DICLECTIN THERAPY FOR NAUSEA AND VOMITING OF PREGNANCY: EFFECTS OF OPTIMAL DOSING

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Abstract

Objectives: (1) To quantify rates of suboptimal use of pyridoxine hydrochloride-doxylamine (Diclectin); and (2) to study responses to optimal doses of Diclectin in women previously taking a suboptimal dose.

Methods: Women who called the Motherisk NVP helpline, and were taking only Diclectin (vitamin B_6 10 mg and doxylamine 10 mg), were enrolled in the study and assessed for the severity of nausea and vomiting of pregnancy (NVP) with the Motherisk-PUQE (pregnancy-unique quantification of emesis and nausea) scoring system. Their Diclectin doses were subsequently increased according to body weight and individual symptoms. A follow-up phone call occurred within 1 to 3 weeks after the intervention, at which time the overall PUQE score was repeated, along with individual scoring of symptoms of nausea, vomiting, and retching.

Results: Sixty-eight women were enrolled and completed the study. Despite moderate to severe NVP, defined by the validated PUQE scoring system, most women (50/68) were receiving 2 tablets a day of Diclectin instead of the recommended dose of 4 tablets a day. Following a mean doubling of the dose to 4 tablets a day, there was a significant decrease in length of nausea (from 4 to 3 hours, $P < 0.001$), frequency of vomiting (from mean 1.6 to 1.3 a day, $P = 0.02$), and overall PUQE score (from mean 7.5 to 6.1, $P < 0.001$).

Conclusion: Women suffering from NVP are often given subtherapeutic doses of Diclectin. Women should receive a dosage according to their body weight and severity of their symptoms.

Résumé

Objectifs : (1) Mesurer les taux d'utilisation sous-optimale du chlorhydrate de pyridoxine et du succinate de doxylamine (Diclectin); et (2) étudier les réactions à des doses optimales de Diclectin chez des femmes antérieurement traitées selon une dose sous-optimale.

Méthodes : On a inscrit dans cette étude des femmes qui avaient téléphoné à la ligne-info NVG de Maternité sans risque et qui ne prenaient que du Diclectin (10 mg de vitamine B_6 et 10 mg de doxylamine); on a évalué la gravité de leurs nausées et vomissements de grossesse (NVG) au moyen du système de cotation Motherisk-PUQE (*pregnancy-unique quantification of emesis and nausea*). Par la suite, leurs doses de Diclectin on été augmentées selon leur poids corporel et leurs symptômes individuels. De 1 à 3 semaines après l'intervention, les participantes ont reçu un appel téléphonique au cours duquel on a réévalué le score global PUQE, ainsi que les scores individuels sur les symptômes de nausées, de vomissements et de haut-le-cœur.

Résultats : Soixante-huit femmes ont été inscrites à l'étude et l'ont terminée. En dépit du fait qu'elles avaient des NVG allant de modérés à graves, selon le système de cotation validé PUQE, la majorité des femmes (50/68) prenait 2 comprimés par jour de Diclectin, plutôt que les 4 comprimés par jour recommandés. Après avoir doublé la dose moyenne à 4 comprimés par jour, on a constaté une baisse statistiquement significative de la durée des nausées (de 4 à 3 heures, $p < 0,001$), de la fréquence des vomissements (de 1,6 à 1,3 par jour en moyenne, $p = 0,02$) et du score global PUQE (de 7,5 à 6,1 en moyenne, $p < 0,001$).

Conclusion : Les femmes présentant des NVG se voient souvent prescrire des doses subthérapeutiques de Diclectin. La posologie administrée devrait être proportionnelle à leur poids corporel et à la gravité de leurs symptômes.

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Key Words
Nausea and vomiting of pregnancy, Diclectin, pyridoxine hydrochloride, doxylamine

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INTRODUCTION

Up to 80% of pregnant women are affected by nausea and vomiting,[1] with 0.5% to 2% suffering from hyperemesis gravidarum,[2] which may lead to dehydration and hospitalization.[2] Symptoms of nausea and vomiting of pregnancy (NVP) usually start 4 to 6 weeks into the pregnancy and peak around 10 to 12 weeks, sometimes persisting throughout pregnancy.[3]

Severe NVP can profoundly affect the health and quality of life of pregnant women.[2] About 50% of working women believe that their daily activities are reduced by NVP and 25% of them are unable to go to work at all.[3] Unfortunately, two-thirds of women have similar symptoms in successive pregnancies.[3]

There are a number of effective pharmacological agents for the treatment of NVP. Diclectin is a combination of 10 mg of doxylamine and 10 mg of vitamin pyridoxine hydrochloride in a delayed-release formulation.[4] The recommended dosage is 2 tablets at night, to combat NVP in the morning, then a third tablet to be taken in the morning and a fourth in the afternoon.[4] Numerous studies, including 2 large meta-analyses, have shown the reproductive safety of Diclectin.[5,6] We have recently shown the fetal safety of doses larger than 4 tablets a day, as well as their tolerability by the mother.[7]

The Motherisk Program is a counselling service for women and their health-care professionals regarding the safety of drugs, chemicals, radiation, and infectious diseases during pregnancy and lactation. The Nausea and Vomiting helpline was established in 1996 to counsel women and their health-care providers in Canada and the United States on the evidence-based management of this condition. It became apparent that a significant number of the women calling the Motherisk NVP helpline were prescribed subtherapeutic doses of Diclectin, possibly due to misperception regarding risk to the fetus.[8]

The objective of this study was to evaluate the efficacy of Diclectin when used in optimal doses.

METHODS

Women who called the Motherisk NVP helpline between 2001 and 2002, and had been taking only Diclectin in addition to prenatal vitamins, were approached to be enrolled in the study. Those women who were concomitantly taking other antiemetic drugs, or had medical conditions that may affect nausea and vomiting, were excluded, as were women who had taken Diclectin for less than 3 days prior to their call (based on the data that at least 3 days are required for an adequate response to Diclectin).[9]

The severity of nausea and vomiting was measured by the Motherisk-PUQE (pregnancy-unique quantification of emesis and nausea) scoring system. Recently created and validated by our team,[10] the system scores nausea, vomiting, and retching separately, as reported by women in the last 12 hours prior to their call (Table 1).[10] In addition to description of the symptoms as continuous variables (hours of nausea and frequency of vomiting and retching), the scoring system allows categorization of the NVP into mild, moderate, and severe, based on clinical presentation. The mg/kg of body weight dose of Diclectin and severity of each symptom were also recorded.

Based on actual body weight and severity of NVP as measured by PUQE, each woman was advised to increase her dose of Diclectin. Women were advised to communicate this advice to their physicians, and, as needed, we communicated the information to the physicians. The increased dosage was calculated such that each woman received at least 0.6 mg/kg/day of each component of Diclectin.[4] For example, a woman with a PUQE score of 8, weighing 65 kg or more, and taking 2 tablets a day, was instructed to increase her Diclectin intake to 4 tablets a day. A woman with a PUQE score of 10, weighing 90 kg, was advised to take 6 tablets a day. We then informed the participating women that they would receive a follow-up phone call in 3 weeks to assess changes in symptoms by repeating the PUQE and individual scores of each symptom. In the follow-up phone call, the women were also asked if they had suffered any side effects from the increased dose of the drug.

The primary outcome of interest was the change in PUQE score. Secondary endpoints were changes in each symptom. A paired *t*-test was used to compare changes between first and second measurements of severity of nausea and vomiting (PUQE and individual symptoms). The Bonferroni correction was used to account for multiple comparisons. A sample size of

TABLE 1

PUQE (PREGNANCY-UNIQUE QUANTIFICATION OF EMESIS AND NAUSEA) SCORE[10]

Question	Descriptors (score assigned)				
1. In the last 12 hours, for how long have you felt nauseated or sick to your stomach?	**Not at all** (1)	**1 hour or less** (2)	**2–3 hours** (3)	**4–6 hours** (4)	**More than 6 hours** (5)
2. In the last 12 hours, have you vomited or thrown up?	**7 or more times** (5)	**5–6** (4)	**3–4** (3)	**1–2** (2)	**I did not throw up** (1)
3. In the last 12 hours, 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 or more** (5)
Total score* <6: mild; 7–12: moderate; ≥13: severe.					

*The categorical cut-off (mild, moderate, severe) is based on the original method described by Rhodes *et al.*[13]

TABLE 2

EFFECTIVENESS OF DICLECTIN (MEAN ± SD OF THE FIRST CONTACT VS FOLLOW-UP)*

	1 Call	2 Calls	P
Diclectin dose mg/kg/day	0.40 ± 0.22	0.66 ± 0.21	<0.0001
Nausea hours/day	4.01 ± 1.29	3.19 ± 1.63	<0.001
Vomiting number/day	1.59 ± 0.97	1.26 ± 0.61	0.021
Retching number/day	1.88 ± 1.25	1.63 ± 1.20	0.107
PUQE score	7.48 ± 2.46	6.06 ± 2.69	<0.001

*Paired Student's *t*-test with Bonferroni correction using SigmaStat (version 2.03).

50 women was needed to show a difference of 1 unit in PUQE score (pre and post) with a power of 80% and alpha of 0.05. Seventy women were recruited to correct for potential attrition.

The study was approved by the Research Ethics Board at the Hospital for Sick Children.

RESULTS

Of the 70 women who called the Motherisk NVP helpline between 2001 and 2002, met the inclusion criteria, and were enrolled, 68 completed the study. The mean age of the women was 31 ± 3 years and the mean gestational age at the time of first contact was 9 ± 2 weeks. Most of the women (91%) were Caucasians and 57% had a college or university education. None of the women reported smoking cigarettes or consuming alcohol. One woman reported using cocaine. Most of the women (88%) were taking prenatal vitamin supplements. Thirty-five women were cared for by a family physician, 15 by an obstetrician, and 18 by a midwife.

Although the women in the study were suffering from NVP rated as moderate to severe, based on the validated PUQE score, at the time of enrollment the mean dose of Diclectin that they had been taking was 2 tablets a day (0.40 mg/kg/day), which is half of the recommended dose of 4 tablets a day. Following enrollment, the dose was increased to a mean of 4 tablets a day (0.66 mg/kg/day). Some of the women (26.4%) needed 5 to 8 tablets a day to control their symptoms.

This increased dose resulted in a significant decrease in the PUQE score ($P < 0.001$) and in the severity of nausea ($P < 0.001$) and vomiting ($P < 0.02$) at the follow-up time of 1 to 3 weeks (mean 1.9 ± 1.4 weeks), as shown in Table 2. The retching score was not significantly changed in follow-up ($P = 0.11$). Most of these changes were reported as occurring within 3 days of the increased dose (Table 3). The most commonly reported adverse effects of Diclectin were drowsiness and sleepiness (31%).

DISCUSSION

To our knowledge, this is the first interventional study to document that pregnant women suffering from NVP are taking subtherapeutic doses of Diclectin. The women who contacted the Motherisk NVP helpline suffered from unresolved symptoms, yet on average they were prescribed and received only half (2 tablets/day) of the label-recommended dose or even less

TABLE 3

CHANGES IN SYMPTOMS AND PUQE SCORE AFTER OPTIMIZING DOSE OF DICLECTIN (N = 68)

	Improvement of Symptoms	The Same	Symptoms Worse
Symptoms	**No. of Women (%)**	**No. of Women (%)**	**No. of Women (%)**
PUQE	39 (56.7)	12 (17.9)	17 (25.4)
Nausea	30 (42.6)	28 (42.0)	10 (14.7)
Vomiting	20 (27.9)	40 (58.8)	9 (13.2)
Retching	19 (28.4)	39 (57.3)	10 (14.9)

(1 tablet/day). Our intervention shows that when these women were prescribed the recommended dose of Diclectin according to individual body weight, overall symptoms improved significantly. The improvement of 1.4 points in the PUQE score represents a medium to large effect size (i.e., 0.56 of the standard deviation of the score).

Previous studies[11] have found that antiemetic drugs are often more efficacious for vomiting than for nausea, despite the fact that women complain that constant nausea exerts a heavier toll on them than vomiting (which often provides relief).[1] In the present study, women reported that when they were taking an optimal dose of Diclectin, their nausea was also significantly improved. These results suggest that, in many cases, a higher dose of an antiemetic may be required to alleviate nausea, which may be an important finding for women suffering from constant nausea during pregnancy.

There are limitations to our study, the main one being that this was not a population-based sample, as the women who called the Motherisk NVP helpline were self-selected. Women often call the helpline as their last resort after being unable to control their NVP symptoms on their own. Consequently, our data may not be easily extrapolated to the general population. We speculate that women and their health-care providers are reluctant to increase the dose when necessary, probably due to fears of teratogenicity.

It could be argued that, with a lack of a control group, it is possible that the improvement merely represents the natural course of many cases of NVP. However, the improvement was recorded within 3 days of the increased dose in all cases, strongly suggesting that the improvement in symptoms was a treatment-related effect. It will be important to repeat this study with a control group.

Despite the large evidence of fetal safety,[5,6] Bendectin (the original form of Diclectin) was removed from the United States' market due to litigation cost. The Food and Drug Administration and Health Canada repeatedly reaffirmed the safety of this preparation.[14] Similar results have been found with the prescribing of antidepressants in pregnancy, where women were taking subtherapeutic doses despite the fact that they were suffering from severe depression.[12]

In summary, it is critical that women with NVP be treated optimally according to their body weight, severity of symptoms, and response to treatment. This will ensure the best possible outcome in controlling this common condition of pregnancy that can exert heavy physical, emotional, and economic burdens on the pregnant woman.

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REFERENCES

1. Goodwin TM. Nausea and vomiting of pregnancy: an obstetric syndrome. Am J Obstet Gynecol 2002;185:5184–9.
2. Attard CL, Kohl MA, Coleman S, Bradley C, Huyx M, Atanackovic G, et al. The burden of illness of severe nausea and vomiting of pregnancy in the US. Am J Obstet Gynecol 2002;S215–9.
3. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. Br J Gen Pract 1993;43(371):245–8.
4. Levichek Z, Atanackovic G, Oepkes D, Maltepe C, Einarson A, Magee L, et al. Nausea and vomiting of pregnancy. Evidence-based treatment algorithm. Can Fam Physician 2002;48:267–8, 277.
5. Einarson T, Leeder S, Koren G. A method for meta-analysis of epidemiological studies. Drug Intell Clin Pharm 1988;22:813–24.
6. McKeigue P, Lamm S, Linn S, Kutcher J. Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. Teratology 1994;50:27–37.
7. Atanackovic G, Navioz Y, Moretti M, Koren G. The safety of higher than standard dose of doxylamine-pyridoxine (Diclectin) for nausea and vomiting of pregnancy. J Clin Pharmacol 2001;41:842–5.
8. Koren G, Levichek Z. The teratogenicity of drugs for nausea and vomiting of pregnancy: perceived versus true risk. Am J Obstet Gynecol 2002;186:S2498–252.
9. Bishai R, Mazzotta P, Atanackovic G, Levichek Z, Pole M, Magee LA, et al. Critical appraisal of drug therapy for nausea and vomiting of pregnancy: II. Efficacy and safety of Diclectin (doxilamine-B6). Can J Clin Pharmacol 2000;7(3):138–43.
10. Koren G, Boskovic R, Hard M, Maltepe C, Navioz Y, Einarson A. Motherisk-PUQE (Pregnancy-Unique Quantification of Emesis and nausea) scoring system for nausea and vomiting of pregnancy. Am J Obstet Gynecol 2002;186:S228–31.
11. Zhou Q, O'Brien B, Relyea J. Severity of nausea and vomiting during pregnancy: what does it predict? Birth 1999;26(2):108–14.
12. Bonari L, Einarson A, Jasper JD, Einarson TR, Koren G. Determinants of decision making regarding the use of antidepressants during pregnancy [abstract]. Annual meeting of the Canadian Psychiatric Association. Banff, Alta, Canada; November 2002.
13. Rhodes VA, Watson PM, Johnson MH. Development of reliable and valid measures of nausea and vomiting. Cancer Nurs 1984;7:33–41.
14. Arsenault MY, Lane CA. The management of nausea and vomiting of pregnancy. SOGC Clinical Practice Guideline No. 120, October 2002. J Obstet Gynaecol Can 2002;24(10):817–23.