

Bendectin

How a Commonly Used Drug Caused Birth Defects - Part One

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Nausea and occasional vomiting is often one of the first symptoms heralding pregnancy. It is a discomfort women have coped with for millennia. Up to 50% of all pregnant women may experience these symptoms at some time during pregnancy. Although popularly called "morning sickness", the condition may also occur in the evening or throughout the day.

The precise cause of morning sickness is not known. Some experts have attributed the condition to human chorionic gonadotropin and estrogen which is produced in increasing amounts approximately ten days after fertilization of the egg. This does not explain, however, why many women never experience morning sickness or have it in one pregnancy and not another. Additionally, morning sickness may have a kind of protective effect on the unborn, since some studies have shown that the rate of miscarriage in pregnancies with morning sickness is lower than in those where no nausea and/or vomiting occurred.

Morning sickness usually occurs during the first three months of pregnancy, the period of organogenesis, when all the important organs and structures of the baby's body are being formed. It is during this time that the developing embryo is most at risk for external insults that may result in major structural defects.

Until the proliferation of new drugs on the market in the 1950's, morning sickness was usually treated with a pat on the hand and admonitions to eat dry crackers every few hours and avoid fatty, greasy or highly seasoned foods. However, as "a pill for every ill" became a popular credo, morning sickness began to receive attention as an affliction with great marketing potential.

From 1950 to 1960, Dr. Raymond C. Pogge was Director of Medical Research for the Merrell Pharmaceutical Company. In an October 26, 1953 memorandum to the company president, he explored the possibility of a new product specifically designed for nausea and vomiting of pregnancy.

"Between three million and four million pregnancies occur annually in the United States and will continue within that range for some time to come," Dr. Pogge wrote. "About half the pregnant women I used to see in the prenatal clinic, when I was obstetrical resident, complained of enough nausea and vomiting to justify writing a prescription for some safe and probably effective medication."¹

Pogge went on to suggest the development of a delayed release tablet that would allow the patient to take the medicine at bedtime when she was not nauseated. The multi-layered coating on the tablet would slowly dissolve during the night so that the active ingredients could go to work to control symptoms before the patient arose in the morning.

The original formulation of Bendectin contained Bentyl (dicyclomine hydrochloride) an antispasmodic used to control the nausea and vomiting of nervous stomach; Decapryn (doxylamine succinate) an antihistamine that had been used to alleviate nausea following radiation therapy in cancer patients; and pyridoxine (vitamin B-6) which was thought by some physicians to have a beneficial effect on the nausea of pregnancy.²

In 1953 the regulations for marketing a new drug were not as restrictive as they are today. Since both Decapryn and Bentyl were Merrell products that had prior approval for marketing, the individual animal safety studies from these separate ingredients were accepted as proof of Bendectin's relative safety. Additional testing in animals was not required for the three-part combination and no specific studies were made of the drug's effects on the offspring of test animals.^{2a}

Although Bendectin was designed for use specifically in pregnancy, only one clinical study was undertaken prior to marketing. In this study some 277 patients were given samples of Bendectin to evaluate the drug's ability to reduce symptoms of nausea and vomiting. In addition to pregnant women with morning sickness, the study population also included several children and women with motion sickness. There was no follow-up of the pregnant patients to determine any possible adverse affects to their babies.³

Merrell filed a new drug application for Bendectin in June 1956. This NDA was approved by the Food and Drug Administration in just 28 days.

In January 1959, the Merrell Company obtained the exclusive rights to market another drug. Thalidomide had been developed by a West German pharmaceutical company. It was rapidly gaining popularity all over Europe as a "safe" sedative. Thalidomide was also included in some 50 over-the-counter products used for everything from colds and flu to the morning sickness of pregnancy.

Four months after obtaining the license for thalidomide from its German manufacturer, Richardson Merrell began testing the drug by distributing 2,528,412 thalidomide tablets to 1,267 private physicians who gave them to 20,000 patients. At the same time these human studies were underway, the company also began animal testing. Although one of the indications for thalidomide was nausea and vomiting of pregnancy, no specific tests were done to look for possible adverse effects to the developing fetus.⁴

Dr. Frances Kelsey was the medical officer at the Food and Drug Administration who was assigned to review Merrell's New Drug Application for thalidomide. She was not fully satisfied with the data that had been submitted on the drug so she proceeded with the review process very cautiously."

The first reports of problems with thalidomide reached the FDA in 1961. A letter in the British Medical Journal warned of a possible toxic hazard with the new sedative involving peripheral neuritis, a serious nervous disorder, in patients who had received the drug for more than six months. This information was enough for Dr. Kelsey to delay her approval of thalidomide's New Drug Application, a decision that was to save untold thousands of American children from tragedy.⁵

In 1961, another more ominous warning about possible adverse effects of thalidomide had also been made. Dr. William McBride had called the office of the Australian company marketing thalidomide to report his suspicions that the drug might be causing drug-induced malformations in babies. Dr. McBride was an obstetrician-gynecologist who had delivered three infants with limb malformations to patients who had taken thalidomide early in pregnancy.⁶

On the other side of the world in Germany, Professor Widukind Lenz, the head of the children's clinic at Hamburg University was also investigating clusters of phocomelia, a previously rare birth deformity in which limbs are totally absent or grossly shortened to appear like little flippers directly attached to the trunk. Since 1957, the deformity had been appearing with increasing frequency and in 14 cases the mothers reported taking thalidomide during the early part of pregnancy.

Stories of other thalidomide associated birth defects began to appear in reports from Canada (where Merrell was actively marketing the drug), Scotland, Sweden, Belgium, Lebanon, Israel and Peru. On November 26, 1961, thalidomide was withdrawn from the German market. All further consideration of Merrell's application to market the drug in the United States was suspended.

Although thalidomide was never approved for sale in the United States, millions of tablets had been distributed to physicians during the clinical testing program. It was impossible to know how many pregnant women had been given the drug to help alleviate morning sickness or as a sedative.

As the horror of the thalidomide tragedy made headlines around the world, the Food and Drug Administration started making an investigation of its files of adverse reaction reports searching for thalidomide-related deformities.

It was this investigation that was to lead to the first questions about Bendectin's safety.

In a letter dated December 17, 1962, the Director of the FDA's Bureau of Field Administration, A.E. Rayfield wrote to Frederic Lamb, General Counsel for the Wm. S. Merrell Company. His letter affirmed that the thalidomide investigation had turned up four reports to the Food and Drug Administration of infants with birth defects whose mothers had taken Bendectin during pregnancy. These reports included:

Infant born 1/15/61 Missing left thumb and right thumb. Club foot and heart disorders.

Infant born 12/22/60. Absence of left arm, some metatarsus varus of the left leg, left side of face flattened, both hands missing index fingers, bilateral club foot.

Infant born 5/10/62 Nasal bone with no airway. Fibulars missing from both legs, no knee caps or ankle bones, red mark on forehead between eyes.

Infant died 4/10/62 Atresia of extremities, imperforate anus.⁷

Reports of Bendectin associated birth defects were coming in from other parts of the world as well. In an interoffice memo dated September 17, 1963, a Dr. Gerald Morson of Merrell wrote to his associate in Australia regarding two reports of malformations: "... in cases like this, it is hardly possible to be sure one way or the other whether any drug given during the pregnancy was directly or indirectly involved."

In a 1962 report in the American Journal of Obstetrics and Gynecology, Dr. P.M. Dunn reported the cases of four infants who were born with phocomelic limb malformations. In two cases, the mothers had taken thalidomide, but in the third case of twins with phocomelia the mother had taken Debendox, the British name for Bendectin. Dr. Dunn speculated, "... Thalidomide is only one of many new sedative and antiemetic drugs. It may well be that more than one has this teratogenic action."⁹

Dr. Frances Kelsey, who had been instrumental in preventing the sale of thalidomide in the United States, also had concerns about the safety of Bendectin. On November 28, 1962, she wrote a memo to Dr. Ralph G. Smith, Acting Medical Director for Richardson-Merrell.

"During investigation of congenital defects possibly related to thalidomide, at least 4 cases were reported in which the physician stated the mother received Bendectin during pregnancy, but not thalidomide. Two obstetricians using thalidomide widely have also reported on Bendectin (Drs. Nulsen and Woodbull). Although there may be reason to doubt that no thalidomide was used in these cases, I believe they raised a question concerning the safe use of Bendectin in pregnancy."¹⁰

Reports of malformations being associated with Bendectin eventually reached the Medical Letter, a prestigious newsletter for physicians. The publication notified Richardson Merrell that they were planning to investigate the possibility that Bendectin was associated with birth defects."

Merrell responded by informing the Medical Letter that the company was undertaking animal studies and an epidemiological survey to assess Bendectin's safety for the developing fetus.

The "Bunde and Bowles" study was Richardson Merrell's first epidemiological survey to determine whether Bendectin was associated with an increased risk of birth defects. Dr. Carl Bunde, the company's Director of Medical Research devised a technique to survey case records of pregnant patients treated with Bendectin during the first trimester of pregnancy and compare the incidence of congenital abnormalities in this treated group with untreated controls.

Physicians who were known to prescribe Bendectin frequently were contacted. From this group, twenty-one physicians were asked to cooperate in the study. A worker in each office was paid to survey the physician's patient records and to match as many treated patients and controls as possible. A total of 2,218 pairs were matched covering approximately six years.

The published results of the study reported only 11 cases of malformation in the infants of mothers who were treated with Bendectin and 21 cases of malformation in the untreated control population. 12

Although the "Bunde and Bowles" study was cited over the years as proof of Bendectin's safety, it has been severely criticized by many reviewers. Dr. Bernard St. Raymond, a Medical Officer at the Food and Drug Administration reviewing the study wrote the following:

"The results (of this study) would indicate that Bendectin is not teratogenic. However, I believe it would be erroneous to draw such a conclusion from this study ... I feel that this study is of practically no value and could be misleading." 13

Other medical experts who reviewed the raw data for the study discovered that the ingestion of Bendectin could not be confirmed from approximately 369 (1/6) of the cases and that at least one Bendectin exposed newborn listed as "normal" was deformed.¹⁴

The reliability of the data provided by two of the physicians participating in the study was also called into question. If the data from these two investigators were excluded, the "Bunde and Bowles" study changed from a negative to a positive relative risk of 1.8. A risk factor of 1.8 means that a woman taking Bendectin is 80% more likely to have a malformed baby than a woman in the control group who did not take the drug.¹⁵

In addition to the "Bunde and Bowles" study, the Richardson Merrell Company was also performing laboratory tests to determine whether Bendectin could cause birth malformations in the offspring of rabbits. In the first study, all but two rabbits died because of adverse environmental conditions. However, the negative results of this study were released to the company sales force as further proof of Bendectin's safety.

In 1962, Dr. Robert Staples was a young researcher at Richardson Merrell who had been trained as a teratologist. In the aftermath of the thalidomide tragedy, he was studying the teratogenic potential of thalidomide and several other drugs in Dutch-Belted rabbits. One of these drugs was Bendectin.

In a September 11, 1963 memo, Dr. Staples made the following statement regarding the results of the Bendectin studies:

"The sternal changes noted involving shifted ossification centers among kits of Bendectin-treated females by past experience of the laboratory, could point to the possibility of more severe alteration should increased dosages be employed. This is considered of particular importance since this type of change was noted only at the highest dose administered ..."

"These possibilities can be answered only upon further experimentation employing increased dosage. Such experimentation would also provide additional information concerning the biological importance of the abortions seen following Bendectin administration in this study, as well as the significance of the slight increase in the incidence of intrauterine death and resorptions.""

By past experience, Dr. Staples was referring to his laboratory experience with thalidomide. In parallel teratology experiments with thalidomide using DutchBelted rabbits, he had obtained a large number of abnormal young. Skeletal abnormalities induced in the young of the thalidomide-treated rabbits

included club hand and abnormal fusion of sternebrae. These malformations were seen in the kits of rabbits treated with large doses of thalidomide (150 m/p/k/) from day 8 to 16 of pregnancy.

In the Bendectin teratology study, clubbed limbs and sternal malformations were also produced, but at much lower doses than with thalidomide.

Despite Dr. Staples recommendation to repeat the Bendectin teratology study at higher doses, the study was never repeated. The original "Staples Study" was the only animal teratology study ever done with three-part Bendectin.

Years later, researchers reviewing the raw data from the original Staples Study discovered additional unreported malformations in Bendectin treated kits that had been aborted or born dead.

The results of all animal studies assessing the safety of a drug are supposed to be reported immediately to the Food and Drug Administration. However, the Staples Study did not reach the FDA until 1966 and by that time the results had been modified substantially. Notations of clubbed limbs were changed to flexed limbs (a less significant anomaly) and Staples' recommendation for further testing was eliminated from the summary."

One FDA medical officer, Dr. Frances Da Costa testified in 1980 that if she had seen the Staples memorandum when she was reviewing Bendectin in 1968, she would have recommended that marketing should be stopped until further testing could be completed.

In the years since the original Staples Study, both company and government researchers have tested the separate ingredients of Bendectin in various species of pregnant animals. But, no one has ever reported another teratology study with three-component Bendectin, a drug that was given to millions of women for more than twenty years.

It is well known in the scientific community that testing the separate ingredients of a drug is not the same as testing a combination. Drugs have the potential to interact. In Bendectin's case, the antihistamine doxylamine succinate potentiates the effect of the antispasmodic-anticholinergic dicyclornine hydrochloride.

According to Saxon and Rappola's comprehensive text *Congenital Defects*, "if teratogens potentiate each other's effect, their simultaneous use results in a higher incidence of malformations that would be expected from mere summation of their separate effects."¹⁹

There are substantial questions of safety for both of Bendectin's active ingredients, Bentyl (dicyclomine hydrochloride) and Decapryn (doxylamine succinate).

According to court documents, Dr. Raymond Pogge submitted Merrell's New Drug Application for Bentyl to the Food and Drug Administration in 1950. The NDA was not approved, because the FDA had determined that the information provided was incomplete, a legal way of saying that the FDA did not agree that the data submitted proved the drug was safe for commercial distribution.

Instead of conducting additional studies, Dr. Pogge reviewed the existing data, prepared a series of tables and summary paragraphs and resubmitted the same NDA to the FDA. The New Drug Application for Bentyl was approved and marketing of the drug began in 1952. 20

Bentyl is an antispasmodic drug recommended for the treatment of peptic ulcer and for relief of discomfort resulting from muscle spasm of the gastrointestinal tract.

The product information provided by the manufacturer includes a long list of potential adverse reactions including nausea and vomiting. Bentyl also has anticholinergic effects meaning that it can cause reactions similar to atropine. 21

In 1985, a new warning was added to Bentyl's list of adverse effects. In addition to indications for stomach problems and as an ingredient in Bendectin, Bentyl was also marketed as a colic syrup for infants. Reports of severe reactions including respiratory distress, convulsions, coma and even deaths in infants after treatment with Bentyl colic syrup prompted new warnings on dicyclonine containing products.

In a world-wide communique, the company advised, "... Merrell Dow considers it prudent to contraindicate Bentyl syrup in infants under six months of age and to delete the indication of infant colic..." 22

Although the warning about Bentyl colic syrup was sent to physicians and added to the product information, no public announcement was made to warn mothers not to use any of the colic syrup still in their medicine cabinets.

If Bentyl was not safe for babies from birth to six months, how could it be safe for the developing fetus?

Following the thalidomide tragedy in 1962, Congress passed the Kefauver-Harris Amendments which required that all drugs be proven efficacious as well as safe before marketing. As the result of these new Drug Efficacy Study Implementation (DESI) requirements, Merrell had to prove that each ingredient of Bendectin was effective.

As a result of the company's "8-Way Efficacy Study", Merrell removed Bentyl from the Bendectin formulation beginning in 1977. The official position of the company and the Food and Drug Administration was that the Bentyl was removed because it did not contribute to the effectiveness of the combination product.

Internal documents from the FDA, however indicate that Bendectin's safety was also an issue. On October 14, 1976, special assistant to the director of the Bureau of Drugs at FDA wrote: "The consensus of the meeting seemed to be that although the name Bendectin does not connote the presence of Bentyl in the mind of most prescribers, dispensers and patients, as in the case of almost all reformulations of prescription drugs, steps should be taken to inform these individuals that a reformulation has taken place and to minimize confusion. These steps should include a 'Dear

Doctor/Dear Pharmacist' letter, some indication on the label to remind the pharmacist of the reformulation, and a retrieval of stocks of Bendectin containing Bentyl in the same manner in which other reformulated DESI drugs have been handled.

Concern was expressed by Compliance that the approval of the improved, safer product should not be unnecessarily delayed for labeling purposes."²³

There were questions about Bentyl's safety in the Bendectin combination from other parts of the world as well.

Dr. T. Da Silva, Chief of the Central Nervous System Division at the Canadian Food and Drug Directorate sent this urgent letter to Dr. T.B. O'Dell, Director of Drug Regulatory Affairs at Merrell:

"We have noted that only a summary of the findings of the additional studies which were conducted to determine the efficacy and safety of Bendectin were provided in the data which we received on June 10, 1977."

"However, in view of the findings in these studies which question the contribution of some of the ingredients of Bendectin towards efficacy and safety of this product, we hereby request your cooperation in filing Supplemental New Drug Submission for Bendectin with a view to reformulating as urgently as possible, the product available on the Canadian market. "²¹

In an RCA Global communication a Merrell official in Sydney wired the company's New York office ...

TRIBIANO UNOFFICIAL DISCUSSIONS HEALTH DEPARTMENT INDICATES REPORT OF POSSIBLE TERATOGENIC PROBLEMS WITH DICYCLOMINE IN DEBENDOX STOP INFORMATION APPARENTLY SUPPLIED BY NON COMPETITIVE PHARMACEUTICAL OVERSEAS REPRESENTATIVES DURING RECENT AUSTRALIA VISIT STOP I SUSPECT MOTIVE BUT MUST CHECK WHETHER ANY DRUG SUSPICION EXISTS STOP WOULD YOU PLEASE INFORM ME FULL DETAILS IF ANY AVAILABLE MORGAN 25

A query about the safety of dicyclomine to the World Health Organization brought this response from Dr. J.F. Bertaux, Medical Officer, "... a number of case reports have been published in the literature postulating a possible causal relationship between the use of dicycloverine (another name for dicyclomine) during pregnancy and congenital malformations."²⁶

In the "8-Way Efficacy Study", the efficacy of each of Bendectin's ingredients alone and in combination was compared to placebo. The study was also analyzed to evaluate the safety of each of these single or combination ingredients for the developing baby. In a Retrospective Survey of Outcome of Pregnancy of Patients Enrolled in Bendectin Efficacy Studies, each pregnancy was followed through to the birth of the child. Twice as many malformations were reported in the infants of mothers who took dicyclomine alone as those who took doxylamine, pyridoxine or placebo alone .²⁷

As a result of these studies, Merrell removed Bentyll from the Bendectin formulation. Following a large meeting at the Food and Drug Administration on October 15, 1976, it was decided that "a type 2 NAS/NRC recall of the old formulation product should be undertaken."²⁸ Despite the decisions made at this meeting, no recall of three-part Bendectin was ever made. Since the product had a shelf life of up to five years, it is possible that women in the United States received Bendectin containing Bentyll as late as 1982.

FOOTNOTES

1. Memorandum (Oct. 26, 1953), Dr. Raymond Pogge to Merrell President Frank Getman.
2. Deposition of Dr. Raymond Pogge (July 26, 1976), *Mekdeci vs. Merrell National Laboratories*, case #77-255 Ore-Civ-Y, pp. 19-22.
3. *Ibid*, pp. 50-51.
4. *Ibid*, p. 42, pp. 50-51.
5. The Insight Team of the Sunday Times, *Suffer the Children: The Story of Thalidomide* (London; Andre Deutch, 1979), pg. 70.
6. *Ibid*, p. 74.
7. *Ibid*, pg. 76.
8. *Ibid*, pp. 86-88.
9. 7. Letter (Dec. 17, 1962), A.E. Rayfield, Director, Bureau of Field Administration FDA to Frederic D. Lamb, Wm. S. Merrell Company.
10. Interoffice Memo (Sept. 17, 1963), Dr. Gerald Morson (Merrell) to associate in Australia.
11. Dunn, P.M. et al, *Phocomelia*, *Am. J. Obst. & Gynec.*, Aug. 1, 1962, pp. 352-353.
12. Memorandum (Nov. 28, 1962), Frances O. Kelsey, M.D., Division of New Drugs FDA to Ralph G. Smith, M.D., Acting Medical Director, Richardson Merrell.
13. Personal communication from Alan T. Eaton, Esq.
14. Bunde, Carl A.; Bowles, D.M., "A Technique for Controlled Survey of Case Records", *Current Therapeutic Research*, Vol. 5, No. 5, May 1963, pp. 245-248.
15. FDA Review (May 19, 1967), Bernard St. Raymond, M.D., FDA Medical Officer.
16. Manard, Barbara Ph.D., "Does Bendectin Cause Diaphragmatic Hernia in Humans?", *Bendectin and Congenital Diaphragmatic Hernia: An Overview of the Evidence and the Issues*, presented: April 8, 1982 to the Office of the Surgeon General of the United States, p. 1.
17. Appeal from the Superior Court of the District of Columbia (Civil Division) No. 83-1055, *Mary Virginia Oxendine vs. Richardson Merrell*, pg. 15.
18. Interdepartment Memo (Sept. 11, 1963), R.E. Staples to D.E. Holtkamp (Richardson Merrell) p. 2.
19. FDA Summary Animal Reproduction & Teratology Tests for Bendectin and to Component Parts, (Mar. 28, 1966).
20. Hartsborn, E.A. Ph.D., *Handbook of Drug Interactions*, 1973, "Classes of Drugs and Their Interactions", pg. 21; *Bendectin Product Information* (7-30-56).
21. Saxen, L.; Rapola, J., *Congenital Defects*, Holt, Rinehard and Winston, Inc 1969, p. 188.

22. Deposition of Dr. Raymond Pogge (July 26, 1976) Mekdeci vs. Merrell National Laboratories, case #77-255 Ore-Civ-Y, pp. 12-13.
23. Physicians Desk Reference, 1983, Medical Economics Co., pp. 1346-1347.
24. Dear Doctor Letter (April 1985), Phillip M. Altman, Ph.D. Director, Medical Services Merrell Dow, Australia/ New Zealand.
25. Memo to Division of Neuropharmacological Drug Products (HFD-120) Oct. 14, 1976, James C. Morrison, Special Assistant for the Director FDA Bureau of Drugs.
26. Letter (July 25, 1977), T. Da Silva, M.D., Chief Central Nervous System Division Bureau of Drugs, Canadian Food and Drug Directorate to T.B. O'Dell M.D., Director Drug Regulatory Affairs, Merrell National Laboratories.
27. RCA Global Communication.
28. Letter (Mar. 1, 1979), J.F. Bertaux, M.D., Medical Offices Pharmaceuticals, World Health Organization to Betty Mekdeci.
29. Retrospective Survey of Outcome of Pregnancy of Patients Enrolled in Bendectin Efficacy Studies - Final Report - Dicyclomine/Doxylamine (IND-7620), Sept. 30, 1977.
30. Bendectin Chronology (Oct. 15, 1976); Summary of phone call from Roger Gregorio, FDA to T.B. O'Dell, Richardson Merrell regarding meeting of Oct. 15, 1976.