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Allergic rhinitis during pregnancy

Abstract

● During pregnancy, the first-choice drugs for allergic rhinitis are nasal or oral “non-sedating” antihistamines without antimuscarinic activity, in particular *cetirizine*, or *loratadine* after the first trimester.

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Nasal antihistamines: little evaluation data in pregnancy

Nasal solutions containing antihistamine have similar efficacy to *sodium cromoglicate*. Antihistamine solutions provoke local adverse effects. Their systemic adverse effects depend on the antihistamine used and the quantity administered and absorbed. At the doses recommended in their summaries of product characteristics (SPCs), oral forms carry a higher risk of systemic adverse effects than nasal solutions (1).

Antihistamine nasal solution: preferably azelastine. In late 2015, the antihistamines available in France in nasal spray form are *azelastine* and *phenyltoloxamine* combined with the antiseptic *cethexonium bromide*. Some of these nasal solutions contain the quaternary ammonium *benzalkonium chloride* as a preservative. Some *azelastine* products contain no preservatives.

Phenyltoloxamine is a sedating antihistamine.

The main adverse effects of *azelastine* are local irritation and altered taste sensation (2). Rare cases of drowsiness, headache and dry mouth have been reported (3). Its efficacy is similar to other, oral antihistamines (2).

Skeletal malformations and fetal deaths were reported in some animal studies after exposure to *azelastine* at doses 300-fold to 500-fold higher than those used in human therapy. We identified no animal studies of

phenyltoloxamine in our literature search (4-7).

We found no epidemiological studies of *azelastine* exposure during pregnancy in our literature search (4-7).

Follow-up data are available on 45 pregnant women who took *phenyltoloxamine* during the first trimester of pregnancy and 142 pregnant women who took this drug during pregnancy, with no significant safety signals (4-7).

Preservatives can provoke local reactions (congestion, irritation) (3). No significant safety signals emerged from follow-up data on about 50 women exposed during the first trimester of pregnancy to *benzalkonium chloride*, and about 50 other women exposed during the second and third trimesters of pregnancy (4,5). We found no data on pregnancies exposed to nasal *cethexonium bromide* in our literature search (4-7).

When used during the second and third trimesters of pregnancy or close to birth, the fetus then the neonate are exposed to the adverse effects of antihistamines. But given the small quantities absorbed systemically during nasal use, no major effects are expected.

In practice. Antihistamines administered intranasally provoke more adverse effects than *sodium cromoglicate* and have been less well studied in pregnancy (4). They provoke fewer adverse effects than oral antihistamines.

When local antihistamine therapy is considered the best option, it is better to choose a preservative-free *azelastine* solution.

Women may have been exposed to another antihistamine during the first trimester before realising they are pregnant. There are no data indicating that this poses a significant risk, but plenty of unknowns.



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Mildly sedating oral antihistamines: cetirizine or loratadine

Antihistamines only relieve allergic symptoms and have only modest efficacy (1). The antihistamines differ in particular in the intensity of their sedative and antimuscarinic effects (1).

In non-pregnant patients, oral “non-sedating” antihistamines without antimuscarinic activity are an alternative to local treatments. *Cetirizine* and *loratadine* are the best established among them (8).

Other “non-sedating” antihistamines without antimuscarinic activity are *desloratadine* (the major ►►

► active metabolite of *loratadine*), *bilastine*, *ebastine*, *fexofenadine*, *mizolastine*, *rupatadine* and the *cetirizine* enantiomer *levocetirizine*. Their harm-benefit balance in pregnancy is no better than that of *cetirizine*.

The adverse effect profile of mildly sedating antihistamines.

The adverse effect profiles of antihistamines are variable due to the heterogeneity within this class. The so-called non-sedating antihistamines without antimuscarinic activity can have a sedative action in certain patients. Their adverse effects mainly comprise arrhythmias with QT prolongation, bradycardia, tachycardia with *ebastine*, *mizolastine* and perhaps *rupatadine*; and rare hypersensitivity reactions (1).

There are no data to suggest a high risk of QT prolongation with *cetirizine*, *fexofenadine* or *loratadine*. However, it is better to err on the side of caution by avoiding these drugs in patients with risk factors for torsades de pointes or with renal impairment and by not combining them with enzyme inhibitor drugs (1).

First trimester: no significant safety signals for cetirizine, loratadine teratogenic in animal studies. *Cetirizine* and *levocetirizine* are not teratogenic in animals.

Loratadine is teratogenic in mice, provoking hypospadias, an abnormality of the male urethra. No teratogenicity was reported in the other animal species tested. *Desloratadine* is not teratogenic in animals.

Bilastine, *ebastine*, *fexofenadine*, *mizolastine* and *rupatadine* are not teratogenic in animals.

A large body of data has been collected from tens of thousands of women exposed to various antihistamines in the first trimester of pregnancy, and no notable safety signals have emerged.

Six cohort studies and follow-up data in about 1400 women exposed to *cetirizine* during the first trimester of pregnancy found no increase in the incidence of malformations. *Cetirizine* is a metabolite of *hydroxyzine*, a drug that has long been in clinical use.

With *loratadine*, an initial Swedish cohort study from 2002 in nearly 1800 neonates exposed in utero during the first trimester of pregnancy showed an increased risk of hypospadias (4-7). The same team

later published an additional study in about 3400 exposed neonates which found no significant safety signals.

A meta-analysis of three case-control studies and seven cohort studies, including a total of almost 2700 newborn boys exposed to *loratadine* in utero during the first trimester of pregnancy and nearly 500,000 controls, showed that 1.4% of the exposed neonates had hypospadias, versus 0.9% in the control group (9). The difference was not statistically significant. Other epidemiological studies found no significant safety signals. These data do not prove a causal link with *loratadine*, but justify avoiding exposure to *loratadine* during the first trimester of pregnancy.

A single cohort study has been conducted in about 30 children exposed in utero during the first trimester to *fexofenadine*, without significant safety signals.

We found no epidemiological studies in pregnant women exposed to *bilastine*, *desloratadine*, *ebastine*, *levocetirizine*, *mizolastine* or *rupatadine*. However, pregnant women exposed to *loratadine* have necessarily also been exposed to *desloratadine*, and those exposed to *cetirizine* have been exposed to *levocetirizine*.

Second and third trimesters and close to delivery.

In the second and third trimesters of pregnancy, the fetus is exposed to the adverse effects of "non-sedating" antihistamines, and arrhythmias are therefore foreseeable with *ebastine*, *mizolastine*, and perhaps *rupatadine*. There is little data to suggest that *cetirizine*, *levocetirizine*, *fexofenadine* or *loratadine* increases the risk of QT prolongation.

In practice. For pregnant patients with troublesome allergic rhinitis, if therapy with a "non-sedating" antihistamine without antimuscarinic activity seems the best option, *cetirizine* (and therefore *levocetirizine*) is an acceptable choice throughout pregnancy, for which no significant safety signals have emerged. It should be avoided in patients with renal impairment.

Loratadine should be avoided in the first trimester of pregnancy due to the risk of hypospadias reported in animal studies and which has not been ruled out in humans.

In the event of exposure to *loratadine*, *desloratadine*, *bilastine*, *ebastine*,

fexofenadine, *mizolastine* or *rupatadine* during the first trimester of pregnancy, before the woman realised she was pregnant, there are no data indicating any particular risks, but plenty of unknowns.

Sedating antihistamines with antimuscarinic activity: unknowns

Compared with the "non-sedating" antihistamines without antimuscarinic activity, antihistamines with sedative and antimuscarinic effects, used orally, have a less favourable harm-benefit balance in allergic rhinitis on account of these adverse effects (1).

The drugs include *carbinoxamine*, *cypheptadine*, *dexchlorpheniramine*, *chlorphenamine*, *doxylamine*, *meclozine*, *dimenhydrinate*, *diphenhydramine*, *brompheniramine*, *bucizine*, *niaprazine*, *pizotifen*, *ketotifen*, *mepyramine* and *triprolidine*. *Chlorphenamine* is a racemic mixture of two isomers: *chlorphenamine* and *dexchlorpheniramine* (10).

Some of these drugs have a clearly unfavourable harm-benefit balance in pregnancy (see inset on p. 103).

Adverse effects. The adverse effects of sedating antihistamines with antimuscarinic effects mainly consists of sedation and antimuscarinic disorders.

Peripheral antimuscarinic effects are mainly: mydriasis, blurred vision due to impaired accommodation, dry mouth, nausea, constipation or even ileus, urinary retention, reduced sweating, transient bradycardia followed by tachycardia, and sometimes acute angle-closure glaucoma. Central antimuscarinic effects are mainly: confusion, disorientation, visual hallucinations, agitation, irritability, delirium, memory disorders, aggression and tremor.

The antihistamines have variable adverse effects due to the heterogeneity within the group, including: balance disorders, memory and concentration disorders, confusion, motor incoordination and tremor with phenothiazines and other sedating antihistamines; hypotension due to an alpha-blocking effect with *carbinoxamine*, *brompheniramine*, *chlorphenamine* and *dimenhydrinate*; seizures; paradoxical central nervous [continued on p. 104] ►►

► [continued from p. 102] system stimulation with agitation, tremor and hallucinations, especially in children; rare hypersensitivity reactions; photosensitivity (1).

During the first trimester: no significant safety signals. *Chlorphenamine* and *dexchlorpheniramine* are not teratogenic in animals, but at high doses can cause embryonic, fetal and neonatal death in mice (4-7). In three cohort studies and follow-up data on 1400 pregnant women whose child was exposed to *chlorphenamine* during the first trimester of pregnancy, one study including about 1000 women showed an increased risk of inguinal hernia and eye and ear abnormalities, but no overall increased risk of serious malformations compared with the general population. No significant safety signals emerged during a cohort study in about 1000 pregnant women whose child had been exposed to *dexchlorpheniramine* during the first trimester.

Animal studies demonstrated no teratogenic effects for *doxylamine* at therapeutic doses (4-7,11). The evaluation data on *doxylamine* for nausea and vomiting of pregnancy in thousands of pregnant women did not indicate an increased risk of malformations in children who had been exposed to the drug in utero (4-7,11).

Tripolidine is teratogenic in rabbits, causing limb abnormalities (4-7). The two main cohort studies and follow-up data including about 1500 children exposed to *triprolidine* during the first trimester of pregnancy produced conflicting results. In one of the studies, in about 900 exposed neonates, a higher rate of major malformations occurred (7.9%) than in the general population, particularly cardiovascular abnormalities (4-7).

We identified no animal studies of *brompheniramine* or *pheniramine* in our literature search (4-7). The results from cohort studies conducted in 800 pregnant women exposed during the first trimester to *pheniramine* and about 400 to *brompheniramine* detected no significant safety signals (4-7).

Second and third trimesters: poorly documented long-term effects. Since the fetus is exposed to the antimuscarinic and sedative adverse effects of sedating antihista-

mines, acceleration of the fetal heart rate would be expected as well as neurological adverse effects such as agitation and tremor that would be undetectable in the fetus. The sedative effects of antihistamines would not be expected to pose a particular risk to fetuses exposed during the second and third trimesters of pregnancy.

The sedating antihistamines with antimuscarinic activity have psychotropic effects and only limited long-term data are available on the development of children exposed to these drugs in utero. Two prospective studies in an unspecified number of young children exposed in utero to *doxylamine* have been conducted (12). No evidence of cognitive or behavioural disorders were demonstrated at 3 years and 7 years of age (7,8).

Close to birth: monitor the neonate. When the fetus is exposed to a sedating antihistamine with antimuscarinic activity close to delivery, these effects are sometimes observed in the neonate: sedative effects, sometimes interfering with suckling; antimuscarinic effects such as neurological disorders (agitation or tremor), delayed passage of meconium, abdominal distension or even ileus; and withdrawal symptoms (1,4-7).

In practice. The sedating antihistamines with antimuscarinic activity expose pregnant women and their unborn child to a worse adverse effect profile than the non-sedating antihistamines without antimuscarinic activity. There is also some uncertainty over their long-term effects. When an oral antihistamine is considered the best option to treat allergic rhinitis, the drug chosen will depend on the stage of pregnancy: *cetirizine* in the first trimester, or *doxylamine* if the woman also has nausea and vomiting provided its sedative effects are acceptable; and *cetirizine* or *loratadine* from the second trimester onwards.

When a sedating antihistamine with antimuscarinic activity is continued until delivery, it is better to inform the medical team so that the neonate receives appropriate monitoring and care.

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Literature search and methodology

Our literature search was based on continuous monitoring at the *Prescrire* library and systematic consultation of textbooks (Briggs *Drugs in Pregnancy and Lactation* 10th ed., Martindale *The Complete Drug Reference*, UpToDate). We also systematically searched the databases Reprotox, Shepard's Catalog of Teratogenic Agents, and TERIS, and the websites of the ANSM, CRAT, EMA and FDA up to 5 June 2015. The data obtained on each drug from these various sources were collated, in particular in order to estimate the number of pregnant women exposed during each trimester of pregnancy and then followed up.

This literature review was prepared using the standard *Prescrire* methodology, which includes verification of the sources and of their analysis, external review, and multiple quality controls.

- 1- Prescrire Rédaction "24-1. Patients allergiques" *Rev Prescrire* 2014; **34** (374 suppl. interactions médicamenteuses).
- 2- Prescrire Rédaction "Rhume des foins, alias rhinite allergique saisonnière" *Rev Prescrire* 2008; **28** (300): 755.
- 3- "Azelastine". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 6 October 2015; 4 pages.
- 4- "Reprotox". reprotox.org accessed March 2015.
- 5- "Teris Teratogen Information System". depts.washington.edu/terisdb accessed March 2015.
- 6- "Shepard's Catalog of Teratogenic Agents". depts.washington.edu/terisdb accessed March 2015.
- 7- "Briggs *Drugs in Pregnancy and Lactation*. A reference guide to fetal and neonatal risk" 10th ed. Lippincott Williams and Wilkins, Philadelphia 2011.
- 8- Schatz M et al. "Recognition and management of allergic disease during pregnancy" UpToDate. www.uptodate.com accessed 28 June 2015; 22 pages.
- 9- Prescrire Rédaction "Anti-histaminiques H1 au cours de la grossesse: loratadine ou pas?" *Rev Prescrire* 2010; **30** (315): 75-76.
- 10- "Chlorphenamine Maleate". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 10 August 2015; 16 pages.
- 11- Prescrire Rédaction "Femmes enceintes et médicaments oraux des nausées-vomissements modérés" *Rev Prescrire* 2013; **33** (358): 595-600.
- 12- Koren G et al. "Neurocognitive development of children exposed to doxylamine-pyridoxine combination in utero for morning sickness" *Ob Gyn* 2014; **23** (5) Suppl: 151S.

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