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REVIEW ARTICLE

The Pharmacokinetics of Drugs Delivered to the Upper Nasal Space

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Abstract

Pharmacokinetics (PK) includes how a drug is absorbed, distributed, metabolized and eliminated. The compartment providing this information is usually the plasma. This is as close to the tissue of interest that we can get, although biopsies may be obtained to give "tissue levels" of drugs. Ultimately, the goal of PK is to understand how long the drug is actually engaged with the target in the tissue of interest after a dose has been administered. Most drugs at some point in their development will have been administered intravenously (IV), which acts as the standard for 100% bioavailability. By comparing various routes of administration to IV, the percentage of drug delivered to the plasma, on a dose-normalized basis, can be calculated and is referred to as the "absolute bioavailability". As pharmacology has advanced and more drugs have become available, many older products have been reformulated to be given by routes other than those originally intended (often oral). As the drawbacks of oral (or IV) administration have become better appreciated, non-oral, non-IV formulations and methods of administration have become more popular. Nasal administration is one route that has historically been overlooked as an alternative to oral administration—particularly for products needing rapid and non-invasive access to the target tissue—mostly via the blood stream. But attention is now focused on nasal administration for direct access to the brain, as that has the potential to bypass the blood-brain-barrier (BBB), which not even IV administration can always achieve. Assessing PK for these drugs targeting the brain may require serial sampling of the cerebrospinal fluid (CSF), making PK assessments of CNS drugs more invasive and complex, but still possible in future product development. However, we are now seeing more drugs reformulated for nasal delivery to gain faster systemic levels than oral administration (especially in patients with known or suspected gastrointestinal dysmotility), while avoiding the use of needles. For example, in recent years several different formulations and delivery methods for an old drug, dihydroergotamine (DHE), have been developed and these show very different characteristics, suggesting that delivery to different parts of the nose may have very different PK profiles. This review summarizes the systemic PK of different nasal DHE options that have been, or are being, developed and suggests that delivery of drugs to the upper nasal space (UNS) may represent an optimal target. Further research is required to ascertain if this route could also be utilized for direct administration to the CNS (as an attractive alternative to intrathecal delivery) via the olfactory or trigeminal nerves—but already preclinical data (and some human data) suggest this is entirely possible.

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Key Points

More drugs are being discovered and developed for CNS diseases with many of these, especially peptides, proteins, and other large molecules unable to readily cross the blood-brain-barrier (BBB).

"Nose-to-brain" (N2B) delivery might allow these drugs to enter the CNS directly, raising interest in how to deliver to the olfactory epithelium of the upper nasal space (UNS) (or potentially the respiratory epithelium of the lower nasal space and access the underlying branches of the 2nd division of the trigeminal nerve).

Not all nasal delivery is the same—as evidenced by distinct pharmacokinetic differences of UNS delivery versus lower nasal space with the same liquid drug formulation.

1 Introduction

Pharmacokinetics (PK), or what the (human) body does to a drug, dates back to two German scientists Michaelis and Menten, who, in 1913, described the kinetics of enzymes, but the actual term, pharmacokinetics, was only adopted some 40 years later by another German, Dost [1]. Nowadays, all drugs must establish their PK, principally how they are absorbed, distributed, metabolized and finally eliminated from the body, collectively called ADME. First in animals before the human dosing may commence [2]. The most widely used PK parameters are the maximum plasma concentration reached (C_{max}) and the time taken to reach it (T_{max}), the area under the time vs concentration curve (AUC), which can be over a specified time (e.g., 2 h or $AUC_{0–2}$), to infinity ($AUC_{0–inf}$) or to last measured concentration ($AUC_{0–last}$), the drug's estimated half-life in the plasma ($T_{1/2}$), elimination rate and volume of distribution [3].

Providing the raw data to enable the calculation of the various PK parameters is the job of the bioanalytical team. Bioanalytical processes evolve over time, typically becoming more reliable with a greater range of detection. Sometimes that leads to quite different results from earlier techniques and analyses making it difficult to compare results from different bioanalytical methods and different laboratories. The most rigorous comparison compares results from identical processes conducted by the same laboratory and preferably in the same or adjacent batches run through the same calibrated equipment.

2 Why the Nose?

The nose has long been the target of drug delivery, dating back to ancient Chinese [4] and Persian [5] practices but with little change to the administration device compared to perfume atomizers that were popularized in many countries in the 19th century. An atomizer was first adopted for medicinal purposes by DeVilbis, an otolaryngologist from Ohio in 1887 [6]. More recently, local nasal disease, especially allergic rhinitis, a relatively benign but distressing local allergic disease of the nose, has been treated with local anti-inflammatory sprays (specifically corticosteroids and cromoglycate) or decongestants and antihistamines. The steroid, beclomethasone dipropionate was launched first in 1972, but was soon followed by flunisolide and triamcinolone and subsequently by other nasal steroids, budesonide, fluticasone propionate, mometasone furoate and ciclesonide. But the treatment was always designed to target the edematous, allergen-responsive respiratory epithelium of the lower nasal space (LNS), and especially the nasal turbinates. This is also the area of the nose targeted for other local sinu-nasal diseases, such as chronic rhinosinusitis (CRS), and does not require (indeed would prefer to avoid), corticosteroid being systemically absorbed. Most of the aerosol sprays use a pump to ensure a metered dose of product is delivered, but most deliver a diffuse cloud, or broad plume of spray with much depositing in the non-absorbing stratified squamous epithelium of the vestibule, or the (absorptive) ciliated respiratory epithelium of the middle and inferior turbinates [7].

Recently, much more interest has focused on the olfactory epithelium, which in humans occupies about 10% of the nasal cavity [8] and is located in the upper nasal space (UNS). The UNS includes the superior nasal septum (medially), the medial surface of the superior turbinate and sections of the middle turbinate (laterally), and the cribriform plate (superiorly) [9] (see this illustrated in cross section in Fig. 1) [10].

Depositing drugs on olfactory epithelium, with its rich supply of olfactory dendrites descending through the cribriform plate from the olfactory bulb may lead to direct "nose-to-brain" (N2B) delivery (as has been reported in animals for nearly 30 years [11–13]) and its highly vascular bed, which can lead to faster systemic absorption [14].

Obtaining systemic administration via nasal delivery has several appealing aspects, namely:

- Low risk of pain.
- Potentially reduce systemic side effects (for some preparations).
- Avoids first-pass metabolism by the liver, improving bioavailability (over oral and rectal administration).

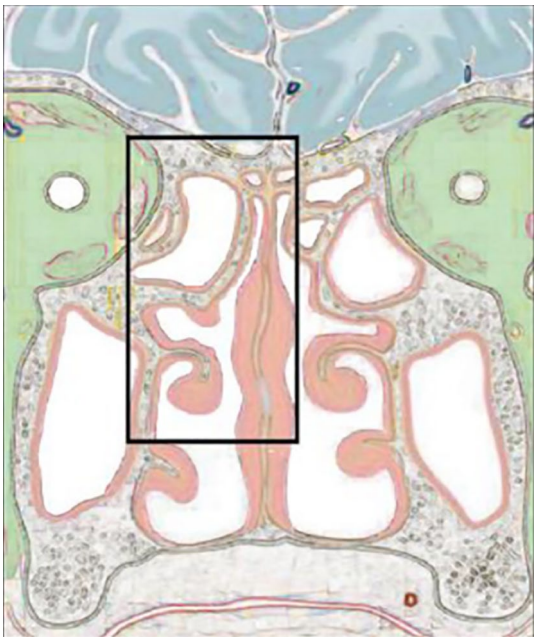

Fig. 1 Cross-section of the frontal portion of the human head, representing the posterior third of the nasal cavity, with outlined region highlighting areas commonly enriched with olfactory epithelium. Adapted from Salazar I, Sanchez-Quinteiro P, Barrios AW, López Amado M, Vega JA. *Handb Clin Neurol.* 2019; 164: 47–65 [2], with original adaptation from Schünke M, Schulte E, Schumacher U, et al. *Prometheus: Texto y Atlas de Anatomía.* 3a edición, vol. 3. Madrid: Panamericana; 2014

- Easy and fast delivery that increases patients' compliance.
- May allow rapid absorption and rapid onset of action.
- Sterile administration technique not required.
- Immediately and readily available for all patients.
- Useful for drugs that are effective at low doses.
- Suitable for self-, caregiver- or health care provider-administration.
- Can be used when nauseous or by patients with gut disorders [14].

For this review the focus will be on the PK of drugs specifically delivered to the UNS, which highlights the importance of understanding that delivering drugs to different parts of the nose may generate very different PK profiles. As an example, the PK of UNS delivery versus traditional nasal delivery of dihydroergotamine mesylate (DHE) for acute treatment of migraine will be used. Several liquid sprays have been developed and approved, including a recent program using the same liquid formulation as an approved traditional product, but delivering to the UNS, and a powder formulation, which has recently completed its clinical development.

Within the nose, local delivery of DHE to the V2 branches of the trigeminal nerve supplying the LNS may be an, as yet, under investigated route of direct N2B providing benefit, but that is not the focus of this article.

3 Dihydroergotamine (DHE)

3.1 Liquid spray (LS): Traditional LNS Delivery (STOP 101 Study)

Appreciating the potential benefits outlined above, a liquid nasal spray (LS) DHE formulation was developed and approved in the 1990s. As bioanalytical methods have evolved since the product was approved, and to provide a current comparison against UNS delivery (and IV delivery), the PK parameters, for this "traditional" LS formulation at a dose of 2.0 mg were recently investigated in the STOP 101 study (NCT03401346) [15], which was a randomized, open label, 3-arm, 3-period, 3-way crossover study in health volunteers, dosed with consecutive single doses of 1.0 mg of IV DHE, 2.0 mg of the approved LS formulation to the LNS using a traditional spray and 1.45 mg of the same formulation by Precision Olfactory Delivery (POD®) to the upper nasal space in 6 treatment sequences [15]. A lower dose (of the same formulation) was delivered by POD compared to the LS, as it was predicted that it would lead to greater absorption through the UNS mucosa – as was shown to be the case. The device is actuated by pressing up with the thumb under the assembled device while holding the actuator between 2nd and 3rd fingers in a scissor grip. For further information about the technology, and how it is administered, see Cooper et al. [16].

Subjects were domiciled for 48 h after each dose for safety assessments and PK blood draws and waited 7 days until the next dose [15].

The product was self-administered by the 34 healthy volunteers (the safety population), after reading the instructions for use, by spraying a broad plume of spray once into each nostril, waiting 15 min and then spraying a second spray into each nostril. The PK results showed a T_{max} (median) of 0.78 h, with a C_{max} of 299.6 pg/mL, and a coefficient of variation (CV) of 91.8%. The $AUC_{0–inf}$ was 2199 h*pg/mL (with CV 74.7%) and $T_{1/2}$ 10.4 h (Table 1). One of the recognized problems of delivery using the "traditional" LS device is that much of the spray plume coats the non-absorbing squamous epithelium of the nasal vestibule and does not land on the absorptive epithelium of the LNS, with very little penetrating through the nasal valve to enter the UNS. This leads to the loss of drug via gravity both out on to the upper lip and down the back of the throat causing complaints of unpleasant taste. Both of these situations, which reduce the amount of

Table 1 Pharmacokinetics of various DHE products from STOP101 study [15] and STS101-006 study [22]

DHE	STOP 101			STS101-006	
	LS 2.0 mg (liquid)	POD 1.45 mg (liquid)	IV 1.0 mg	STS101 6.0 mg (powder)	LS 2.0 mg (liquid)
	$n = 34$	$n = 31$	$n = 31$	$n = 35$	$n = 33$
C_{max} (pg/mL)	299.6	1301	14,190	2090	417
T_{max} (h)	0.78	0.5	0.08	0.5	1.0
AUC_{0-inf} (h*pg/mL)	2199	6275	7490	10100	3450
$T_{1/2}$ (h)	10.4	11.8	14.2	Not reported	Not reported
AUC_{0-2} (h*pg/mL)	428.7[a]	1595[a]	3019[a]	2710	550

AUC_{0-inf} area under (concentration vs time 0 to infinity) curve, *AUC_{0-2}* area under (concentration vs time 0 to 2 h) curve, *C_{max}* maximum plasma concentration, *DHE* dihydroergotamine, *IV* intravenous, *LS* liquid spray, *POD* precision olfactory delivery, *STS101* Satsuma powder DHE product in development, *$T_{1/2}$* half-life, *T_{max}* time to C_{max}

[a]PK population ($n = 27$ received all 3 treatments)

drug product on the LNS epithelium available for absorption, were observed and reported, by 77% (dripping) and 56% (running down back of throat) in the STOP 101 study with the LS [15]. In addition, the epithelium of the LNS has a strong rostral-caudal mucociliary clearance (MCC) towards the nasopharynx, which sweeps the mucus and entrapped drug to the back of the nasopharynx with a clearance time of ~ 10 min, in rodents [17], and estimated to be a mean 8 mm/min in humans, ranging from 1 to > 20 mm/min [18].

3.2 Liquid Spray: Upper Nasal Space (UNS) Delivery (STOP 101 Study)

After a 7-day washout, the same formulation was again self-administered using the novel POD device [15]. The device was assembled in much the same way as the traditional spray but the POD is activated by pushing the bottle into the body of the device, which triggers a release of propellant [16], which gently pushes the liquid dose through narrow channels in the tip, creating a narrow plume that passes through the nasal valve and into the UNS [16]. That is then followed by the release (from the single dose) of more propellant that pushes the delivered dose further into the UNS and spreads the dose over the epithelium [16]. The 3-period, 3-way crossover study was conducted in 6 sequences, 2 of which received the POD DHE first. Thirty-one subjects provided data showing T_{max} 0.5 h with C_{max} 1301 pg/mL (CV 51.4%), AUC_{0-inf} was 6275 h*pg/mL (with CV 41.8%) and $T_{1/2}$ 11.8 h [15] (Table 1). In total, 32% reported nasal dripping and 32% reported product running down the back of the throat with POD DHE [15]. The olfactory epithelium of the UNS has cilia but these are non-motile, making MCC much slower from the UNS, estimated at several days [19].

3.3 IV Administration (STOP 101 Study)

In a third period of the same study, 31 volunteers received 1.0 mg of DHE by IV infusion over 1 min [15] giving T_{max} 0.08 h with C_{max} 14,190 pg/mL (CV 37.0%), AUC_{0-inf} was 7490 h*pg/mL (with CV 16.6%) and $T_{1/2}$ 14.2 h (Table 1). The absolute bioavailability of IV DHE is assumed to be 100% and using the PK population (i.e., results from the volunteers who received and provided data from all 3 treatments), the absolute bioavailability of POD DHE was 58.9% and for traditional LS DHE 15.2% in this study, a 4-fold improvement with the same formulation when delivered to the UNS, despite the lower dose [15].

3.4 DHE Metabolites

Most drugs are metabolized in the liver giving rise to one or more metabolites some of which may be bioactive, while others are not. Dihydroergotamine was first approved in 1946 but it was not until 1984 that its five metabolites were characterized [20], with one, the 8′hydroxy DHE (8′OH-DHE), being the major metabolite. The other metabolites are: 8′,10′-dihydroxy-dihydroergotamine (8′,10′-OH-DHE), 2,3seco,N(1)formyl,3-keto,8′-hydroxy-dihydroergotamine (8′-OH,N(1)formyl-DHE), dihydrolysergic acid amide (DH-LSA) and dihydrolysergic acid (DH-LS) all present at much lower concentrations and not considered to contribute to efficacy (or safety) of the administered DHE product.

It had been believed that the high levels of metabolite were responsible for the recognized long duration of action of DHE. However, as reported, even the levels of the main metabolite 8′OH-DHE are low, of the order of 5%–10% of the parent molecule [15]. More recently, it has been suggested that the long duration of DHE action was due to slow dissociation kinetics from the serotonin receptors ($5\text{-}HT_{1B}$ and $5\text{-}HT_{1D}$) [21], being only one of the classes of

receptors to which DHE binds. Notwithstanding that mechanistic explanation for DHE's well known long duration of action, there has been continued interest (and a regulatory requirement) to characterize the PK profile of the 8′OH-DHE metabolite, if not for the potential efficacy of the compound, then certainly from a safety perspective. This was done in the STOP 101 trial [15]. As can be seen, the plasma concentrations for 8′OH-DHE (Table 2) were of an order of magnitude lower than for the parent molecule (Table 1), which was an important result considering the new route of administration, with the T_{max} for both nasal administrations being longer than the parent (as would be expected to give the liver time to metabolize the parent).

3.5 Powder Spray: Lower Nasal Space (STS101-006 Study)

Satsuma conducted a separate DHE program with two PK studies with slightly different formulations of DHE from slightly different devices [22]. Both STS101 powder formulations incorporated a proprietary bio-adhesive drug carrier and specially engineered drug particles in an attempt to increase residence time on the mucosa and hence facilitate a greater degree of absorption.

The second program, which incorporates a slightly different plastic bottle delivery device, with thinner walls making it easier to squeeze and expel the powder and incorporated revised training and updated instructions for use (IFU) for the device. Both of the STS101 plastic bottle devices come fully assembled and before use require the plastic tab to be removed from the top of the nose tip, device inserted into a nostril and then a forceful squeeze between 2nd finger and thumb given to the plastic bottle. The revised program with the improved device and IFU included a PK study with a dose of dihydroergotamine base of 5.2 mg (equivalent to a 6.0-mg dose of the mesylate salt), which provided the following results in 35 healthy volunteers: T_{max} 0.50 h with C_{max} 2090 pg/mL (CV 37.8%), $AUC_{0–inf}$ was 10,100 h*pg/mL (with CV 74.7%). The $T_{1/2}$ was not reported [23] (Table 1). Although assessment of the 8'OH-DHE levels, specifically AUC, were an important secondary endpoint in both PK studies, as stated on ClinicalTrials.gov (NCT03874832 and NCT05337254) and confirmed in the primary publication from the first PK study [22], that (8'OH-DHE) data have not been abstracted or otherwise reported to date.

Table 2 Pharmacokinetics of 8'OH-DHE from the STOP 101 study (safety population) [15]

	STOP 101		
	LS DHE 2.0 mg (liquid)	POD DHE 1.45 mg (liquid)	IV DHE 1.0 mg
	$n = 34$	$n = 31$	$n = 31$
C_{max} (pg/mL)	38.8	55.9	387.4
Median T_{max} (h)	1.93	1.33	0.08
$AUC_{0–last}$ (h*pg/mL)	351.3	414.5	500.9
$T_{1/2}$ (h)	18.8	16.9	10.5

AUC_{0-inf} area under (concentration vs time 0 to infinity) curve, *C_{max}* maximum plasma concentration, *DHE* dihydroergotamine, *IV* intravenous, *LS* liquid spray, *POD* precision olfactory delivery DHE product in development, *$T_{1/2}$* half-life, *T_{max}* time to C_{max}

3.6 Liquid Spray: Lower Nasal Space Delivery (STS101-006 Study)

In the same study the "traditional" LS formulation at a dose of 2.0 mg in 33 healthy volunteers provided the following results: T_{max} (median) was 1.00 h, with a C_{max} then of 417 pg/mL, with a coefficient of variation (CV) of 155%. The $AUC_{0–inf}$ was 3450 h*pg/mL (with CV 74.7%), $T_{1/2}$ 10.4 h [23] (Table 1). The product was self-administered by the volunteers after reading the instructions for use; however, it is not clear what degree of device training patients received prior to administration. It is also unclear if the same bioanalytical methodology was used in the STS101-006 study, or laboratory conducting it, as the STOP 101 study, which highlights an important point when conducting a PK study. It is necessary to compare results with different products from within the same study using the same subjects, the same bioanalytical methods run by the same laboratory and analyzed by the same scientists with the same methods at the same time. Despite that the results for the same standard dose of LS DHE across the two programs are not too dissimilar given the high degree of variability observed with the LS DHE in both studies. The bioavailability of STS101 is 2- to 6-fold greater than the LS based on the ratios of the geometric means for C_{max} (5-fold) or AUC ($AUC_{0–inf}$ 2.9-fold) [23], but that does not allow for the difference in dose, 6.0 mg vs 2.0 mg and in neither of the STS101 PK studies was an IV arm included to give the 100% absolute bioavailability results. However, within each of the above two studies, comparing different nasal products show the following:

STOP 101: despite delivering less than 75% of the dose, when DHE was delivered by POD to the upper nasal space, it increased the C_{max} 4-fold and the $AUC_{0–inf}$ 3-fold, with much reduced variability compared to the LS DHE [15]. Across all 3 DHE products, the major bioactive metabolite, 8'OH-DHE, generated both C_{max} and $AUC_{0–last}$ data that were an order of magnitude lower than the parent molecule.

STS101-006: delivering 6.0 mg powder increased the C_{max} 5-fold compared to 2.0 mg of the traditional nasal spray (but with much reduced variability). Adjusting for the greater dose of STS101 (6.0 mg), the C_{max} of the powder may represent a 1.7-fold improvement in C_{max} [23]. The

$AUC_{0–inf}$ of the 6.0-mg powder product increased 2.9-fold, compared to the 2.0-mg traditional nasal spray. Adjusting for the 3-fold increase in dose, there appears to be little difference in the amount of DHE absorbed over time between the two formulations when both were delivered, presumably, to the LNS. The data for 8′OH-DHE have not been reported.

There were high hopes that STS101 would be effective; however, two large Phase 3 single migraine attack efficacy studies failed to show statistical superiority versus placebo in the standard co-primary endpoints of pain freedom and most bothersome symptom freedom both at 2 h; EMERGE in 2020 [24] (NCT03901482) with 1065 patients in the modified intent-to-treat (mITT) population and SUMMIT in 2022 [25] (NCT04940390) with 1424 patients in the mITT population. Neither study has been fully published. In the initial study it was reported that patients failed to squeeze the plastic bottle device adequately, with patients only getting a mean of 73% of the intended dose out of the device and into their nose. It is not clear why the SUMMIT trial failed to demonstrate efficacy.

A previous orally inhaled formulation of DHE (MAP0004) was developed but never gained regulatory approval. In a Phase 2 study, the highest dose tested, 2.0 mg nominal (1.0 mg systemic equivalent), was not effective, whereas the lower 1.0 mg nominal (0.5 mg systemic equivalent dose) was [26] and was taken forward to a successful, large Phase 3, FREEDOM 301 study [27]. It was speculated during the development program that C_{max} was not the best predictor of subsequent clinical efficacy, but that there might be a "sweet spot" of AUC_{0-2} [28] that would be a better predictor, based on the results with MAP0004. The $AUC_{0–2}$ of MAP0004 was reported as 1513 h*pg/mL [28], which was closely matched by POD DHE in the STOP 101 study at 1595 h*pg/mL [15] (Table 1).

In contrast (to the STS101 development), POD DHE performed an open-label safety study of 360 patients (as requested by FDA) (NCT03557333) for Phase 3 [29]. The satisfactory PK results showed that the C_{max} and AUC with POD DHE lay between the two approved DHE products (IV DHE as D.H.E.45® and LS DHE as Migranal®) [15], which had both previously shown sufficient safety and efficacy, and these two studies (STOP101 and STOP 301) were sufficient to gain regulatory approval of POD DHE NDA in September 2021.

4 Other Programs Delivering Drugs to the Upper Nasal Space

As part of the comprehensive development program for the POD system, various iterations of the technology were especially adapted to deliver either liquid or powder formulations of drug to the UNS of rodents and primates. The nasal architecture and small microsmatic area of primates (compared to rodents and canines) more closely resemble those of humans. This allows more accurate PK predictions when moving from (non-terminal) animal experiments into early clinical studies [30]. Another useful feature of the POD programs is a "Clinical Research Device", which accepts standard pharmaceutical grade capsules (specifically for powder formulations) allowing rapid transition from one powder formulation to another, and even bringing different powder drug products into the same study (once regulatory approval has been received), allowing for faster clinical programs [30]. Two programs (INP105 and INP107) have already run clinical PK studies with the "Clinical Research Device" using powder formulations [31].

4.1 Olanzapine: INP105 (SNAP 101)

Olanzapine (OLZ) is a second-generation atypical antipsychotic, approved as a chronic oral formulation, but with clinical benefit offset by metabolic concerns and often significant weight gain. It is also available as an intramuscular (IM) injection for patients with acute agitation and is approved for use in patients with schizophrenia and bipolar disorder, but not infrequently requiring restraint for safe administration. It is also used for other causes of acute agitation, e.g., in patients with autism, but then often the oral disintegrating tablet (ODT) is used to avoid the use of needles and restraint.

A PK study was run in healthy adult volunteers comparing an early spray dried OLZ formulation to both the IM injection and the ODT (NCT03624322) [32]. Pharmacokinetic data were generated for 2 IM doses (5 mg and 10 mg—although the latter was quickly abandoned as it led to unacceptable postural hypotension in the healthy volunteers), 3 POD doses (5 mg, 10 mg and 15 mg) and a 10-mg dose of OLZ ODT (Table 3). Comparing POD OLZ dose to the same mg dose delivered IM, the 5-mg doses showed slightly higher C_{max} with POD (28.7 ng/mL vs 24.8 ng/mL), faster time to achieve that C_{max}, median T_{max} 15 min (POD) versus 20 min (IM), and at least similar extent of absorption measured by $AUC_{0–inf}$ (5 mg POD OLZ 328 h*ng/mL vs 314 h*ng/mL with 5 mg IM) [32]. Similar encouraging results were seen for the 10-mg dose, C_{max} (74.5 ng/mL vs IM 73.1 ng/mL), at median T_{max} (10 min vs 15 min) and $AUC_{0–inf}$ (POD OLZ 720 h*ng/mL vs 470 h*ng/mL with IM). These were also significantly different from the OLZ ODT results (C_{max} 17.5 ng/mL, at median T_{max} 120 min and $AUC_{0–inf}$ of 563 h*ng/mL) [32].

These results suggest that according to PK, it would be anticipated that in an acute situation, effective blood levels of OLZ could be achieved at least as quickly with non-invasive POD delivery of OLZ to the upper nasal space as with the equivalent IM injection and much faster than with the OLZ ODT. A clinical study recently had set out to test this

Table 3 Summary of SNAP 101 PK parameters (of selected doses) (PK population) [31]

	POD OLZ 5 mg (powder) $n = 10$	POD OLZ 10 mg (powder) $n = 9$	IM OLZ 5 mg $n = 20$	IM OLZ 10 mg $n = 2$	OLZ ODT 10 mg $n = 18$
C_{max} (ng/mL)	28.7	74.5	24.8	73.1	17.5
Median T_{max} (mins)	15	10	20	15	120
$AUC_{0–inf}$ (h*ng/mL)	328	720	314	470	563
$T_{1/2}$ (h)	40.5	36.8	41.2	33.2	37.1

$AUC_{0–inf}$ area under (concentration vs time 0 to infinity) curve, *C_{max}* maximum plasma concentration, *DHE* dihydroergotamine, *IM* intramuscular, *IV* intravenous, *LS* liquid spray, *OLZ* olanzapine, *POD* precision olfactory delivery, *$T_{1/2}$* half-life, *T_{max}* time to C_{max}

hypothesis in acutely agitated adolescent and young adult patients with autism (NCT05163717) but was terminated for business reasons.

4.2 Levodopa (INP103) and Carbidopa/Levodopa (INP107)

Another program (INP103/INP107) demonstrating the versatility of the POD device was conducted in patients with Parkinson's disease suffering from severe and frequent off episodes when the level of levodopa (LD) drops below that needed to keep dopaminergic neurons fully functional. This study (THOR 201), conducted at 5 centers in Australia (NCT03541356) [31], started with a spray dried formulation of just LD at three ascending dose levels 35 mg, 70 mg and 140 mg (preceded by an oral dose of dopa decarboxylase inhibitor [DCI]) [31]. The powder formulation was developed and provided in standard pharmaceutical grade capsules, which could be opened and inserted onto the dosing tip of the "clinical research" POD device. This allowed a formulation of combined carbidopa/levodopa to be developed during the early phase of the study and, once regulatory approval had been obtained, provided for dosing of a final cohort at 7 mg carbidopa (CD), 70 mg LD. This formulation allowed the discontinuation of the oral DCI pretreatment. Generally, the results showed dose proportional increases in both C_{max} and $AUC_{0–2}$ once plasma levels were corrected for baseline LD (which all patients were receiving but had not had for at least 8 h at the time of dosing in this study). However, the median T_{max} was disappointingly longer than expected, or desired (Table 4). Further work on optimizing the formulation would be needed before further clinical work would be contemplated—and understanding why LD (taken by patients already on chronic oral LD) provides significantly slower T_{max} than seen with either liquid DHE or powder OLZ. In addition, this study did not compare the speed and extent of rising LD levels obtained from their usual morning dose of LD—or any other formulation or route of administration of LD. One hypothesis is that the much higher payloads of drug, 35 mg, 70 mg, 140 mg and a combined 77 mg (of LD+CD) might limit the rate of absorption (from the small surface area of the UNS) compared to the 1.45 mg of DHE or 5 mg (or 10 mg) of OLZ. Another is that the formulation of combined LD+CD still needs work for it to be optimal.

4.3 Other Nasally Delivered Drugs

Increased interest in the non-invasive delivery of drugs by the nasal route has led to several other programs in development over the recent years [33–44] (Table 5), although not specifically targeting the UNS. Some of these have led to successful product approvals. Much of the current interest in nasal delivery relates to "nose-to-brain" drug delivery, which may not see drugs enter the systemic circulation at all. Although exactly how the amount of drug

Table 4 Summary of THOR 201 PK parameters (of baseline corrected) levodopa and carbidopa (PK population)

	POD LD 35 mg (powder)	POD LD 70 mg (powder)	POD LD 140 mg (powder)	Combined LD/CD (powder)	
				POD LD 70 mg	POD CD 7 mg
	$n = 6$	$n = 6$	$n = 6$	$n = 6$	
C_{max} (ng/mL)	185.8	362.7	643.7	466.5	80.2
Median T_{max} (min)	45.5	50	60.5	90.5	44.5
$AUC_{0–2}$ (h*ng/mL)	240.7	463.5	725.3	552.8	114.8

AUC_{0-2} area under (concentration vs time 0 to 2 h) curve, *CD* carbidopa, *C_{max}* maximum plasma concentration, *LD* levodopa, *POD* precision olfactory delivery, *T_{max}* time to C_{max}

Table 5 Summary of absolute bioavailability (i.e., compared to IV delivery) of nasally delivered products in development, or recently approved

Product [Reference]/manufacturer device (formulation) (if known)	Bioavailability	Indication	Status
Zavegepant [32] Pfizer (liquid)	~5%	Migraine	Approved 2023
Oxytocin (TTA-121) [33] Teijin Pharma Ltd. (liquid)	N/A (but 3.6 × AUC of existing Syntocinon® spray in rabbit)	Autism spectrum disorder	Clinical—Phase 2 (Japan)
Sumatriptan [34] GSK (liquid)	~17%	Migraine	Approved 1992
Sumatriptan [35]/BiDirectional Optinose device OptiNose (powder)	N/A (but higher C_{max} and "early (first 30 min) exposure" than liquid spray)	Migraine	Approved 2016
Zolmitriptan [36] Perrigo (liquid)	102%—relative to oral BAV	Migraine	Approved 2003
Insulin[a] [37] Multiple insulin suppliers (liquid)	N/A	Alzheimer's disease	In development
Benzgalantamine [38] Alpha Cognition (liquid)	N/A	Alzheimer's disease	In preclinical development
Esketamine [39] Janssen (liquid)	~48%	Treatment-resistant depression	Approved 2019
Fentanyl [40] Archimedes Pharma (liquid)	~70%	Cancer breakthrough pain	Approved 2011
Diazepam [41]/ Aptar UDS/Neurelis (liquid)	97%	Seizures	Approved 2020
Dexmedetomidine [42] MAD nasal (device only) (liquid)	74–89%	Sedation (for non-invasive procedures)	Clinical—Phase 2
Midazolam [43]/Aptar UDS/UCB (liquid)	44%	Acute repetitive seizures	Approved 2019

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AUC area under (concentration vs time) curve, *BAV* bioavailability, C_{max} maximum plasma concentration, *IM* intramuscular, *IV* intravenous, *MAD* mucosal atomization device, *N/A* not available, *UDS* unit dose spray

[a]In fact bioavailability of insulin in the systemic circulation is NOT desired—but direct access to the brain is desired

accessing the CNS directly can be measured has yet to be proposed and agreed, other than through imaging and/or clinical endpoints. The (systemic) bioavailability (when known) of these products is summarized in Table 5.

Previous studies have compared differential PK of sumatriptan nasal delivery [36] but in this case it was between different formulations—powder (through the BiDirectional Optinose device) and liquid (through a traditional nasal spray)—and compared with both oral and SC administration, although the Optinose product also claims some delivery to the UNS. The absolute bioavailability (BAV) (compared to IV administration) of sumatriptan from either nasal formulation was not reported from this study but the PK curves for both nasal formulations showed a bimodal distribution showing an earlier initial peak following absorption through the nasal mucosa, followed by a second peak, presumed to be unintended gastrointestinal absorption of the swallowed fraction of drug in the normal healthy volunteers [36]. This device was the first to win approval that suggested differential delivery within the nose was important, although this required patients to blow into their own nose and the device has, so far, not been a huge commercial success.

As Table 5 shows, there has been considerable interest, and several successful clinical development programs for nasal products over the past 3 decades intended for patients with migraine, where both acute symptoms (of nausea and vomiting) often accompany a migraine attack and asymptomatic gastrointestinal dysmotility even between attacks may be exacerbated within an attack [45]. Other indications targeted include seizures where drug levels are required rapidly to abort the ongoing seizure activity. The programs that have so far led to approvals benefit from the rapid absorption and systemic distribution of drug from the nose (be it from the LNS or the UNS), rather than direct "nose-to-brain" delivery, although it is tempting to think that these CNS drugs approved, or in development (Table 5), may benefit from early and direct distribution of the drugs involved to the brain.

5 Summary

Understanding the PK of a drug is a key step in a successful development program—not just for new chemical entities (NCEs), but also for old molecules that have never been

optimally delivered and a new route of administration is being explored—as has been the case with DHE. Originally approved in 1946, it has remained arguably the gold standard drug for acute administration to patients with episodic migraine ever since, but by injection. A traditional nasal spray version was approved in 1996 but even during that Phase 3 program, inconsistent efficacy results were apparent across 4 studies. In 2008–2013, an orally inhaled version, MAP0004, with an attractive PK profile showed that more was not always better, when an optimal dose in a Phase 2 dose-ranging study was found to be the middle of 3 doses. The high C_{max} "spike" of an IV injection of DHE is responsible for the higher incidence of adverse events reported, especially nausea. Indeed, even pre-medicating with metoclopramide in the STOP 101 PK study both nausea and vomiting were reported after the IV injection by the healthy volunteers.

Since the traditional LS spray was approved, other routes of administration have been tried but the orally inhaled (MAP0004) product, despite a successful Phase 3 study, was unable to obtain regulatory approval due to Chemistry Manufacturing and Controls (CMC) challenges.

More recently, delivery of the approved liquid DHE formulation (manufactured by the same company on the same equipment as the approved product) by POD to the UNS has been approved. This was a deliberate decision to avoid potential concerns that a new liquid formulation, manufacturing process, or manufacturer might encounter. It showed a dramatically different PK profile to the originator—and a very close $AUC_{0\text{-}2}$ match to the MAP0004 product.

This has been followed by a powder DHE program, STS101, delivering 6.0 mg (three times the approved LS product dose) to the LNS. Although absolute PK results were encouraging, when corrected for dose administered they were little different from the LS directed to the LNS and two very large Phase 3 efficacy studies have both failed to show a statistical difference to placebo with the important co-primary endpoints. Powder products may indeed benefit from bio-adhesives and absorption enhancers to overcome some of the challenges of gravity and rapid MCC from the LNS and indeed much work has focused on trying to slow clearance of drug deposited in the LNS to allow for greater absorption. Some nasal delivery projects (with or without these additional complexities) have indeed born fruit, with substantial bioavailability for some recently approved nasal products (Table 5), although differential delivery within the nose was mostly not investigated.

6 Conclusion

Drug delivery to the richly vascularized UNS with either liquid or powder drug products allows rapid and extensive absorption and may offer a promising alternative route for drugs that are needed for acute situations when slow absorption from an oral dose, or the lack of necessary equipment, staff or an appropriate location or patient compliance make an IM injection unfeasible. The PK profile of drugs so far in development with POD delivery is encouraging and guided by PK, this route of administration may have many other opportunities ahead to deliver drugs rapidly and extensively to the systemic circulation. Targeting the olfactory epithelium of the UNS may also be the necessary first step to potential "Nose-to-Brain" delivery, which will be required for the many CNS drugs in development that will otherwise need invasive delivery to bypass the BBB.

Declarations

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Conflict of interest Dr Stephen B. Shrewsbury was Chief Medical Officer to Impel Pharmaceuticals at the time the above studies were conducted and during the initial development of this manuscript, but not during the subsequent review and revision process.

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