

MAP0004, an Orally Inhaled Formulation of DHE, Delivers Faster and More Consistent Blood Levels of the Drug Compared to Traditional Oral, Subcutaneous, Intramuscular, and Intranasal Formulations of DHE

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OBJECTIVES

To review literature and compare published time to maximum serum concentration (t_{max}) data for various methods of DHE delivery.

BACKGROUND

Intravenous (IV) DHE is extensively used and is effective in treating both acute and resistant migraine attacks. Despite being an inconvenient and invasive mode of delivery, speed of onset and consistency of response, provided by IV DHE, are valuable attributes for migraine treatments for both patients and prescribers. Attempts to develop more convenient routes of administration for DHE have not been successful to date, in part due to the high variability of the rate of absorption of the drug resulting in inconsistent response, even in the same individual. Absorption of oral tablets is dependent on the degree of gastric stasis, which is common in migraineurs and highly variable. Subcutaneous and intramuscular injections also show a wide variation in their absorption rates. Rate of absorption from intranasal administration depends on the ratio of the amount of drug swallowed to that of the drug absorbed through the mucosa of the nasal epithelium, which differs significantly from administration to administration even in the same individual.

MAP0004, a novel orally inhaled DHE product candidate, has demonstrated consistent serum concentrations in clinical trials because it delivers the drug to the pulmonary circulation through the lung, the function of which is not affected by the underlying migraine. A published study has demonstrated that orally inhaled DHE serum concentrations were similar to that of DHE administered IV.

This report was undertaken to compare the published t_{max} data, and their coefficients of variation, for different formulations of DHE administrations including IV, intranasal, intramuscular, subcutaneous and oral inhalation.

METHODS

A comprehensive literature search of published PK results for several formulations of DHE was performed. Studies which had documented t_{max} and had sufficient information to calculate the coefficient of variation (CV) were included. T_{max} and CV data from these studies were compared with data from a recent Phase 1 pharmacokinetic study of IV DHE versus orally inhaled DHE (MAP0004). The 1 mg nominal dose of MAP0004 in this Phase 1 study corresponded to a systemic equivalent dose of approximately 0.44 mg; the 2 mg nominal dose of MAP0004 corresponded to a systemic equivalent dose of 0.88 mg.

Coefficient of variation is a measure of dispersion of a probability distribution. It is defined as the ratio of the standard deviation to the mean. It is often reported as a percentage by multiplying the above ratio by 100. The coefficient of variation is a dimensionless number, and is directly proportional to the variability of the factor studied.

In the case where only the standard error (SE) was stated in the literature, the SD was calculated as the product of SE and the \sqrt{n} , where n is the sample size, or the number of subjects.

RESULTS

The mean t_{max} and CV for various formulations of DHE were: 0.5 mg subcutaneous injection (20 minutes and 77%); 0.5 mg intramuscular injection (34 minutes and 74%); 1 mg intramuscular injection (23 minutes and 79%); 2 mg oral (75 minutes and 67%); 1 mg intranasal (56 minutes and 68%); 2 mg intranasal (42 minutes and 43%); 1 mg intravenous injection (5 minutes and 0%); 1 mg orally inhaled MAP0004 (12 minutes and 40%); and 2 mg orally inhaled MAP0004 (12 minutes and 30%).

Table 1. Mean t_{max} and Corresponding CV for Different Routes of Administration of DHE

	0.5 mg SQ	0.5 mg IM	1 mg IM	2 mg PO	1 mg Nasal	2 mg Nasal	1 mg IV	1 mg MAP0004 (0.44 mg systemic equivalent)	2 mg MAP0004 (0.88 mg systemic equivalent)
Mean t_{max} (minutes)	20	34	23	75	56	42	5	12	12
CV	77%	74%	79%	67%	68%	43%	0%	40%	30%

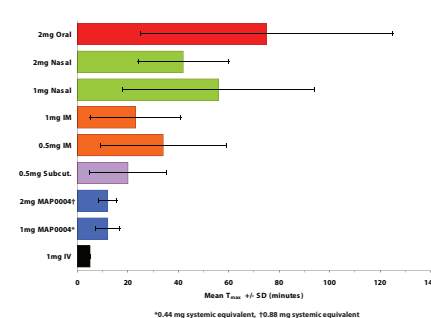
- MAP0004 had t_{max} closest to IV, better than SQ and IM injections
- MAP0004 had the least variability of non-IV administrations

RESULTS continued

Table 2. Reported Pharmacokinetic Parameters for DHE

Reference	Dose Route	No. of Subjects	Mean C_{max} \pm SE or SE (mg/mL)	Mean T_{max} \pm SE or SE (h)	Mean AUC 0 to infinity (ng/mLh)
de Hoon et al. Br J Clin Pharmacol 2007	0.5 mg SQ	10 healthy males	1.619 \pm 0.088 (SE)	0.33 \pm 0.08 (SE)	5.825 \pm 0.667 (SE)
Humbert et al. Clin Pharmacol Ther 1996	1 mg nasal	10 healthy males	1.02 \pm 0.42 (SD)	0.93 \pm 0.63 (SD)	5.32 \pm 2.30 (SD)
	1 mg IM	10 healthy males	4.44 \pm 1.23 (SD)	0.38 \pm 0.30 (SD)	13.57 \pm 4.45 (SD)
Van der Kuy PHM, Lohman JHM; Hooymans PM; Ter Berg JWM, Merkus FWHM: Bioavailability of intranasal formulations of Dihydroergotamine. Eur J Clinical Pharmacology. 1999; 55, 677-680.	0.5 mg IM	3 female, 6 male	1.9 \pm 0.4 (SD) (95%CI: 1.2-2.1)	34 \pm 25 min (SD) (95%CI: 20-48)	AUC _{0-24h} 13.7 \pm 3.0 (SD) (95%CI: 20-146)
	2 mg po		0.4 \pm 0.2 (SD) (95%CI: 0.3-0.5)	79 \pm 50 min (SD) (95%CI: 46-102)	AUC _{0-24h} 8.9 \pm 3.3 (SD) (95%CI: 5.1-141)
	2 mg nasal		1.8 \pm 1.1 (SD) (95%CI: 1.2-2.4)	42 \pm 18 min (SD) (95%CI: 32-52)	AUC _{0-24h} 25.6 \pm 10.4 (SD) (95%CI: 109-311)
Scherer and Taylor Clin Pharmacol & Ther 1983	1.5 mg SQ	6 healthy volunteers	3 to 8	15 to 45 min	NA
	1 mg IM		2.9	24 min	NA
Saper and Silberstein Headache 2006	1 mg IV		<10	1-2 min	NA
	1 mg nasal		1.0	54 min	NA
Shrewsbury et al. Headache 2007	1 mg MAP0004 (0.44 mg systemic equivalent)	6 healthy volunteers	1.257 \pm 0.670 (SD)	0.2 \pm 0.06 (SD)	3.219 \pm 0.921 (SD)
	2 mg MAP0004 (0.88 mg systemic equivalent)	12 healthy volunteers	3.888 \pm 1.498 (SD)	0.2 \pm 0.06 (SD)	8.281 \pm 1.851 (SD)

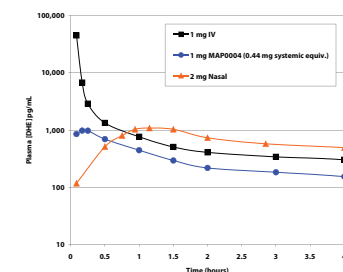
Figure 1. Comparison of Mean t_{max} and SD for Different Routes of Administration of DHE



- MAP0004 had the shortest t_{max} of non-IV administrations
- MAP0004 had the least standard deviation of non-IV administration

RESULTS continued

Figure 2. PK Curves for IV, Nasal and Orally-Inhaled DHE



- MAP0004 t_{max} is faster than intranasal administration and similar to IV
- MAP0004 C_{max} is similar to intranasal and lower than that of IV

CONCLUSION

Based on our review of the available literature, we conclude that orally inhaled MAP0004 delivers DHE at a rate and consistency closest to IV DHE compared to other delivery routes. Both MAP0004 and IV DHE systemically deliver DHE faster and more consistently than other available methods of DHE administration, but MAP0004 is delivered without the inconvenience and the invasiveness of IV infusion which may translate into improved clinical outcomes. Additional clinical evaluation of MAP0004 is ongoing.

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