The Egyptian Journal of Medical Human Genetics (2015) **16**, 287–290

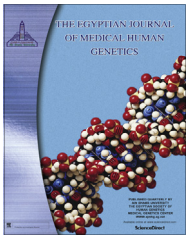
HOSTED BY

ELSEVIER

Ain Shams University

The Egyptian Journal of Medical Human Genetics

www.ejmhg.eg.net
www.sciencedirect.com



REVIEW

The relation between antihistamine medication during early pregnancy & birth defects

Rabah M. Shawky [a,*], **Neveen S. Seifeldin** [b]

[a] *Genetics Unit, Pediatric Department, Ain Shams University, Egypt*
[b] *Dermatology, Venereology and Andrology Department, Ain Shams University, Egypt*

Received 6 April 2015; accepted 16 April 2015
Available online 11 May 2015

KEYWORDS

Antihistamine;
Birth defects;
Congenital malformation;
H_1 antagonist;
Early pregnancy;
Dermatological conditions

Abstract Antihistamines are a group of medications which can inhibit various histaminic actions at one of two histamine receptors (H_1 or H_2). H_1 receptor antagonists are used for the relief of allergic dermatological and nondermatological conditions. We will review classes of antihistamines (H_1 antagonists) and the relationship between specific antihistamines and specific birth defects. Although many findings provide reassurance about the relative safety of many antihistamine drugs and that any malformation reported is most probably caused by chance, studies are still required to assure fetal safety. As pruritus is sometimes troublesome for pregnant women topical medications like emollients should be tried first in the first trimester of pregnancy. Also pregnant women should be advised to consult their health care provider before taking any medication.

Contents

1. Introduction

Antihistamines are a group of medications which possess the ability to inhibit various histaminic actions. Histamine is released by our body during an allergic reaction and acts on

* Corresponding author.
E-mail address: shawkyrabah@yahoo.com (R.M. Shawky).
Peer review under responsibility of Ain Shams University.

http://dx.doi.org/10.1016/j.ejmhg.2015.04.003

a specific receptor. They act principally by preventing histamine – receptor interaction through competition with histamine for histamine receptors. Thus they prevent and not reverse histamine actions. Antihistaminic drugs inhibit the action of histamine at one of the two histamine receptors (H_1 or H_2) but not at both receptors. H_2 receptor inhibitors inhibit histamine induced gastric secretion and so are used to treat gastric ulceration [1]. H_1 receptor inhibitors are used for the relief of allergic dermatological and nondermatological conditions [2].

Pruritus is one of the most common dermatological symptoms during pregnancy [3], whether due to specific dermatoses of pregnancy or due to atopic dermatitis, urticaria, angioedema, infections, drug induced or due to various systemic diseases [4].

Also antihistamines can be used for the relief of allergic rhinitis, allergic conjunctivitis, upper respiratory tract infections as well as the treatment of pregnancy symptoms of nausea and vomiting, motion sickness, dizziness and insomnia [5]. The antihistamine use during pregnancy ranges from 4 to 10% during the first trimester and from 8 to 15% at any time during pregnancy in various studies [6,7]. Some antihistamines require a prescription, but most are available over the counter (OTC). They are among the most commonly used drugs during pregnancy [8].

Several studies have indicated an association between the maternal use of some antihistamines during early months of pregnancy and some birth defects [9]. In 1960 Bendectin (containing doxylamine and dicyclomine hydrochloride) which is commonly used at that time as antinausea preparation was suspected to be associated with congenital malformations. Although it is pulled from the market in the years following, the rate of birth defects remained stable [10].

We will review classes of antihistamines (H_1 antagonists) and the relationship between specific antihistamines and specific birth defects if reported in literature.

2. Classification of H_1 antihistamines

They are classified as older or 1st generation, 2nd and 3rd generation antihistamines targeting histamine – type 1 (H_1) receptors.

2.1. First generation histamine H_1 receptor antagonists include [11]:

1- Ethylene diamines which are the first group of clinically effective H_1 antihistamines. This class includes Mepyramine, Antazoline and Tripelennamine.
2- Ethanolamines which has significant anticholinergic side effects and sedation with reduced gastro-intestinal side effects. This class also includes Diphenhydramine (Benadryl), Carbinoxamine (Clistine), Doxylamine, Clemastine (Tavist), Dimenhydrinate (Dramamine), Orphenadrine and Bromazine.
3- Alkylamines which have fewer sedative and gastrointestinal adverse effects, but greater incidence of CNS stimulation. This class includes Brompheniramine (Dimetane), Triprolidine, pheniramine (Avil), Dexchlorpherniramine, Chlorpheniramine (Chlortrimeton) Dexbrompheniramine, and Cimetidine.
4- Piperazines which have significant anticholinergic adverse effects. Compounds from this group are often used for motion sickness, vertigo, nausea and vomiting as Cyclizine, Chlorcyclizine, Hydroxyzine, Meclizine, [12].
5- Tricyclics and tetracyclics which are structurally related to tricyclic & tetracyclic antidepressants, explains why they have cholinergic side effects. This class includes promethazine (phenergan), Alimemazine (vallergan), Cyproheptadine, Azatadine (Optimine or Trinalin) and Ketotifen (Zaditor) [13].

This group (first generation antihistamines) has a very potent effect but are short acting as they have poor selectivity for H_1 receptors and they cross the blood brain barrier. They have also anticholinergic activity. They are metabolized in the liver. They have many adverse side effects mostly due to CNS depression (sedation, dizziness, tinnitus, blurred vision, euphoria, incoordination, anxiety, insomnia, tremors, nausea and vomiting, dryness of the mouth, constipation, blurred vision, dry cough, and urinary retention [14].

- FDA classified antihistamines into:

Category A: A risk to the fetus has not been demonstrated in controlled studies in women in the first trimester and there is no evidence of risk in later trimester and the possibility of fetal harm appears remote e.g. cyproheptadine [7].

Category B: A fetal risk has not been demonstrated in animal studies and no controlled studies in pregnant women have been done or there are some adverse effects in animal studies that were not confirmed in controlled studies in women in first trimester e.g. Chlorpheniramine, Diphenhydramine, Dexchlorpheniramine, Clemastine and Tripelennamine, [15].

Category C: Animal reproductive studies have shown adverse effects on the fetus and there are no well controlled studies in humans e.g. Promethazine and Hydroxyzine [15].

Seto et al. [16] and Gilbert et al. [17], reported no increased fetal risks or birth defects from this class (1st generation antihistamines) of drugs when used during any time of pregnancy. The same was also reported with a meta-analysis which involved more than 200,000 women in early pregnancy [18]. However Hydralazine was linked to cleft palate [19,20], cleft lip with or without cleft palate, neural tube defects, spina bifida, limb reduction defects and gastroschisis [18]. Also chlorpheniramine was linked to eye and ear defects, spina bifida and cleft lip with or without cleft palate [18,19]. Doxylamine was also linked to oral clefts [21], pyloric stenosis, [22,23], hypoplastic left heart syndrome, spina bifida and neural tube defects[18]. Bendectin (an antinausea preparation containing doxylamine succinate, dicyclomine hydrochloride and pyridoxine hydrochloride) used in early pregnancy was minimally associated with congenital heart [24].

Also an increased risk of retrolental fibroplasias was reported in 21% of premature infants exposed in utero to Diphenhydramine during the last 2 weeks of pregnancy compared to 11% in premature infants not exposed [19]. Also Diphenhydramine use in early pregnancy was also reported in relation to cleft palate, cleft lip with or without cleft palate, neural tube defects, spina bifida, limb reduction defects and gastroschisis [18,19]. Diphenhydramine has also an oxytocin