Safety of Dihydroergotamine for the Acute Treatment of Migraine: Reality vs Perception

Alan M. Rapoport, MD[1]; Shannon Strom, PhD[2]; John Kollins[2]; Detlef Albrecht, MD[2]
[1]UCLA, Los Angeles; [2]Satsuma Pharmaceuticals Inc., South San Francisco, CA, USA;

Objectives

To evaluate the misperceptions about the safety and tolerability of dihydroergotamine (DHE) for the acute treatment of migraine, we investigated the history of ergot alkaloids, product label language, and case reports of serious clinical events with various DHE dosage forms; this is particularly with respect to nausea and vomiting, cardiovascular and fibrosis risk, and use during pregnancy or concomitantly with potent CYP3A4 inhibitors.

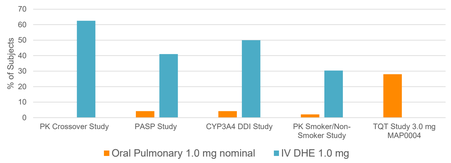
Methods

A literature search was performed to examine the safety of various DHE dosage forms, including oral, intravenous (IV), intramuscular (IM), intranasal (IN) liquid spray, orally inhaled, and IN dry powder, for the acute treatment of migraine. The specific focus was on cardiovascular risk, use during pregnancy, concomitant use with potent CYP3A4 inhibitors and fibrosis.

Results

Nausea is more prominent with IV DHE than various other formulations and possibly C_{max} related

Figure 1. Nausea after Single Doses of DHE from Phase 1 Studies



C_{max} from Phase 1 Studies (pg/mL)		
MAP0004 Phase 1 Study	**MAP0004 1.0 mg nominal**	**IV DHE 1.0 mg**
PASP Study	2,357	57,558
CYP3A4 DDI Study	2,583	27,771
PK Smoker/Non-Smoker Study	2,551	48,428
TQT Study with 3.0 mg MAP0004	8,757	

Sources: Shrewsbury, 2008; Kellerman, 2013; and Jividen, 2011

Risk of Rare Cardiovascular or Fibrotic Complications with DHE Use is Associated with Other Risk Factors or Dosage Forms

- ✓ Most were single case reports, associated with excessive dosage, other risk factors, or use of concomitant medication (Silberstein, 1995).
- ✓ Orally inhaled MAP0004 Phase 3 long-term safety study showed no increase in CV adverse events (Kellerman, 2011).
- ✓ In a retrospective chart review, 38 patients received 5 or more infusion cycles (one IV infusion cycle is 9 mg DHE given over 5 days).
  - No cases of cardiac valvular, pleural, or retroperitoneal fibrosis were observed over the treatment period of up to 4 years (McDonald, 2019).
- ✓ Rare reports of fibrotic complications seem linked to long-term daily use of oral DHE formulations that are not available in the US (CHMP Assessment Report 2013).

Risk Associated with DHE Use During Pregnancy is Similar to Triptan and Lower than NSAID Use

- ✓ DHE is contraindicated during pregnancy.
- ✓ Animal data showed delayed skeletal ossification and decreased fetal body weights.
- ✓ Quebec Pregnancy Registry data (Table 1) show DHE use during pregnancy was not statistically significantly associated with risk of spontaneous abortion (SA), major congenital malformation (MCM) or low birth weight (LBW) but it did correlate with increased risk of prematurity (Bérard and Kori, 2012).
  - Triptans associated with statistically significant increased risk of SA.
  - NSAIDs associated with statistically significant increased risk of SA, MCM, and LBW.
- ✓ Data corroborated by Swedish Medical Birth Register that found no increased risk of MCM with DHE or sumatriptan use (Kallen, 2011).

Table 1. Risk Associated with DHE Use During Pregnancy is Similar to Triptan and Lower than NSAID Use

Treatment	MCM Adjusted OR (95% CI)	Prematurity Adjusted OR (95% CI)	LBW Adjusted OR (95% CI)	SA Adjusted OR (95% CI)
DHE	0.97 (0.22-4.28)	4.18 (1.34-12.99)	1.41 (0.25-7.80)	1.97 (0.21-18.57)
Triptans	1.49 (0.89-2.52)	0.76 (0.34-1.66)	0.83 (0.31-2.25)	2.65 (1.57-4.48)
NSAIDs	1.20 (1.06-1.36)	1.10 (0.95-1.26)	1.29 (1.08-1.54)	2.97 (2.63-3.36)

Adapted from Bérard and Kori, 2012.

Oral DHE use has been linked to drug-drug interactions with potent CYP3A4 inhibitors while non-oral formulations have not

- ✓ Black box in the product insert warns that serious and/or life-threatening peripheral ischemia may occur when DHE is co-administered with potent CYP3A4 inhibitors
- ✓ Risk seems to be based on rare single case reports, primarily with oral ergotamine and oral DHE (Francis, 1984; Rosenthal, 1999; Montero, 1999).
- ✓ DDI study of oral DHE showed increased bioavailability in presence of the CYP3A4 inhibitor ponsinomycin (Couet, 1991).
- ✓ DDI study with the CYP3A4 inhibitor ketoconazole had little to no effect on PK of oral pulmonary DHE (MAP0004) (Kellerman, 2013) (Table 2).

Table 2. Oral pulmonary DHE showed no drug-drug interaction with a potent CYP3A4 inhibitor

Treatment	N	C_{max} (pg/mL)	T_{max} (median hr)	$AUC_{0\text{-}inf}$ (pg*hr/mL)	$t_{1/2}$ (hr)
MAP0004 pre-ketoconazole	23	2,583	0.17	3,784	13.5
MAP0004 post-ketoconazole	23	2,495	0.17	4,323	11.2
IV DHE 1.0 mg	20	27,771	0.08	9,592	11.1

Adapted from Kellerman, 2013

Summary of DHE safety misperceptions and reality

MISPERCEPTION	REALITY
DHE causes nausea	• Nausea is C_{max} related & typically seen with IV • Minimal nausea with other administration routes
DHE causes coronary artery constriction	• DHE is primarily a veno-constrictor • Less coronary artery constriction than triptans
DHE exposure during pregnancy has a higher risk than other migraine medications	• DHE has a similar risk during pregnancy to triptans and a lower risk than NSAIDs
DHE may cause fibrosis	• Existing evidence suggests that rare cases of fibrosis are primarily linked to chronic, long-term use of oral DHE
DHE has significant CYP3A4 mediated drug interactions	• Drug interaction studies in humans report increased DHE concentrations only with oral route

Conclusion: DHE is safe for acute treatment of migraine

- Misperceptions of DHE safety are not supported by existing evidence.
- Adverse event severity and frequency depend on the administration route and duration of exposure.
- Reports of serious adverse events are rare.
- DHE for migraine is safe when used in recommended doses & in patients without contraindications (AAN Panel 1995).
  - DHE should not be given to patients with uncontrolled hypertension, coronary or peripheral arterial disease.
  - DHE use is not recommended during pregnancy; however, data suggest inadvertent early exposure during 1st trimester prior to confirmation of pregnancy has low risk similar to triptan exposure

References

- Bérard A and S Kori. Headache. 52:1085-1093, 2012.
- CHMP Referral Assessment Report. Procedure Number. EMEA/H/A-31/1325, 27 September 2013.
- Couet W, Mathieu HP, JB Fourtillan. Fundam Clin Pharmacol. 5:47-52, 1991.
- Francis H, Tyndall A, J Webb. Clinical rheumatology. 3(2):243-246, 1984.
- Jividen H, Kellerman D, Kori S, A Forst. American Headache Society annual meeting, 2011.
- Kallen B, Nilsson E, PA Olausson. Drug Sat. 34(8):691-703, 2011.
- Kellerman D, Chang J, Reppine A, Kori S. American Headache Society annual meeting, 2011.
- Kellerman D, Forst A, Combs DL, Borland S, Kori S. J Aero Med Pulmon Drug Del. 26(5):297-306, 2013.
- Lipton RB. Headache. 37(suppl 1):S33-S41, 1997.
- McDonald M, Dickson G, Gorrie G, et al. Intl Headache Conference Annual Meeting 2019 IHC-LB-007.
- Montero A, Giovannoni AG, Tvrde PL. Annals of Internal Medicine. 130(4):329, 1999.
- Rosenthal E, Sala F, Chichmanian RM, et al. JAMA. 281(11):987, 1999.
- Shrewsbury SB, Cook RO, Taylor G, et al. Headache. 48:355-367, 2008.
- Silberstein SD and WB Young. Neurology. 45:577-584, 1995.
- Young WB. Headache. 37(suppl 1):S42-S45, 1997.

Abbreviations

DDI = drug-drug interaction; LBW = low birth weight; MCM = major congenital malformation; PASP = pulmonary arterial pressure study; PK = pharmacokinetic; SA = spontaneous abortion; TQT = thorough QT study