Valium: An Oral Cleft Teratogen?

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Retrospective case-control studies in three countries have recently shown an association between oral clefts and maternal exposure to Valium (diazepam) during the first trimester of pregnancy (1-4). We will briefly describe these studies and discuss their implications.

Saxén (1975a) compared 599 cases of oral clefts reported to the Finnish Register of Congenital Malformations between 1967 and 1971 to carefully matched controls. She reported that antineurotic drugs, mostly Valium, were used more frequently during the first trimester of pregnancy by the mothers of infants with cleft palate and cleft lip with or without cleft palate (CL±CP) than by the control mothers. Saxén and Saxén later (1975b) confirmed a more specific association between the antineurotic drugs of the benzodiazepine class (diazepam, oxazepam, nitrazepam, and chloridiazepoxide) and oral clefts. They found that 5.4% (25/464) of the mothers of infants with oral clefts without other major anomalies had a history of exposure to these drugs compared with 2.0% (9/456) of the mothers in the control group. The relative risk was 3 for both the cleft palate and CL±CP groups, but the association was statistically significant only for the cleft palate group.

Since 1970, we have routinely interviewed mothers of infants with certain categories of major malformations, including oral clefts, ascertained by the Metropolitan Atlanta Congenital Defects Program (Safra and Oakley, 1975). The interview is designed to obtain a medical, socioeconomic, genetic, and environmental profile on each woman, without regard to any particular etiologic hypothesis. Beginning in 1972, we supplemented the standard interview by showing the mothers a card containing samples of various tranquilizers, including Valium. Of the women interviewed and shown the drug sample card, 5.8% (16/278) gave a history of first-trimester exposure to Valium. The exposure rate among mothers of infants with CL±CP was 14.3% (7/49) compared with a rate of 3.9% among both the mothers of children with all other defects (9/229) and among the mothers of the infants with Down’s syndrome (2/52). The exposure rate for the mothers of infants with CL±CP with no other major anomalies was 17.6% (6/34). We were not able to account for this fourfold increase in relative risk on the basis of racial distribution, family history, common drug exposures, or other confounding variables. For the mothers of infants with cleft palate, the exposure rate was 5.0% (1/20).

Aarskog (1975), as part of another study, mailed questionnaires to 130 mothers of children who had been treated for oral clefts without other defects at Children’s Hospital in Bergen between 1967 and 1971. He recently reported a 6.1% (6/99) rate of first-trimester exposure to Valium in the responding mothers.

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of children with CL±CP and an 8.3% (1/12) rate of exposure in the responding mothers of children with cleft palate. The author compared these exposure rates to the 1.1% (4/362) first-trimester exposure rate in the general population, as ascertained by a sample of records of normal births between 1972 and 1975 by the Medical Birth Registry of Norway. The validity of this comparison is open to some criticism, however, because exposure among controls was not ascertained by the same questionnaire method used for the cases.

The finding of an association between a drug and a birth defect does not necessarily mean the drug caused the problem. All three studies examined a variety of associations. Chance alone would be expected to lead to some statistically significant associations in such exploratory studies. However, the data for the three studies were collected at a time when there was no concern or bias that the drug might be associated with oral clefts. Furthermore, they were done in three different countries by investigators using different case-control designs. That they all showed an association of similar strength for CL±CP decreases the likelihood that chance is responsible. In the case of cleft palate, only one study looked at enough cases to make a meaningful statement about the association of the defect with first-trimester Valium exposure. In the absence of supporting data from other studies, chance must still be considered a possible explanation for the association.

In spite of the consistent results from the three studies, one might dismiss the idea of causality simply because neither systems that monitor birth defects nor clinicians who care for infants with clefts have perceived an increased incidence. Such an outright dismissal of causality is unjustified, though, because the increased risk, if real, is so low that, even with considerable exposure, the incidence would be expected to change very little as the following example shows. If the first-trimester exposure to Valium doubled from 2% in 1970 to 4% in 1973 as the number of new prescriptions nationally almost doubled (Table 1), one would predict that the incidence of CL±CP would have increased by 6%. Clinicians would not be likely to notice a change of this magnitude, and the Birth Defects Monitoring Program, the largest birth defect registry in the country (Center for Disease Control, Report, 1975), would not perceive it as significant (at the .05 level).

Now that the hypothesis that Valium is a teratogen has been raised,

### Table 1: Valium Sales Trends vs. Secular Trends in Rates of CL ± CP and Cleft Palate in the United States.

<table>
<thead>
<tr>
<th>year</th>
<th>Valium new prescriptions (millions)*</th>
<th>CL ± CP cases/1,000 births United States</th>
<th>Cleft palate cases/1,000 births United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>1968</td>
<td>18.6</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>1969</td>
<td>24.9</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>1970</td>
<td>31.7</td>
<td>0.97</td>
<td>0.51</td>
</tr>
<tr>
<td>1971</td>
<td>40.6</td>
<td>1.01</td>
<td>0.50</td>
</tr>
<tr>
<td>1972</td>
<td>50.0</td>
<td>0.99</td>
<td>0.56</td>
</tr>
<tr>
<td>1973</td>
<td>58.4</td>
<td>1.03</td>
<td>0.56</td>
</tr>
<tr>
<td>1974</td>
<td>59.3</td>
<td>0.92</td>
<td>0.53</td>
</tr>
</tbody>
</table>

* Data supplied by I.M.S. America, Ltd., 1975
monitoring data should be reviewed for trends that may not be statistically significant. The data in Table 1 show that there is no upward trend in the incidence of CL±CP or cleft palate. The lack of an increase is a strong argument against a causal relationship, although still not strong enough to dismiss the idea. It is possible that the first-trimester use of Valium has remained relatively stable since 1970 and has not followed the general trend in new prescriptions. Unfortunately, national data on first-trimester use are not available.

There has been some debate (Milchovich and van den Berg, 1974, and Hartz, et al., 1975) in the recent medical literature over the possibility that some of the other minor tranquilizers may be low-level teratogens as well. Clearly more data are needed before these hypotheses can be accepted or rejected. In the meantime, the Food and Drug Administration (1975) has prudently suggested that, since minor tranquilizers are "rarely a matter of urgency" during the first trimester, "the benefit-risk considerations are such that their use during this period should almost always be avoided."

Some pregnant women already exposed to Valium during their first trimester may seek abortion counseling. They should be told that no causal relationships have yet been established and, even if they exist, a fourfold increase in relative risk implies an actual risk of only 0.4% for having a child with CL±CP and 0.2% for having a child with cleft palate. To put this risk in its proper perspective, it is important to mention that the overall risk of giving birth to an infant with a major anomaly evident at birth is around 2%, and that isolated oral clefts are repairable by plastic surgery.

Clearly, more research is needed. Many readers of the Cleft Palate Journal will undoubtedly have the case loads and the expertise to do it.

Authors' Note: Since we wrote the editorial, a retrospective case-control study from Hungary by Czeizel compared the first-trimester Valium use by mothers of infants with neural tube defects to that of mothers of infants with oral clefts and found them similar. This report further complicates the issue, pointing out the need for a definitive study.

References

Czeizel, A., Diazepam, phenytoin, and etiologic of cleft lip and/or cleft palate, Lancet 1, 810, 1976.

Editor's Comment: This invited editorial serves to remind us not only of the vast amount that is unknown about teratogens but of the value of interaction among researchers with similar interests in different parts of the world.

B.J.M.