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

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The Egyptian Journal of Medical Human Genetics

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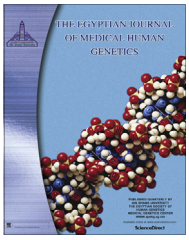

REVIEW

The relation between antihistamine medication during early pregnancy & birth defects

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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

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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

like effect in animals and human uteri especially in high doses [25].

2.2. Second generation histamine H_1 receptor antagonists:

These are the newer drugs and they are long acting with high selectivity for the peripheral H_1 receptors involved in allergies as opposed to H_1 receptors in the central nervous system. They are also less lipophilic than first generation drugs and do not cross the Blood Brain Barrier (BBB). Therefore these drugs provide the same relief with less sedation and performance impairment [26].

These drugs also have an anti-inflammatory activity which can help in the treatment of inflammation in allergic airway disease [27]. Rare side effects of second generation antihistamines include photosensitivity, tachycardia and prolongation of QT interval [28].

This class includes Loratadine Acrivastine (Semprex-D), Terfenadine (Seldane), Azelastine (Astellin or Optivar), Levocabastine (Livostin), Olopatadine (Patanol), and Cetirizine (Zyrtec) [29].

2.3. Third generation histamine H_1 receptor antagonists:

These drugs are derived from second generation antihistamines. They are either the active enantiomer or metabolite of 2nd generation drugs designed to increase the efficacy of the drugs with lesser side effects [30].

This class includes levocetirizine (Xyzal), which is the active form of cetirizine, Desloratadine (Clarinex), the active metabolite of loratadine, Fexofenadine (Allegra) which is developed as an alterative to Terfenadine with a decreased risk of cardiac arrhythmia [13]. However there is some controversy associated with the use of the term third generation antihistamines [30]. So these drugs will be referred to in this review as 2nd generation antihistamines [31].

FDA categorized Fexofenadine, Desloratadine as pregnancy category C, while Cetirizine, Loratadine and Levocetirizine as category B [15].

Based on the available pregnancy data Cetirizine is unlikely to increase the incidence of major or minor malformations in neonates. There are also no significant differences in miscarriage or birth rate with first trimester exposure [32,33]. However additional studies on larger number of pregnancies are still needed [32]. Although sedation of Cetirizine is dose dependent, it is less than that of first generation antihistamines, but more sedating than Loratadine or Fexofenadine [34].

Loratadine is the most studied 2nd generation antihistamine and there is no reported increased risk of major malformations when used in early pregnancy. However some cases of hypospadias were reported with the use of this drug in early pregnancy [7,35,36]. The majority of infants had mild glandular hypospadias which makes the association with early pregnancy use of this drug questionable [37]. Also animal studies did not support this association as McIntyre [38] reported no increase in the incidence of hypospadias or other androgen mediated end points in animals that are given up to 120 times the human dose. At the same time several studies in humans reported no association between loratadine and desloratadine and hypospadias, premature delivery or still birth [7,35]. However both drugs are still considered as category B drugs by FDA and performance impairment has been reported with higher than the recommended doses [39].

No major malformations were reported in infants whose mothers had taken Fexofenadine in their early pregnancy although one case of positional talipus was reported which is unlikely to be caused by the drug [40]. Also reduction in pup weight and survival was observed in rat pups with this drug. It is to be noted that this drug is no longer available in some countries' markets owing to the clinically significant QT prolongation [2] Fexofenadine is a metabolite of Terfenadine. As regards Terfenadine, the Swedish Medical Birth Registry reported no higher rates of congenital anomalies in neonates of pregnant women treated with it than in the general population [6]. However birth weight of infants was also reported to be less than 10th percentile for gestational age [41]. On the other hand animal studies by the manufacturer have not shown an increase in birth defects in up to 30 times the human dose [42] although rat pups had dose related decreased weight gain and survival. Additional studies are needed to clarify if this drug causes a decrease in birth weight or not.

We have to consider that most pregnancies are unplanned and the fetus is vulnerable to drug induced teratogenesis from the day a woman's period is due [8].

Also we have to consider the popular use of antihistamines during pregnancy and that most of them are available without prescription and even a small increase in the risk of specific birth defects may have considerable clinical and public health implications. In Egypt no definite guidelines have been given by the government (Health Officials) for the use of antihistamines as over the counter medicine or prescription purposes, so we advice practitioners to follow FDA criteria.

Although no definite teratogenic effects have been associated with the intake of antihistamines during pregnancy and they are not licensed by FDA as category A or safe drugs, much investigations are still required to prove fetal safety of these drugs. Women should also be advised to consult their health care provider before taking any medication.

As pruritus is sometimes troublesome for pregnant women in the first trimester of pregnancy, topical medications like emollients should be tried first together with drinking plenty of water to overcome anticholinergic side effects. If antihistamines have to be prescribed, first generation agents have to be given as they are relatively safe and well studied [4].

Also the National Asthma Education and prevention program recommended the use of 1st generation antihistamines as chlorpheniramine and tripelennamine due to reassuring animal and human studies [43]. However in allergic rhinitis and its impact on Asthma (ARIA) guidelines recommends that first-generation antihistamines should no longer be prescribed because of poor selectivity and their sedative and anticholinergic effects [44].

If a 2nd generation antihistamine has to be used loratadine or cetirizine should be preferred as they are categorized as category B and they are preferably used after the first trimester.

3. Conclusion and recommendations

While many findings provide reassurance, about the relative safety of many of these antihistamines and any malformation reported is most probably caused by chance, studies are still required to assure fetal safety. Efficacy of the agent should also

be considered to assure optimal well-being of both the mother and her infant.

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