Nigerian Journal of Paediatrics, **8(1)**, 29–33

Primary Reduction Malformation with Bendectin

O O Ogunye*

Summary

Ogunye O O Primary Reduction Malformation with Bendectin. *Nigerian Journal of Paediatrics*, **1981; 8: 29.** Animal and human studies of the teratogenic effects of anti-histaminic anti-emetics have yielded conflicting results. We report here, the case of an infant with multiple congenital anomalies of the appendicular skeleton born to a mother who was exposed to Bendectin** at the critical time of limb development in first trimester of pregnancy. While a cause-and-effect relationship cannot be positively proved, this association raises the possibility that Bendectin may be teratogenic in man. The observed low incidence of congenital malformations seen with this drug may reflect pharmacogenetic differences of the population at risk.

Introduction

In 1964 and 1965, the British literature carried many accounts of birth defects in association with the ingestion of meclizine, cyclizine and dicyclomine used for the treatment of hyperemesis gravidarum.[1 2] The prospective study of Yerushalmy and Milkovich[3] however, showed no significant increase in major birth defects in the group treated with these drugs. In contrast, Lenz[4] showed that among 3,333 infants whose mothers received meclizine during the first trimester, there was a two-to-three fold increase in the incidence of cleft lip or cleft palate or both. Thus, there is conflicting evidence on the possible teratogenicity of these widely-used drugs.

University of Ife, Ile-Ife.
Department of Paediatrics
*Senior Lecturer in Paediatrics

**Bendectin: Merrell National Laboratories.
Bentyl (Dicyclomine hydrochloride) 10mg.
Decapry (doxylamine succinate) 10mg.
Pyridoxine hydrochloride 10mg.

The thalidomide experience[5] and the increasing importance of birth defects as a paediatric problem have made it important to report cases where environmental influences, whether chemical, physical or biological may be teratogenic.

Case Report

The infant was a term product of a 39-year old gravida 4, para 4, mother. The pregnancy was complicated by severe emesis which was treated with Bendectin. The mother started taking this drug from the twenty-eighth post-menstrual day at a dosage of three tablets per day and continued taking it throughout her pregnancy. This unrelated couple had had three children all of whom were in good health. Family history was negative for congenital anomalies.

On examination, the patient, a female, weighed 2,500 gm and measured 43 cm. The head and chest circumferences were 34.5 cm and 32.5 cm, respectively. She was appropriate for gestational

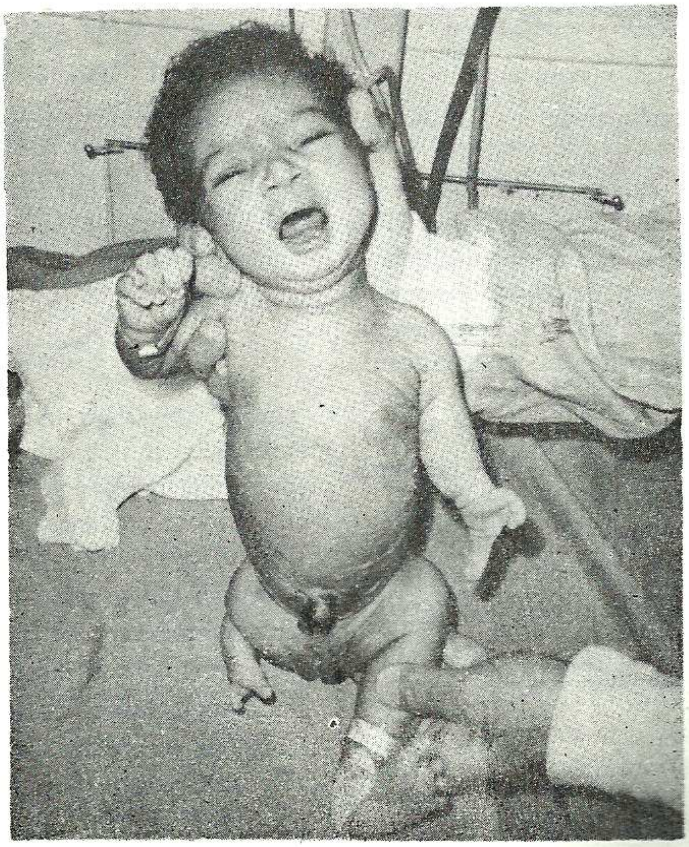
age. Both the left upper and the right lower extremities showed ectrodactyly and marked proximal reduction malformation (Fig.). The right lower extremity showed attachment of the digits to the axial skeleton in the classic complete phocomelic fashion. The right upper extremity, the axial skeleton and the rest of the physical examination were normal.

Radiographic studies showed the right lower extremity to be underdeveloped with total absence of the right femur. A rudimentary right tibia and fibula as well as right tarsal bones were present. The left upper extremity showed deformity of the left humerus, fusion of the rudimentary left radius to the distal end of the humerus, and complete absence of the ulna. A split hand deformity was noted with only two bony digits identified. The left femur was hypoplastic and the proximal tibial epiphyses were absent.

The haematocrit was 54%, haemoglobin, 19.0 gm %, WBC, 22.9×10^9/ l ($22{,}900/mm^3$) with a normal differential count. Platelets were 162.0×10^9/l ($162{,}000/mm^3$) and normal in shape and size. Chromosome analysis from short-term culture of peripheral lymphocytes using both routine and G-banding techniques showed normal 46XX complement with no structural abnormalities.

Discussion

Before the implication of a possible aetiological role of environmental factors in cases of dysmorphogenesis, it is important to show that the birth defect in question does not represent a previously



Photograph of an Infant showing ectrodactyly, proximal reduction malformation of the left upper and the right lower extremities

described "syndrome" with known or suspected genetic transmission. Thus, primary limb aplasias can be secondary to genetic and exogenous factors. For example, reduction malformation of the upper extremities occur in the Holt-Oram syndrome[6] and in Fanconi pancytopenia.[6] Similarly, a syndrome of split hand and foot is known to be inherited in a dominant mendelian fashion. The absence of cardiac anomalies, and of pancytopenia and the negative family history in the present case make these considerations unlikely even though they cannot be completely ruled out.

A second necessary condition that must be satisfied before a chemical agent can be considered a teratogen is that the foetus must have been exposed to the suspected teratogen at the critical time of the development of the malformed parts. Limb buds of human embryos appear at four weeks fertilization age[7] and the introduction of Bendectin in the present case at the twenty-eighth post-menstrual day satisfies this condition. Experience with thalidomide[8,9] showed that the sensitive period lasts from the thirty-fourth to the fiftieth post-menstrual day and that after this period, thalidomide is not teratogenic. Supportive experiments on *Macaca Mulatta* have also shown that the susceptible period for thalidomide teratogenesis extends from the twenty-fifth through the thirtieth day after mating when the limb buds first appear in the monkey embryo.[10]

For more than two decades, it has been suspected that histamine antagonists can interfere with rat pseudopregnancy. Shelesnyak[11] reported that antihistamines applied topically to the rat uterine lumen inhibited the development of deciduomata of the traumatized endometrium of pseudopregnancy. In a very careful study, King, Weaver and Narrod[12] showed that antihistamines in which the ethylamine grouping is present as a ring structure, e.g., meclizine and chlorocyclizine induced micromelia, microstomia and branchygnathia in Sprague-Dawley rats.

The question always arises, however, whether the results of these animal experiments can be extrapolated to man. This is particularly important here since histamine acts differently in humans than it does in the rat. In the human, it dilates arterioles and elicits oedema, but in rodents, it constricts arterioles[12] and, therefore, the vascular effect of the antihistamines in the rodents would be expected to be the opposite of that in the human. Contradictory reports of the possible teratogenicity of this class of antiemetics in man have appeared in the literature. In 1972, Freeman[13] reported two unrelated infants with hemimelia in which one of the mothers took Bendectin early in the first trimester during the critical time of limb development. However, Bunde's retrospective analysis of 4,436 pregnancies in half of which Bendectin was administered in the first trimester did not show any statistically significant difference in the incidence of congenital malformation in the treated and the control groups.[14]

It may be argued that if these antiemetics are in fact teratogenic there should be a very high incidence of congenital limb malformations, judging from the frequency of their usage. The problem with this argument is that it is not always clear whether it is the drug or its metabolite which is teratogenic. The level or even the type of metabolite may therefore be a reflection of pharmacogenetic differences in the population at risk. Such genetically determined variations in response to drugs include the effect of acetamides and barbiturates in precipitating attacks of porphyria in genetically susceptible persons,[15] and the effect of cortisone in pregnant mice upon the incidence of cleft palate in the progeny.[16] This interesting possibility is highlighted by the family reports of Walker[17] where it was concluded that sibships appear to contain genetically predisposed individuals who, when exposed to a combination of hyperemesis gravidarum and certain antiemetic agents in the first trimester, may express a major malformation syndrome.

The apparent discrepancy between the results of the studies of Yerushalmy and Milkovick[3] on one hand and Lenz[4] on the other can, therefore, be reasonably explained by differences in the incidence of the "genetic susceptibility factor" in the populations studied. The nature of such

susceptibility factor, if it exists, is still unclear. It may be monogenic and enzymic or polygenic and structural. Analysis of the families reported by Walker[17] also suggests that such a factor may be inherited in an autosomal dominant fashion with variable expressivity.

We believe that while the case of Bendectin being a teratogen has not been proven conclusively, there is enough evidence now to classify this drug under the "suspicious" group of potential teratogens. The observed low incidence of congenital malformations seen with this drug may reflect pharmacogenetic differences of the population at risk.

References

1. Smithells RW and Chinn ER. Meclizine and foetal malformations: A prospective study. *Brit Med J* 1964; **1**: 217–30.
2. Sadusk JF and Palmisano PA. Teratogenic effect of meclizine, cyclizine and chlorcyclizine. *JAMA* 1965; **194**: 139–42.
3. Yerushalmy J and Milkovich L. Evaluation of the teratogenic effect of meclizine in man. *Am J Obst Gynec* 1965; **93**: 553–62.
4. Lenz W. Malformations caused by drugs in pregnancy. *Amer J Dis Child* 1966; **112**: 99–105.
5. Pfeiffer RA and Kosenow W. Thalidomide and congenital abnormalities. *Lancet* 1962; **1**: 45–7.
6. Smith DW. Recognizable patterns of human malformation. Philadelphia: WB Saunders, 1970: 130–5.
7. Langman J. Medical Embryology. Baltimore: Williams and Wilkins, 1963: 56–8.
8. Lenz W and Knapp K. Die Thalidomid-Embryopathie Dentsche. *Med Wchnschr* 1962; **87**: 1232–5.
9. Nowack E .Die Sensible Phase Beider Thalidomid–Embryopathie. *Humangenetik* 1965; **1**: 516–20
10. Wilson JG and Gavan JA. Congenital malformations in non-human primates: Spontaneous and experimentally induced. *Anat Rec* 1967; **158**: 99–106.
11. Shelesnyka MC. Antihistamines and teratogenicity. *Amer J Physiol* 1952; **70**: 522–31.
12. King CTG, Weaver SA and Narrod SA. Antihistamines and teratogenicity in the rat. *J Pharm Exp Ther* 1965; **147**: 391–8.
13. Freeman R. Limb deformities: possible association with drugs. *Med J Austral* 1972; **1**: 606–7.
14. Bunde CA and Bowles DM. A technique for controlled survey of case records. *Curr Ther Res* 1963; **5**: 245–8.
15. Talman EL, Labbe RF and Aldrich RA. Porphyrin metabolism IV. Molecular structure of acetamide derivatives affecting porphyrin metabolism. *Arch Biochem Biophys* 1957; **66**: 289–300.
16. Fraser FC and Fainstat TD. Production of congenital defects in offspring of pregnant mice treated with cortisone. *Pediatrics* 1951; **8**: 527–34.
17. Walker FA. Familial spina bifida associated with antiemetic ingestion in the first trimester. *Birth defects* 1974; **10**: 17–21.