A History of Dihydroergotamine in Migraine

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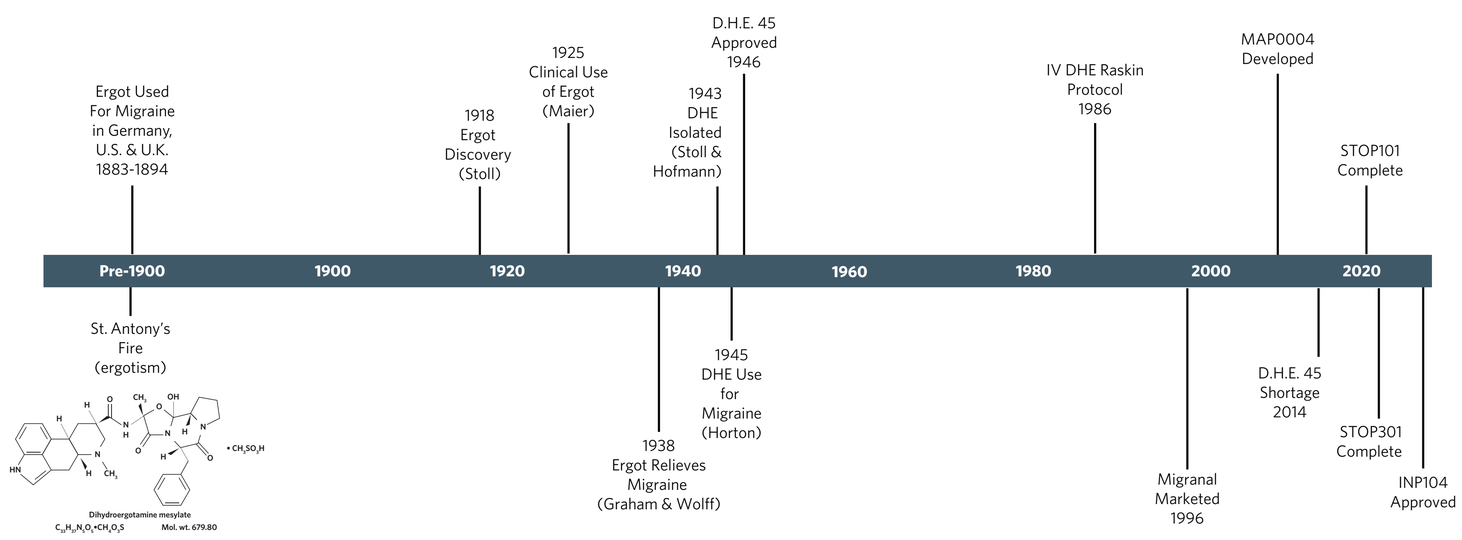
Background

Figure 1. Historical Timeline of Development of Ergot Alkaloids for Medicinal Use (Then and Now)



- Ergot use in obstetrics dates back to 1100 BC in China, 370 BC noted by Hippocrates and 1808 in the U.S.
- Ergotamine was isolated in 1918, subsequently modified to DHE, and approved in 1946 for the treatment of migraine (**Figure 1**).
- DHE remains a dependable choice for neurologists and headache specialists for acute migraine, status migrainosus and cluster headache.

Objective

- We provide a history of DHE from its synthesis in 1943 to modern day formulations and routes of administration.
- This review highlights existing evidence for the effectiveness of DHE for acute migraine with a focus on a new route of administration for DHE.

History of DHE for Migraine

- The chemical structure of DHE is similar to many naturally occurring neurotransmitters, including epinephrine, norepinephrine, dopamine, and serotonin (**Figure 1 inset**).

Migraine

- The worldwide prevalence of migraine is 14.3% and along with severe headache is estimated to affect 1 in 6 adult Americans.
- Migraine remains one of the leading causes of disability worldwide.
- In the U.S., annual costs for healthcare and lost productivity from migraine are estimated at $36 billion. In Europe, annual costs are estimated at €27 billion.

Treatment of Migraine

- Acute migraine treatment remains a significant challenge.
- Although the ditans and the calcitonin gene-related peptide (CGRP) antagonists, or gepants are launching, these new classes of drugs are not more effective than the triptans or DHE (**Table 1**).
- Additional treatment options are needed for acute episodic migraine that overcome current medication limitations.

Table 1. Rates of Pain Relief, Pain Freedom, and Treatment Effects (Active Minus Placebo Rates) at 2 Hours With Acute Non-Injected Migraine Drugs

Drug/Dose (Reference)	Relief (%)	Treatment Effect (%)*	Freedom (%)	Treatment Effect (%)*
Levadex [Orally inhaled DHE 1.0 mg][1]	59	24	28	18
Migranal 2.0 mg [Study 1][2]	61	38	Not reported	Not reported
Migranal 2.0 mg [Study 3][2]	32	12	Not reported	Not reported
Sumatriptan 100 mg[3]	59	30	29	19
Rizatriptan 10 mg[4]	88.1	No placebo	60.9	No placebo
Ubrogepant[5]			25.5	16.6
Rimegepant [Study 301][6]			19.2	5.0
Rimegepant [Study 302][6]			19.6	7.6
Lasmiditan 200 mg[7]			32.2	16.9

*Treatment Effect = active treatment minus placebo.

DHE – Then

- DHE was approved for migraine in 1946.
- DHE is recommended as an alternative to triptans for treating acute migraine.[8]
- DHE binds to multiple receptor sites with a long half-life and has a rapid onset and sustained effects lasting up to 48 hours and may be effective in patients with:[9]
  - Waking with migraine
  - Triptan-resistance
  - Menstrual migraine
  - Allodynia
  - Severe and/or prolonged migraine
  - Cluster headache

D.H.E. 45

- DHE is available for intravenous, subcutaneous (SC), intramuscular (IM), and nasal administration.
- IV DHE is used most often in the emergency room or by headache specialists after other treatments have failed.
- IV DHE, because of its high peak plasma concentration (C_{max}), has more systemic side effects than other formulations (**Table 2**).

Table 2. Comparison of PK Parameters for Different Formulations of DHE [10](PK Population Data)

Parameter	IV[10]	INP104[10]	Migranal[10]	IM/SC[11]	Orally Inhaled[12]
Dose (mg)	1	1.45	2	1	1
T_{max} (h)	0.083	0.5	0.667	0.37-0.40	0.15
C_{max} (pg/mL)	14190	1281	300	2900-3200	2720
$AUC_{0\text{-}inf}$ (h*pg/mL)	7490	6153	2199	9210-9360	4472
$AUC_{0\text{-}2}$ (h*pg/mL)	3022	1595	388	Not available	1447

MAP0004 (Levadex/Semprana)[9]

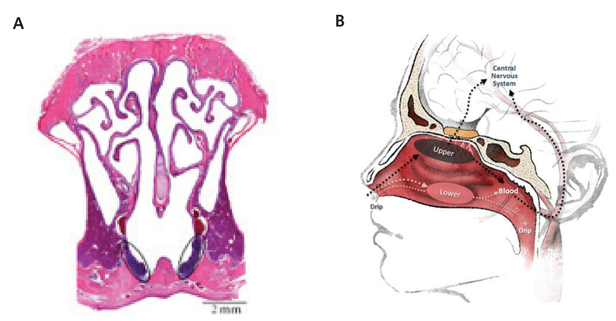
- Orally inhaled DHE (MAP0004) was developed for systemic delivery using a breath-actuated device.
- MAP004 demonstrated a rapid T_{max} and lower C_{max} for orally inhaled DHE vs. IV DHE, but comparable exposure (AUC) and improved tolerability
- $AUC_{0\text{-}2h}$ proposed as key PK measure predicting DHE efficacy[12]
- Although the clinical program for MAP0004 reported migraine pain relief as early as 10 minutes and good tolerability, MAP0004 was not approved because of manufacturing issues.

DHE – Now

Pharmacology of Nasal Drug Delivery

- Nasal sprays have low bioavailability and large inter- and intrasubject variability and a long time to peak concentration (T_{max}) that limits overall efficacy.[9]
- Drug delivery via the highly vascularized olfactory epithelium of the upper nasal cavity leads to more consistent and predictable systemic absorption.
- Delivery to the olfactory epithelium decreases the likelihood of dripping out of the front of the nose, or down the back of the throat and dripping may be reduced (**Figure 2**) compared to traditional nasal sprays.
- At least 3 companies are currently developing nasal DHE (mesylate) products: Impel with liquid INP104 1.45 mg well advanced in phase 3; Satsuma with powder 6 mg just enrolling a preliminary safety and efficacy study, and Promius believed to be in Phase 1 with a liquid (dose and formulation unknown)

Figure 2. A) Cross Section of the Nose; B) Disposition of Drugs Administered by Nasal Delivery (Lower Nasal Space – Targeted by Traditional Atomizers and Upper Nasal Space – Targeted by POD)

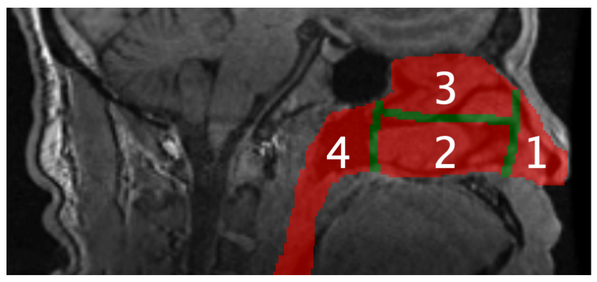


INP104

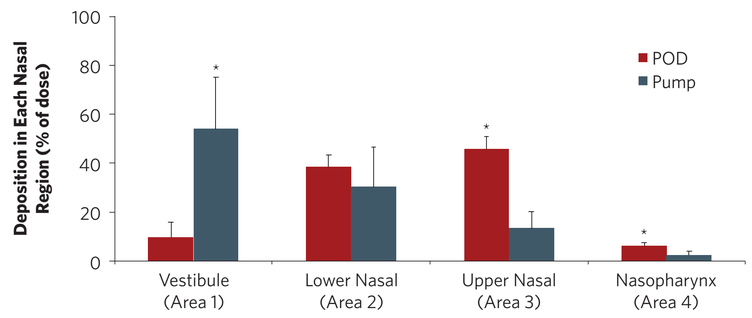
- The Precision Olfactory Delivery or POD® nasal drug delivery platform delivers a large fraction of DHE to the upper nasal region, above the middle turbinate (Area 3 in **Figure 3**).
- POD utilizes the rich vasculature found in the olfactory region for consistent, predictable delivery and increased bioavailability.

Figure 3. Intranasal Delivery of MAG-3 (Technetium-^{99m} Labeled Peptide) by POD Versus a Nasal Pump (SPECT Imaging) in 7 Healthy Subjects[13]

A. (1) Nasal vestibule (2) lower turbinate region (3) upper turbinate/olfactory region (4) the nasopharynx.

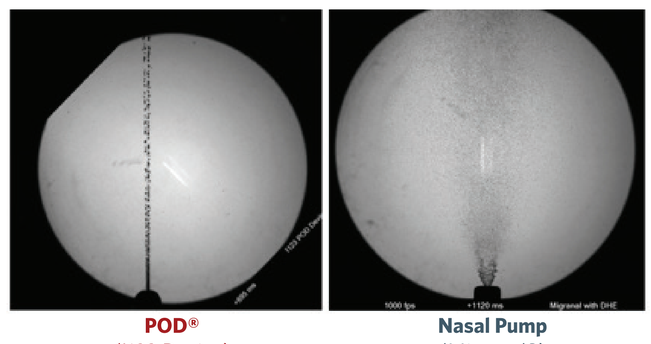


B. Nasal deposition quantitation. The POD device significantly (*p<0.05) increased deposition in the upper nasal cavity/olfactory region (upper nasal) Region 3 in **Figure 3A**. compared to the traditional pump. A majority of the PUMP dose was administered into the vestibule region.



- Delivery of DHE into the upper nasal cavity by a following, low velocity jet of ambient temperature propellant, with a narrow, focused plume of DHE (**Figure 4**) produces a different PK profile compared to the same formulation delivered by a "traditional" nasal spray.

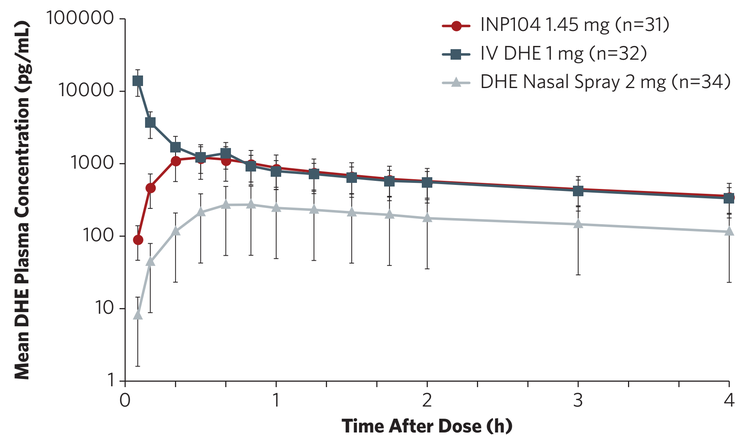
Figure 4. Contrasting Plumes of DHE Propelled From POD (left panel) and Migranal Nasal Spray (right panel)



POD® (I123 Device) | **Nasal Pump** (Migranal®)

- A Phase 1 study of INP104 vs. IV DHE and Migranal demonstrated lower peak plasma DHE concentrations but comparable exposure (AUC) with INP104 vs. IV DHE.[9]
- Peak plasma concentrations of DHE have been correlated with AEs (**Figure 5**).[10]

Figure 5. Plasma DHE Concentrations Following Administration of Single Doses of INP104, IV DHE, and DHE Nasal Spray[10]



- STOP 301, a Phase 3 study with INP104 for the treatment of acute migraine, has been initiated to assess the safety and tolerability of intranasal administration of DHE.

Summary

- DHE has a valuable role in the treatment of migraine.
- In spite of recent injectable DHE shortages, the US physicians are writing approximately 50,000 prescriptions for DHE a year (all formats combined), showing that there is still a demand for this drug.[14]
- INP104 may unlock the potential of DHE delivery for acute migraine, in the home setting, by utilizing targeted upper nasal cavity delivery.
- The safety of INP104, a nasal DHE by the POD device, is being investigated in a Phase 3 study assessing safety by nasal endoscopy and olfactory function tests.

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