OBSTETRICS

Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial

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OBJECTIVE: To evaluate the effectiveness of Diclectin (doxylamine succinate 10 mg-pyridoxine hydrochloride 10 mg, delayed-release preparation) as compared with placebo for nausea and vomiting of pregnancy.

STUDY DESIGN: A randomized, double-blind, multicenter placebo controlled trial studying pregnant women suffering from nausea and vomiting of pregnancy, analyzed by intention to treat. Women received Diclectin (n = 131) or placebo (n = 125) for 14 days. Nausea and vomiting of pregnancy symptoms were evaluated daily using the pregnancy unique quantification of emesis scale.

RESULTS: Diclectin use resulted in a significantly larger improvement in symptoms of nausea and vomiting of pregnancy compared with placebo based on both the pregnancy unique quantification of emesis score (-4.8 ± 2.7 vs -3.9 ± 2.6; $P = .006$) and quality of life. After the trial, 64 (48.9%) women receiving Diclectin asked to continue compassionate use of their medication, as compared with 41 (32.8%) of placebo-treated women ($P = .009$).

CONCLUSION: Diclectin delayed release formulation of doxylamine succinate and pyridoxine hydrochloride is effective and well tolerated in treating nausea and vomiting of pregnancy.

Key words: doxylamine, effectivenss, nausea and vomiting of pregnancy, pyridoxine, safety

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Nausea and vomiting of pregnancy (NVP) is the most common medical condition during gestation, affecting up to 80% of expecting mothers. Whereas changes in nutrition and lifestyle may alleviate the symptoms of some women, pharmacotherapy is needed in many cases.[1,2]

The delayed-release combination of doxylamine succinate and pyridoxine hydrochloride (Bendectin; Merrell Dow Pharmaceuticals, Kansas City, MO) was the most commonly used antiemetic for NVP and the only one approved by the Food and Drug Administration (FDA) until its voluntary removal from the market in 1983, after a large series of lawsuits alleging an excess of birth defects.[3] Since that time, no other product has been marketed in the United States with labeling to support its safe and effective use for NVP.[4] In 1983[4] and again in 1999,[5] the FDA determined that the combination of doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg (Bendectin), had not been withdrawn from sale for reasons of either safety or effectiveness. Indeed, its effectiveness was supported by the observation that hospitalizations of pregnant women for the severe form of NVP, hyperemesis gravidarum, increased 2-fold, after its removal from the American market.[6,7] Over the last 3 decades many studies and 2 metaanalyses have confirmed the fetal safety of this drug combination.[8,9] This same drug combination, reformulated as Diclectin (Duchesnay Inc, Blainville, QC, Canada), is widely used in Canada. The delayed-release characteristics of this combination are designed to allow dosing at bedtime, when NVP tend to be minimal, in order to counteract the typically increased symptoms in the morning.[10,11] Because no randomized control trial has evaluated the effectiveness of this new formulation of doxylamine succinate-pyridoxine hydrochloride for NVP to allow its reintroduc-

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TABLE 1
Pregnancy unique-quantification of emesis and global assessment of well-being[12-14]

Motherisk PUQE Scoring System (*please tick box and write total score)*					
1. In the last 24 h, for how long have you felt nauseated or sick at your stomach,	Not at all (1)	≤1 h (2)	2-3 h (3)	4-6 h (4)	>6 h (5)
2. In the last 24 h, have you vomited or thrown up,	≥7 times (5)	5-6 (4)	3-4 (3)	1-2 (2)	I did not throw up (1)
3. In the last 24 h, how many times have you had retching or dry heaves without bringing anything up,	No time (1)	1-2 (2)	3-4 (3)	5-6 (4)	≥7 times (5)
Global assessment of well-being					
How many hours have you slept out of 24 h?					
If this is not your normal sleep hours, why?					
On a scale of 0-10, how would you rate your *Well Being* in the last week?					
Reference Scale 0 (Worst possible) to 10 (The best you felt before pregnancy)					
Can you tell me what causes you to feel that way?					

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tion to practice in the United States, we undertook this randomized, double-blind trial, comparing Diclectin and placebo to treat NVP.

Materials and Methods

This was a double-blind, randomized, multicenter, placebo-controlled study of the delayed-release combination of doxylamine succinate (10 mg) and pyridoxine hydrochloride (10 mg) (Diclectin) in the treatment of NVP. Women were recruited in 2008-2009 in 3 university medical centers: The University of Texas in Galveston, TX, University of Pittsburgh, Pittsburgh, PA, and Georgetown University, Washington, DC. All subjects were pregnant, at least 18 years of age, in the gestational age range of 7-14 weeks, had a NVP, had a pregnancy unique quantification of emesis (PUQE) score ≥ 6 (Table 1),[12-14] and had not responded to conservative management consisting of dietary/lifestyle advice according to the 2004 American College of Obstetrics and Gynecology (ACOG) practice bulletin.[15] Women treated with other antiemetics, having chronic medical conditions, or those who could not communicate in either English or Spanish, were excluded. After normal physical examination and laboratory tests (hemoglobin and blood count, liver function tests, electrolytes, amylase), and after confirming in utero singleton pregnancies by ultrasound, women were randomly assigned to receive Diclectin or a similar-appearing placebo. Interactive voice response system (IVRS) provided study sites the ability to randomly assign a subject, report a study clinic visit, early termination of a subject, report receipt of drug, manage drug supply, replace lost or damaged drug, report an unscheduled visit, report study completion, report a compassionate visit, and report compassionate use subject discontinuation.

In recent studies on the effect of 500 mg ginger or 10 mg vitamin B6 on "nausea score" and on number of vomiting episodes, a sample size of 64 per group showed significant differences at power of 90% and alpha of .001. Therefore, for this study, 280 patients (140 patients per treatment group) were enrolled to achieve 200 evaluable patients.

Two tablets of study drug (Diclectin or placebo) were administered at bedtime on day 1. If symptoms of nausea and vomiting persisted into the afternoon hours of day 2 (ie, PUQE score >3), the subject was directed to take her usual dose of 2 tablets at bedtime and an additional tablet the next morning on day 3. Based on assessment in the clinic on day 4 (± 1 day), the subject might have been directed to take an additional (fourth) tablet in the midafternoon to control evening symptoms. Therefore, the minimum assigned dose of study medication was 2 tablets daily at bedtime, increasing when indicated to the maximal dosage of 4 tablets per day according to the timing, duration, severity, and frequency of the symptoms experienced by the subject. This was a 15-day study, which included 14 days on which study drug was administered. Telephone contact was made on days 2, 6, 12, and 14 to assess subject diary information, adverse events (AEs), concomitant medications, and compliance with the study medication. Patients returned to the clinic in the morning prior to their morning dose on day 4 (± 1 day), day 8 (± 1 day), and on day 15 (± 1 day; end of study visit) to collect diary report and complete all study-related data.

Subjects completed the PUQE score and the study diary once daily every morning before study dose at approximately the same time each day. Subjects completed the global assessment of well being scale of the PUQE on days 1, 8, and 14 at the same time that the PUQE score was completed.

AEs and concomitant medications were recorded at all visits and follow-up phone calls. A follow-up phone call was conducted 30 days after last dosing to capture any serious AEs for patients completing the treatment period or early termination. At the end of the 2-week trial, patients were offered compassion-