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Intranasal drug delivery: An efficient and non-invasive route for systemic administration
Focus on opioids

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ABSTRACT

Intranasal administration is a non-invasive route for drug delivery, which is widely used for the local treatment of rhinitis or nasal polyposis. Since drugs can be absorbed into the systemic circulation through the nasal mucosa, this route may also be used in a range of acute or chronic conditions requiring considerable systemic exposure. Indeed, it offers advantages such as ease of administration, rapid onset of action, and avoidance of first-pass metabolism, which consequently offers for example an interesting alternative to intravenous, subcutaneous, oral transmucosal, oral or rectal administration in the management of pain with opioids. Given these indisputable interests, fentanyl-containing formulations have been recently approved and marketed for the treatment of breakthrough cancer pain. This review will outline the relevant aspects of the therapeutic interest and limits of intranasal delivery of drugs, with a special focus on opioids, together with an in-depth discussion of the physiological characteristics of the nasal cavity as well as physicochemical properties (lipophilicity, molecular weight, ionisation) and pharmaceutical factors (absorption enhancers, devices for application) that should be considered for the development of nasal drugs.

Contents

1. Introduction

Intranasal (IN) drug delivery is usually associated with the production of a local effect. A typical example is the treatment of allergic or infectious rhinitis with antihistamines, corticoids and/or vasoconstrictors. However, the nasal mucosa's high degree of vascularisation and high permeability also enable systemic drug administration via this route—making the

Abbreviations: IN, intranasal; i.v., intravenous; MW, molecular weight; P-gp, P-glycoprotein.

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Table 1
Intranasally administered drugs for systemic delivery.

Drug	Brand	Indications
Buserelin	Suprefact nasal®	Prostate cancer
Nafarelin	Synarel®	Endometriosis
Desmopressin	Minirin®	Prevention and control of polydipsia, polyurea and dehydratation in patients with diabetes insipidus
Calcitonin	Miacalcin®	Post-menopausal osteoporosis
Dihydroergotamine	Diergo-spray®	Migraine and cluster headache
Sumatriptan	Imigran®	Migraine and cluster headache
Butorphanol	Stadol NS®	Management of pain, including migraine headache pain
Fentanyl	Instanyl®, PecFent®	Breakthrough pain in patients with cancer
Estradiol	Aerodiol®	Hormone replacement therapy
Nicotine	Nicotrol NS®	Smoking cessation
Oxytocin	Syntocinon®	Labour induction and lactation stimulation
Cyanocobalamin	Nascobal®	Vitamin B12 deficiency
Influenza vaccine	FluMist®	Seasonal or H1N1 flu prevention

nose both a therapeutic target and a portal for drug delivery. Hence, IN drug formulations have been developed for a wide range of indications, including hormone replacement therapy, osteoporosis, migraine, prostate cancer and even an influenza vaccine (Table 1) (Pires et al., 2009). The main advantages (Table 2) of IN delivery are ease of administration, a rapid onset of action and the avoidance of gastrointestinal and hepatic first-pass effects; accordingly, the nose constitutes a very valuable route for the administration of active principles with low oral bioavailability. Conversely, the limitations of IN administration (Table 2) are related to the need to cross the nasal mucosa—the physiological properties of which (including some disease-related alterations) influence drug absorption. Several general reviews on IN drug delivery have already been published (Behl et al., 1998; Illum, 2003; Graff & Pollack, 2005; Costantino et al., 2007; Pires et al., 2009) but none has covered all the determinant physicochemical, pharmaceutical and physiopathological parameters in the absorption of drugs via this route, their pharmacokinetic consequences in man and the methods that can be used to modulate systemic exposure. After having presented the parameters that govern the pharmacokinetics of intranasally administered drugs, we shall address the IN absorption of opioids in general and fentanyl in particular; the latter's pharmacokinetic profile via the IN route enables its use in the treatment of breakthrough cancer pain.

Table 2
Advantages and limitations of intranasal administration of drugs for systemic delivery. Adapted from Arora et al.

Advantages	Limitations
High absorption for lipophilic drugs with MW<1 kDa	Poor permeability for hydrophilic drugs or drugs with MW>1 kDa (peptides, proteins…)
Avoidance of gastrointestinal and hepatic first-pass effect	Absorption time limited by mucociliary clearance
Plasma profile similar to the intravenous route: fast onset of action	Low absorption surface in comparison to intestinal mucosa
Ease of administration, non-invasive: self-medication	Enzymatic activity of the nasal mucosa, especially with proteins- and peptides-degrading enzymes
Ease of use in patients with nausea and vomiting	Variability in the absorption in case of chronic alterations of the nasal mucosa or with simultaneous administration of vasoconstrictive drugs
Cheap drug delivery devices	Local intolerance towards nasal mucosa

2. Mechanisms involved in intranasal drug delivery

The four pharmacokinetic steps that influence the fate of drugs in the body are absorption, distribution, metabolism and elimination. The specific, valuable features of IN administration are mainly related to the drug absorption step and depend on anatomical, physiological and compound-related factors.

2.1. Anatomical and physiological factors

Each nasal fossa is divided into three segments: the vestibule, the atrium and the turbinate (which in turn is divided into the superior, middle and inferior turbinate) (Fig. 1). The respiratory zone (around the inferior turbinate) is the main site for systemic entry of drugs because of its high surface area (120 to 150 cm^2) and its highly vascularised and permeable chorion. The latter contains many glands responsible for secreting most of the nasal mucus. The epithelium covering the nasal fossae is mainly constituted of basal cells, ciliated cells and mucus-secreting goblet cells (Fig. 2). The epithelial cells are held together by intercellular tight junctions. Beating cilia transport the mucus towards the oropharyngeal junction, where it is swallowed.

The nose's arterial blood supply comes from the external carotid system (via the sphenopalatine and facial arteries) and from the internal carotid system (via the ophthalmic artery). The arterial blood flow irrigates a dense bed of capillaries and then capacitance vessels (i.e. large venous sinusoids) near the turbinate respiratory zone. The venous return involves the sphenopalatine, facial and ophthalmic veins and then the internal jugular vein, which in turn drains (via the subclavian vein and the superior vena cava) into the right heart chambers; this explains the absence of a hepatic first-pass effect. Nasal blood flow is partly controlled by the autonomic nervous system. Stimulation of vascular alpha-adrenergic receptors by the noradrenaline released by sympathetic nerves has a predominant role in the neuronal control of blood flow and leads to significant vasoconstriction and a decrease in blood flow. Treatment with α_1-adrenergic antagonists induces nasal congestion in less than 5% of patients, demonstrating indirectly the catecholamine-mediated control of the nasal vasculature. In humans, endothelially generated endothelin also has a major role in controlling nasal vascular tone, as shown by the occurrence of nasal congestion as a side effect of treatment with endothelin antagonists. Conversely, the stimulation of muscarinic or peptidergic receptors (e.g. with calcitonin gene-related peptide and the tachykinins) induces vasodilatation (Devillier et al., 1988; Al Suleimani & Walker, 2007). Changes in local vascular homeostasis (combined with over-secretion of mucus) can have significant repercussions on the absorption of intranasally administered drugs; the impact on therapeutic management must therefore be carefully assessed.

The olfactory epithelium (Fig. 1) has a small surface area (1 to 5 cm^2, accounting for only 3 to 5% of the nasal cavity's total surface area (Morrison & Costanzo, 1990) and is thus not significantly involved in the systemic absorption of drugs. However, it can enable direct access to the central nervous system (CNS) by by-passing the blood–brain barrier (Illum, 2004). Although the mechanisms and physicochemical properties that govern drug deposition in the olfactory zone are the same as those in the respiratory zone, the former has a much lower surface area in humans than in the animal; hence, studies in animal models are less relevant (Illum, 1996, 2004). A few clinical, pharmacodynamic studies suggest that CNS drugs can be absorbed directly through this zone (Born et al., 2002; Illum, 2003). However, the results of a recent study showed that sprays reached the olfactory epithelium in only 1 in 15 patients (Scheibe et al., 2008). The partial obstruction of the nasal fossa by the turbinates prevents the deposition of drugs on the olfactory epithelium as well as the nasopharynx. A general review on steroids concluded that most of the spray is deposited in the nasal cavity's anterior segment (the nasal floor and preturbinate zone) and middle segment (the turbinate zone) (Benninger et al., 2004). Furthermore,

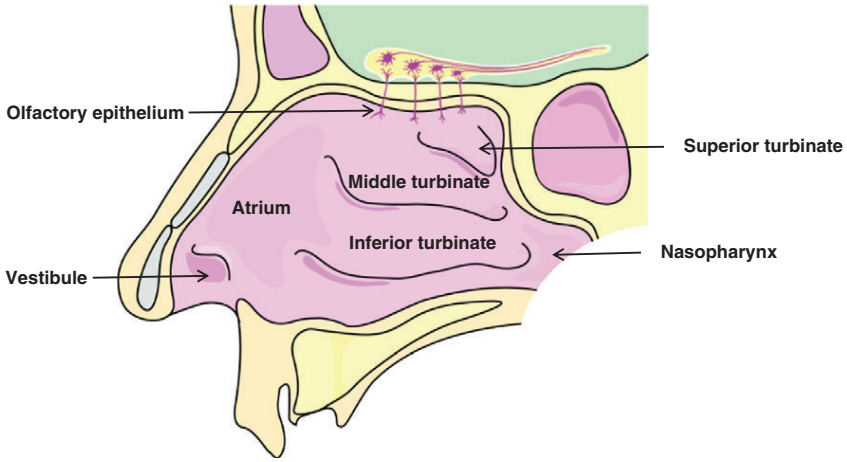

Fig. 1. Representation of the different areas of the nasal cavity: vestibule, atrium, inferior, middle and superior turbinates; olfactive region and nasopharynx. Drug deposition following intranasal administration mainly occurs in the respiratory zone around the inferior turbinate. Partial obstruction of the nasal cavity by the turbinates prevents at least in part the deposition on the olfactory epithelium and on the nasopharynx.

the mechanisms of transport to the CNS through the olfactory zone are poorly known; they may involve either diffusion through the subarachnoid area or internalization of the active principles by olfactory neurons and then axonal transport up to the olfactory bulb (Born et al., 2002). This transport mechanism is slow (about 2.5 mm/h in the monkey) and thus cannot explain the rapid appearance of active principles in the brain or the cerebrospinal fluid after IN administration (Illum, 2000).

2.2. Sources of variability in intranasal absorption

Absorption through the nasal epithelium takes place after deposition of the drug by local spray administration. The proportion of the drug that actually crosses the epithelium thus depends variously on physiological, molecular and pharmaceutical factors.

2.2.1. Factors influencing the site and surface area of drug absorption

In the chronological sequence of events, the initial limitations on absorption are related to the drug's pharmaceutical formulation and the characteristics of the spray created by the pump.

2.2.1.1. The volume administered. The nasal mucosa's low surface area limits the administration of active principles to volumes below 200 μL, in order to avoid direct loss of the drug via anterior or posterior run-off. For insulin preparations of between 80 and 160 μL in volume, it has been shown that the entire administered dose is deposited in the nasal cavities, with no passage to the lungs (Newman et al., 1994). The unit volume administered is also important because it appears that the administration of a single volume of 100 μL leads to deposition over a greater surface area than that obtained with the administration of two 50 μL volumes (Newman et al., 1994; Kundoor & Dalby, 2011).

2.2.1.2. The particle diameter. For drugs in solution administered as a nasal spray, the aerodynamic diameter of the particles emitted by the spray device must be greater than or equal to 10 μm, in order to ensure impaction of the particles on the nasal mucosae and to prevent them from being drawn into the lower airways by inspiratory flow.

2.2.1.3. The solution's viscosity. By using an anatomically accurate silicone model of the human nose and nasal cavities, Kundoor and Dalby showed that the deposition area decreased with sprays of increasing viscosity. Thus was probably due to an increase in the droplet size at higher viscosities (Kundoor & Dalby, 2011).

2.2.1.4. The spray administration angle and plume angle. The spray administration and plume angles are key determinants of optimal drug delivery. The combination of an administration angle of 30° and a plume angle of 30° led to deposition primarily in the anterior

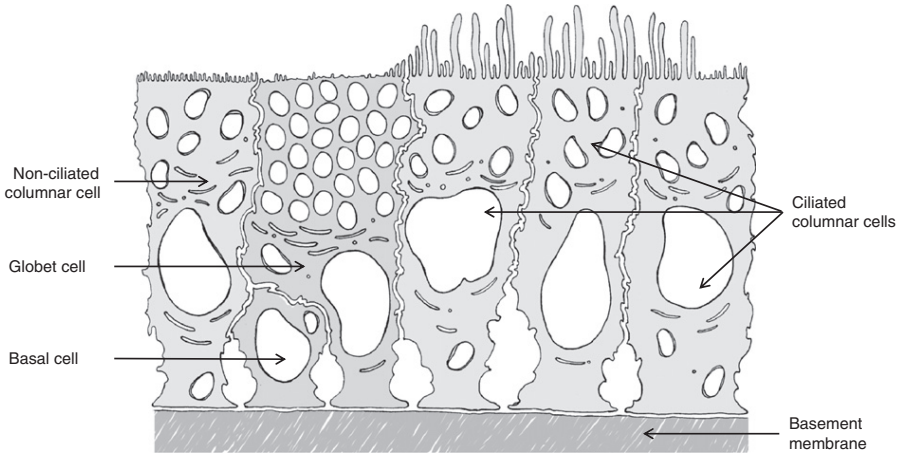

Fig. 2. Representation of the different cell types constitutive of the nasal epithelium.

region of the nose, with a deposition efficiency close to 90% (Foo et al., 2007).

2.2.1.5. Respiratory flows. By using a device similar to the silicone nose mentioned above, another group showed that variations in inspiratory flow at the time of drug administration had only a minor influence on the efficacy of deposition in the turbinate zone. The absence of an effect of intense inhalation at the time of spraying has also been demonstrated (Homer & Raine, 1998).

2.2.2. Factors influencing transepithelial passage

After being deposited on the respiratory mucosa, the active principle must cross the epithelium to reach the systemic circulation. This mucus-coated anatomical barrier is notably constituted of beating, ciliated cells that ensure efficient mucociliary clearance.

2.2.2.1. Mucociliary clearance. Mucociliary clearance limits the drug–mucosa contact time by ensuring effective drainage and thus can constitute a limiting factor in the absorption of active principles. Hence, inhaled particles that deposit on the mucus are eliminated by this mechanism in 15 to 30 min (Marttin et al., 1998; Illum, 2003). More exactly, it is possible to distinguish an initial, 15- to 20-minute clearance phase (during which about 50% of the administered dose is eliminated from the respiratory mucosa) and a second, slower phase that enables elimination of drug molecules deposited on the non-ciliated epithelium of the vestibule and on the nasal cavity's anterior segment (Marttin et al., 1998). Major variations can be observed, since over 55% of the total dose may still be present at the initial spraying site 30 min post-administration (Newman et al., 1987). Furthermore, the presence of active principle in the nasal tissue and secretions up to 24 h after administration of a single dose has already been documented with a corticosteroid in aqueous solution—perhaps because of this compound's slow dissolution and high tissue binding (Bonsmann et al., 2001).

2.2.2.2. Transepithelial routes. After deposition, a drug may cross the epithelium via the transcellular route (i.e. though the epithelial cells themselves) and the paracellular route (i.e. through the tight junctions between the epithelial cells), depending on the compound's intrinsic physicochemical properties. For the transcellular route, the molecules can cross the cells by passive diffusion down a concentration gradient or via active, receptor- or membrane transporter-mediated processes. Many transporters responsible for the influx or efflux of peptides and organic anions and cations have been identified (including P-glycoprotein (P-gp), the organic anion transporter (OAT) and the organic cation transporter (OCT)) and the corresponding transport mechanisms have been characterised in various organs (Koepsell, 1998; Meijer et al., 1999; Inui et al., 2000; Mizuno et al., 2003), including the human nasal mucosa (Agu et al., 2011). The paracellular route involves crossing the tight junctions, the role of which is not only to ensure mechanical cohesion of the epithelial cells but also to regulate molecular transport through the paracellular space.

2.2.2.3. Physicochemical properties of active principles. The three main physicochemical criteria involved in the epithelial passage of active principles are the molecular weight (MW), hydrophilicity/lipophilicity and degree of ionisation, which all affect the routes and mechanisms of transepithelial passage. The solubilization rate is also involved but also depends (at least in part) on the afore-mentioned physicochemical properties. Schematically, lipophilic molecules take the transcellular route, whereas hydrophilic molecules can take the transcellular or paracellular routes (depending on their MW) (Fig. 3). High MW is the limiting factor for paracellular passage through the tight junctions. For drugs with a MW below 300 Da, nasal absorption is rapid and hardly influenced by the other physicochemical properties, whereas molecules with a MW above 1 kDa absorb very slowly (with a bioavailability of between 0.5% and 5%) (McMartin et al., 1987; Arora et al., 2002; Illum, 2003; Costantino et al., 2007). For the molecules with a MW of between 300 Da and 1 kDa (which is the case for the great majority of active principles), liposolubility is an important property for resorption (Arora et al., 2002; Labiris & Dolovich, 2003; Costantino et al., 2007) because it influences passive diffusion across the epithelium. Lipophilic molecules can diffuse freely, whereas hydrophilic molecules have to use the paracellular route to cross the epithelium. Hence, there is a strong, positive relationship between lipophilicity and the transepithelial transport rate in in vitro models based on cultured porcine or human epithelial cells (Lin et al., 2005).

Although the degree of ionisation has a weaker influence on IN absorption, this parameter is also involved in diffusion of the drug compound because only the non-ionized fraction is diffusible and thus more easily absorbed (Costantino et al., 2007). It is easy to understand that for molecules like proteins (which have a high MW and, in most cases, a non-zero net charge at physiological pH), the diffusion mechanism is not appropriate for crossing biological barriers and that alternative mechanisms (via transporters or the paracellular

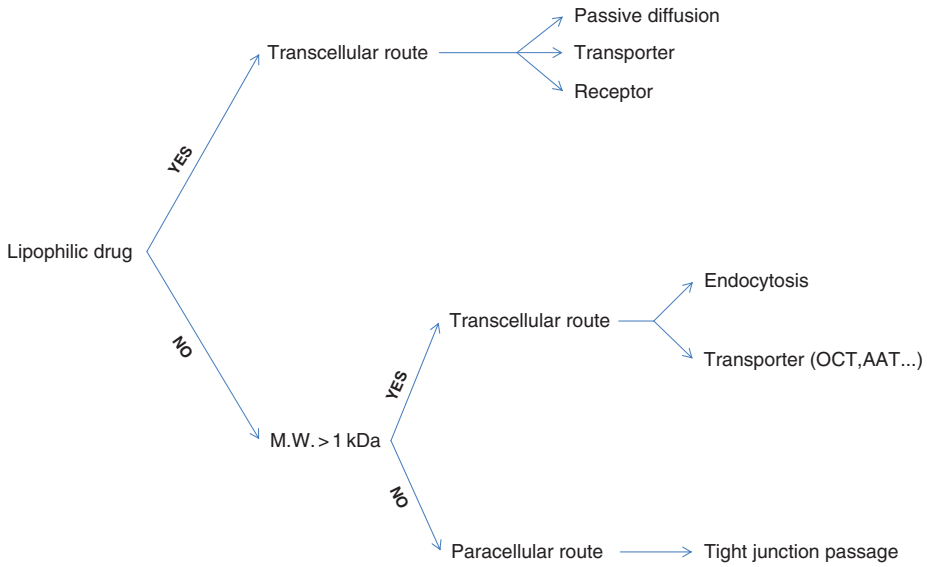

Fig. 3. Mechanisms involved in the crossing of the respiratory epithelium by xenobiotics, in function of their physicochemical properties. OCT = organic cations transporters, AAT = amino acids transporters.

route) are involved. However, for small molecules that are weak acids or bases, the degree of ionisation can partly be controlled during solubilization of the active principle by using the pH of the vehicle solution to produce a non-ionized, more readily diffusible state. Since the average pH in the anterior and posterior nasal cavities is around 6.3 (Washington et al., 2000), basic drugs with a pKa above 7.3 will be predominantly (90%) in a charged state in the absence of a buffer. The proportion of neutral molecules rises when the active principle is solubilised in a basic buffer, which thus favours membrane diffusion.

The rate of dissolution in the mucus may become an absorption-limiting factor in terms of mucociliary clearance and is especially important for drugs administered as a powder or suspension. A molecule whose dissolution time is greater than the time required for mucociliary drainage to the oropharyngeal junction cannot be absorbed locally. The dissolution rate depends not only on the compound's pharmaceutical formulation (i.e. as a solution or a suspension) but also on its liposolubility and degree of ionisation. Hydrophilic molecules are very soluble in mucus (which is mainly constituted of water) and are thus most sensitive to mucociliary clearance, especially since their transmembrane diffusion rate is low.

2.2.2.4. Nasal blood flow. Nasal blood flow is a key factor in maintaining a concentration gradient at the absorption site, which in turn is essential for promoting drug diffusion. Vasoconstrictor or vasodilator drugs influence the nasal blood flow and thus induce variability in the absorption of compounds at this site. This aspect will be discussed in more detail below.

In any case, a molecule intended for IN administration would ideally have the following properties: a low MW, high lipophilicity and zero net charge at physiological pH. It must be soluble enough to enable delivery of the entire effective dose in a volume of 100 μL per nostril (i.e. a total of volume of 200 μL).

2.2.3. Degradation and excretion of nasally administered drugs

Before a drug enters the systemic circulation, several specific, IN elimination mechanisms come into play. In addition to purely physical phenomena (such as sneezing or anterior or posterior run-off), local degradation of the active principle can occur. In fact, the epithelium barrier has an impact on three levels. The first two are related to mucociliary clearance and tight junctions, which counter the crossing of this defensive barrier by external agents and xenobiotics. Thirdly, epithelial cells are equipped with protein and enzymatic machineries that are involved in the degradation and transcellular efflux of molecules. In fact, this could be termed a “nasal first-pass effect”. The nasal epithelium is equipped with enzymes responsible for the degradation of native molecules (e.g. the endopeptidases or carboxypeptidases that degrade bradykinin or neuropeptides; Ohkubo et al., 1995, 1994) but also contains a large pool of enzymes involved in drug metabolism. The presence of many P450 cytochrome isoforms (mainly isoforms 3A, 2A6, 2A13, 1B1, 4B1, 2C and 2F1; Ding & Kaminsky, 2003; Zhang et al., 2005) and other biotransformation enzymes (such as dehydrogenases, esterases, UDP-glucuronosyltransferase and glutathione S-transferases) (Ding & Dahl, 2003; Zhang et al., 2005) demonstrates the nasal mucosa's significant metabolic capacity. Efflux systems also contribute to the excretion of xenobiotics. The latter's main component (P-gp, a member of the superfamily of ATP-binding cassette transporters) is expressed in the nasal mucosa in man (Henriksson et al., 1997; Wioland et al., 2000). The protein's 12 transmembrane domains form a pore in the cytoplasmic membrane that serves as an ATP-dependent pump for the specific cellular efflux of certain substrates. It is well known that cells in the blood–brain barrier express P-gp, which is involved in the efflux of drugs crossing endothelial cells; this limits the access of drugs to the CNS, as has been observed with antidepressants (O'Brien et al., 2012). Likewise, OCTs have been identified in the human nasal mucosa and may be responsible for the efflux of organic cations such as antihistamines, opioids and antibiotics (Agu et al., 2011). Even though the exact role of metabolic enzymes and efflux systems in the degradation and excretion of intranasally administered drugs is not yet fully understood, these mechanisms promote drug biotransformation and efflux into the extracellular milieu and thus decrease bioavailability (Graff & Pollack, 2003).

3. The pharmacokinetics of intranasally administered drugs

3.1. The main pharmacokinetic characteristics

As mentioned above, a drug's physicochemical properties are key determinants of its ability to cross the nasal mucosa efficiently and thus providing adequate bioavailability for achieving the desired systemic effects, in terms of both intensity and onset of action.

A few studies have compared the respective pharmacokinetic profiles for oral or parenteral vs. IN administration of a given compound. When administered intranasally as drops (0.5 mL per nostril), the very hydrophilic drug zanamivir (log P: −3.2; MW: 332 Da) has a bioavailability of about 11%. The maximum plasma concentration (C_{max}) after IN administration was only 3% of that observed with the intravenous (i.v.) route and occurred (at T_{max}) after 1.8 h, versus 0.3 h with the i.v. route (Cass et al., 1999). The migraine drug sumatriptan (which is more lipophilic (log P: 0.9) than zanamivir but has a similar MW (295 Da)) also shows low IN bioavailability (about 16%), when compared with the subcutaneous route (about 100%) (Duquesnoy et al., 1998). It is also noteworthy that T_{max} for IN administration is 1.5 h, versus 0.17 h for the subcutaneous route—again reflecting slower IN absorption of this molecule. In another study, midazolam (a compound that is even more lipophilic than sumatriptan (log P: 2.5; MW: 326 Da)) administered as an IN spray (0.5 mg/100 μL in each nostril) was found to have a bioavailability of 88% (Haschke et al., 2010). T_{max} is 10.6 min (vs. 2.1 min when given i.v.) and the C_{max} is about 33% of the i.v. value. Similar results were obtained with lorazepam (another member of the benzodiazepine family, with similar physicochemical properties, (log P: 2.4; MW: 321 Da)) when administered as an IN spray (1 mg per 100 μL in each nostril). A bioavailability of 78% was reported, with C_{max} and T_{max} values of 21.4 ng/mL and 0.5 h respectively (compared with 47.6 ng/mL and 0.1 h, respectively, for the i.v. route) (Wermeling et al., 2001). Lastly, the bioavailability of the very lipophilic antipsychotic haloperidol (log P: 3.2; MW: 376 Da) when administered as an IN spray (2.5 mg in 100 μL in one nostril) in a pilot study was 64%, with a T_{max} of 15 min (the same as for i.v. administration) (Miller et al., 2008). These latter examples with small molecules illustrate well the importance of lipophilicity in obtaining optimal IN bioavailability.

The IN route also has some distinctive characteristics during the pharmacokinetic phase that follows absorption, i.e. distribution. In fact, after absorption at the venous plexus that drains into the facial, sphenopalatine and ophthalmic veins, drugs pass through the jugular veins, the superior vena cava, the right heart, the lungs and the left heart. They are then expelled into the arterial blood flow that irrigates the various organs. The latter are able to extract a proportion of the active principle and release the rest into the venous circulation. This explains the arterial vs. venous differences observed in the blood concentrations of various administered intranasally molecules, such as nicotine and fentanyl. In such cases, arterial T_{max} occurs earlier and thus measurement of the arterial concentration appears more appropriate for explaining the drug's pharmacodynamics (Gourlay & Benowitz, 1997; Guthrie et al., 1999; Moksnes et al., 2008).

In conclusion, the unusual aspects of the pharmacokinetics of intranasally administered drugs are mainly due to physiological causes and the molecules' physicochemical properties, which lead to the observed variations in absorption. However, it may be preferable to modulate these phenomena and thus improve the bioavailability of certain active

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