated with fractures in children [58, 59]. Another synthetic opioid, sufentanil, has also been administered intranasally for analgesia and sedation in children [60, 61].

Recently, the use of intranasal ketamine in children has received attention [40, 62]. Ketamine is a pediatric analgesic and sedative. It has recently become the focus of research for intranasal administration. Roelofse et al. compared the intranasal administration of 20 Hg sufentanil and 0.3 mg/kg midazolam in healthy children weighing between 15 and 20 kg undergoing dental surgery [63]. They found that the two treatment groups had the same sedative effects.

11.5.2 Seizure Control

Intranasal midazolam also provides an effective treatment option for patients with epilepsy. Midazolam easily crosses the nasal mucosa and blood brain barrier, causing a rapid increase in plasma and cerebrospinal fluid concentrations [64, 65]. Fisgin et al. compared rectal administration with intranasal midazolam and found intranasal midazolam work faster and is more effective at interrupting seizures (60% vs 87%) [48]. Compared to intravenous diazepam, intranasal midazolam has a similar effect (92% vs 88%) and was faster at ceasing seizure activity [66, 67]. In addition, the use of intranasal midazolam and lorazepam is safe for the treatment of seizures for use by patients. Ahmad et al. compared intranasal lorazepam and intramuscular injection of lorazepam in 160 pediatric patients in rural Africa, most of whom had long-term seizures due to cerebral malaria or bacterial meningitis [68]. Intranasal lorazepam stopped 75% of seizures within a few minutes, while intramuscular paraldehyde was effective only 61% of the time. Holsti et al. compared the treatment of seizures with rectal diazepam or intranasal midazolam in children [49]. Pre-hospital seizure control rate (62% vs 28%), emergency intubation rate (11% vs 42%), admission requirements (40% vs 89%) and ICU admission rate (16% vs 59%). Compared to rectal administration of diazepam, the intranasal midazolam group had significantly better outcomes [32, 34]. Family epilepsy treatment by parents at home is also effective, and safer than rectal diazepam [69, 70]. Cumulatively, these findings suggest that intranasal midazolam is a favorable treatment option for epilepsy in children.

11.5.3 Opioid Antagonists

Rapid administration of naloxone can alleviate the symptoms of respiratory depression caused by opioid overdose. Traditionally, naloxone is administered intravenously [71, 72]. Excess opioid use in the pediatric population is usually due to accidental intake. However, since peripheral venous access is often difficult to obtain in people who abuse opioids, intranasal administration of naloxone may be a

simple and rapid alternative. Intranasal delivery of naloxone provides a similar bioavailability and onset time [73]. In addition, compared to intravenous administration, intranasal administration can reduce the potential for needle stick injuries [74]. Because patients with a history of intravenous drug abuse tend to have a higher risk of infectious disease, this situation requires the protection of medical personnel from puncture injuries [74]. In adult prehospital patients, Barton et al. found no difference in time to onset between intranasal and intravenous naloxone administration by paramedics [75]. Robertson et al. found that although the clinical response of intravenous naloxone was faster than that of intranasal, there is no significant difference in the time from initial contact to clinical response to cessation of clinical response [76]. This may be due to the time needed to establish venous access [77].

11.5.4 Anti-Migraine

Migraine is a common chronic and recurrent headache disorder in the pediatric population. The age of onset is commonly 6–12 years old. The incidence in males is slightly more than that in females before the age of 10, however, the rate in adolescent females is higher than that in males. Oral medication is usually administered as a first line of therapy. When oral treatment fails, intranasal drugs can be used instead of intravenous therapy in certain situations. The most common intranasal anti-migraine drug is sumatriptan [78]. A comparison of intranasal sumatriptan at 5, 10, and 20 mg with normal saline placebo found that sumatriptan offered more relief than placebo at 1 h for those receiving 10 and 20 mg and more relief than placebo at 2 h for those receiving 5 mg [79]. Ahonen and Lewis found that intranasal sumatriptan was more effective in relieving migraine than placebo [80, 81]. The side effects of intranasal triptans include unpleasant taste, nasal discomfort, and congestion [82]. The use of intranasal lidocaine for the treatment of acute migraine has not been fully studied in children. Some studies in adults have shown that lidocaine can be used to stop migraine, however, the data is limited [83, 84].

11.6 Conclusions

Intranasal delivery offers an attractive alternative to invasive drug delivery for delivering analgesia, anxiolytics, and anticonvulsants to pediatric patients. The major advantages of intranasal delivery include the straightforward and needle-free application modality and the permeable application site in the nasal cavity that allows for a rapid onset of local and systemic drug activity. Furthermore, intranasal delivery may reduce medical staff resource use, eliminate needle-stick exposure risk, and lead to improved patient and parent satisfaction. Pediatricians, pediatric emergency physicians, and emergency medical services should consider adopting this delivery method for medications and indications that are appropriate to their practice setting.

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