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Second generation antihistamines and pregnancy

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Inquiries to health care providers about the use of antihistamines during pregnancy are common since 20-30% of pregnant women have allergic symptoms (Ellegard et al., 2006). Avoiding known triggers (pets, mold, dust mites, and cigarette smoke), elevating the head end of the bed, and using a nasal saline spray may help avoid or alleviate symptoms (Blaiss, 2003). If these recommendations are not helpful, then providing judicious treatment with antihistamines may benefit the pregnancy by aiding in asthma control, and promoting better sleep and emotional status in pregnant women (Keles, 2004).

The first generation antihistamines (i.e. chlorpheniramine which can be found in Chlor-Trimeton Allergy) are preferred for pregnancy because they have been around longer and better studied during pregnancy. However, second generation antihistamines may be preferred by women due to their lower rates of CNS side effects, such as sedation and performance impairment (Blaiss, 2003). Therefore, this Risk Newsletter will discuss pregnancy outcomes following use of the second generation antihistamines, cetirizine (Zyrtec), fexofenadine (Allegra), and loratadine (Claritin).

Cetirizine

Cetirizine is marketed as Zyrtec. Sedative effects of this medication have been disputed; sedation seen with this medication appears to be dose dependent. While cetirizine is less sedating than the first generation antihistamines, it may be more sedating than loratadine or fexofenadine (Horak and Stubner, 1999).

The frequency of malformations was not increased among the offspring of pregnant rats or rabbits treated with up to 500 times the maximum human dose of cetirizine (Kamijima et al., 1994).

A controlled prospective study by a Canadian teratology service found no significant differences in miscarriage, birth weight, or the rates of major or minor malformations in 33 infants with first trimester cetirizine exposure (Einarson, et al., 1997). No major malformation were identified in another clinical series of 16 infants whose mothers took cetirizine during the first trimester (Wilton, et al., 1998). While reassuring, these studies are of limited value since at least 800 pregnancies would need to be evaluated to identify a 2-fold increase in congenital anomalies (Einarson, et al., 1997).

In Sweden, medicine exposures are entered into a national database following an interview with a midwife in early pregnancy. The pediatrician subsequently updates the registry with the resulting pregnancy outcomes. This dataset identified 917 women who were taking cetirizine in early pregnancy. This group did not have a significant increase in congenital anomalies (Kallen, 2002). Although the study is large, specific timing, dose, and duration of medication is not available.

Cetirizine is also a metabolite of hydroxyzine, which has not been associated with major malformation in several clinical series totaling 187 infants who were exposed during the first trimester (Heinonen et

al., 1977; Erez et al., 1971; Diav-Citrin et al., 2003; Einarson et al., 1997).

In summary, based on available pregnancy data, cetirizine is unlikely to increase the chance for congenital anomalies. Additional studies on larger numbers of pregnancies are still indicated.

Fexofenadine

Fexofenadine is marketed as Allegra. The sedative properties of fexofenadine are thought to be negligible (Horak and Stubner, 1999).

There are no published animal studies on fexofenadine. Animal studies done by the manufacturer have not shown an increase in birth defects at doses 4-30 times the human dose (Sanofi-Aventis, 2006). However, rat pups had dose related decreased weight gain and survival.

A post-marketing cohort study in England identified 23 infants whose mothers had taken fexofenadine in the first trimester. There were no major malformations although one case of “positional talipes” was reported, which is unlikely to be caused by a medicine (Craig-McFeely, et al., 2001).

Fexofenadine is a metabolite of terfenadine. Administration of terfenadine (which is no longer on the market) and fexofenadine lead to similar serum concentrations of the active metabolite so pregnancy outcomes are likely to also be similar (Loebstein et al., 1999) The Swedish Medical Birth Registry identified 1164 women treated with terfenadine in early pregnancy, and they did not have rates of congenital anomalies any higher than the general population (Kallen, 2002).

Similarly, a multicenter prospective controlled study found no congenital anomalies in 65 infants with terfenadine first trimester exposure (Loebstein et al., 1999). The mean daily dose ranged from 30-120 mg. Duration of use was not reported. While reassuring, this study has only an 80% power to rule out a 6.5-fold increased risk for malformations. Of note is that the birth weights were lower in the exposed group. However, the authors pointed out that the birth weight rates <10th percentile for gestational age did not differ between the exposed and control groups, which argues against a major clinical effect. Daily dose, duration of therapy, time of exposure, concomitant maternal asthma or steroid use did not correlate with the lower birth weight. Additional studies would need to address whether terfenadine plays a causative role in low birth weight.

While the animal and human metabolite data does not suggest an increase in birth defects, further studies on larger numbers of pregnant women are needed.

Loratadine

Loratadine is marketed as Claritin. Several studies have not seen a significant sedative effect with loratadine (Horak and Stubner, 1999). Performance impairment has been reported at doses higher than the recommended dose (Horak and Stubner, 1999).

Concern of an association between early pregnancy use of loratadine and hypospadias was raised by the Swedish Medical Birth Registry when an incidence of hypospadias twice that of the general population (but an absolute risk of <1%) was reported (Kallen, 2002). This dataset from 1995-2001 found 15 infants with hypospadias out of 2,780 loratadine exposed infants. The majority of infants had mild glandular hypospadias which makes the association with early pregnancy medicine exposure questionable in terms of biological plausibility (Diav-Citrin, et al. 2003).

Additional surveillance from 2001-2004 found only two more cases of hypospadias out of 1911 infants when 4.3 cases were expected (Kallen and Olausson, 2006). This negative follow-up study led the authors to note that the most likely explanation of the discrepancy was that the first finding was a chance event based on multiple analyses of the data.

Furthermore, two case control studies with 558 and 227 cases of hypospadias also found no association with maternal loratadine use (Werler et al., 2004; Pedersen et al., 2006). Animal data also did not

support an association since McIntyre et al. (2003) reported no increase in hypospadias or other androgen mediated endpoints in animals given up to 120 times the human dose.

A prospective controlled study by the Israeli Teratogen Information Service did not find an increase in major malformations with 126 infants with exposure to loratadine during the first trimester or in the case of 175 infants with exposures at anytime during pregnancy (Diav-Citrin, et al., 2003). This study had the power to detect a 3-fold increase in major anomalies. There were also no cases of hypospadias in this study. The median daily dose was 10 mg with a median duration of 8 days.

Additionally, there was no significant differences in birth weight, premature delivery, or stillbirth. There was a significantly higher rate of miscarriage in the loratadine group, although the loratadine miscarriage rate of 11.4% was within general population rate. The authors felt a likely explanation was that the loratadine group contacted the teratogen service significantly earlier in gestation and also had higher maternal ages compared to the control groups.

Finally, another multicenter study that also investigated the use of loratadine in the first trimester did not find an increase in congenital anomalies in 143 infants (Moretti et al., 2003). This study had an 80% power to detect a 3.5- fold increase in malformations. No cases of hypospadias were observed in the exposed group either. There was also no significant increase in miscarriage, birth weight, or gestational age at delivery. The median daily dose was 10 mg and median total dose in the first trimester was 50 mg (range of 10-1470 mg).

Based on the combined animal and human studies, loratadine does not appear to significantly increase the risk of hypospadias or non-genital congenital anomalies.

Pseudoephedrine

All of these second generation antihistamines can be purchased in formulation with pseudoephedrine, i.e. Zyrtec-D, Allegra-D, and Claritin-D. Studies have not associated pseudoephedrine with congenital anomalies in over 2000 pregnancies (Jick et al., 1981; Aselton et al., 1985; Heinonen et al., 1977; Rosa, 1993).

However, weak associations with vascular disruptions, such as gastroschisis, have been reported, and cigarette smoking may further exacerbate the risks. (Werler et al., 1992, 2002, 2004). Although weak, these associations have not been entirely discounted due to the vasoactive properties of decongestants. If truly causative, absolute risks would still be <1%. Preferentially, antihistamines are taken alone, especially during the first trimester.

Summary

The use of first generation antihistamines is preferred in pregnancy over the use of second generation antihistamines due to their longer availability on the market. However, women who do not respond to chlorpheniramine can be counseled that the available studies for cetirizine, fexofenadine, and loratadine do not show an increased risk for congenital anomalies. Larger numbers of human pregnancies are still needed, particularly for fexofenadine. Avoidance of combination therapy with pseudoephedrine, at least in the first trimester, is also preferred.

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