Pregnancy Outcome After Gestational Exposure to Cinnarizine: a Case Series

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DISCLOSURES

- Bitton Yossi: none (at the time of study)*
- Diav-Citrin Orna: none

*currently works for Sanofi-Aventis Israel LTD (this work was done and completed before joining Sanofi-Aventis Israel LTD)
Sanofi-Aventis Israel LTD does not market any product that contains cinnarizine

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Introduction

- Cinnarizine, a piperazine derivative, has been widely used in the treatment of vestibular disorders such as vertigo, tinnitus and Ménierè's disease.
- It acts by multiple mechanisms of action: L-type Ca^{2+} channels blockage, slight antihistaminergic (H_1) action, and pressure-sensitive potassium channel blockage[1,2].
- It improves microcirculation by preventing tissue-selective vasoconstriction and blocks Ca^{2+} entry into RBC, (which promotes their flexibility leading to reduced blood viscosity).
- Cinnarizine has also demonstrated labyrinthine depressant effects and diminishes nystagmus[1,3]

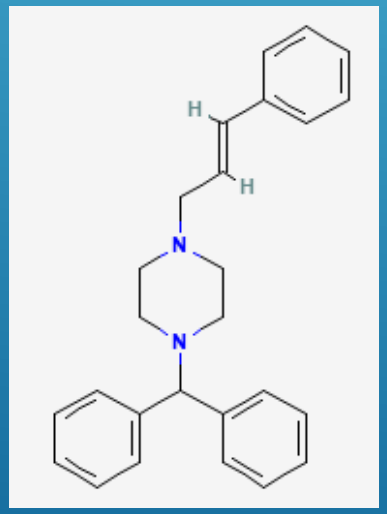

Image credit: https://pubchem.ncbi.nlm.nih.gov/compound/Cinnarizine

1. Israeli physician's leaflet, available at: https://data.health.gov.il/drugs/alonim/Rishum_17_463239820.pdf
2. Soto E, Vega R. Neuropharmacology of vestibular system disorders. Curr Neuropharmacol. 2010;8(1):26-40.
3. Kirtane MV, Bhandari A, Narang P, Santani R. Cinnarizine: A Contemporary Review. Indian J Otolaryngol Head Neck Surg. 2019;71(Suppl 2):1060-1068

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Introduction

- It is not known if cinnarizine crosses the human placenta. However, its molecular weight of approximately 3699, elimination half-life of 4 to 241 hours and plasma protein binding of 91%[1] suggests that embryo-fetal exposure should be expected.
- Meclizine, another piperazine derivative is generally considered compatible in pregnancy[4,5].

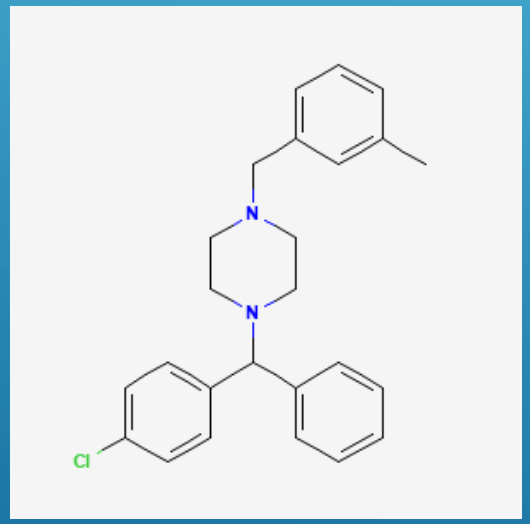

Image credit: https://pubchem.ncbi.nlm.nih.gov/compound/Meclizine

4. Briggs GG, Freeman RK, Towers CV, Forinash AB. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Philadelphia: Lippincott Williams & Wilkins Health; 11th edition, 2017. 5. Schaefer C, Peters P, Miller RK. Drugs during pregnancy and lactation: treatment options and risk assessment. Amsterdam: Academic Press imprint of Elsevier; 3rd edition, 2015.

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Introduction

- Although cinnarizine has been used for a few decades – registered in Israel since 1976 [7], there is paucity of data on its safety in pregnancy.
- Animal studies do not suggest teratogenicity[1,6]
- There is one case report of ectromelia following human intrauterine exposure to cinnarizine[7].
- Data from the Swedish Medical Birth Registry regarding pregnancy exposure to oral decongestants, did not show an increased risk for any congenital malformation when 2474 first trimester exposures were compared with 1771 women who were prescribed an oral decongestant later in pregnancy. 136 reported using phenylpropanolamine in combination with cinnarizine in early pregnancy, and 46 women later in pregnancy[8].
- However, data on cinnarizine could not be extracted or evaluated since they were reported in a large group dominated by phenylpropanolamine and in combination[9].

6. Israeli Ministry of Health website: https://data.health.gov.il/Drugs/index.html#!/medDetails/031%2026%2021879%2000 Accessed June 15th 2022. 7. Kovatsis A, Dozi-Vassiliades J, Kalogirou M, Kokalla N, Kounenis G. Experimental study on the permeability of placental barrier to cinnarizine in pregnant guinea pigs and its distribution in several tissues. Pharm Delt Epistem Ekdosis 1972;2:3-20. 8. Litta R, Rainone R, Zingariello L A case of incomplete amelia. [Italian] Pediatria (Napoli). 1983;91:287-93.
9. Källén BA, Olausson PO. Use of oral decongestants during pregnancy and delivery outcome. Am J Obstet Gynecol. 2006;194(2):480-485.

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Introduction

- Although vestibular disorders occur predominantly in the elderly, epidemiologic survey in 70 million individuals revealed that unspecific **vertigo and dizziness are common among women of reproductive age**, 20-24 to 45-49 years old, with reported prevalence of approximately **4%**[10].
- In addition, in some countries such as the United Kingdom, reduced strength, 15mg cinnarizine tablets indicated for the prevention of travel sickness are available for purchase without prescription (**prescription strength is 25mg**; triple strength of 75mg is available in some countries), which may increase its inadvertent early pregnancy use.
- **Hence, our goal is to provide more data on the pregnancy outcome following gestational exposure to cinnarizine.**

10. Hülse R, Biesdorf A, Hörmann K, Stuck B, Erhart M, Hülse M, et al. Peripheral Vestibular Disorders: An Epidemiologic Survey in 70 Million Individuals. Otology & Neurotology. 2019;40(1):88–95.

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Methods

- The Israeli Teratology Information service (TIS) database had been searched for queries on cinnarizine from January 2001 until the end of May 2019.
- The characteristics of the inquiries were analyzed, and women who has called the TIS about cinnarizine were contacted by telephone for a follow-up interview using a structured questionnaire.
- Only women who were over **18** years of age at the date of call were included in this study.
- The following information was recorded at the initial contact: maternal demographics, medical and obstetric histories, as well as exposure details (dose, duration, and timing in pregnancy, additional exposures).
- Exposure was documented during the inquiry (time of pregnancy) and before the outcome was revealed.

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Methods

- All neonates in this study were delivered in hospitals except for one neonate delivered at home.
- Follow-up was conducted after the expected date of delivery to obtain details on pregnancy outcome, gestational age at delivery, birth weight, congenital anomalies, and neonatal complications.
- Major anomalies were defined as structural abnormalities in the offspring that have serious medical, surgical, or cosmetic consequences.
- Gestational age was defined from the last menstrual period.
- Due to the relatively small sample size, only descriptive statistics were applied.

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Results

- From a total of 52 pregnancy exposures, 14 were excluded since they occurred in the "all or none" period, 23 were in the period of organogenesis, and 15 in the 2nd and / or 3rd trimesters.
- Pregnancy outcome: 33 deliveries resulting in 34 live-born infants due to one set of twins, 31 term and 2 preterm deliveries, 2 spontaneous abortions, 3 elective terminations of pregnancy, of whom two were performed due to cytomegalovirus (CMV) infection and one due to personal reasons.

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Results

Details on pregnancy outcome, maternal and offspring characteristics are presented in the table.

	Number / median	Range (if applicable)
Pregnancy outcomes (n=38)		
Delivery of live-born infant	33	
Term delivery	31	
Preterm delivery (<37 gestational weeks)	2	
Spontaneous abortion	2	
Elective termination of pregnancy	3	
Stillbirth	0	
Gestational age at birth (n=31)	39	**35-41**
Birth weight (n=31), grams	3270	**2100-4500**
Maternal age (n=31), years	32	**23-40**
BMI (n=23)	22.9	**17.6-31.3**
Congenital malformations		
major	0	**0**
minor	0	**0**

Results

- **No major or minor congenital malformations were reported.**
- **No fetotoxic effect was reported.**
- 6 women reported cinnarizine use around delivery; no neonatal effects were reported among them.
- Efficacy: interviewed women reported the beneficial effect of cinnarizine on their condition; few described themselves as bedridden without it.

Discussion

- This case series provides preliminary outcome data on cinnarizine exposure in pregnancy. No congenital malformations were reported in neonates of women who were exposed to cinnarizine.
- Similar results were reported with first trimester exposure to its di-fluorinated derivative flunarizine[11].

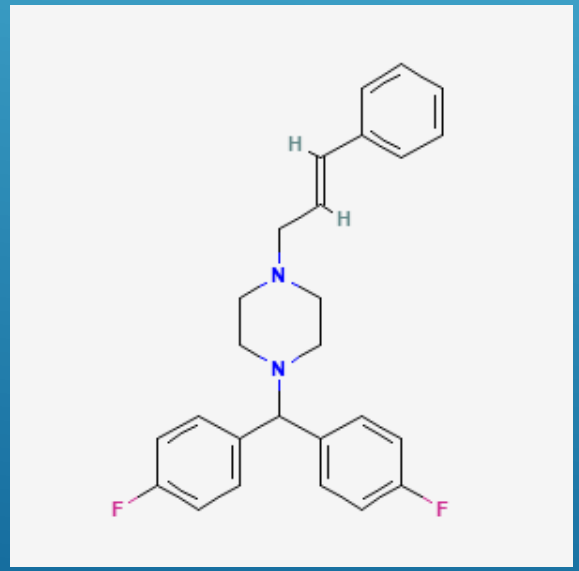

Image credit: https://pubchem.ncbi.nlm.nih.gov/compound/Flunarizine

11. Weber-Schoendorfer C, Hannemann D, Meister R, et al. The safety of calcium channel blockers during pregnancy: a prospective, multicenter, observational study. Reprod Toxicol. 2008;26(1):24-30.

Discussion

Strengths of the study:

- To the best of our knowledge, our case series is the first one on cinnarizine exposed pregnancies.
  It includes detailed documentation of exposure, which was obtained in the initial intake and before pregnancy outcome is obtained => minimizes potential recall bias.
- Drug exposure was verified and assigned to gestational age allowing assessment of exposure during time periods critical for organ formation, excluding exposure in the "all or none" period.
- Our study includes data on pregnancy losses and on elective termination of pregnancies.

The major limitations of the present study are its small sample size and lack of a comparison group.

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Discussion

- It is worth noting that two pregnancies in this case series were terminated due to CMV infection.
- Two cases in such a relatively small group raises a question about a possible relationship between active CMV infection and vestibular disorders.
- However, the exposure to cinnarizine preceded the diagnosis of CMV infection.
- In addition, Hanci et al. (2015) found an association between benign paroxysmal positional vertigo and serologic evidence of viral infections such as HSV1, adenovirus, VZV, influenza, and CMV[12]

12. Hanci D, Ulusoy S, Muluk NB, Cingi C. Do viral infections have a role in benign paroxysmal positional vertigo?. B-ENT. 2015;11(3):211-218.

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Conclusions

- In our case series, cinnarizine exposure during pregnancy was not associated with congenital anomalies nor with fetotoxic or neonatal effects.
- However, the small sample size calls for caution with the generalization of these results.
- Larger denominator-based studies are needed in order to draw definitive conclusions.

- **We hope that our preliminary findings will prompt more research on this drug use during pregnancy!**

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THANK YOU!