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Update: Benzodiazepines in Pregnancy

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Benzodiazepines (BZDs) are frequently prescribed during pregnancy to treat anxiety or panic disorder. As a class, the BZDs are central nervous system depressants that have anxiolytic, sedative, hypnotic, muscle relaxant and occasionally anti-epileptic properties. They are well absorbed in the body and cross the placenta easily (Kanto, 1982); elimination half-lives for the BZDs range significantly (8-48 hours), with active metabolites often remaining in the body for longer periods of time (Gilman, 1990).

Initial concern regarding BZD exposure in pregnancy arose because they act upon GABA receptors; GABA is an amino acid neurotransmitter that may be related to palatal development (Kellogg, 1988). Early studies on Valium (diazepam), a commonly prescribed BZD, showed an increased risk for oral clefting in both animals (Zimmerman, 1984) and in retrospective and case-control studies in humans (Saxon and Saxon, 1975; Safra and Oakley, 1975). This has, however, been contradicted by several recent prospective and case-controlled studies and a meta-analysis that all uniformly found no association between diazepam use and clefting (Altshuler et al., 1996; Bracken, 1986; Czeizel, 1988; Ornoy et al., 1998; Pastuszak et al., 1994; Rosenberg et al., 1983; Shiono and Mills, 1984). In recent years, several prospective studies have addressed the potential teratogenicity of multiple BZDs. The association between BZDs and clefting, and birth defects in general, remains unclear, and it will be reviewed in more detail in this RISK/NEWSLETTER. BZDs were reviewed in the September, 1995 (RISK/NEWSLETTER 4(2)); this newsletter serves as an adjunct to that issue.

General studies on BZDs

Many of the studies on BZD exposure in pregnancy have lumped various drugs into a single analysis, making it difficult to determine if specific medications pose teratogenic risk in pregnancy. McElhatton (1994) provides an excellent review of many of the studies on BZDs. While there have been mixed findings, these studies do not suggest an overall increase in malformations after in utero exposure to BZDs. Pastuszak et al. (1994) prospectively ascertained 137 women exposed to BZDs, primarily diazepam (N=43) and lorazepam (N=33) and found no differences from control groups in frequency of malformations or miscarriage, birth weight, gestational age or measures of the Denver developmental scale at various ages. Johnson et al. (1995) presented an abstract reporting 272 women exposed to alprazolam, lorazepam and clonazepam; of the 186 liveborns, 15 had malformations, including four cardiac defects and six inguinal hernias, which the authors speculated may be secondary to the muscle relaxant properties of BZDs. In a separate abstract, Godet et al. (1995) reported on 187 malformed infants exposed to BZDs; while no anomaly was more frequent in this group as compared to a control group of over 10,000 malformed infants, associations between lorazepam and anal atresia and between bromazepam and urinary anomalies were noted, but there was no association between clefting and any

BZD. Most recently, Ornoy et al. (1998) prospectively reported 460 pregnancies exposed to BZDs in the first trimester and found no increase in birth weight, gestational age or malformations, but more cardiac defects were present in the exposed versus control group; a slight increase in miscarriage and induced abortions was also observed.

Aside from the concerns regarding malformations after in utero exposure to BZDs, there are reports of transient neonatal withdrawal symptoms and even of a possible syndrome of BZD exposure after significant maternal exposure (Laegrid et al., 1989; Bergman et al., 1992). Laegrid et al. (1989) described facial dysmorphology similar to fetal alcohol syndrome, involving impaired growth, hypotonia, developmental and motor delays and transient neonatal withdrawal after significant maternal BZD exposures. Other studies have failed to support this association, suggesting that perhaps chronic use at high dosages is required to produce this syndrome. There has also been controversy about whether an autosomal recessive condition (Zellweger syndrome) explains some of the physical and developmental features noted. The confounding effect of other maternal drug use in Laegrid's studies has also been raised. Most recently, the Michigan Medicaid study (Bergman et al., 1992) looked at 80 women who filled over 10 benzodiazepine prescriptions during a pregnancy and saw no increase in malformations among those exposed in utero. Concurrent maternal alcohol and substance exposure in pregnancy significantly biases all of the above studies. While no long term studies have been performed to assess neurodevelopment in exposed children, the potential exists for neurobehavioral teratogenicity after exposure to BZDs, and this has been noted in animal studies (Schardein, 1993).

Reproductive Data on Specific BZDs

Alprazolam (Xanax)

Several human studies exist on alprazolam exposure in pregnancy. Postmarketing research of 411 women with first trimester exposure to alprazolam did not suggest an increased frequency of malformations (St. Clair et al., 1992). Separate prospective studies of 133 and 149 women, respectively, found no increased risk of malformations nor any pattern to the malformations described (Johnson et al., 1995; Ornoy, 1998). Neonatal withdrawal symptoms have been noted after exposure to alprazolam in late pregnancy (Barry and St.Clair, 1987) and breast-feeding (Anderson and McGuire, 1989). Alprazolam has a relatively short half-life (<12 hours) compared to other BZDs.

Chlordiazepoxide (Librium)

Data on chlordiazepoxide exposure in pregnancy has been contradictory. 175 pregnancies exposed to chlordiazepoxide showed an increased frequency of malformations (Milkovich, 1974). In contrast, two studies of 257 and 136 women using Librium in the first trimester found no increase in malformations (Hartz, 1975; Crombie, 1975). This was supported by a large retrospective study of 788 women (Rosa, cited in Briggs, 1998) that also showed no increase in malformations, but there was a slight increase in cardiac anomalies (10 vs. 7 expected). A case-control study of infants with cardiac defects also showed a slight association with chlordiazepoxide exposure (Rothman et al., 1979), but it is unclear what to make of this association. Animal studies involving rats and mice show no increase in malformations at doses lower than the maternal toxicity levels; however, there is some evidence of low birth weight and behavioral changes at doses 2-7X the human dose. Withdrawal symptoms have been noted after exposure to chlordiazepoxide near term (Briggs, 1998).

Clonazepam (Klonopin)

Clonazepam has not been shown to increase malformations in rats or rabbits. A single retrospective study of 19 women exposed in the first trimester showed 3 malformations (including 2 heart defects); because of the small study size, the implications of this finding are unclear (Briggs, 1998). Prospective studies of 60 and 69 women each found a slight increase in malformations, but given the small number

of women in each study, it remains difficult to determine causality from these studies (Johnson et al., 1995; Ornoy, 1998). One complicating factor is that clonazepam is also used to treat seizure disorder and therefore, an increase in malformations may be due to epilepsy rather than medication use. A case control study of anti-epileptic medications, including clonazepam, did not show an association with malformed infants and clonazepam use during pregnancy (Czeizel, 1992). Clonazepam has a relatively long half-life (20-40 hours) compared to other BZDs (McElhatton, 1994), and withdrawal symptoms have been observed after exposure late in pregnancy (Fisher et al., 1985).

Clorazepate (Tranxene)

While clorazepate crosses the placenta in a limited amount, its metabolite nordiazepam is related to diazepam and crosses the placenta easily. Clorazepate is not teratogenic in mice, rats or rabbits, but there are no human studies available. There is a single case report of multiple malformations in an infant whose mother took clorazepate during the first trimester; the relevance of this is unknown (Patel, 1980). As such, clorazepate has an undetermined risk during pregnancy.

Diazepam (Valium)

Most reproductive studies on BZDs involve diazepam, and its reproductive risks are well reviewed (McElhatton, 1994). As previously discussed, several early case controlled studies on diazepam showed an increased risk of oral clefts, with relative risks of approximately 3-4 times the baseline risks (Aarskog, 1975; Safra and Oakley, 1975; Saxen, 1974). These early studies were criticized for their study design and other confounding factors. Studies since that time have contradicted these results, showing no increase in clefting (Rosenberg et al., 1983; Shiono and Mills, 1984; Czeizel, 1988). Prospective studies of 43 and 89 women exposed to diazepam did not show any increased risk for malformations, specifically for oral clefts (Pastuszak et al., 1994; Ornoy et al., 1998). Thus, it appears that if there is a risk of oral clefting after exposure to diazepam, it is likely to be a insignificant.

Flurazepam (Dalmane)

Human studies on flurazepam are limited to a retrospective study following 73 women exposed in the first trimester (Briggs, 1998). No increase in malformations was seen. Animal studies have not shown an increased risk for malformations (McElhatton, 1994). However, because of the paucity of information on flurazepam in pregnancy, its risks remain undetermined.

Lorazepam (Ativan)

Lorazepam crosses the placenta more slowly than diazepam, and also has a short half life (12-16 hours). Lorazepam is not considered teratogenic in mice or rats, but human reproductive data is limited. Small prospective studies (N=30; N=112) have not shown an increase or pattern to the malformations observed in women exposed to lorazepam in the first trimester (Johnson et al., 1995; Ornoy, 1998). Much of the human information has reviewed use around labor, and shows an increase in respiratory distress, decreased APGARS, problems with temperature regulation and poor feeding (McElhatton, 1994).

Oxazepam (Serax)

Oxazepam is a metabolite of diazepam. It has not been shown to increase malformations in rats, rabbits or mice (Owens et al, 1970; Miller and Becker, 1973). No malformations were noted in 89 women exposed to oxazepam in a prospective study (Ornoy, 1998). Oxazepam was, however, one of the benzodiazepines that Laegrid (1987) associated with "fetal benzodiazepine syndrome" and neonatal withdrawal.

Triazolam (Halcion)

Data on triazolam is limited to manufacturers data and a retrospective study on 138 women exposed in the first trimester; neither showed any significant increase in malformations or pattern to these malformations (Briggs, 1998), although withdrawal symptoms have been noted (Barry and St. Clair, 1987; Sakai et al. 1996).

Virtually no data is available on Halazepam (Paxipam) or Prazepam (Centrex). Animal studies on these medications do not show an increase in malformations at non-toxic levels. As such, these medications have an undetermined risk for use during pregnancy.

Summary

Use of benzodiazepines, specifically diazepam, was previously thought to be associated with an increased frequency of cleft lip and/or palate; this finding has not been supported by the majority of recent studies. Although the balance of evidence from human studies of the benzodiazepines (chiefly, diazepam) does not show first trimester usage to be teratogenic, animal studies have shown an increase in abnormal behavioral patterns after in utero exposures at levels comparable to the usual human doses. At this point, there is still no conclusive data regarding the possible behavioral teratogenicity of benzodiazepine use during pregnancy. Withdrawal symptoms can occur after fetal exposure late in pregnancy.

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