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Determinants of Adherence to Delayed-Release Doxylamine and Pyridoxine in Patients with Nausea and Vomiting of Pregnancy

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Abstract

Objective—Women often hesitate to take medications in pregnancy due to fears of perceived potential fetal damage. The authors' objective is to identify the determinants of adherence to delayed release doxylamine-pyridoxine (Diclectin®) in patients with nausea and vomiting of pregnancy (NVP).

Methods—The authors performed a pre-specified secondary analysis of a multicenter double blind randomized controlled trial of Diclectin® vs. placebo for the treatment of NVP. Data on adherence to study medication were collected in all patients. The primary outcome of this analysis was adherence with study medication, which was determined by pill counting and patient diaries. The treatment regimen in the original trial was not fixed and depended on patient's symptoms. There was no difference in the adherence rates between subjects in the Diclectin® or placebo arms of the study, so the 2 arms were analyzed as one cohort. The degree of adherence was analyzed in the various subgroups. Subsequently, a multiple linear regression model was constructed to identify predictors to adherence.

Results—258 women were included in this analysis. There was no difference in adherence rates according to ethnicity, race or the presence of adverse events. Gravidity, average number of prescribed tablets per day, site of enrollment, and change in NVP severity measured by the pregnancy unique-quantification of emesis (PUQE) score were associated with adherence. In multivariable analysis, average number of tablets per day, change in PUQE, number of treatment days, site of enrollment were significantly predictive of adherence, with the former being negatively correlated.

Conclusion—adherence to antinauseants for NVP is affected by number of tablets prescribed per day, and treatment duration and effectiveness.

Keywords

adherence; nausea and vomiting of pregnancy; pyridoxine; doxylamine

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INTRODUCTION

Nausea and vomiting of pregnancy (NVP) is a common condition that affects the quality of life and health of up to 70%–85% of pregnant women.¹ It combines a spectrum of symptoms, and in its most extreme form, can lead to hyperemesis gravidarum (HG). HG affects 0.5%–2% of pregnant women and manifests as persistent NVP associated with weight loss (>5% of prepregnancy weight), electrolyte imbalances, ketonuria, and dehydration. HG is the most common indication for admission to the hospital in early pregnancy.¹ NVP, and HG in particular, impose a large economic burden (direct and indirect), particularly as it relates to productivity losses.² Although mild NVP may be managed with dietary and life style modification, more severe forms and HG often require pharmacological treatment.³ Most commonly, women will continue their medications until their symptoms improve, at that point they switch to medications on an “as needed” basis. Further review on the management of NVP in pregnancy is described elsewhere. (1, 3) A delayed-release combination of doxylamine succinate and pyridoxine hydrochloride has not been marketed in the US since 1983 despite its efficacy and proven safety.^{3–7} Recently, the Obstetric Pharmacology Research Unit Network, Eunice Kennedy Shriver National Institute of Child and Human Development, and the Mothersick Program of the Hospital for Sick Children and University of Toronto conducted and reported a randomized and placebo-controlled clinical trial of a similar doxylamine succinate-pyridoxine hydrochloride delayed-release formulation [Diclectin (Duchesnay Inc, Blainville, QC, Canada)],⁸ providing the data for this secondary analysis focused on adherence. In that trial, pregnant women treated with Diclectin had greater improvement in their nausea and vomiting symptoms, as well as overall quality of life score compared with those who received placebo. In addition, Diclectin was well tolerated by pregnant women.⁸

Understanding the factors that influence pregnant patients' adherence to study medications may aid clinicians in identifying patients at risk for poor adherence and resultant suboptimal treatment response in usual clinical practice. Pregnant women often hesitate to use medications in pregnancy due to perceived fetal risk, even for medications proven safe during gestation. Our objective in this study was to identify determinants of adherence to study medications in this cohort of pregnant women with NVP.

METHODS

Study Design

This was a planned secondary analysis of a multicenter, double blind randomised controlled trial of the delayed-release combination of doxylamine succinate (10 mg) and pyridoxine hydrochloride (10 mg) (Diclectin®, Duchesnay Inc., Blainville, QC, Canada) vs. placebo for the treatment of NVP. Women who had singleton pregnancies between 7 and 14 weeks with NVP, and who had not responded to conservative management of lifestyle and dietary modifications, were randomized to receive either Diclectin® or a similar appearing placebo.⁸ Women were excluded if they had previously received other antiemetics or had other medical conditions during the current pregnancy. Women were enrolled at three university medical centers in the US between 2008 and 2009. The treatment regimen was not fixed and depended on patient's symptoms. Briefly, the minimum assigned dose of study medication was 2 tablets per day, and it was increased by the provider to a maximal dosage of 4 tablets per day according to the severity, duration and frequency of symptoms experienced by the patient. Details about the trial design and treatment regimen are described elsewhere.⁸ Subjects enrolled in the trial and who had available data on adherence to study medication were included in this secondary analysis. The current study is a secondary analysis of de-identified data from a published study (clinical trial registration no.

NCT00614445) where ethics has been specified and IRB approval was obtained from all participating sites.⁸

The primary outcome of this analysis was adherence with study medication, determined by tablet counting at each visit, compared with the number of tablets prescribed. In addition, the participants filled a daily diary of their drug therapy and symptoms. Overall adherence percentage was calculated by counting the number of tablets remaining at day 14 of the Diclectin study and comparing it to the number of tablets that were prescribed during the whole Diclectin randomized clinical trial (RCT) period. We also determined the average number of tablets taken per day by dividing the number of total prescribed tablets by the number of treatment days. This was needed as some patients discontinued their treatment before day 14 of the study, with the most common reason was improvement in their symptoms. For those who got better and stopped their medications, they were considered compliant if they took their medications until the day of discontinuation. The diary log was used to corroborate the adherence rate determined from the pill count.

Data retrieved from the Diclectin RCT were used. Data retrieved and used in this study were comprised treatment arm (Diclectin or placebo), maternal age, ethnicity, race, obstetric history including gravidity and presence of NVP in previous pregnancies, and adverse effects during the diclectin RCT. The validated pregnancy unique-quantification of emesis (PUQE) score at enrollment and last available PUQE score were retrieved as well, and the change in the score (Delta PUQE) between these two time points was calculated. PUQE is a scoring system that assesses symptoms of nausea and vomiting as well as global well being.^{9,10}

Statistical Analysis

Data are reported as mean $\pm$ standard deviation, or median and interquartile range, when appropriate. The degree of adherence to study medication was compared between different groups using Student *t* test, 1-way ANOVA, or Kruskal-Wallis test as appropriate. The relation between adherence and various variables was assessed using Pearson correlation coefficient and Spearman correlation coefficient as appropriate. We subsequently constructed a multivariable linear regression model using the ENTER method in order to identify predictors to adherence. The covariates included in the model were treatment group (drug or placebo), number of tablets per day, Delta PUQE, gravidity, number of treatment days, NVP presence in previous pregnancies, and site of enrollment. Statistical analyses were performed using SPSS software, (IBM SPSS, version 17, Somers, NY).

RESULTS

Two hundred eighty women were randomly assigned to Diclectin® (n=140) or placebo (n=140). Seven (6.4%) subjects in the Diclectin® group and 12 (12.9%) in the placebo group withdrew their consent before receiving study medication, leaving 133 women in the Diclectin®-treated group and 128 in the placebo group for inclusion in the intent-to-treat effectiveness analysis. In the Diclectin® group, seven women were lost to follow-up, and 21 women discontinued treatment before day 14. In the placebo group, 19 women were lost to follow-up, and 30 women discontinued treatment.⁸ Of those who discontinued treatment before day 14, the majority stopped their medications because their symptoms improved, and those were considered compliant. For the current analysis, data were available for 131 and 127 women in the Diclectin and placebo arms, respectively.

There was no difference in the adherence rates between subjects in the Diclectin or placebo arms of the study (90.0 ± 14.5 vs. 86.5 ± 18.2 ; $P=0.08$) (Table 1); therefore, we combined the two arms and analyzed them as a single cohort. The overall rate of adherence in the study

was $88.2 \pm 16.5\%$. In univariable analysis, adherence was not associated with ethnicity, race, or the occurrence of adverse events. Patients who had experienced NVP in prior pregnancies had lower adherence rates in univariate analysis compared with those who did not experience it (86.1 ± 15.2 vs. 91.2 ± 17.7 ; $P=0.01$) (Table 1).

Patients' age, gravidity and gestational age at enrollment were 25.4 ± 5.8 years, 2 [0–8], and 9 [7–14] weeks respectively. There was no correlation between age and adherence (Pearson $r=-0.06$; $p=0.30$) or gestational age at enrollment and adherence (Spearman $r_s=-0.030$; $p=0.63$). However, gravidity and average number of tablets per day were negatively associated with adherence, whereas the delta PUQE score was positively associated with adherence (Table 2).

In multiple linear regression, we used the adherence rate as the dependent variable and treatment group, average tablets per day, delta PUQE, gravidity, number of treatment days, adverse effects, NVP in previous pregnancies, and site of enrollment as covariates. The model was statistically significant ($P<0.001$, $r=0.73$, $r^2=52.9\%$), with the following variables being significantly predictive of adherence: average tablets per day, delta PUQE, number of treatment days, and enrollment site (Table 3).

DISCUSSION

In this cohort of pregnant women with NVP, we found that the daily average number of tablets, the change in PUQE score from baseline to the end of study, and the number of treatment days were all predictive of adherence, with the former being negatively correlated. The rate of adherence was also different between the various enrollment sites. On the other hand, treatment assignment, gravidity, and presence of NVP in prior pregnancies were not associated with adherence to medication in this trial.

Adherence is defined as the extent to which patients take prescribed medications as directed by their health care providers.¹¹ Factors that have been shown to affect medication adherence may be grouped into patient-related (age, awareness of benefit of treatment, difficulty swallowing pills, inconvenience, remembering to take the drug, presence of depression or other comorbidities), therapy-related (drug adverse effects or benefits), and health-care-provider-related factors (explanation of importance of adherence, health care system, and ease of appointments and follow-up visits). Identifying predictors of adherence is important clinically, as poor adherence may lead to suboptimal treatment effectiveness or treatment failure, leading to worsening of disease, prolonged hospitalization, or a need for more aggressive management, as well as increased hospitalization and health care costs.^{12–14} Poor adherence to medications has been found to contribute from one- to two-thirds of all medication-related hospitalizations in the United States, resulting in additional cost of approximately \$100 billion a year.^{13–15} In pregnancy, this issue is further enhanced, as women often have anxiety due to real or perceived teratogenic effects of medications.

Based on our analysis, we believe that in the setting of NVP, and to improve adherence with treatment, the clinician should attempt to prescribe the lowest possible and most effective number of pills since the average number of tablets per day was found to be negatively associated with adherence: the higher the number of tablets, the lower the adherence to therapy. This relation has been demonstrated with iron supplementation in pregnant women with anemia, in whom adherence to iron supplements declined as the dosage of the medication increased,^{16,17} as well as to that of many medications outside of pregnancy and in various medical conditions.^{18–20} Additionally, we found that patients who responded better and had the most improvement in their PUQE score had the higher adherence. This perceived treatment efficacy has been previously reported to be a predictor of medication

adherence in multiple settings and disorders.^{21–23} This association between the change in PUQE score and adherence was found despite the fact that there was no difference in the adherence rates between subjects in the Diclectin® or placebo arms of the study. This may be related to the complex multifactorial etiology of adherence to medications. If this relation was simple, one would expect that adherence rates should have been higher in the Diclectin treatment arm than in the placebo arm. On the other hand, the positive relation of number of treatment days with adherence could have been confounded by patients who were lost to follow-up and thus had the lowest number of treatment days and lower adherence. The different adherence rates in the three sites of the study may be related to differences in practices and/or cultural differences at these sites.

The high rate of adherence in our study ($88.2 \pm 16.5\%$) is comparable to other clinical trials and, at least in part, may be inherent to the nature of the study. Women in this study were all part of a randomised trial in which they explicitly consented to take these medications, had an informed consent process which carefully discussed treatment safety, and had repeated, close, and supportive follow-up from study personnel. This may be different from usual clinical practice. High adherence rates are also observed more often among patients with acute and symptomatic conditions.^{11, 24}

The major strength of our study is that it was based on a multicenter randomised blinded trial where the outcomes were clearly defined and rigorously ascertained, and the data carefully collected in a standardised fashion. Patients were excluded if they had previously received other antiemetics. Our data were also considerably more accurate compared to the many adherence studies that rely on registry or administrative databases since data in the latter may be incomplete or missing, and the methods for ascertainment and data verification may be variable and inaccurate. However, our study suffered from being a secondary analysis, with all its inherent limitations, and no formal power analysis was performed. It relied on both pill count and patient diaries for measuring adherence, which may be biased. We additionally did not correct for loss to follow-up, as the analysis was based on the intent-to-treat principle, and we did not assess possible associations with other medical and psychiatric comorbidities (eg, depression), sociocultural and socioeconomic factors (eg, financial difficulties in obtaining the medications, language barriers, fear of taking medications during pregnancy), or genetic variances that may interfere with medication adherence.^{11, 25}

Various methods are used to assess adherence to medication, but none is considered to be a gold standard.^{11,25} Direct methods, such as direct observed pill intake and measurement of metabolites or drugs in blood, are considered more accurate and/or objective but are usually impractical for routine clinical use, are expensive, and may be biased by various patient behaviors.^{26, 27} In addition, measurement of drug and/or metabolite levels may be affected by the false-positive and false-negative rates of the test used to measure serum levels, as well as errors in experimental assays and pharmacokinetic and dosage variations of the drug. On the other hand, indirect measures of medication adherence include patient questionnaires, diaries, self reports, pill counts, electronic databases of prescription refills, medication electronic monitoring systems, and assessment of clinical response or measures of physiologic markers. Most are easy to perform (such as pill count), and some provide objective measures; however, each method has its own limitations. For example, the self reports and pill counts may suffer from patient recall errors, self-report distortion, or data altering, as patients tend to exaggerate the degree of adherence to their health care providers.^{11, 21, 28, 29} Also, the degree of clinical response or change in physiologic markers is also dependent on many other parameters besides adherence.^{11, 25}

Study medication adherence is an important parameter when evaluating a treatment trial since poor compliance can reduce the power of the study and cloud the interpretation of the results. Conversely, good compliance strengthens the confidence in the results and supports the conclusions. In this cohort of pregnant women with NVP, we found the rate of adherence to treatment to be high and identified factors that influenced it, which may assist clinicians in usual practice.

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Table 1

Rates of adherence to study medications in the entire cohort.

	Adherence (%)	P
Treatment group		
Diclectin (n=131)	90.0±14.5	0.08*
Placebo (n=127)	86.5±18.2	
Sites of enrollment:		
Washington Hospital Center, Washington, DC (n=57)	88.1±17.6	0.04**
University of Texas Medical Branch, Galveston, TX (n=131)	91.8±11.4	
Magee-Women's Hospital, Pittsburg, PA (n=70)	84.4±18.4	
Ethnic groups		
Hispanic or Latino n=109	89.0±17.94	0.57*
non Hispanic or Latino n=149	87.8±15.4	
Race		
Black or African American n=98	88.0±15.4	0.30***
White n=154	89.0±16.9	
Others n=6 [¶]	75.2±19.1	
Adverse effects		
With AE n=139	87.3±14.6	0.28*
No AE n=118	89.5±18.4	
NVP in previous pregnancies		
With n=146	86.1±15.2	0.01*
Without n=112	91.2±17.7	

P was calculated using: Student's t-test *, One way ANOVA ** or Kruskal-Wallis *** test

[¶]Asians=3, 3 unknowns

Table 2

Correlation of different variables with adherence to study medication.

Variable	Correlation with adherence	P
Age *	-0.06	0.30
Gravidity **	-0.17	0.006
Delta PUQE *	0.38	<0.001
Average tablets per day *	-0.54	<0.001

* Pearson correlation,

** Spearman correlation;

Delta PUQE = delta of pregnancy unique-quantification of emesis score (mean = 4.3 ± 2.8)

Table 3

multivariable linear regression of adherence to study medication

Variable	Beta	P
Gravidity	−0.26	0.61
Treatment group	−0.29	0.85
Delta PUQE	0.73	0.02
Average tablets per day	−8.55	<0.001
Number of treatment days	1.70	<0.001
NVP in prior pregnancies	−2.37	0.17
Site of enrolment		
Washington Hospital Center, Washington, DC (reference)	1	
University of Texas Medical Branch, Galveston, TX	4.52	0.019
Magee-Women's Hospital, Pittsburg, PA	7.0	0.001

Delta PUQE = delta of pregnancy unique-quantification of emesis score; NVP = nausea and vomiting of pregnancy