Should Doxylamine-Pyridoxine Be Used for Nausea and Vomiting of Pregnancy?

Navindra Persaud, MSc, MD,1,2,3 Jessica Chin, MD,2 Mark Walker, MSc, MD4,5

1Department of Family and Community Medicine, St. Michael’s Hospital, Toronto ON
2Keenan Research Centre of the Li Ka Shing Knowledge Institute, St Michael’s Hospital, Toronto ON
3Department of Family and Community Medicine, University of Toronto, Toronto ON
4Ottawa Hospital Research Institute, Ottawa ON
5Department of Obstetrics and Gynecology, University of Ottawa, Ottawa ON

Abstract

Doxylamine-pyridoxine is the first-line agent for the treatment of nausea and vomiting of pregnancy (NVP) according to Canadian guidelines, and this combination is commonly prescribed to pregnant women. There is limited evidence that doxylamine-pyridoxine is more effective than pyridoxine alone. There is stronger support for the safety of pyridoxine monotherapy than for the combination of doxylamine-pyridoxine during pregnancy, and some conflicting evidence links doxylamine-pyridoxine use to pyloric stenosis and childhood malignancies. The role of doxylamine-pyridoxine as the first-line pharmacological treatment for NVP in Canada should be reconsidered.

INTRODUCTION

Nausea and vomiting commonly occurs early in pregnancy, and affects up to 80% of pregnancies.1,2 According to guidelines published by the Society of Obstetricians and Gynaecologists of Canada3 and by Motherisk (an organization that provides clinicians and patients with information about drug safety during pregnancy),4 doxylamine-pyridoxine is currently the first-line pharmacological therapy for nausea and vomiting of pregnancy (NVP). The Public Health Agency of Canada has stated that doxylamine-pyridoxine “has been studied in over 200 000 pregnant women and has not been shown to increase the risk of teratogenicity.”5 A 1999 survey indicated that 95% of Canadian physicians caring for pregnant women have prescribed doxylamine-pyridoxine,6 and the manufacturer claims that this combination has been used in more than 33 million pregnancies.7

The SOGC guideline gives doxylamine-pyridoxine a I-A recommendation (indicating good evidence from at least one randomized control trial) and depicts it in the algorithm as the first-line treatment; pyridoxine alone, which also receives a I-A recommendation, is not shown in the treatment algorithm.3 The Motherisk guideline mentions pyridoxine as an adjunct treatment (with ginger and acupressure).4,8 In contrast, pyridoxine monotherapy is recommended as a first-line treatment for NVP in the United States9 and Australia.10 British guidelines do not mention doxylamine-pyridoxine.11 In this article we examine the primary studies that form the basis of the Canadian guideline recommendations.

Key Words: Nausea and vomiting of pregnancy, evidence-based medicine, clinical practice guidelines
Competing Interests: None declared.
Received on December 3, 2013
Accepted on January 15, 2014

HISTORICAL CONTEXT

Doxylamine-pyridoxine was marketed under the trade names Bendectin and Debendox in the United States and United Kingdom respectively in the 1950s. It initially contained the antispasmodic dicyclomine until it was reformulated in the late 1970s. Many studies on whether doxylamine-pyridoxine was teratogenic were published during the 1980s. Bendectin was voluntarily removed from the United States market by its manufacturer in 1983 following several lawsuits alleging that it caused birth defects. During the period Bendectin was off the market, there was a 37% increase in admissions to hospital for nausea and vomiting of pregnancy. The United States Food and Drug Administration subsequently concluded that “Bendectin was not withdrawn from the market for reasons of safety or effectiveness.” A delayed-release formulation of doxylamine-pyridoxine, Diclectin (Duchesnay Inc., Blainville QC), has been marketed in Canada since 1978.

Pyridoxine has been used in the treatment of NVP since before 1942.

TREND OF DICLECTIN PRESCRIPTIONS

The prescription rate of Diclectin was 503 prescriptions per 1000 live births in 2010, according to data from seven Canadian provinces (Alberta, Manitoba, New Brunswick, Newfoundland, Nova Scotia, Ontario, and Quebec), and this represents a 2.4-fold increase since 2001 (Figure 1). The rise in Diclectin prescription rate was highest from 2002 to 2003 (an increase of 27%) and the SOGC NVP guideline was published in 2002. Quebec had the highest rate of Diclectin prescriptions per 1000 live births in 2010 among the seven provinces (Figure 2).

EVIDENCE OF EFFICACY

Doxylamine-Pyridoxine

There is limited evidence for the efficacy of doxylamine-pyridoxine for NVP. A 2010 Cochrane review concluded that two older studies provided insufficient evidence supporting the efficacy of Bendectin over placebo. A 1959 double-blind study of Bendectin (n = 53) versus placebo (n = 57) found a treatment effect or symptom improvement in 50 patients given Bendectin (94%) versus 37 patients given placebo (65%) (P < 0.001). The method for determining clinical response was not described. A 1971 double-blind randomized control trial of Debendox (n = 41) versus placebo (n = 40) employed a five-point symptom scale. The fraction of patients who were “better” did not significantly differ between the Debendox (71%) and placebo (55%) groups after 14 days (P = 0.17). Despite this negative finding, the results were reported as positive because the response rate in the Debendox group was “significantly better than the theoretical 50% improvement that would be expected from purely random fluctuations in severity.”

In a double-blind randomized trial published after the Cochrane review and Canadian guidelines, 131 women were given Diclectin and 125 a placebo for 14 days. Symptoms were assessed using daily ratings on the 15-point pregnancy unique quantification of emesis (PUQE) scale. A score of 3 represented no symptoms and 15 represented the most severe state of symptoms including greater than six hours of nausea, at least seven instances of retching and at least seven episodes of vomiting daily. The ANCOVA of the symptoms scores yielded a significant difference between Diclectin and control patients (P = 0.006). The difference in mean symptom score changes between women given Diclectin (−4.8 ± 2.7) and placebo (−3.9 ± 2.6) was 0.9 on the 15-point PUQE symptom scale.

Of these three studies, two showed statistically significant differences between patients receiving doxylamine-pyridoxine and placebos. In all three studies, the response magnitude in the placebo groups was three to five times larger than the difference between the active and placebo groups. The two older studies employed formulations containing dicyclomine in addition to doxylamine-pyridoxine, so no studies of the efficacy of doxylamine-pyridoxine were available at the time the Canadian guidelines were published.

Pyridoxine

The evidence supporting the efficacy of pyridoxine for NVP is similar in amount to that supporting doxylamine-pyridoxine. In a double-blind randomized trial, 169 women were given pyridoxine and 169 a placebo. The reduction in reported severity of nausea, as measured on a 10-cm visual analogue scale on five consecutive days, was significantly (P < 0.001) greater in the pyridoxine group (2.9 ± 2.2 cm), compared with the placebo group (2.0 ± 2.7 cm). There was also a reduction of vomiting episodes as a secondary outcome, but this was not statistically significant (P = 0.055). In another double-blind randomized trial, 31 women were given pyridoxine and 28 a placebo. In this three-day study, the reduction in reported nausea (2.9 ± 2.4) in the pyridoxine group was not significantly greater than in the placebo group (1.9 ± 2.0) on a 10-cm visual analogue scale, but there was a significant (P < 0.01) reduction in the proportion of women who reported vomiting after taking pyridoxine versus placebo. A recent Cochrane review cautioned against over-interpretation of these two small positive studies.
Should Doxylamine-Pyridoxine Be Used for Nausea and Vomiting of Pregnancy?

Figure 1. Diclectin prescriptions in seven Canadian provinces from 2001 to 2010

Figure 2. Diclectin prescription rates in seven Canadian provinces in 2010

The total number of registered live births for each of the seven Canadian provinces (Alberta, Manitoba, New Brunswick, Newfoundland, Nova Scotia, Ontario, and Quebec) were obtained from the Vital Statistics—Birth Database on the Statistics Canada website for the years 2001 to 2010. The total number of Diclectin prescriptions in each of the seven Canadian provinces for the years 2001 to 2010 was provided by IMS Brogan.
Since the effect sizes of pyridoxine and doxylamine-pyridoxine in RCTs are similar—and both are much smaller than the response to placebos—the utility of doxylamine must be questioned. The clinical significance of these effects (0.9 on a 15-point scale and 0.9 cm on a 10 cm visual analogue scale) is also debatable.

**Direct Comparisons of Doxylamine-Pyridoxine Components**

There are no high quality studies comparing the efficacy of the individual components of doxylamine-pyridoxine and/or the combination. One study compared the effects on NVP of Debendox plus an extra 10 mg of pyridoxine (for a total of 20 mg) to 10 mg of pyridoxine alone in a crossed-over fashion, making it difficult to determine whether doxylamine or the higher dose of pyridoxine was responsible for the significantly greater symptom reduction in the former group. An unpublished 1970s RCT conducted by Merrell Dow (Bendectin’s manufacturer) seemed to show that doxylamine-pyridoxine had greater efficacy than pyridoxine alone. The fraction of patients who experienced an excellent or moderate response was significantly different (P = 0.01) between pyridoxine (66%, 126/191) and doxylamine-pyridoxine (77%, 165/213). However, this study had limited internal validity because 31% of patients (709/2308) dropped out of the six-day trial or were excluded from the analysis. It is unclear how physicians classified the response to treatment (excellent, moderate, slight, or none). The results of the completed study were never published.

**Malformations**

Three meta-analyses of safety data for Diclectin have concluded that its use during pregnancy is not associated with an overall increase in malformations. Two of these meta-analyses each included more than 100 000 pregnancies and reported summary odds ratios for overall malformation rates near unity. The third meta-analysis reportedly included more than 200 000 pregnancies and indicated a summary odds ratio significantly below unity (indicating that doxylamine-pyridoxine use is associated with a lower risk of malformations), but these conclusions have been questioned. A recent re-analysis of the data in the third meta-analysis showed that the number of women included was lower than reported and that the odds ratio for malformation was higher than reported. Following the publication of this article, the Public Health Agency of Canada took down its statement about the safety of Diclectin.

One potential limitation of the included studies is that some women had taken other teratogenic medications such as tetracycline. Exposure to other medications was not reported in all studies. Some older studies employed questionable methodologies. In the General Practitioner Research Group trial (1963), physicians were invited to provide information about patients seen during a nine-month period but they were also given the option of including patients seen during the previous six months. The number of patients recruited in each period is not reported so the effect of any selection bias in the retrospective group is unknown. In a study reported in 1963 by Bunde and Bowles, 21 physicians who frequently prescribed Bendectin were asked by the manufacturer to complete questionnaires about recent patients. This study’s odds ratio for Bendectin exposure and birth defects, 0.52 (95% CI 0.25 to 1.1), is substantially lower than those in other studies.

**Pyloric Stenosis**

There are conflicting findings regarding an association between doxylamine-pyridoxine exposure and pyloric stenosis. In a cohort study of 13 346 children, 3835 of whom were exposed prenatally to doxylamine-pyridoxine, a pyloric stenosis risk ratio of 2.5 (95% CI 1.2 to 5.2) was found, and there was a relative risk of 7.59 (95% CI 4.95 to 11.64; P = 0.01) when more than five prescriptions were filled. A case–control study of 1427 cases and 3001 control subjects found the odds of exposure to doxylamine-pyridoxine for any malformation were not significantly increased (OR 1.4; 95% CI 0.95 to 2.0), but subanalyses identified a statistically significant association for pyloric stenosis (OR 4.3; 95% CI 1.75 to 10.75). Another case–control study that used two control groups consisting of different malformations found no increased exposure to Bendectin in 325 cases with pyloric stenosis (OR 0.9; 95% CI 0.6 to 1.2 and OR 1.0; 95% CI 0.7 to 1.4). A meta-analysis of five studies found no increased risk (OR 1.04; 95% CI 0.85 to 1.3). Subanalyses of two large cohort studies revealed (in the first) a relative risk for pyloric stenosis of 3.3 (95% CI 1.6 to 7.2) with seven cases in the exposed and 88 in the unexposed groups and (in the second) a relative risk of 1.7 (95% CI 0.21 to 14) with one case in the exposed and six in the control groups. Another large cohort study did not report any cases of pyloric stenosis in either group.

**Childhood Malignancies**

A paired case–control study of 204 mothers of children with acute non-lymphoblastic leukemia found a non-significant odds ratio of 1.75 (95% CI 0.98 to 3.20) for use of Bendectin, but there was a significant dose–response
relationship.\textsuperscript{36} Another case–control study of 555 patients with childhood malignancies (including solid tumours) and 1110 control subjects found an odds ratio of 0.99 for prenatal exposure to Bendectin/Debendox.\textsuperscript{37} A subanalysis in that study showed an odds ratio of 10.04 (95\% CI 1.76 to 57.37) of malignancy if Debendox was taken for one to two months, but there was no significant relationship for longer durations of use. The Diclectin product monograph mentions the negative finding in this latter study.

**Safety of Pyridoxine Alone**

If evidence for the safety of the combination of doxylamine and pyridoxine is also evidence for the safety of pyridoxine alone, there is not greater evidence for the safety of doxylamine-pyridoxine than for pyridoxine alone (as is suggested by Canadian guidelines).\textsuperscript{4,8} In addition, there is separate evidence that pyridoxine monotherapy is not associated with adverse outcomes. A case–control study of 458 children with malformations and 911 control subjects found an odds ratio for pyridoxine exposure of 0.95 (95\% CI 0.57 to 1.6).\textsuperscript{38}

**CONCLUSION**

There is no clear evidence that doxylamine-pyridoxine is more effective in the management of NVP than pyridoxine alone. While large cohort studies have found no association between doxylamine-pyridoxine and malformations, some smaller studies are consistent with an increased risk of pyloric stenosis and childhood malignancies (but the overall risk of these outcomes remains small). If pharmacotherapy is indicated for NVP, pyridoxine may be as rational a choice as doxylamine-pyridoxine because there is no clear evidence of a clinically significant effect of either medication. The grade I-A recommendations for doxylamine-pyridoxine in Canadian guidelines may not be supported by the current evidence. A non-inferiority trial of pyridoxine versus doxylamine-pyridoxine would likely establish if there is a role for the combination.

**ACKNOWLEDGEMENTS**

Navindra Persaud was supported by a Banting Postdoctoral Fellowship and a Randomized Controlled Trials Training Grant from the Canadian Institutes of Health Research as well as by the Department of Family and Community Medicine, St Michael's Hospital, Toronto, Canada.

**REFERENCES**


APRIL JOGC APRIL 2014 ● 347


