

Safety and Efficacy of Doxylamine Succinate 10mg with Pyridoxine Hydrochloride 10gs (Diclectin) for Nausea and Vomiting of Pregnancy (N.V.P)

1. Careful questioning of the patient, early in pregnancy, about the frequency and intensity of the symptoms of nausea and vomiting allows the practitioner to intervene with diet and lifestyle adjustments, as well as medication with the aim of preventing hyperemesis gravidarum.

Doxylamine Succinate 10mg, in combination with Pyridoxine Hcl 10mg (Diclectin), were approved for use in the treatment of nausea and vomiting in pregnancy by the Health Protection Branch of Health and Welfare Canada in 1990. To date, this formulation is the only anti-nauseant approved for such use. Bendectin (Diclectin) which was withdrawn from the market in 1983 in the USA after several unsuccessful lawsuits against it. Despite the most vigorous testing of any drug in pregnancy, no evidence of teratogenicity has been found.

Multiple studies have reviewed Debendox (Bendectin, Diclectin) and concluded that the drug is a safe effective treatment for nausea and vomiting of pregnancy and that there is no evidence that it is a teratogen.

Doxylamine Succinate in combination with Pyridoxine Hcl 10mg (Diclectin) is a delayed release tablet. It is recommended that they start with two tablets at night before bed. If symptoms are not relieved, one tablet in the morning and another mid-afternoon can be added. The dosing regime can be tailored to fit each woman's peak of symptoms. It is recommended that all health professionals should question women early in their pregnancies about the presence of these symptoms, and offer intervention, with advice about diet, lifestyle adjustment and medical treatment.

- Ref 1.** CADDICK R, COLLITON I E, DUSHINSKI B, EZZAT A, GAGNE G-P, MacKINNON C J, SCHUURMANS N, de la RONDE S.
Guidelines for the management of nausea and vomiting in pregnancy. Society of Obstetricians and Gynaecologists of Canada (SOGC).
Clinical Practical Guidelines 1995; 12:1-4.

2. THE MANAGEMENT OF NAUSEA AND VOMITING OF PREGNANCY

Recommendations

1. Dietary and lifestyle changes should be liberally encouraged and women should be counselled to eat whatever appeals to them.
2. Alternative therapies such as ginger supplementation, acupuncture and acupressure, may be beneficial.
3. A doxylamine/pyridoxine combination should be the standard of care, since it has the greatest evidence to support its efficacy and safety.
4. H1 receptor antagonists (certain other antihistamines) should be considered in the management of acute or breakthrough episodes of NVP.
5. Pyridoxine monotherapy supplementation may be considered as an adjuvant measure.
6. Phenothiazines are safe and effective for severe NVP.
7. Metoclopramide is safe to be used for management of NVP, although evidence for efficacy is more limited.
8. Corticosteroids should be avoided during the first trimester because of possible increased risk of oral clefting and should be restricted to refractory cases.
9. When NVP is refractory to initial pharmacotherapy, investigation of other potential causes should be undertaken.

Ref 2. ARSENAULT M-Y, LANE C A. Principal Authors for Clinical Practice Obstetrics Committee and approved by Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.
The Management of Nausea and Vomiting of Pregnancy.
J Obstet Gynaecol Can. 2002; 24 (10): 817-23.

3. The American College of Obstetricians and Gynecologists (ACOG) have issued guidance to Physicians for diagnosing and treating nausea and vomiting (or 'morning sickness') in pregnancy. The new ACOG Practice Bulletin (Nausea and Vomiting of Pregnancy) reviews the prevalence, risk factors and clinical recommendations in treating morning sickness. Whilst the cause of morning sickness is unknown, today there are effective treatments to prevent and treat the problem.

Morning sickness typically begins within the first nine weeks of pregnancy with symptoms ranging from mild to severe. Severe morning sickness (hyperemesis gravidarum) occurs in approximately 0.5-2% of pregnancies. It is the most common indication for hospitalization during early pregnancy and second only to pre-term labour as the most common reason for hospitalization during pregnancy.

Some women do not seek treatment for morning sickness because of concerns about treatment safety. Yet, once symptoms progress, treatment can become more difficult. Mild cases may be resolved with lifestyle and dietary changes, and safe and effective treatments are available for more severe cases.

The following recommendations for the prevention and treatment of nausea and vomiting of pregnancy are based on consistent scientific evidence:

- Taking a multivitamin at the time of conception may decrease the severity of symptoms.
- Taking Vitamin B6 or Vitamin B6 plus doxylamine (an antihistamine) is safe and effective and should be considered a first-line treatment.

The following recommendations are based on limited or inconsistent scientific treatment:

- Ginger has shown beneficial effects and can be considered a non-pharmacological option.
- Antihistamine H1 receptor blockers, phenothiazines and benzamines have been shown to be safe and effective in treating refractory cases.
- Early treatment of symptoms is recommended to prevent progression to hyperemesis gravidarum.
- Treatment with methylprednisolone (a steroid) may be effective in severe cases, but should be a treatment of last resort due to its potential risk to the fetus.

Ref 3. The American College of Obstetricians and Gynecologists (ACOG) news release March 29th 2004. ACOG Office of Communications (202) 484-3321. ACOG Issues Guidance on Treatment of Morning Sickness During Pregnancy.

4. Question. How effective are different treatments for nausea and vomiting in early pregnancy?

Conclusions. Anti-emetic drugs are the most effective interventions for reducing nausea and vomiting in early pregnancy. Insufficient evidence exists to support

the effectiveness of pericardium 6 acupressure. None of the treatments for hyperemesis gravidarum that have been tested shows any benefit.

Doxylamine and vitamin B-6 are among the few medications classified as 'risk factor A' drugs (i.e. controlled studies in women fail to show risk to the fetus in the first trimester, no evidence exists for risk in later trimesters and the possibility of fetal harm remains remote). Because no credible evidence of human or animal teratogenesis or other undesirable effects existed, a Canadian company began to make a generic form of doxylamine - pyridoxine (Diclectin) in 1984. Thus, the pharmacological equivalent to Bendectin has been available to the benefit of pregnant women, at least in Canada, since shortly after the original formulation was withdrawn.

Ref 4. JEWELL D, YOUNG G. Interventions for nausea and vomiting in early pregnancy. *Cochrane Database Syst. Rev* 2002 (1) CD000145 (latest version 15 Jan 2001).

5. Bendectin was first marketed in the US in 1956 and in the UK in 1958 and the company estimates that the drug was used in 33 million pregnancies by 1983. By 1980 10 to 25% of pregnancies in the US were being exposed to Bendectin. On June 9th 1983, Bendectin was voluntarily withdrawn from the market by Merrell Dow Pharmaceuticals Inc. At the time, the company faced 327 pending US product liability suits and insurance premiums were increasing to the point at which manufacture of the drug was unprofitable. Eventually all law suits which went to court were dismissed.

The Canadian hospital discharges for excessive vomiting in pregnancy (ICD-9 643). Both separations per thousand births and days in hospital per thousand births show a sudden increase after 1982. Figure 1 highlights that ratio of hospital separations for excessive vomiting in pregnancy over live births in Canada for the years 1979 to 1989 and compares these ratios with the amounts of Bendectin and Diclectin sold in the same year. The hospitalization ratios for excessive vomiting show a considerable jump coinciding with a drop in Bendectin sales. The total number of days of hospitalization for diagnosis ICD-9 643 increased from just under 20,000 days each year, for the years 1980 - 1982 to 31,295 days in 1984, which is a 50% increase.

The scientific evidence points towards a lack of teratogenic effect of Bendectin. Table III presents the Canadian rates of congenital malformations per live births. There is no indication of sudden decline in the rates of congenital malformation after 1983.

Similar US statistics have been presented in an unpublished report by LAMM produced for a US court case. Again, no evidence of a change in congenital malformations was shown after the decrease in use and withdrawal of Bendectin.

- Ref 5.** NEUTEL C I, JOHANSEN H L. Measuring Drug Effectiveness by Default: The Case of Bendectin. Canadian Journal of Public Health 1995; 86 (1) 66-70.
6. We have conducted a meta-analysis of the thirty years of Bendectin data and birth defects through 1993 and have found that the set of risk estimates indicate neither an increase nor a decrease in birth defects risk, following the first trimester use of Bendectin. The odds ratio of 0.95 with an upper confidence limit of 1.04 provides a very great level of assurance (the meta-analysis included 16 cohort studies and 11 case control studies. No study has shown a statistically significant association). These studies, as a group, showed no difference in the risk of birth defects between infants whose mothers had taken Bendectin during the first trimester of pregnancy and those infants whose mothers had not.
- Ref 6.** McKEIGUE PM, LAMM SH, LINN S, KUTCHER JS. Bendectin and Birth Defects: 1. A Meta-analysis of the Epidemiological Studies. Teratol 1994; 50: 27-37.
7. Bendectin, until its removal from the market in 1983, was the only anti-emetic approved in the USA for nausea and vomiting in pregnancy. Its removal was a direct consequence of negative publicity and financial concerns about litigation and increased insurance premiums. A number of epidemiological studies concluded that Bendectin was not associated with an increased risk of birth defects and were unable to demonstrate a homogenous pattern of defects in offspring exposed to the product in utero.
- Ref 7.** EINARSON T R, LEEDER J S, KOREN G. A Method for Meta-analysis of Epidemiological Studies. Drug Intell Clin Pharm 1988; 22: 813-24.
8. Bendectin was introduced in the United States in 1956 by Merrell Dow Pharmaceuticals as a tri-ingredient product; doxylamine succinate, an antihistamine, dicyclomine hydrochloride, an antispasmodic agent and pyridoxine hydrochloride (vitamin B6) to prevent possible deficits during pregnancy and to synergize the anti-nauseant activity (10). Dicyclomine hydrochloride was dropped from the formulation in 1976 based on results of randomized control trials, comparing each component alone and in combination versus placebo (10). In 1978 the drug Diclectin ® doxylamine and pyridoxine was licensed for use in Canada by a company in Quebec called Duchesnay Incorporated.

Ref 10 for this article is; LEEDER J S, SPEILBERG S P. Teratogenicity and Litigation In: KOREN G ed. Maternal-fetal toxicology; a clinician's guide. New York: Marcel Dekker Inc. 1990: 415-25.

In all pregnancies there is a baseline risk of 1 to 3% of having a baby with a major congenital abnormality. It was estimated that more than 30 million infants were exposed to Bendectin by the time of its removal from the market. With a background malformation rate of 3%, chance alone would account for 900,000 infants born with major defects. Brent pointed out '...the general consensus among teratologists is that Bendectin is one of the best studied drugs of all time for use in pregnancy and the great preponderance of evidence generally exonerates it from any harmful effects. (8)

Ref 8. Editorial. Bendectin/Diclectin for morning sickness; A Canadian follow up of an American Tragedy.
Reprod Toxicol. 1995; 9 (1): 1-6.

9. Diclectin is chemically and pharmaceutically identical to Bendectin. Because it is extremely unlikely that any other drug used to treat NVP will ever be the subject of as many safety studies in pregnancy as Bendectin or Diclectin, it is unlikely that other agents will ever have the same statistical power to discount a potential teratogenic effect.

Several reports have suggested that women with hyperemesis gravidarum (HG) have a vitamin B6 deficiency. Gant H et al (12) proposed that a possible explanation is the increased need for the coenzyme pyridoxal 5 phosphate due to a pregnancy-induced increase in protein metabolism.

Four clinical trials of Debendox=Bendectin. Double-blind placebo controlled with Bendectin 109 patients. Favourable response to Bendectin 94% compared with that of placebo 65% $P<0.001$. 52 patients who received Bendectin 23 had complete relief from nausea. Another double-blind placebo controlled trial, 41 patients received Debendox or placebo. There was an improvement in severity of NVP in 70.7% of the group receiving Debendox, compared to 50.5% in the placebo group ($P<0.05$). (9)

In another randomized double-blind trial by Wheatley (30). Debendox plus 10mg extra of pyridoxine or placebo plus 10mg pyridoxine was given to 57 pregnant women in crossover design. Differences in the severity of nausea were statistically significant ($P<0.001$) when treatment with placebo in the first week was changed to Debendox in the second week. This result was achieved despite that the group treated first with placebo contained relatively higher proportions of mild cases. The severity of retching ($P<0.001$) and vomiting ($P<0.02$) showed a similar pattern.

Another study in 1975 evaluated the efficiency of all components of Bendectin including pyridoxine alone and in various possible combinations compared to placebo in more than 2300 women with NVP. The study confirmed that the efficacy of Bendectin was greater than that of placebo but showed no contribution from dicyclomine, in the association. Doxylamine was the major component, but pyridoxine had a clear effect on nausea but probably not vomiting. (31)

The first prospective post-marketing study on the efficacy of Diclectin. The first interview took place after the onset of symptoms, generally at six to eight weeks. A second evaluation took place at 20 weeks. During the first follow-up 106 patients, 71% reported an improvement in their NVP symptoms temporally, due to Diclectin use. 34 patients (23%) did not report improvement and 2 patients (1%) reported worsening of their symptoms. By 20 weeks gestation, an additional 25 of the original cohort of patients started Diclectin therapy; 21 patients (84%) reported improvement, 3 patients (12%) reported no change and 1 patient (4%) experienced a worsening of symptoms. These results are strikingly similar to those reported in the double-blind trial above, suggesting that Diclectin does not lose efficacy over time in the 'real world' compared with one week of use in tightly controlled trials. It also showed that 11 women who increased their dosage before 20 weeks all reported better NVP. (9)

Ref 9. BASHAI R, MAZZOTTA P, ANTANACKOVIC G, LEVICHEK Z, POLE M, MAGEE LA, KOREN G.
Critical Appraisal of Drug Therapy for Nausea and Vomiting of Pregnancy. II Efficacy and Safety of Diclectin (doxylamine - B6)
Can. J Clin Pharmacol 2000; 7 (3): 138-143

Ref 12 in this article.

GANT H, Reinken L, DAPUNT O, SCHOLZ K.
Vitamin B6 depletion in women with hyperemesis gravidarum.
Wien Klin Wochenschr 1975;87;510-3.

Ref 31 in this article.

Bendectin Peer Review Report 1975. Overall Summary of 8-way Bendectin Study (unpublished study from the FDA databank-DESI 10598).

- 10.** The Food and Drug Administration (F.D.A) has determined that the drug product Bendectin, a tablet composed of pyridoxine hydrochloride 10mg and doxylamine 10mg for the prevention of nausea during pregnancy was not withdrawn for reasons of safety or effectiveness. (10)

Ref 10. Department of Health and Human Services.
Food and Drug Administration - Federal Register 9th August 1999
Volume 64, number 152, page 1-3.

- 11.** Bendectin was withdrawn from the market by its manufacturer which left millions of pregnant women without an approved drug by the food and drug administration (FDA) for the treatment of nausea and vomiting of pregnancy. The rate of

hospitalization for severe NVP increased by a factor of two in both the USA and Canada after Bendectin was withdrawn from the market.

The withdrawal of the drug from the American market did not decrease the rate of any specific category of malformation as would be expected from a truly teratogenic drug estimated to have been used by up to 40% of pregnant women at one time. In Canada, the drug continues to be marketed under the trade name Diclectin. A review committee has advised the Canadian Minister of Health that the drug is safe. Other formulations of doxylamine, in combination with pyridoxine, are available in other countries e.g. South Africa, Spain and Thailand.

Ref 11. KOREN G, PASTUSZAK A, ITO S
Drug Therapy: Drugs in Pregnancy
The New England Journal of Medicine 1998; 338 (16) 1128-1137

This article also has a table of drugs with proven teratogenic effects Table 1, page 1129, in humans.

12. Earlier this month in the United States the manufacturers of Debendox/Bendectin reached agreement with the parents of children with deformities, who had brought court actions on the grounds that the defects had been caused by prescription of the drug for morning sickness. The makers did so, apparently, because to fight might have cost more than to settle and a proviso was that the parents should drop all claims that the drug caused the defect. The Merrell-Dow Settlement does not automatically apply to the United Kingdom and the Debendox Action Group is understandably upset, especially since they lack the funds to mount the sort of legal campaign that U.S. parents did, and in British courts, they would have to prove duty of care, cause and effect and negligence.

It is easy to produce for the television cameras, children with limb or other deformities, whose mothers, as it happened, took Debendox when pregnant, and the emotional impact of this has proved too much for some commentators. But the facts are not there. Debendox is not another thalidomide.

When production of the drug was reluctantly halted in June 1983, after twenty-seven years, Merrell estimated that it had been used in 33 million pregnancies - ample basis for epidemiological studies of cause and effect. In any scientific sense, Debendox is not a proven human teratogen (four refs).

The UK product licence remains in force, and in 1981 the Committee of Safety of Medicines (C.S.M.) confirmed that there is no scientific evidence that Debendox causes harm to the foetus (ref 1). The timing of administration has complicated some studies and the picture in recent years has become confused by reformulations, dicyclomine being removed, and by changes in prescription status. However, the CSM's verdict is the only reasonable one on current

evidence. Compensation for all neonatal handicap, as a matter of public policy, is an entirely different issue.

Ref 12. Editorial Debendox is not Thalidomide.
The Lancet 1984 July 28th 205-206.

- 13.** Women suffering from morning sickness, which is not controlled by non-pharmacological methods can safely use H1 receptor antagonist antihistamines. Twenty-four controlled studies met the inclusion criteria with more than 200,000 participating women. The summary odds ratio of major malformations associated with antihistamines taken during the first trimester was 0.76 (95% ci:0.60-0.94).
(13)

Ref 13. SETO A, EINARSON T, KOREN G.
Pregnancy outcome following first trimester exposure to antihistamines a meta-analysis.
AM J PERINATOL 1997; 14(3): 119-124.