

# INTRA-PULMONARY ARTERY AS COMPARED TO PERIPHERAL VENOUS DOSING OF DIHYDROERGOTAMINE (DHE) IN TELEMETERIZED, AWAKE DOGS

S. Shrewsbury<sup>1</sup>, J. Okikawa<sup>1</sup>, M. Stonerook<sup>2</sup>, N. Ramadan<sup>3</sup>

<sup>1</sup>MAP Pharmaceuticals, Inc., 2400 Bayshore Parkway, Suite 200, Mountain View, CA 94043, USA

<sup>2</sup>Battelle Memorial Institute., Columbus, OH and <sup>3</sup>Rosalind Franklin University of Medicine and Science, North Chicago, IL, USA

## ABSTRACT

**RATIONALE:** MAP is developing the Tempo™ device, a novel, synchronous trigger, plume-controlled inhaler that promises efficient and consistent targeting of peripheral lung with new formulations of drugs, including dihydroergotamine (DHE). Parenteral DHE is used widely in the US for treating acute migraine. Inhaled DHE may deliver systemic levels as rapidly as IV DHE - without an injection. Also, DHE is vasoactive. Accordingly, we evaluated pharmacokinetics and pharmacodynamic measures of fast, bolus delivery of DHE to the pulmonary artery as a surrogate for inhalation.

**METHODS:** 4 instrumented, awake dogs received vehicle and then DHE (0.014mg/kg, repeated at 60 minutes and 0.14mg/kg at 120 minutes) via a peripheral vein [V] or directly into the pulmonary artery [PA] (minimum 2 days washout between V and PA administration). We monitored ECG parameters; systemic and pulmonary arterial BP; left ventricular EDP; heart rate; coronary artery, carotid artery and aortic blood flows. Systemic, pulmonary carotid and coronary vascular resistances; mean systemic and mean pulmonary artery pressures were calculated.

**RESULTS:** We observed no obvious differences between PA and V dosing of DHE for: measured blood flows, blood pressures, PK values or any calculated value (except coronary artery resistance). Systemic vascular resistance changed more from baseline for V than PA dosing at the 1x, 1x repeated and 10x doses (8, 16 and 20 vs 6, 8 and 8 mmHg/mL/min). All dogs demonstrated brief, transient periods of emesis at 10x dosing by both routes.

**CONCLUSIONS:** Coronary vascular effects of inhaled DHE and IV DHE are similar in dogs. Similar results are expected in humans.

## INTRODUCTION

DHE has been used for over 50 years as an effective treatment against migraine headaches. DHE has 5HT<sub>1</sub> agonist activity, but is less selective than the triptans, and also has norepinephrine and dopamine receptor effects which may lead to vasoconstriction. DHE, like the triptans, has the potential for undesirable vasospastic side-effects that may lead to coronary artery spasm in susceptible individuals. High DHE plasma levels in the coronary arteries, which may follow inhaled administration compared to peripheral vein injection, may therefore provoke spasm in "at risk" individuals. Dogs cannot be trained to deeply inhale to reproduce human behavior with a metered dose aerosol, thus a bolus pulmonary artery injection to mimic inhaled delivery may be needed to allow potential cardiovascular effects of inhaled DHE to be compared to that of the accepted mode of intravenous administration.

This study was designed to challenge and evaluate cardiovascular parameters in a patient dose simulation of inhaled bolus dihydroergotamine mesylate (DHE) by administering DHE via pulmonary arterial (PA) dosing with comparison to intravenous (IV) dosing of DHE in beagle dogs. The doses were selected to compare the two routes of delivery at the approved clinical IV dose for DHE (1x), and to determine the safety of delivering ~10x the dose by single bolus delivery.

## MATERIALS AND METHODS

\*The bulk test article for this study was DHE. Vehicle for this study was phosphate buffered saline (PBS) manufactured by Nexell.

\*Four naïve male beagle dogs were used for this study. One naïve male dog was available as a backup animal. Dogs were between 7 and 11 months of age and weighed 9.4 to 11.6 kg at the time of study.

\*Each dog was surgically implanted with a radiotelemetry unit (D70-PCPT, DataSciences).

\*Additionally, a Schwan-Ganz catheter was placed percutaneously under brief anesthesia (propofol i.v.) prior to each dog's first dosing event to provide a dosing route to the pulmonary artery and to measure pulmonary arterial pressures.

Table 1: The following cardiovascular parameters, at a minimum, were measured during the physiological monitoring period or subsequently calculated for evaluation.

Parameters measured	
Systemic arterial blood pressure (systolic, diastolic, mean)	
Pulmonary arterial pressure (Schwan-Ganz catheter)	
Heart rate	
Left ventricular pressure (systolic and end diastolic)	
Coronary Blood Flow ( $Flow_{cor}$ )	
Carotid Artery (Left) Blood Flow ( $Flow_{ca}$ )	
Aortic Blood Flow ( $Flow_{aort}$ )	
Parameters calculated	
MAPs (systemic mean arterial pressure)	
MAPp (pulmonary mean arterial pressure)	
Systemic vascular resistance ( $MAPs - Flow_{aort}$ )	
Pulmonary vascular resistance ( $MAPp - Flow_{cor}$ )	
Coronary artery resistance ( $MAPs - Flow_{cor}$ )	

An initial bolus of vehicle only was administered (either PA or IV) and dogs monitored for 15 minutes. Then at time 0, DHE at a dose of 0.014 mg/kg (1x) was injected. This is a direct equivalent of the approved clinical dose for humans (a single bolus of 1.0 mg in an average 70 kg adult = 0.014 mg/kg). Each dog then received 2 additional doses, a further 1x dose (60 minutes after the first) and then a 10x dose after a further 60 minutes (either PA or IV). All doses were administered by the same PA or IV route on any one dosing day. Animals were restrained in a sling to which they had previously been acclimated for periods of up to 4 hours. Each animal had a recovery period of at least 45 hours before a second dosing when the same doses were administered by the other route (PA or IV).

Blood samples were collected from a peripheral vein (of a different limb to the IV administration) at specified time points to establish the pharmacokinetic profiles of DHE at the various doses/routes.

## RESULTS

Pharmacokinetic parameters were similar at all dose levels between IV and PA delivery of DHE (Table 2). The administration of 0.014 mg/kg DHE as second 1x dose at ~60 minutes from the first dose of 0.014 mg/kg DHE increased  $C_{max}$  and  $AUC_{0-60}$  by almost two-fold. The administration of 0.14 mg/kg DHE (10x) had a  $C_{max}$  that was 15x and an  $AUC_{0-60}$  that was 15-20x the values measured for the first dose of 0.014 mg/kg DHE. At all dose levels the PK parameters were similar between PA and IV doses indicating no difference in systemic exposure due to the route of dosing.

Table 2: Summary of PK parameters following administration of DHE via PA or IV bolus dosing in beagle dogs.

Dose	0.014 mg/kg			0.014 mg/kg			0.14 mg/kg		
	Start Time	0 min	60 min	120 min	0 min	60 min	120 min	0 min	60 min
Intravenous Dose									
Mean	5	1.72	45.70	5	2.34	72.66	5	30.46	795.77
S.E.		0.22	5.20		0.16	5.69		3.28	85.78
Pulmonary Artery Dose									
Mean	5	1.52	44.78	5	2.70	79.66	5	30.17	825.03
S.E.		0.19	4.26		0.36	9.19		3.79	43.13

Clinical observations associated with dosing were limited to emesis after the 0.14 mg/kg DHE (10x) dose at 2 to 5 minutes in 4 of 4 dogs IV route and 3 of 4 dogs PA route (one dog showed muscular contractions of emesis that did not result in full emesis).

Figures 1, 2 and 3 show representative data: the mean Coronary Artery Resistance, Mean Blood Pressure and Aortic Resistance respectively in all four dogs when DHE was administered by either PA or IV, but all parameters measured or calculated (see Table 1) produced similar patterns of response.

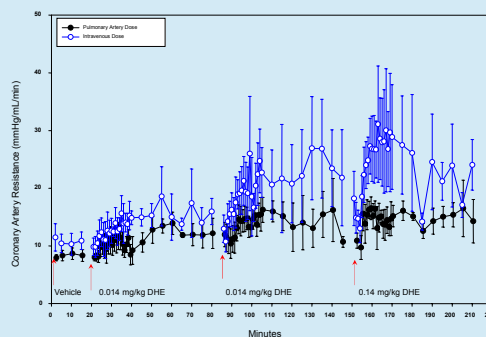


Figure 1: Coronary Artery Resistance (mean ± SE) of Beagle dogs (N=4/dose) receiving sequential bolus doses of vehicle (0 mg/kg), 0.014 mg/kg, 0.014 mg/kg, and 0.14 mg/kg dihydroergotamine (DHE) by peripheral intravenous or pulmonary arterial dosing. The time zero data represent baseline means (± SE).

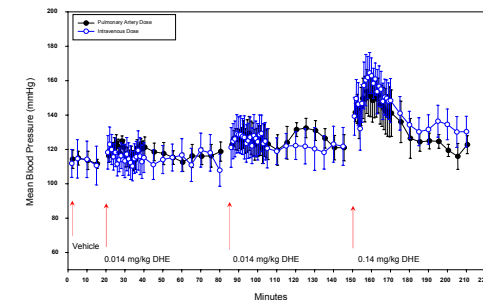


Figure 2: Mean Blood Pressure (mean ± SE) of Beagle dogs (N=4/dose) following sequential bolus doses of vehicle (0 mg/kg), 1x, 1x and 10x DHE by PA or IV dosing. The time zero data represent baseline means (± SE).

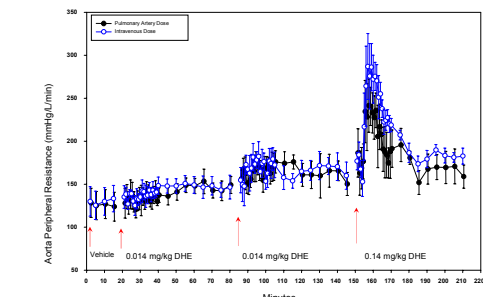


Figure 3: Aortic Resistance (mean ± SE) of Beagle dogs (N=4/dose) following sequential bolus doses of vehicle, 1x, 1x and 10x DHE by PA or IV dosing. The time zero data represent baseline means (± SE).

## CONCLUSION

The changes seen following two sequential clinical doses of 0.014 mg/kg DHE were minimal and were not considered to be adverse. The changes following 0.14 mg/kg DHE (10x the clinical dose) by either route were marked, although short in duration with return to pre-dose values by 20 to 40 minutes post-dose. There were no appreciable differences in most of the parameters examined (pharmacokinetics, heart rate, blood pressures or blood flows) between PA and IV dosing of DHE at any of the dose levels. The only difference noted between the dose routes was a greater increase in aortic and coronary resistance seen in dogs receiving 0.14 mg/kg DHE IV as compared to the PA dose. Coronary vascular effects of inhaled DHE and IV DHE are similar in dogs. Similar results are expected in humans.

This data would indicate that equivalent doses of DHE administered by inhalation can be expected to have comparable pharmacodynamic effects to approved IV administration.

MAP is currently in clinical development with inhaled DHE via Tempo, a novel breath synchronized plume controlled inhaler.