A History of Dihydroergotamine in Migraine

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Background

• Ergot use in obstetrics dates back to 1000 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.

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 $627 billion.

Treatment of Migraine

• Acute migraine treatment remains a significant challenge.
• Although the diarene and the calcium gene-related peptide
  (CRG) 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.

DHE - Then

• DHE was approved for migraine in 1946.
• DHE is recommended as an alternative to triptans for treating
  acute migraine.
• 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.”
• Waking with migraine
• TRIPTAN resistance
• Menstrual migraine
• Migrainous
• Severe and/or prolonged migraine
• Cluster headache

DHE - Now

• DHE is available for IV, subcutaneous (SC), intramuscular (IM),
  and nasal administration.
• Nasal sprays have low bioavailability and large intrasubject
  variability and a long time to peak concentration (T_{max}) that
  limits overall efficacy.
• 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).

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 serotonine, noradrenalin,
  dopamine, and serotonin (Figure 2).

Figure 2. Dihydroergotamine (mesylate) - the Molecule

INPD04

• The Precision Olfactory Delivery or POD® nasal drug delivery
  platform delivers a large fraction of DHE to the upper nasal
  region, above the middle turbinates (Area 3 in Figure 4).
• POD utilizes the rich vascular network found in the olfactory
  region for consistent, predictable delivery and increased bioavailability.

Figure 4. Intranasal Delivery of MAG-3 (Technetium™-
  Labeled Peptide) by POD Versus a Nasal Pump (SPECT
  Imaging) in 7 Healthy Subjects

A. (1) Nasal vestibule (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 4A, compared
to the traditional PLUM. A majority of the PUMP dose was
  administered into the vestibule region.

Figure 5. Contrasting Plumes of DHE Propelled From POD
(small panel) and Migranal Nasal Spray (right panel)

• A Phase 1 study of INPD04 vs. INPD4 and Migranal
  demonstrated lower peak plasma DHE concentrations but
  comparable exposure (AUC) with INPD04 vs. IV DHE.
• Peak plasma DHE concentrations were up to 10-fold lower
  with INPD04 vs. IV DHE (Figure 6).

References

3. Voss T, Lipton RB, Dodick DW, et al. A phase IIb randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment
4. Biohaven Press Release 03/26/2018
7. Voss T, Lipton RB, Dodick DW, et al. A phase IIb randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment
10. Voss T, Lipton RB, Dodick DW, et al. A phase IIb randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment

Figure 6. Plasma DHE Concentrations Following
Administration of Single Doses of INPD04, IV DHE, and
DHE Nasal Spray

• STOP 301, a Phase 3 study with INPD04 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.
• Precision olfactory delivery of DHE provides a viable alternative
  to other formulations of DHE that may allow self-administered,
  in-home treatment.
• The safety of INPD4, an intranasal DHE, is being investigated
  in a Phase 3 study assessing safety by nasal endoscopy
  and olfactory function tests.
• INPD04 may unlock the potential of DHE delivery for acute
  migraine, in the home setting, by utilizing targeted upper
  nasal delivery.