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Calcium Channel Blockers and Pregnancy

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Calcium channel blockers (CCBs) are a highly prescribed class of drugs used for the treatment of angina pectoris, hypertension, and cardiac arrhythmias. These vasodilating agents relax smooth muscle by inhibiting the entry of calcium into muscles or by inhibiting its release from intracellular storages. This relaxation in blood vessel walls results in dilation of arteries and, subsequently, in reduction of blood pressure (Ducsay et al., 1987). The most commonly prescribed calcium channel blockers are nifedipine (Procardia), diltiazem (Cardizem), and verapamil (Calan; Isoptin). Less frequently prescribed are nicardipine (Cardene), felodipine (Plendil), isradipine, and amlodipine.

In addition, CCBs are frequently used during pregnancy for pregnancy-induced hypertension and to inhibit pre-term labor. These agents are helpful in the treatment of pre-term labor because they decrease myometrial contractility in the uterus (Forman et al., 1981). This RISK||NEWSLETTER will evaluate the safety of CCBs in human pregnancy.

TIMING OF EXPOSURE

Generally, calcium channel blockers are administered in the second and third trimesters of pregnancy. Drug exposure usually has only minor effects on the fetus, if any, at this time.

It is in the first trimester when the major organ systems are formed that the fetus is most susceptible to a teratogen. This critical period of development occurs from the fifth week from the last menstrual period through the tenth week of gestation. Since many of the developmental processes in the first trimester are calcium-dependent, there is concern that the use of a calcium channel blocker during this time may cause fetal malformations or other adverse effects. This risk is primarily theoretical as it is based on a study of frog embryos which showed many developmental abnormalities after exposure to CCBs (Nurgess and Vere, 1989).

SPECIFIC CCBS AND THEIR FINDINGS

Frequently prescribed calcium channel blockers:

Verapamil is used in pregnancy for inhibition of pre-term labor and cardiac arrhythmias. The risk to a fetus exposed to this agent is minimal. Magee et al. (1994) studied 57 infants of women treated in the first trimester with verapamil. The frequency of malformations was not significantly increased in this population. Many investigators have looked at the effects of the drug in late pregnancy. No adverse drug-related effects were seen in infants of 137 women with second and third trimester exposures to verapamil (Orlandi et al., 1986; Marlettini et al., 1990).

Animal studies have not indicated an association of birth defects with verapamil use. However, Spatz et

al. (1986) did find decreased litter size and reduced birth weight in the offspring of rats treated with doses similar to those used in humans. Studies in pregnant ewes have shown a decrease in uterine blood flow after injection of verapamil (Murad et al., 1985). This finding prompted the investigators to caution against use when uteroplacental perfusion may be compromised.

Nifedipine is also considered to be of minimal risk to the fetus. It is generally used in the second half of pregnancy for hypertension, cardiovascular disease and pre-term labor. A retrospective study of 102 women who received nifedipine for inhibition of pre-term labor found the drug to be a safe means of therapy (Waisman et al., 1989). In addition, no increase in the frequency of congenital anomalies was observed in 57 infants exposed to nifedipine in-utero in the first trimester (Magee et al., 1994). Clinical trials involving from 20 to 99 infants of women treated with nifedipine in the second and third trimesters also failed to show any treatment-related adverse effects (Read and Wellby, 1986; Ferguson et al., 1990; Meyer et al., 1990; Bracero et al., 1991; Fenakel et al., 1991; Murray et al., 1992; Sibai et al., 1992; Glock and Morales, 1993; Roy and Pan, 1993; Smith and Woodland, 1993; Childress and Katz, 1994).

Animal studies dealing with nifedipine use have shown a dose-response relationship. Increases in the frequency of fetal death, growth retardation, and skeletal and cardiovascular malformations were seen when rats were treated with doses of nifedipine 9-62 times greater than "the human dose" (Fukunishi et al., 1980; Cabov and Palka, 1984; Yoshida et al., 1988; Komai et al., 1991; Richichi and Vasilenko, 1992). Digital abnormalities were observed in the offspring of rabbits exposed to 3.5-14 times the human dose (Danielsson et al., 1989, 1992). It has been hypothesized that these abnormalities may have been the result of decreased uteroplacental blood flow rather than from direct effects of the drug (Yoshida et al., 1995). Cardiac failure and decreased fetal and placental weights were also observed in a dose-related fashion in rats (Momma and Takao, 1989; Furuhashi et al., 1991).

Diltiazem is primarily used in the treatment of premature labor. The teratogenic risk of this calcium channel blocker is undetermined. There have been no reported studies on the effects of this drug in human pregnancy. Adverse effects have been observed in animal studies, however. An increase in the frequency of embryonic loss was seen in studies on pregnant rabbits, mice, and rats (Ariyuki, 1975). Malformations of the tail and limbs were also observed in this study. However, the doses were greater than those used in humans exposures. At doses similar to human doses, no teratogenic effects were noted. Mahalik and Hitner (1992) found an increase in the frequency of palatal defects and hydrocephalus in the offspring of mice treated with doses similar to those used in humans. The relevance of these findings to human pregnancy is unknown at present.

Other calcium channel blockers:

The calcium channel blocker felodipine is used for the treatment of hypertension, angina pectoris and congestive heart failure. Teratogenic effects have been seen in rabbits (Lorimer and Pringle, 1990; Danielsson et al., 1989, 1990). These consisted of digital defects and may have been a result of decreased uteroplacental blood flow. Digital defects were also reported by the manufacturer (Merck Sharp and Dohme) in studies of monkeys. The relevance to human pregnancy is presently unknown.

Use of nicardipine was not associated with a high incidence of adverse outcomes in infants of 60 women treated for hypertension and preeclampsia (Carbonne et al., 1993). This study as well as others have shown nicardipine as an acceptable medication for the treatment of pregnant hypertensive patients (Jannet et al., 1994). Animal studies found digital defects, specifically hyperphalangism, in rats (Yoshida et al., 1989) and decreased uteroplacental blood flow in rabbits treated with this agent (Lirette et al., 1987).

Very little information is available on amlodipine. It has been studied in rats and rabbits by Horimito et al (1991). An increase in the incidence of congenital anomalies was not found when administered

throughout the critical period of organ formation.

Isradipine is structurally related to nifedipine. Human studies regarding this agent have been of limited size and lack longterm follow-up. However, these studies have shown that use of isradipine in late pregnancy for hypertension is safe and acceptable. No adverse effects were seen on uterine activity or uteroplacental blood flow (Feiks et al., 1990, 1991; Ingemarsson et al., 1990; Wide-Svensson et al., 1990, 1995).

RISKS WHEN BREAST-FEEDING

Information on breastfeeding and CCBs is available for verapamil, nifedipine and diltiazem. The WHO Working Group on Drugs and Human Lactation has classified verapamil as compatible with breastfeeding. However, Inoue et al. (1984) recommended not using the agent while breastfeeding because the hearts of infants may be more susceptible to the pharmacologic effects of verapamil. Nifedipine is also transferred to breast-milk. The dose ingested by the infant is so small, however, that it is unlikely to have adverse effects (Murray et al., 1992; Manninen et al., 1991). Diltiazem is also ingested in small amounts from breast milk, but the WHO Working Group has not concluded that it is safe to use while breast-feeding.

SUMMARY

Calcium channel blockers appear to be safe for mother and fetus when used for the treatment of hypertension, cardiac arrhythmias, angina and pre-term labor in pregnant women. Teratogenicity with these agents has been demonstrated in animals, but no cases of possible human malformation or deformity have been reported (Hennessy and Horvath, 1992). However, it must be recognized that human studies have been very limited. It is recommended that a drug only be used during pregnancy if the potential benefit outweighs any potential risk to the fetus.