

Bendectin

NDA 10-598

(DESI 10598)

Dicyclomine/Doxylamine (Bentyl/Decapryn)

(IND 7620)

RETROSPECTIVE SURVEY OF OUTCOME OF PREGNANCY

OF PATIENTS ENROLLED IN

BENDECTIN EFFICACY STUDIES--FINAL REPORT

OVERALL SUMMARY

INTRODUCTION

Two multiclinic studies (IND 7620) of the efficacy of 3-ingredient Bendectin* (dicyclomine, doxylamine, and pyridoxine), each of its ingredients alone and in combination, and placebo in the treatment of nausea and vomiting of pregnancy were conducted since 1971. All investigators of these studies have now been contacted for follow-up of outcome of pregnancy of the patients who participated. The retrospective survey of patients enrolled in the following two efficacy studies was started in February, 1975:

1. "4-Way" study of 3-ingredient Bendectin in which the efficacy of dicyclomine and doxylamine alone and in combination and placebo was evaluated. This study was conducted under Protocol 026-003 submitted in the original IND (7620) dated 1/26/71 and amended 2/23/71. Patients were to be treated for a maximum of 7 days. The efficacy results were submitted on 9/26/72, 12/15/72 (case reports), 6/18/73 and 10/8/73 (statistical only).

*Until November, 1976, commercially available Bendectin contained 3 ingredients: dicyclomine hydrochloride 10 mg., doxylamine succinate 10 mg., and pyridoxine hydrochloride 10 mg. Since November, 1976, commercially available Bendectin contains 2 ingredients: doxylamine succinate 10 mg., pyridoxine hydrochloride, 10 mg.

2. "8-Way" study of 3-ingredient Bendectin in which the efficacy of Bendectin, each of its 3 ingredients alone and in combination, and placebo was evaluated. This study was conducted under Protocol 008-004 as submitted to IND 7620 on 12/11/72. Patients were to be treated for a maximum of 7 days. The results (including case report for evaluation of efficacy were submitted 4/15/75 with a final report being submitted in 1977 providing results on the additional patients on whom data were received after the July 22, 1974 cutoff date for inclusion in the efficacy evaluation.

An outline of the plan for the conduction of this retrospective outcome of pregnancy survey, sample general letter to the investigators, glossary, and sample forms for data were presented in Appendix II of the 8/15/75 progress report to IND 7620. Preliminary summary data of this survey of patients were submitted in an interim status report on 11/26/75 to NDA-10-55 Bendectin (DESI 10598). This submission of 12 volumes is the final report of the survey.

PLAN OF STUDY

All investigators of the "4-way" and "8-way" efficacy studies were contacted for follow-up information on outcome of pregnancy of their patients who had been enrolled in these studies. A general letter and glossary of pertinent terms to be used for this survey went to each principal investigator along with a checklist IBM print-out that listed patient number, name, and date of entry into the study for each of his/her patients. Spaces for his/her checking of type of outcome of pregnancy and for comment for each

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delivery were provided on the form. A computer program was designed to tabulate the information returned by the investigator.

Another form (#060575--16 pages) was made available to those investigators who agreed to supply supplemental follow-up information on adverse pregnancy outcome reports related to spontaneous abortion, stillbirths, neonatal deaths, and birth anomalies.

Representative copies of the general letter, glossary, and data forms are resubmitted in Appendix II of this volume for the convenience of the reviewer.

OVERALL SUMMARY OF RESULTS

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" Twenty-eight of the 31 investigators involved in the "4-way" and "8-way" efficacy studies cooperated by completing the checklist forms of this survey. Twenty-four of the 28 investigators cooperated by completing the follow-up supplemental information form (#060575) for patients who had an adverse pregnancy outcome. (See Tables 6 and 7 of Appendix I of this volume.) One investigator, in addition to the 24, cooperated by providing a supplemental information form on one pregnancy involving a birth anomaly.

Information was obtained on the checklist forms from the 28 cooperating investigators on 2580 of their 3069 patients who had been entered into the study. Of the 2580, 2542 patients* had received identifiable study

*Data received on 38 of 46 patients who did not take medication or for whom medication was not identifiable were excluded from the 2542 patient population. See also page 6 for further comment on source of numeric values in this summary.

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medication of placebo or one or more of the 3 tested ingredients. Table summarizes the incidence of pregnancies with outcome of offspring with birth anomalies of this 2542 patient population according to whether patients did or did not receive the individual ingredients of dicyclomin, doxylamine, or pyridoxine.

No real difference was apparent in the incidence of birth anomalies with or without the presence of any of the three ingredients studied.

Table 1*

Incidence (%) of Pregnancies with Outcome of Offspring
with Birth Anomalies According to
Presence or Absence of Each of the Three Ingredients in the Medication

(Incidence for the total population was 1.2%)??

PLACEBO
0.8% SE
TABLE

Medication	Present	Absent
Dicyclomine	1.5% (19/1278)	0.9% (11/1264)
Doxylamine	1.1% (14/1283)	1.3% (16/1259)
Pyridoxine	1.0% (10/977)	1.3% (20/1565)

*Data from Table 3.

The incidence of reported adverse outcome of pregnancy (stillbirths, neon deaths, spontaneous abortion, induced abortion, and offspring with birth anomalies) is summarized in Table 2, according to types of medication use by the 2542 investigational patients. Table 3 is a summary of the same incidence information according to whether patients did or did not receive

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the individual ingredients of dicyclomine, doxylamine, or pyridoxine.

A general range of incidence rates for the general population for stillbirth, neonatal deaths, spontaneous abortions, and birth anomalies as presented in representative published references is included in Table 2 for comparative purposes.

All observed incidence rates for this study were below or within the published range of rates for each of the four pregnancy outcome indexes. (See also footnote "h" of Table 2.) Copies of the pages cited as references for Table 2 are included in Appendix III of this volume.

Summary descriptions of the reported birth anomalies of 31 offspring with anomalies of this study are presented in Table 4. They are arranged by sequential patient number (mother) within each medication group.

There was no pattern to the type of anomalies reported for the 31 offspring of the 30 mothers of the individual investigational drug groups. Three of the 31 offspring with birth anomalies had limb deformities: 2 with polydactyly and 1 with multiple extremity anomalies. (See Table 5.)

OVERALL CONCLUSION

Overall, the data of this survey provide no evidence of an adverse effect on outcome of pregnancy related to spontaneous abortion, stillbirth, neonatal death, or birth anomaly of offspring by any of the investigational medications (dicyclomine hydrochloride, doxylamine succinate, or pyridoxine hydrochloride alone or in combination) evaluated in the two multiclinic

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efficacy studies that provided the patient population cohort for this survey.

COMMENT ON SOURCE OF DATA FOR THIS SUMMARY

Appendix IV of this volume provides IBM computer tabulations of pregnancy outcome (summary tables and listings) for the population of 3069 patients entered into the efficacy study by the 28 investigators who cooperated in this survey. Tables 1 through 3 and Tables 6 and 7 of Appendix I have data obtained from page 3 of the IBM print-out (p. 74 of this volume).

This page summarizes the survey attempt to obtain information on the 3069 patients entered into both the "4-way" and "8-way" efficacy studies by the 28 cooperating investigators. The 3069 value is given on line "total patients" under column "total patients." Verification and/or identification of medication taken by the mother was not possible for 46 patients and of these 46, pregnancy data were received on 38. The 38 value is the difference of 46 and 8 of lines "untab pts." and "no info." under column "no Rx or unknown." Pregnancy data were not received on 481 patients. The 481 value is the difference between 489 of line "no info" and column "total patients" and 8 of line "no info" and column "no Rx or unknown."

The 2542 patient population who took identifiable medication and on whom pregnancy information was received was therefore obtained by subtraction of the above identified 8, 38, and 481 patients from the total of 3069 patients entered into the two studies.

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The sponsor's summaries, completed checklist forms, follow-up forms, and correspondence are presented by sequence of investigator number in volume 2 through 12 of this submission along with the case reports.* Each of the 12 volumes has a table of contents for this entire submission.

*Curricula vitae for the investigators were submitted along with the efficacy data for which dates of submission are given in the introduction. (See page 1 and 2 of this volume.)

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Table 2
Outcome of Pregnancy by Medication Group

Medication	No. of Patients	Pregnancies Resulting In:				
		Still-birth No./%	Neonatal Death(s) No./%	Spontaneous Abortion No./%	Induced Abortion No./%	Infant(s) with Birth Anomaly No./%
* Dicyclomine ^a	399	6/1.5	1/0.2	25/6.3	17/4.3	3/2.0
Doxylamine ^b	397	4/1.0	2/0.5 ^c	26/6.5	12/3.0	4/1.0
Dicyclomine/ Doxylamine	389	2/0.5	4/1.0 ^d	14/3.6	13/3.3	5/1.3 ^e
Pyridoxine	243	2/0.8	1/0.4	13/5.3	13/5.3	3/1.2
Dicyclomine/ Pyridoxine	237	3/1.3	0/0.0	15/6.3	6/2.5	2/0.8
BENDECTIN (2 PART DRUG) Doxylamine/ Pyridoxine	244	3/1.2	0/0.0	11/4.5	13/5.3	1/0.4
DEBENDOX (3 PART DRUG) Dicyclomine/ Doxylamine/ Pyridoxine	253	5/2.0	4/1.6 ^f	15/5.9	12/4.7	4/1.6
* Placebo	380	5/1.3	2/0.5 ^g	14/3.7	14/3.7	3/0.8
All medications	2542	30/1.2	14/0.6	133/5.2	100/3.9	30/1.2

○ Incidence rates in

1.3

2,3,5

4,6

<1.0-15.6^{7,8}

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Table 2 (cont.)

Footnotes.

^aBentyl.

^bDecapryn.

^c2 pregnancies of which 1 was twin pregnancy (1 of twins neonatal death).

^d4 pregnancies of which 1 was twin pregnancy (both neonatal deaths).

^e5 pregnancies of which 1 was a twin pregnancy (both with anomalies).

^f4 pregnancies of which 1 was a twin pregnancy (1 of twins neonatal death).

^g2 pregnancies of which 1 was a twin pregnancy (both neonatal deaths).

^hCited references may have denominators for rate calculation based on other than number of pregnancies (e.g., births or live births) and are here presented for only general and not for specific comparison for which correction factors would need to be introduced.

References. (Copies of referenced pages in Appendix III of this volume.)

¹Niswander, K.R., Gordon, M., and Editorial Committee: The Collaborative Perinatal Study of The National Institute of Neurological Diseases and Stroke. The Women and Their Pregnancies. Washington, D.C., DHEW Publication No. (NIH) 73-379, 1972, pp. 61-62.

²Ibid, p. 63.

Table 2 (cont.)

Footnotes (cont.).

³Hellman, L.M. and Pritchard, J.A., with Wynn, R.M.: *Williams Obstetrics, Fourteenth Edition*, New York, Appleton-Century-Crofts, 1971, pp. 10-13.

⁴*Ibid*, pp. 494-496.

⁵Taylor, E.S.: *Beck's Obstetrical Practice, Ninth Edition*. Baltimore, Williams & Wilkins Co., 1971, pp. 603-605.

⁶*Ibid*, p. 307.

⁷Warkany, J.: *Congenital Malformations, Notes and Comments*. Chicago, Year Book Medical Publishers, 1971, pp. 38-43.

⁸Myriantopoulos, N.C. and Chung, C.S.: *Congenital Malformations in Singletons: Epidemiologic Survey*. Miami, Symposia Specialists, 1974, pp. 4, 20.

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Table 3

Outcome of Pregnancy by Medication Groups Containing or Not Containing a Specific Ingredient

Medication Groups	No. of Patients	Pregnancies Resulting In:				
		Still-birth No./%	Neonatal Death(s) No./%	Spontaneous Abortion No./%	Induced Abortion No./%	Infant(s) with Birth Anomaly No./%
All medications containing ^a dicyclomine	1278	16/1.2	9/0.7	69/5.4	48/3.8	19/1.5
All medications without ^b dicyclomine	1264	14/1.1	5/0.4	64/5.1	52/4.1	11/0.9
All medications containing ^c doxylamine	1283	14/1.1	10/0.8	66/5.1	50/3.9	14/1.1
All medications without ^d doxylamine	1259	16/1.3	4/0.3	67/5.3	50/4.0	16/1.3
All medications containing ^e pyridoxine	977	13/1.3	5/0.5	54/5.5	44/4.5	10/1.0
All medications without ^f pyridoxine	1565	17/1.1	9/0.6	79/5.0	56/3.6	20/1.3

Table 3 (cont.)

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Footnotes.

- ^a dicyclomine (Bentyl), dicyclomine/doxylamine (Bentyl/Decapryn), dicyclomine/pyridoxine, dicyclomine/
doxylamine/pyridoxine.
- ^b doxylamine, pyridoxine, doxylamine/pyridoxine, placebo.
- ^c doxylamine, dicyclomine/doxylamine, doxylamine/pyridoxine, dicyclomine/doxylamine/pyridoxine.
- ^d dicyclomine, pyridoxine, dicyclomine/pyridoxine, placebo.
- ^e pyridoxine, dicyclomine/pyridoxine, doxylamine/pyridoxine, dicyclomine/doxylamine/pyridoxine.
- ^f dicyclomine, doxylamine, dicyclomine/doxylamine, placebo.

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Table 4

Summary Listing of 32 Pregnancies (Including 2 with No Maternal Ingestion of Investigational Drug) from which 33 Infants Were Born with Reported Birth Anomalies (Includes 1 Set of Twins). Listing Is by Patient Number Sequence in Each Successive Medication Group.

Drug	Patient No.	Birth Anomaly	Living/Dead; Sex
Dicyclomine			
	[REDACTED]	Marked edema, generalized, hydrothorax & ascites, congenital atelectasis, excess lobulations of kidneys, dilatation of pelvis of kidneys, focal constrictions of ureters.	Died at 45 minutes; Male
	[REDACTED]	Congenital anomaly of heart, interventricular septal defect, hypertrophy of right ventricle, dilatation of left ventricle, atelectasis of both lungs, passive congestion (lungs and spleen), cleft palate, bilateral inguinal hernias, bilateral pes equinovarus.	Died at 3 months; Male
	[REDACTED]	"Infant survived with severe brain damage - mother has history of reprod. failures - had severe placental insufficiency. . ." (Summary only; no Form 060575.)	Living; Male
	[REDACTED]	T-E Fistula, imperforate anus.	Living; Female
	[REDACTED]	Bilateral inguinal herniorrhaphy at 3 months.	Living; Male
	[REDACTED]	Left hydrocele.	Living; Male
	[REDACTED]	Complete evisceration; ruptured omphalocele.	Neonatal death; Male
	[REDACTED]	"Hair lip." (Summary only; no Form 060575.)	Living; Female

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Table 4 (cont.)

Drug	Patient No.	Birth Anomaly	Living/Dead; Sex
Doxylamine			
	XXXXXX	Congenital absence of globes (eyes), bilateral.	Died at 10 months; Male
	XXXXXX	Deadborn macerated fetus, 2360 g., 31 weeks gestation. Hemorrhagic necrosis of left kidney.	Stillbirth; Male
	XXXXXX	Epidermolysis bullosa lethalis form - skin peelings from hands and around umbilicus at birth - both parents carriers of autosomal condition.	Neonatal death; Male
	XXXXXX	Pyloric stenosis developed several weeks post-partum (Mother-verbal)	Living; Male
Dicyclomine/ Doxylamine			
	XXXXXX	Double distal right thumb.	Living; Female
	XXXXXX	Enzyme insufficiency. (Summary only; no Form 060575.)	Living; Female
	XXXXXX	Twin #1 - hyaline membrane disease; severe cerebral atrophy; skin wrinkled with generalized raw, weeping eruptions; small, asymmetrical head; webbed neck; ocular abnormality; congenital toxoplasmosis (suggested); large hepatic infarct	Neonatal death; Male

Table 4 (cont.)

Drug	Patient No.	Birth Anomaly	Living/Dead; Sex
Dicyclomine/ Doxylamine (cont.)			
	 	Twin #2 - Hyaline membrane disease; cerebral encephalomalacia; bronchopulmonary dysplasia; hemorrhagic infarction of ileum; acute renal tubular necrosis; "peculiar skin & wide neck"; "cervical spine very abnormal."	Neonatal death; Male
	 	Macerated female fetus. No record of autopsy. "Large abdomen & some type of congenital abnormality."	Stillbirth; Female
	 	Pyloric stenosis; inguinal herniorrhaphy; grade II systolic murmur; VSD seen by cardiology, resolved spontaneously in 5 months.	Living; Male
Pyridoxine			
	 	Macerated male fetus (<500 g.).	Spontaneous abortion; Male
	 	Malrotation of GI tract; rectal & anal atresia; a common urachus & bladder; duplication of left ureter; urethral atresia; absence of a uterus & vagina.	Stillbirth; Female
	 	Large thoracic defect; upper abdominal wall defect.	Neonatal death; Female

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Table 4 (cont.)

Drug	Patient No.	Birth Anomaly	Living/Dead; Sex
Dicyclomine/ Pyridoxine			
	[REDACTED]	Bilateral cleft lip and palate. (Summary only; no Form 060575.)	Living; Male
	[REDACTED]	Aplasia of proximal femurs, bilateral; poor to absent femur heads; missing finger, right hand; syndactyly of second and third toes; hyperbilirubinemia from AB/O incompatibility; respiratory distress syndrome due to prematurity.	Living; Male
Doxylamine/ Pyridoxine			
	[REDACTED]	Webbed neck; mongoloid.	Living; Female
Dicyclomine/ Doxylamine/ Pyridoxine			
	[REDACTED]	Absence of left hemidiaphragm with herniation of abdominal contents; hypoplasia of lungs. Scoliosis of thoracic spine.	Died <1 day; Female
	[REDACTED]	"Heart defect."	Living; Female
	[REDACTED]	Possible CNS problem; brachial cleft; pigeon chest.	Living; Female
	[REDACTED]	Bilateral cleft lip and palate.	Living; Female

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Table 4 (cont.)

Drug	Patient No.	Birth Anomaly	Living/Dead; Sex
Placebo			
	[REDACTED]	Abnormality of foreskin of penis.	Living; Male
	[REDACTED]	Grade II systolic murmur; possible PDA, VSD cardiology consult.	Living; Female
	[REDACTED]	Extra digit right hand, excised at birth.	Living; Female
No Maternal Ingestion of Investigational Drug*			
	[REDACTED]	"Baby had <u>possible</u> heart problem." Patient and baby lost to follow-up.	Living; Male
	[REDACTED]	Transposition of great vessels; ventricular septal defect; hypertrophy of right ventricle; ascites; splenomegaly; patent ductus arteriosus.	Neonatal death; Male

*Excluded from text and tables of this report that relate to type of medication taken by mother.

Table 5^a

Comparison of Total Reported No. of Offspring with Birth Anomalies
to Reported No. of Offspring with Limb Deformity
Birth Anomalies According to Type of Maternal Medication

Maternal Medication	Total Number of Offspring with Anomalies	No. of Offspring with Limb Deformities (and description)
Dicyclomine	8	0
Doxylamine	4	0
Dicyclomine/Doxylamine	6 ^a	1 (polydactyly) ^b
Pyridoxine	3	0
Dicyclomine/Pyridoxine	2	1 (multiple extremity deformities) ^c
Doxylamine/Pyridoxine	1	0
Dicyclomine/Doxylamine/ Pyridoxine	4	0
Placebo	3	1 (polydactyly) ^d
Total	31	3

^aData from Table 4.

^b2 of 6 were twins of same pregnancy (Patient No. 121-353).

^cPatient No. 004-015.

^dPatient No. 133-320.

^ePatient No. 005-054.

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