

# Critical appraisal of drug therapy for nausea and vomiting of pregnancy: II. Efficacy and safety of Diclectin (doxylamine-B6)

Key Words: *Doxylamine; Morning sickness; Nausea; Nausea and vomiting of pregnancy; Pregnancy; Pyridoxine; Vomiting*

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R Bishai, P Mazzotta, G Atanackovic, Z Levichuk, M Pole, LA Magee, G Koren. 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. Nausea and vomiting of pregnancy is the most common condition in pregnancy and affects up to 80% of all pregnant women. There are a large number of pharmacological agents that are effective for the treatment of nausea and vomiting associated with conditions such as motion sickness and gastrointestinal conditions; however, their use in pregnancy is limited by the lack of sufficient data on their potential teratogenic effects. The efficacy of the delayed-release combination of doxylamine and pyridoxine (Bendectin, Diclectin) has been shown in several randomized, controlled trials. The present review aims to refute the unsubstantiated beliefs that Diclectin is unsafe when used in the treatment of nausea and vomiting of pregnancy.

**Évaluation cruciale de la pharmacothérapie pour les nausées et les vomissements gravidiques : 2 partie; l'efficacité et l'innocuité de Diclectin (doxylamine-B6) contre les nausées matinales de la grossesse**

**RÉSUMÉ :** Les nausées et les vomissements constituent le trouble le plus fréquent de la grossesse et touchent jusqu'à 80 % des femmes. Il existe un large éventail de médicaments qui sont efficaces contre les nausées et les vomissements associés à certains troubles comme le mal des transports et les affections gastro-intestinales; cependant, leur utilisation durant la grossesse est limitée étant donné qu'on ne dispose pas suffisamment de données sur leur effet tératogène potentiel. L'efficacité des médicaments retard associant la doxylamine et la pyridoxine (Bendectin, Diclectin) a été démontrée dans plusieurs essais comparatifs avec hasardisation. Le présent examen vise à réfuter les croyances non fondées selon lesquelles Diclectin présente des risques pour le traitement des nausées et des vomissements de la grossesse.

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Nausea and vomiting of pregnancy (NVP) affects up to 80% of all pregnant women (1). Although in the majority of cases the symptoms are worse in the morning and subside by 12 weeks' gestation, some women are affected by these symptoms throughout

the day, and in some cases the condition may continue beyond the first trimester of pregnancy (2).

There are a large number of pharmacological agents that are effective for the treatment of nausea and vomiting associated

with motion sickness and gastrointestinal conditions, or induced by cancer chemotherapy; however, their use in pregnancy is limited by the lack of sufficient data on their potential teratogenic effects.

Only the combination of doxylamine and vitamin B6 (Diclectin; Duchesnay Inc, Canada) has proved to be effective and safe based on large cohort and case-control studies. This combination was known in the United States as Bendectin (Merrell Dow Pharmaceuticals, USA) and is available in Canada as Diclectin, a delayed-release formula.

In the United States, Bendectin was first introduced in 1956 by Merrell Dow Pharmaceuticals. It was the most frequently prescribed antiemetic drug for the treatment of NVP from 1956 to 1983. According to several studies, up to 40% of pregnant women took the drug during their first trimester in the late 1970s and 1980s (3). However, due to unsubstantiated fears created by misinformation and misperceptions, most women who presently suffer from NVP cannot benefit from Bendectin.

Since Bendectin was removed from the American market in 1983, the rate of hospitalization of pregnant women for severe NVP has almost doubled (4), demonstrating the risks associated with the loss of benefits of pharmacotherapy in pregnancy.

Because the drug has been off the American market for 16 years, a whole generation of physicians and patients has been led to believe that there is no safe and effective therapy for NVP.

In 1975, Diclectin was licensed for the treatment of NVP in Canada by Duchesnay Inc. Diclectin is chemically and pharmaceutically identical to Bendectin. Diclectin is a delayed-release tablet, so a woman who takes the drug before sleep will receive optimal antiemetic effects in the morning, when the symptoms of NVP are typically at their peak.

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. The present review aims to refute the unsubstantiated belief that Bendectin/Diclectin is unsafe by critically analyzing the available data on the safety and efficacy of Diclectin for NVP.

## **NVP**

NVP was first documented in an Egyptian papyrus dated 2000 BC (5). The term 'NVP' denotes the whole range of the clinical condition, from mild nausea to severe and frequent vomiting and retching. The term 'hyperemesis gravidarum' describes the severe end of the spectrum, and is associated with dehydration, electrolyte imbalance, ketonuria and weight loss.

## **ETIOLOGY**

NVP is the most common condition in pregnancy; however, its etiology is obscure, with several hypotheses being proposed.

## **Endocrine etiologies**

Because the incidence of hyperemesis is higher in multiple gestations and in molar disease, a relation to the concentration of human chorionic gonadotropin (hCG) has been postulated (6). Further evidence for this relation is that the time during which hCG levels are highest (six to 12 weeks after the last menstrual period) coincides with the time when hyperemesis is most common. Women who suffer from NVP, on average, have heavier placentae, which further supports a hormonal cause (7). However, measurements of serum and urine hCG concentrations in women with hyperemesis gravidarum have yielded conflicting results (8). Serum concentrations of maternal adrenocorticotrophic hormone, cortisol, estrogen, progesterone, follicle stimulating hormone, thyroid stimulating hormone, growth hormone and prolactin did not show consistent differences between patients with NVP and those without.

Measurements of serum thyroxine in women with hyperemesis are also inconsistent. Transient biochemical evidence of thyrotoxicosis has been shown in about one of three patients with hyperemesis gravidarum. Several study results showed increased concentrations of free thyroxine and impaired thyroid stimulating hormone response to thyrotropin releasing hormone in patients with hyperemesis upon admission to the hospital. The free thyroxine concentrations normalized when the pregnant patients improved, and remained normal in the postpartum period. The significance of this observation in the cause or effect of the condition remains unresolved. The transient nature of the disturbed thyroid function tests should be recognized before thyrotoxicosis is diagnosed and treated in a patient with hyperemesis gravidarum (6).

## **Psychological factors**

Farkas and Farkas (9) stated in 1972 that hyperemesis gravidarum represented "a protest reaction against pregnancy as a result of physical conflicts, especially from familial and home environment."

In 1988, Iatrakis et al (10) linked NVP with unsuitable diets, poor communication between the patient and her partner and/or obstetrician, stress, doubts and inadequate information about pregnancy. None of the above theories has been proved using acceptable methods of epidemiology; however, they have led to tremendous shame and guilt among women, and have helped to perpetuate folkloristic beliefs that place the blame for the condition on the mother. Our clinical experience suggests that this approach is often used as an excuse for delayed pharmacotherapy in women suffering from NVP.

## **Vitamin B6 deficiency**

Several reports have suggested that women with hyperemesis gravidarum have a vitamin B6 deficiency (11). Gant et al (12) proposed that a possible explanation is the increased need for the coenzyme pyridoxal phosphate due to a pregnancy-induced increase in protein metabolism.

### Gastric dysrhythmias

Koch et al (13) showed, for the first time, that gastric dysrhythmias are present in patients with NVP. The intensity of the nausea was significantly greater in pregnant women with gastric dysrhythmias than in pregnant women who presented with normal electrogastrogram patterns. However, these observations cannot prove a cause and effect relationship.

### CLINICAL PHARMACOKINETICS OF DICLECTIN

Originally, Bendectin contained doxylamine succinate (10 mg), vitamin B6 (10 mg) and dicyclomine hydrochloride (10 mg). Results of studies, required by the United States Food and Drug Administration in the early 1970s, failed to show an additive effect of dicyclomine, and this constituent was removed in 1976.

Because the two constituent compounds in Diclectin are very different, their pharmacological characteristics are discussed separately.

#### Doxylamine succinate

Doxylamine succinate is structurally related to histamine and antagonizes the effects of histamine on H<sub>1</sub> receptor sites. It is an ethanolamine, a class of first generation antihistamines. The drugs in this group have substantial antimuscarinic activity, but are associated with few gastrointestinal side effects (14).

Doxylamine succinate has antiemetic and antiallergic effects. Its sedative effects are believed to be due to its ability to cross the blood-brain barrier and to its high affinity for H<sub>1</sub> receptors in the brain (15). If taken in large doses, doxylamine succinate may cause anticholinergic effects, as seen with any other H<sub>1</sub> blocker.

Similar to other H<sub>1</sub> antagonists, doxylamine succinate is well absorbed from the gastrointestinal tract.

After oral administration of doxylamine succinate, peak plasma concentrations are typically achieved within 2 to 3 h (this is different with the delayed-release form, as in Diclectin), and the therapeutic effects usually last for 4 to 6 h (14). Doxylamine is biotransformed in the liver by *N*-dealkylation to its principle metabolites *N*-desmethyl and *N,N*-didesmethyldoxylamine, which are excreted by the kidney (16,17).

Few studies have examined the pharmacokinetic effects of doxylamine succinate in female patients. Twelve young, healthy, female volunteers, who served as a control group in two studies published in 1989, were given a single oral dose of doxylamine succinate 25 mg (18,19). Mean peak plasma concentration was 103±8 µg/mL, and was reached 2.4±0.4 h after ingestion. The half-life was 10.1±1.1 h and the apparent clearance was 3 s±0.4 mL/min/kg. These findings were similar to those found in a previously published study of 16 healthy male volunteers (20).

Although pharmacokinetic studies of pregnant women are not available, one study investigated the effects of the drug in pregnant primates (21). The objectives of the study were to evaluate whether any significant differences in the pharmacokinetics of doxylamine exist among baboons, cyno-

molgus monkeys and rhesus monkeys; whether the pharmacokinetics of doxylamine are altered by pregnancy in comparison with previously published data on pharmacokinetic effects of doxylamine in nonpregnant rhesus monkeys; and whether multiple dose administration of doxylamine results in alterations of doxylamine pharmacokinetics (22). The dosage used in this study (7 mg/kg/day) was 10 times the maximum human dosage and was administered from days 22 to 50 of pregnancy.

The results showed that the pharmacokinetic effects of doxylamine do not significantly differ among baboons, cynomolgus monkeys and rhesus monkeys. Comparison of these early pregnancy pharmacokinetic values with those recorded in the nonpregnant rhesus monkey showed no significant changes in the disposition of doxylamine as a consequence of early pregnancy. The pharmacokinetic effects of doxylamine after multiple doses had been administered (day 50) did not differ significantly from those documented with the administration of a single dose of doxylamine on day 22.

These observations are of substantial importance and indicate that during the first trimester of pregnancy, the major changes in distribution volume, protein binding and clearance rate, seen later in pregnancy, have not yet occurred with many drugs. Although one should be careful not to overinterpret from doxylamine to other drugs, these findings suggest that pharmacokinetic studies in fecund, nonpregnant women may reflect the disposition characteristics during the first trimester.

#### Pyridoxine hydrochloride

Pyridoxine, pyridoxal and pyridoxamine are related natural compounds with the same biological properties and, thus, all are collectively known as vitamin B6 (15). In pharmaceutical preparations, vitamin B6 is generally used as pyridoxine hydrochloride (23). In vivo, it is converted to pyridoxal 5'-phosphate. As a coenzyme, it is active in over 100 known metabolic reactions of diverse compounds, including amino acids, nucleic acids, unsaturated fatty acids, carbohydrates, glycogen, neurotransmitters and porphyrin (24).

As pyridoxine requirements increase during pregnancy, its use as an ingredient of Diclectin constitutes a supplement of vitamin B6 that can prevent potential pyridoxine deficiency.

Pyridoxine is readily absorbed in the gastrointestinal tract, mainly in the jejunum (15). The absorption is not affected by aging but may be impaired in alcoholic patients (23). Pyridoxine is primarily metabolized in the liver; following phosphorylation, its main active metabolite, pyridoxal 5'-phosphate, is released into the circulation and is highly protein bound. The major metabolite 4-pyridoxic acid is inactive and is excreted in urine (15,25,26). The elimination half-life of pyridoxine has been estimated to range from 20 to 46 h (27). In terms of relating serum concentrations and drug effects, a steady state may not be achieved during a typical six- to eight-week course for NVP, unless a loading dose of vitamin B6 is given. No study has evaluated the efficacy of a loading regimen of this vitamin, and it is given as a fixed maintenance dose.

**TABLE 1**  
Reported effectiveness of Diclectin in a prospective cohort

Reported effect of Diclectin	First call	Second call* (week 20 follow-up)
Better	106 (71%)	21 (84%)
Same	34 (23%)	3 (12%)
Worse	2 (1%)	1 (4%)
Missing data	7 (5%)	0
Total number of patients using Diclectin	149	25 (6%)

*Patients were already taking the drug during their first consultation (typically at six to 10 weeks). \*Patients who started or changed the dose of Diclectin after the first call*

### EFFICACY OF DICLECTIN

The efficacy of the delayed-release combination of doxylamine and pyridoxine has been documented in several randomized, controlled trials (RCTs) and postmarketing studies.

In addition, the results of the removal of Bendectin from the American market, and its continuous use in Canada as Diclectin, have offered population-based evidence of its effectiveness.

Four clinical trials of doxylamine hydrochloride or doxylamine with pyridoxine (Debendox; Merrell Dow, USA [Bendectin]) compared with a placebo have been published.

Geiger et al (28) published the results of a double-blind, placebo controlled trial with Bendectin. In this group of 109 patients, there was a favourable response to Bendectin (94%) compared with that of the placebo (65%) ( $P < 0.001$ ). Of the 52 patients who received Bendectin, 23 had complete relief from nausea.

In another double-blind, placebo controlled trial, 41 patients received either Debendox or placebo (29). There was an improvement in the severity of the NVP in 70.7% of the group receiving Debendox compared with 50.5% in the placebo group ( $P < 0.05$ ).

In another randomized, double-blind trial by Wheatley (30), Debendox plus 10 mg extra of pyridoxine, or placebo plus 10 mg pyridoxine was given to 57 pregnant women in a 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 (30). This result was achieved despite that the group treated first with placebo contained a relatively higher proportion of mild cases. The severity of retching ( $P < 0.001$ ) and vomiting ( $P < 0.02$ ) showed a similar pattern.

The manufacturer of Bendectin, Merrell Dow Pharmaceuticals, evaluated the efficacy of all components of Bendectin individually and together, compared with placebo in two studies (31).

The first study compared the efficacy of doxylamine plus dicyclomine, doxylamine, and dicyclomine and placebo for

**TABLE 2**  
Week 20 report of patients who started Diclectin after the first counselling session, or those who increased their doses

Drug changes at 20 weeks	Better	Same	Worse	Total
Initiated Diclectin therapy de novo	10	3	1	14
Diclectin dose changed	11	0	0	11

the treatment of NVP in 716 patients. Doxylamine plus dicyclomine was more effective than placebo for the treatment of NVP. However, the effect appeared to be secondary to doxylamine because dicyclomine was not significantly better than placebo in the treatment of NVP.

The other study evaluated the efficacy of all components of Bendectin, including pyridoxine alone and in various possible combinations compared with 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. Because of the absence of an effect of dicyclomine, this ingredient was removed from Bendectin.

We have recently analyzed the first prospective postmarketing study on the efficacy of Diclectin. All previous studies were conducted with Bendectin. One of the shortcomings of previous RCTs was their short duration (typically one week), which did not allow evaluation of long term effectiveness. This is especially important in view of the possibility of decreased compliance due to potential adverse effects, such as sedation. Our study was conducted in women counselled by the Motherisk NVP program in Toronto, Ontario. Women were advised to take two tablets before sleep; if NVP symptoms became apparent in the afternoon despite the previous evening dose, they were advised to take an additional tablet in the morning. A fourth tablet was taken at noon if NVP symptoms were apparent in the late afternoon or evening. The first interview took place after the onset of symptoms, generally at six to eight weeks. A second evaluation took place at 20 weeks' gestation.

During the first follow-up, 106 patients (71%) reported an improvement in their NVP symptoms, temporally related to Diclectin use; 34 patients (23%) did not report improvement and two 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, three patients (12%) reported no change and one patient (4%) experienced a worsening of symptoms. These results are strikingly similar to those reported in the double-blind trials reported above, suggesting that Diclectin does not lose efficacy over time in the 'real world' compared with one-week use in tightly controlled trials (Tables 1, 2).

A very convincing body of evidence on the effectiveness of Bendectin/Diclectin came from population-based studies in the United States and Canada. Neutel and Johansen (4) showed that the removal of Bendectin from American and Canadian markets was temporally related to a two- to threefold increase in the rate of hospitalization of women due to severe forms of NVP. These data suggest that the doxylamine-pyridoxine combination is capable of not only eradicating mild and moderate forms of NVP, but also of preventing severe cases. It may be argued that other factors, and not necessarily the removal of Bendectin from the market, led to the tripling of the hospitalization rate in the United States due to NVP.

However, new data by Neutel and Johansen (32) (Figure 1) indicate that during the past few years, the substantial increase in use of Diclectin by Canadian women has been associated with a decrease in their hospitalization rate for severe NVP. This 'challenge-dechallenge' proof provides very powerful evidence for the strong impact of Diclectin on the health of thousands of pregnant women in Canada.

### THE EFFICACY OF VITAMIN B6 AND MULTIVITAMINS

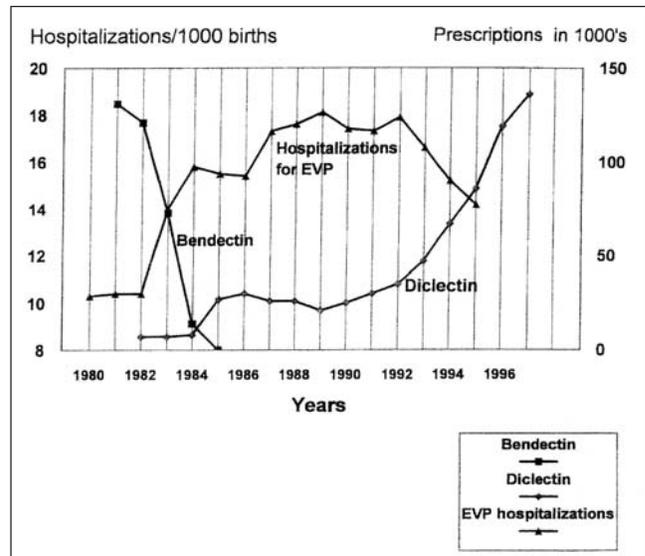
Two RCTs using pyridoxine alone compared with placebo were conducted during the past decade. The first trial comprised 59 women (33). Following one week of therapy, there was a significant difference in nausea score (measured on a scale from zero to 10) between patients with severe nausea receiving vitamin B6 (mean  $1.8 \pm 2.2$ ) and those receiving placebo (mean  $4.3 \pm 2.1$ ) ( $P < 0.01$ ). In patients with mild to moderate nausea and in the group as a whole, no significant difference between vitamin B6 and placebo was observed.

In the other RCT, 342 pregnant women were randomly assigned to receive placebo ( $n=169$ ) or pyridoxine ( $n=173$ ). Similar to the smaller study, the mean change in nausea scores in the pyridoxine group was significantly greater ( $P < 0.001$ ) (34).

The apparent effectiveness of a multivitamin preparation over a mineral preparation before conception was reported in a double-blind, randomized, placebo controlled trial (11). Czeizel and colleagues (11) treated these women in an attempt to prevent spina bifida by the administration of folic acid. In a post-hoc analysis, they realized that the women randomly assigned to receive multivitamins had a significantly lower rate of NVP. Moreover, the incidence of severe forms of NVP was also reduced.

### SAFETY OF DICLECTIN DURING PREGNANCY

In 1969, the first allegations regarding possible teratogenic effects of Bendectin resulting in congenital malformations were filed in the United States (3). During the following years, scores of similar cases were brought to court, claiming Bendectin to be teratogenic. As a result of escalating legal costs, Merrell Dow stopped manufacturing the drug in 1983. This decision was made despite that a convincing body of scientific evidence showed Bendectin to be safe in pregnancy. How-



**Figure 1** Hospitalization for excessive vomiting in pregnancy (EVP) by Bendectin or Diclectin use\* in Canada. \*Canadian Compuscript, 1981 to 1997. Reprinted with permission from reference 32

ever, an expert panel convened by the United States Food and Drug Administration unequivocally refuted the claims of teratogenicity (35).

To address the question of potential teratogenicity of Bendectin in humans, two separate meta-analyses, combining all controlled studies of pregnancy outcome following the use of Bendectin during the first trimester, were conducted. Both studies failed to show a general increase in the malformation rate or in specific malformations. In Toronto, all case-control and cohort studies, including 200,000 patients were analyzed (36). The overall summary odds ratio (OR) was 1.01 with a 95% confidence interval of 0.66 to 1.55 (when a confidence interval includes unity, it indicates no increased risk). When the studies were separated according to their design, the summary OR for cohort studies was 0.95 with a 95% confidence interval of 0.62 to 1.45, and for case-control studies the summary OR was 1.27 with a 95% confidence interval of 0.83 to 1.94.

Subsequently, a second meta-analysis, conducted in Washington, DC, incorporated 16 cohort and 11 case-control studies (37). The pooled estimate of the relative risk for any malformation at birth, in association with exposure to Bendectin in the first trimester, was 0.95 (95% confidence interval 0.88 to 1.04). Separate analyses were done for cardiac defects, limb defects, oral clefts and genital tract malformations. In these categories, the pooled estimates of relative risk ranged from 0.81 for oral clefts to 1.11 for limb defects, with no differences between Bendectin and controls. As a group, these studies showed no differences in the risk of birth defects between infants whose mothers had taken Bendectin during the first trimester of pregnancy and infants whose mothers had not.

In addition to the epidemiological data summarized above, at least five studies in experimental animal and in vitro studies failed to detect teratogenic effects of Bendectin in the therapeutic range and, in most instances, even when the dose was considerably greater than the therapeutic range (38). The

general consensus among teratologists is that Bendectin and Diclectin are the best studied drugs for use in pregnancy, and the great preponderance of evidence confirms its documented efficacy and safety profile (38).

## CONCLUSIONS

Because it is extremely unlikely that another drug to treat NVP will ever be shown to be effective in a similar number of safety and efficacy studies in pregnancy as Bendectin or Diclectin, it is unlikely that other agents will ever have the same statistical significance to discount a potential teratogenic effect. Hence, the most logical solution is to find ways to introduce Diclectin for the benefit of pregnant women worldwide.

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