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

Karen Craig,[1] John Hoekman,[1] Maria Jeleva,[1] Kelsey Satterly,[1] Stephen Shrewsbury[1]
[1]Impel NeuroPharma

Introduction

- Dihydroergotamine (DHE), a synthetic derivative of ergotamine, has been marketed since 1946 to treat migraine. In comparison to ergotamine, DHE has less vasoconstrictive and uterotonic activity. However, DHE may cause peripheral vasoconstriction via 5-HT_{2A} and alpha-adrenergic receptors so DHE should not be given to patients with cardiovascular risk factors.
- Triptans, first introduced in the 1980s, are generally considered 'safer' acute migraine medications as they bind less broadly to 5-HT receptor subtypes, and in particular not to 5-HT_{2A}. However, sumatriptan does show contraction in proximal and distal coronary arteries, similar to DHE.[1]
- Up to 30% of patients report a poor response to triptans and rebound headache is thought to occur more often with the triptans than with DHE,[2] therefore DHE might be a suitable alternative for these non-responders. DHE has been reported to have slow dissociation from target receptors, correlating with better sustained relief compared to triptans. Since DHE is only available as an injection (IV, IM, SC) or as a variably effective nasal spray, there is a need for a more accessible, and easy-to-use, DHE product.
- Impel NeuroPharma has been developing the Precision Olfactory Delivery (POD) device to increase both the speed and extent of systemic absorption of DHE when delivered to the upper nasal space. This combination product, INP104, is shown assembled and ready for actuation in **Figure 1**. In a Phase I, comparative bioavailability trial,[3] INP104 administration achieved approximately 4 x greater absolute bioavailability of DHE compared to Migranal Nasal Spray. INP104 (1.45 mg DHE delivered in one divided dose, ie one spray in each nostril) also achieved an impressive 74% of the $AUC_{0\text{-}inf}$ of D.H.E 45® for Injection, 1 mg, delivered intravenously. Additionally, INP104 administration was associated with fewer adverse events than IV DHE and did not cause the same degree of peripheral blood pressure changes as seen with IV DHE.

Figure 1. The Assembled INP104 Combination Product

The subject is holding her thumb beneath the drug vial and has her index and middle finger on the finger grips. A downward motion on the finger grips actuates the device.

Results

Trial Design

- This was a Phase I, open-label, 3-way, 3 period cross-over, safety, tolerability and comparative bioavailability study of INP104 (1.45 mg), D.H.E. 45 for Injection (IV) (1.0 mg), or Migranal Nasal Spray (2.0 mg).[3]
- Thirty-six subjects received at least one dose of either INP104, IV DHE or Migranal and comprised the Safety Population. Twenty-seven subjects received all three treatments and had sufficient plasma samples for determination of PK parameters and comprised the PK population.

Blood Pressure Changes

- It was noted during data analysis that subjects given IV DHE experienced a statistically significant increase in both diastolic and systolic blood pressure (BP), which abated after approximately one hour (**Figure 2** and **Table 1**). INP104 treatment led to only a minimal increase in blood pressure, yet INP104 achieved similar plasma levels of DHE compared to IV DHE within 30 minutes (**Figure 3**). There appeared to be a lag in blood pressure returning to baseline levels in the IV DHE treatment arm, incongruous to the plasma DHE levels observed from 30 minutes onward since they matched those of the INP104 treatment arm which did not display these same blood pressure effects. This may be attributable to the high C_{max} of IV DHE (**Figure 3**; 14,190 pg/mL at 5 min) and a slow off rate of DHE at target receptors. A persistent cardiovascular effect after 0.5 mg IV DHE administration on brachial artery diameter and compliance, which did not correlate with free plasma levels of DHE has been observed.[4]

Figure 2. Mean Systolic (top) and Diastolic (bottom) Blood Pressure for Each Treatment (PK population)

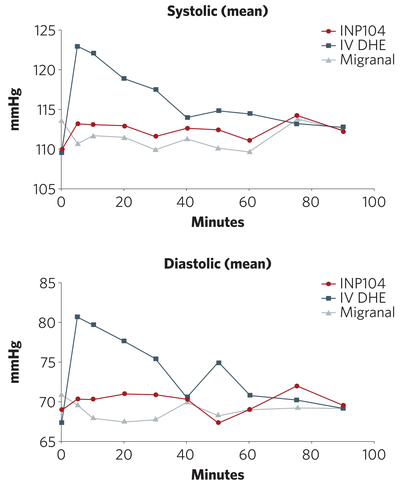
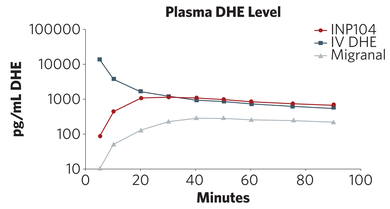


Figure 3. Mean Plasma DHE Concentrations (semi-log) for Each Treatment (PK population)



- Analysis of the change from baseline for the Safety population revealed IV DHE treatment (n=32) resulted in mean increases in BP of 11.4 and 13.3 mmHg, INP104 (n=31) of 3.7 and 1.5 mmHg, and Migranal (n=34) of -1.8 and -1.8 mmHg, respectively, for systolic and diastolic BP at 5 min post-dose (data not shown). In an analysis of the PK population (n=27), performed to remove any potential outliers who had received only one or two of the treatments, IV DHE treatment resulted in a mean change from baseline of 13.2 and 13.4 mmHg, INP104 of 3.2 and 1.4 mmHg, and Migranal of -3.0 and -1.3 mmHg, respectively, for systolic and diastolic BP at 5 min post-dose (**Table 1**). Significant differences were noted for IV DHE compared to baseline measurements from 5 min to 30 min ($p < 0.05$) for both systolic and diastolic BP. The small increase in BP seen with INP104 was not statistically significant (**Table 1**).

Table 1. Mean Change From Baseline in Systolic and Diastolic BP and Associated p Values

	Systolic						Diastolic					
	INP104		IV DHE		Migranal		INP104		IV DHE		Migranal	
Time (min)	Change[a]	p Value[b]	Change	p Value	Change	p Value	Change	p Value	Change	p Value	Change	p Value
5	3.22	0.26	13.19	5.6×10^{-5}	-3.04	0.30	1.37	0.49	13.37	1.2×10^{-5}	-1.30	0.53
10	3.11	0.29	12.44	0.00011	-1.93	0.50	1.37	0.50	12.30	2.0×10^{-5}	-2.96	0.18
20	2.93	0.34	9.22	0.00044	-2.19	0.47	2.04	0.34	10.26	3.4×10^{-5}	-3.44	0.16
30	1.63	0.59	7.89	0.0016	-3.70	0.21	1.96	0.39	8.04	0.00090	-3.15	0.16
40	2.59	0.43	4.33	0.075	-2.33	0.41	1.30	0.58	3.26	0.16	2.00	0.36
50	2.41	0.43	5.22	0.048	-3.52	0.23	1.59	0.49	7.74	0.0012	0.33	0.88
60	1.11	0.72	4.81	0.073	-4.00	0.16	0.07	0.98	3.44	0.19	1.07	0.63
75	4.22	0.15	3.59	0.15	0.11	0.97	3.04	0.16	2.81	0.22	1.30	0.54
90	2.41	0.43	3.15	0.16	-1.19	0.68	0.56	0.80	1.93	0.38	1.26	0.59

Shaded boxes represent p values less than 0.05.
[a]Change from baseline in mmHg
[b]Two tailed t test for significance of change from baseline. Only subjects who received all 3 treatments were included in the analysis.

- An additional analysis was performed to examine the BP changes directly between treatment groups at each time point (**Table 2**). IV DHE treatment resulted in a statistically significant, higher mean systolic and diastolic blood pressure compared to Migranal or INP104 from 5 to 30 minutes ($p < 0.05$, excluding 30 min time point for IV DHE vs INP104 where $p = 0.06$).

Table 2. P Values for the Difference Between the Population Means Between Each Treatment

	Systolic Comparison (p value)			Diastolic Comparison (p value)		
Time (min)	IV DHE vs INP104	IV DHE vs Migranal	INP104 vs Migranal	IV DHE vs INP104	IV DHE vs Migranal	INP104 vs Migranal
0	0.88	0.12	0.24	0.46	0.12	0.39
5	0.0026	0.00054	0.33	0.00016	7.9×10^{-6}	0.70
10	0.0055	0.0020	0.60	0.00037	3.9×10^{-5}	0.23
20	0.039	0.013	0.63	0.0031	0.00013	0.13
30	0.037	0.0085	0.56	0.060	0.0014	0.16
40	0.65	0.33	0.67	0.88	0.75	0.88
50	0.41	0.11	0.43	0.0026	0.0040	0.70
60	0.27	0.10	0.60	0.55	0.48	0.99
75	0.69	0.84	0.87	0.43	0.66	0.17
90	0.90	0.92	0.98	0.92	0.96	0.89

Shaded boxes represent p values less than 0.05.

Adverse Events Related to IV DHE Not Observed With INP104

- Treatment-related adverse events reported in at least 2 or more subjects treated with IV DHE from the INP104-101 study are reported in **Table 3**. There were no specific treatment-related adverse events associated with either INP104 or Migranal reported in more than one subject. The adverse events listed in **Table 3** can largely be attributed to DHE agonism at receptors involved in vasoconstriction (5-$HT_{2B/1B/1D}$ and alpha-adrenergic), nausea and vomiting (5-HT_{1A} and dopamine D2).[5] The mean peak level of DHE in plasma observed after INP104 treatment (C_{max} = 1,301 pg/mL) is considered too low to induce nausea.[6] Pretreatment of all subjects in all treatment arms with metoclopramide did not completely prevent incidents of nausea, in particular after IV DHE administration (C_{max} = 14,190 pg/mL). A close examination of ECG changes from baseline data did not reveal any significant changes in association with any of the 3 treatments.

Table 3. Treatment-related Adverse Events Reported in at Least 2 Subjects Treated With IV DHE

	Treatment		
Adverse Event	INP104 (n=31)	IV DHE (n=32)	Migranal (n=34)
Headache	1 (3.2%)	5 (15.6%)	1 (2.9%)
Dizziness	1 (3.2%)	5 (15.6%)	1 (2.9%)
Somnolence	1 (3.2%)	4 (12.5%)	1 (2.9%)
Nausea	0	3 (9.4%)	1 (2.9%)
Hot Flush/Feeling Hot	0	3 (9.4%)	0
Vomiting	0	2 (6.3%)	1 (2.9%)
Restlessness	0	2 (6.3%)	1 (2.9%)
Myalgia/Musculoskeletal discomfort	0	2 (6.3%)	0

Conclusions

- Statistically significant blood pressure increases were observed in subjects receiving IV DHE which were not seen after INP104 administration.
- INP104 was well tolerated and had fewer treatment-related adverse events in comparison to IV DHE.
- No ECG changes were observed for any treatment arm.
- INP104 matched IV DHE plasma DHE levels by 30 min, yet the cardiovascular effects of IV DHE were still greater than observed for INP104 at 30 min and thereafter. This might be attributable to the high C_{max} of DHE at 5 min (14,190 pg/mL) after IV administration, which is 10 x the C_{max} after INP104 administration, in combination with a slow dissociation rate of DHE from bound receptors.
- INP104 is expected to have an improved cardiovascular safety profile compared to IV DHE.

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