

Evaluation of the Efficacy and Safety of Bi-Daily Combination Therapy with Pyridoxine and Doxylamine for Nausea and Vomiting of Pregnancy

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ABSTRACT: **Background:** Diclectin® (pyridoxine 10 mg and doxylamine 10 mg) has traditionally been used to treat nausea and vomiting of pregnancy (NVP); however, this drug is unavailable in many countries.

Objectives: To evaluate the efficacy and safety of a simple bi-daily treatment regimen with the combination of pyridoxine (50 mg twice daily) and doxylamine (25–50 mg) as an alternative treatment for NVP.

Methods: A prospective case-controlled observational study of mother-infant pairs was conducted between February 2008 and December 2010. All women who contacted the Beilinson Teratology Information Service (BELTIS) regarding treatment of NVP were eligible for inclusion. Using data on NVP severity, treatment efficacy and outcomes, we compared the two groups of women: those treated with the combination of pyridoxine and doxylamine (treatment group, n=29) and those treated with metoclopramide (control group, n=29).

Results: Moderate to severe symptoms were present in 97% of the treatment group women vs. 69% of control group women ($P < 0.01$). Despite increased symptom severity in the treatment group, the combination regimen was efficacious: 20/29 (69%) vs. 18/25 (72%) in the treatment vs. control women respectively ($P = 0.65$). There were no congenital anomalies in the treatment group. Follow-up was normal for all infants.

Conclusions: Bi-daily combination therapy with pyridoxine and doxylamine for NVP is safe, has comparable efficacy to metoclopramide, and is a treatment alternative in countries where Diclectin is not available. Despite symptoms warranting counseling by a teratology information service, more than a third of women do not take the suggested treatment.

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KEY WORDS: pyridoxine, doxylamine, nausea and vomiting of pregnancy (NVP)

[1]. Although self-limited, this condition may have a serious impact on women's health, leading to dehydration, electrolyte imbalance and hospitalization [2]. However, the management of NVP is often suboptimal and only a small percentage of women receive appropriate treatment. A recent study reported that of 283 women who reported nausea and vomiting during the first trimester, only 27% received an anti-emetic prescription from their caregivers [3].

One of the most effective treatment options for NVP in the past was Bendectin (Debendox®, MMD, USA) introduced in 1956 [4,5]. Bendectin was initially a tri-ingredient product comprising doxylamine succinate (an antihistamine with anti-emetic properties of the ethanolamine class, dicyclomine hydrochloride (an antispasmodic agent), and pyridoxine hydrochloride (vitamin B6), which has synergistic anti-nauseate activity with the other components. In 1976, dicyclomine hydrochloride was removed because studies found it to have no independent effect, and Bendectin was reformulated to contain 10 mg doxylamine and 10 mg pyridoxine, to be taken 3–4 times per day. Bendectin was used by 25–30% of pregnant women in the United States during the 1970s. In the early 1980s, lawsuits alleging that Bendectin caused teratogenic effects, followed by extensive media coverage, resulted in the voluntarily removal of the drug from the U.S. market in 1983 by the manufacturer [6]. This was unfortunate because Bendectin has been shown to be both safe and efficacious. Despite its removal from the U.S. market, a similar formulation is marketed in other locations under different brand names (e.g., Diclectin®, Duchesnay, Canada).

Because neither Diclectin nor Bendectin is commercially available in our country, we decided to use the combination of doxylamine and pyridoxine taken from the commercially available preparations in Israel: pyridoxine 50 mg (1/2 tablet of 100 mg) and doxylamine succinate 25 mg (1 tablet of 25 mg). These substances are available over the counter in our country. The aim of the present study was to evaluate the relative efficacy and safety of this combination treatment.

NVP = nausea and vomiting of pregnancy

Nausea and vomiting of pregnancy is a very common phenomenon, occurring in 50% to 80% of pregnancies with symptoms peaking between 8 and 12 weeks gestation

PATIENTS AND METHODS

A prospective case-control observational study was conducted through the Beilinson Teratology Information Service (BELTIS), a free call-in center for queries regarding drug use during pregnancy and lactation. At the initial phone conversation, information was obtained using a standard questionnaire and included maternal age, parity, number of gestations, smoking habits, alcohol or drug use, and use of other medications. In the initial phone conversation mothers were informed that a follow-up call would follow, and consent was obtained for this follow-up interview.

Mothers who contacted BELTIS between February 2008 and December 2010 regarding NVP received consultation on the various treatment options available. BELTIS recommends a stepwise approach to NVP [Figure 1] based on a modification of the 2004 guidelines published by the American College of Obstetricians and Gynecologists [7]. Our standard recommendation was to start with dietary changes (small frequent meals) and, if vomiting continued, to start treatment with pyridoxine at a dose of 50 mg twice daily. If vomiting persisted then doxylamine was added at an initial dose of 25 mg taken at night, with two additional doses of 12.5 mg if required. If symptoms were still present, a third-line therapy, metoclopramide (Pramin[®], Rafa, Israel) was added. If symptom control was still

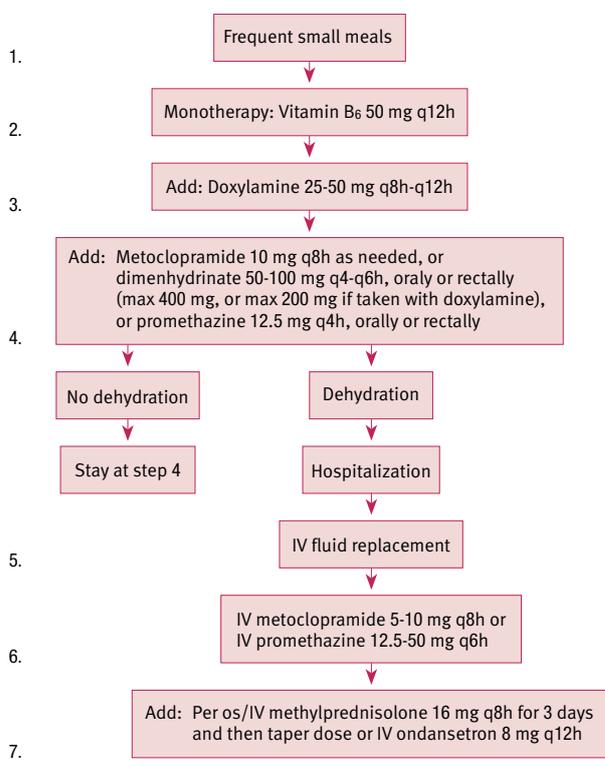
not achieved, additional anti-emetic medications and/or fluid replacement was recommended. In most cases, the resulting combination regimen comprised a daily dose of 100 mg pyridoxine and 25–37.5 mg doxylamine compared to the daily dose of 30–40 mg pyridoxine and 30–40 mg doxylamine in the slow-release formulation Diclectin. Oral use of a solution of these two drugs was previously shown to have similar bioavailability, but with much earlier peak time in comparison to Diclectin [8].

The mothers were contacted up to 2 years after the initial phone conversation for a follow-up telephone interview using a structured questionnaire. Maternal report on the severity of NVP (mild, moderate, severe) and efficacy of treatment (no or mild, moderate, high) were obtained. Data regarding duration of treatment, fetal growth, mode of delivery, gestational age at delivery, birth weight, gender, congenital birth defects, and infant age and development at follow-up were recorded. The treatment group (mothers treated with the combination regimen of doxylamine and pyridoxine only) was compared to a control group (mothers who used metoclopramide only). The control group was followed similarly to the treatment group. Women treated with both doxylamine and pyridoxine and metoclopramide were not included in the study analysis. The study was approved by the Rabin Medical Center Research Ethics Board.

STATISTICAL ANALYSIS

Continuous variables were compared by group using analysis of variance (ANOVA). Discrete variables were compared by group using Pearson's chi-square test. The Mann-Whitney test was used to compare the efficacy of treatment between the two groups. Multivariate analysis was used to evaluate the independent effect of treatment, correcting for disease severity. $P < 0.05$ was considered statistically significant. The data were analyzed using BMDP Statistical Software (1993, Chief Editor: W.J. Dixon, University of California Press, Los Angeles, USA).

Figure 1. Algorithm for treatment of nausea and vomiting of pregnancy



RESULTS

Follow-up data were available for 136 of the 163 women (83.4%) who contacted BELTIS because of NVP during the study period. Of the 136 women, 87 had not received treatment or consultation and were offered treatment with doxylamine and pyridoxine, and 49 had prior knowledge of treatment and had either started treatment with metoclopramide or wanted non-combination therapy. Of the 87 women offered combination treatment, 29 were treated with doxylamine and pyridoxine, 21 were treated with other drug regimens (Diclectin n=6, pyridoxine only n=8, multiple drugs or "alternative" therapy n=7), and 37 were not pharmacologically treated. Of the 49 additional women who contacted our service regarding NVP, 29 were treated with metoclopramide, 6 were treated with other drug regimens (doxylamine, pyridoxine and metoclopramide n=4, Diclectin n=1, pyridoxine only n=1), and 14 were not

pharmacologically treated. The treatment group comprising 29 women (30 infants) treated with doxylamine and pyridoxine was compared with a control group comprising 29 women (29 infants) treated with metoclopramide alone. The characteristics of the mothers and infants included in the treatment and control groups are presented in Table 1.

Most women started treatment during the first trimester (26 of 29 treatment women and 21 of 27 control women). The average duration of therapy in the treatment and control women was 6.2 ± 6.0 and 3.5 ± 3.2 weeks, respectively (*P* = 0.07). The mean gestational age at delivery was 38.9 ± 2.2 weeks in the treatment group, including a twin delivery at 36 weeks gestation, and 39.6 ± 1.1 weeks in the control group.

In the combination doxylamine-pyridoxine group, one woman reported concomitant treatment during pregnancy with sertraline, one with oseltamivir, ceftriaxone and cephalixin, and one with an unknown anti-fungal medication.

EFFICACY OF ANTI-EMETIC TREATMENT

Moderate to severe symptoms were present in 28/29 women in the treatment group (97%) vs. 18/26 in the control group (69%) (*P* < 0.01). Despite increased symptom severity in the treatment group, a comparison of the treatment vs. control women showed similar efficacy in 20/29 (69%) vs. 18/25 (72%) of women (*P* = 0.65) [Table 1]. Multivariable analysis did not change the efficacy results. A severe degree of NVP was reported by all seven women treated with the combination of doxylamine, pyridoxine and metoclopramide. In this group, overall efficacy of treatment with these three drugs was reported to be moderate to high by three women and mild by four women. No adverse effects were reported among these women.

OUTCOMES

There were no significant differences between the two groups with respect to type of delivery, birth weight, and spontaneous first-trimester abortions [Table 1]. The treatment group had a higher rate of late preterm delivery (*P* = 0.03), but this was due to delivery at 36 weeks for three of five late preterm infants (including one case of twin delivery), and no complications of prematurity were noted for any of the preterm infants. There were no congenital birth defects among the treatment infants; in a control infant there was a single congenital anomaly (hypospadias). Development and growth was considered normal for all infants in both groups.

DISCUSSION

Despite the high incidence of NVP, this condition is often inappropriately managed. This is perhaps due to an unjustified perception of teratogenic risk by the medical team as well as by the general population. In our study, despite initially seeking medical advice regarding treatment for NVP, more than a third

Table 1. Characteristics of mother-infant pairs treated for nausea and vomiting of pregnancy

| Treatment during pregnancy | Pyridoxine-doxylamine* (n=29) | Metoclopramide** (n=29) | P value |
|--|-------------------------------|---|---------|
| Mean maternal age (yrs) (SD) | 30.7 (4.5) | 30.4 (5.1) | NS |
| Moderate to severe NVP (%) | 28/29 (97%) | 18/26 (69%) | < 0.01 |
| Treatment duration (wks) (SD) | 6.2 (6.0) | 3.5 (3.2) | 0.07 |
| Spontaneous 1st trimester abortion (%) | 2/29 (7%) | 1/29 (3%) | NS |
| Cesarean section (%) | 2/27 (7%) | 4/28 (14%) | NS |
| Mean birth weight (g) (SD) | 3118 (501) | 3305 (354) | NS |
| Low birth weight### (%) | 3/28 (10%) | 0/28 (0%) | NS |
| Mean gestational age (SD) (wks) | 38.9 (2.2) | 39.6 (1.1) | NS |
| Late preterm births (%) | 5/28 (18%) | 0/28 (0%) | 0.03 |
| Male gender (%) | 14/28 (50%) | 12/28 (43%) | NS |
| Maternal pregnancy complications | 1 (chorioamnionitis) | 1 (preeclampsia) 1 (oligohydramnion) | NS |
| Congenital malformations | 0 | 1 (hypospadias) | NS |
| Age at infant follow-up (mos) (SD) | 10.2 (4.5) | 17.4 (5.5) | < 0.001 |
| Normal infant development | 27/27 (100%) | 28/28 (100%) | NS |

*Anacrodyne® (Rekah, Israel) +Tonight® (CTS, Israel) or Sleep Aid® (Perrigo, Israel)

**Pramin (Rafa, Israel)

###Low birth weight = birth weight < 2500 g

§34–36 weeks gestation

of women did not use any pharmacological therapy. Similarly, Baggeley et al. [9] noted that 34% of women who were informed of the safety of Diclectin refrained from using medication, and of those who took Diclectin 26% used less than the recommended dose. The under-treatment of women with NVP should encourage researchers to investigate other treatment alternatives that may be more acceptable to the public and would therefore improve the management of this common phenomenon.

Bendectin was a widely used anti-emetic drug in the 1970s in the USA and its effectiveness and safety have been extensively studied [4-6,10-12]. The use of combination therapy as an alternative to Bendectin or Diclectin has been recommended by ACOG guidelines [7]. The combination of pyridoxine and doxylamine used in our study is similar to Diclectin in its components; however, the dose of both components is higher and they are not delayed-release formulations. Our twice-daily regimen is simple, is likely to achieve a higher compliance than the three to four times a day recommended regimens, and was chosen based on available drug formulations. To the best of our knowledge, although combination treatment has been recommended for NVP by care-

ACOG = American College of Obstetricians and Gynecologists

givers [7,10,13,14], its properties have not been sufficiently studied. This preliminary study found that the combination of pyridoxine and doxylamine was efficacious and seems as effective as metoclopramide. A study of Diclectin by Boskovic et al. [11] found that women who took suboptimal doses of Diclectin had higher levels of nausea, and that an increase in dosage to the recommended dose of 40 mg pyridoxine with 40 mg doxylamine per day (4 tablets Diclectin per day) led to significant amelioration of symptoms. Thus, the use of a higher drug dosage, as in our study, can be expected to achieve better control of symptoms. Atanackovic and co-workers [15] reported the safety of a higher than standard dose of Diclectin, with doses ranging from 0.1 to 2.0 mg/kg (1–12 tablets Diclectin per day). Their findings are in accordance with our study, showing significant lack of adverse effects among mothers and exposed infants.

In the present study we noted a somewhat increased rate of preterm delivery among women treated with pyridoxine and doxylamine. This was due to three women who delivered at 36 weeks (including one twin delivery) and another woman who delivered at 34 weeks due to chorioamnionitis, which was not related to drug therapy. It is not clear whether this mild degree of prematurity has any clinical significance. Also, the relationship to drug treatment is unlikely since the treatment ended at 15 weeks gestation. The 7% rate of spontaneous abortions at < 12 weeks gestation was similar to that in the general population and was not different in control women.

Women in the treatment group were treated for twice as long as the control group. This increased duration was likely related to the increased disease severity in the treatment group.

This study has some limitations. The sample size was moderate and precludes evaluation of uncommon side effects. Assuming a power of 80% and alpha 0.05, the sample size was sufficient to show a difference in drug efficacy not greater than 50% between groups. Secondly, the choice of treatment was determined by mothers and not by randomization, allowing for possible bias. Thirdly, due to the time elapsed from treatment to the follow-up call, there is a possibility of recall bias. Finally, the follow-up period in this study was insufficient to identify minor developmental difficulties.

In conclusion, our results show that twice-daily combination treatment with pyridoxine and doxylamine is an effective and safe treatment option for NVP, especially in countries where Diclectin is not available. Larger studies are needed to estab-

lish the efficacy and safety of this treatment. Maternal anxiety regarding drug use during pregnancy leads to more than a third of women not being treated for NVP despite severe symptoms and adequate counseling by a teratology information service.

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“Health is the greatest gift, contentment the greatest wealth, faithfulness the best relationship”

Buddha (563-483 BC), spiritual teacher from India and founder of Buddhism, a religion that encompasses a variety of traditions, beliefs and practices. Two of the most important teachings are dependent origination and no-self

“That sorrow which is the harbinger of joy is preferable to the joy which is followed by sorrow”

Sa'adi (1213-1291), Persian poet, famous not only in Persian-speaking countries, but has also been quoted in western sources. He is recognized for the quality of his writings and for the depth of his social and moral thoughts