

Cardiovascular Profile of Dihydroergotamine Mesylate (DHE) Delivered by the POD® Device Compared to D.H.E. 45® for Injection from the INP104-101 Clinical Trial

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Objective:

To investigate the cardiovascular effects of INP104 1.45 mg compared to D.H.E. 45® intravenous (IV) injection 1.0 mg and Migranal® Nasal Spray 2.0 mg in healthy subjects.

Background:

IV DHE is effective for acute migraine. The approved label warns of potential cardiovascular effects although the clinical experience of DHE in 70 years of use has been good¹. Work has shown the high C_{max} of IV DHE may account for a different safety profile through increased adrenergic receptor binding². Conversely, Migranal is an easy-to-use, tolerable nasal spray formulation of DHE, but with poor bioavailability.

Design/Methods:

We conducted a Phase I trial to assess safety, tolerability and comparative bioavailability of a single dose of DHE delivered to the upper nasal cavity by the novel POD® device to D.H.E. 45 (IV) and Migranal in a randomized, 3-period, 3 way cross-over study³. This abstract summarizes the cardiovascular data obtained from that study.

Results:

Thirty-six healthy volunteers received at least one dose of DHE; IV DHE caused a transient increase from baseline in mean systolic and diastolic blood pressure (BP) (11.4 and 13.3 mmHg, respectively) at 5 minutes not observed to this degree with INP104 (3.7 and 1.5 mmHg, respectively) or Migranal (-1.8 and -1.8 mmHg, respectively) at 5 minutes or any other timepoint. This BP rise may be associated with the approximately 10-fold higher C_{max} of IV DHE. The vascular TEAE of flushing was reported in 2 subjects after IV DHE treatment, but in none after INP104. No clinically significant changes in ECG or other cardiovascular TEAEs were observed with IV DHE, INP104 or Migranal.

Conclusions:

INP104 dosing caused no significant changes in BP compared to noticeable elevations with IV DHE. INP104 is expected to be an excellent alternative to the IV route of DHE administration, with short T_{max} , and no untoward cardiovascular impacts.