PHARMACOKINETIC COMPARISON OF A DELAYED- RELEASE COMBINATION OF DOXYLAMINE SUCCINATE AND PYRIDOXINE HYDROCHLORIDE (DICLECTIN®) AND ORAL SOLUTIONS OF THESE DRUGS IN HEALTHY WOMEN OF CHILDBEARING AGE

Irena Nulman, Gideon Koren

The Motherisk Program, Division of Clinical Pharmacology & Toxicology, The Hospital for Sick Children; University of Toronto, Toronto, Canada

Corresponding Author: gkoren@sickkids.ca

ABSTRACT

Background
The delayed-release combination of doxylamine succinate and pyridoxine hydrochloride was the most commonly used antiemetic (Bendectin) approved by FDA for nausea and vomiting of pregnancy (NVP) until its removal of the market in 1983. The drug is widely used today in Canada (Diclectin®). The pharmacokinetics of Diclectin® has never been described in humans.

Objectives
To compare the pharmacokinetics of Diclectin® to oral solutions of its two components.

Subjects and Methods
A randomized, cross over, open label design, comparing the pharmacokinetics of Diclectin® to those of the oral solutions of the two components in 18 healthy adult, non pregnant women of childbearing age.

Results
Diclectin® exhibited similar oral bioavailability to those of the oral solutions. In contrast, the time-to-peak, (Tmax), reflecting the rate of absorption, was 3-6 times longer for the two components of the delayed-release drug confirming its delayed-release characteristics.

Conclusion
The pharmacokinetic profile of Diclectin® well explains its documented delayed efficacy.

Keywords*: Nausea and vomiting of pregnancy; pregnancy; pharmacokinetics; doxylamine succinate; pyridoxine chloride; pyridoxal, pyridoxamine, pyridoxal-5 phosphate*

The delayed-released combination of doxylamine succinate and pyridoxine hydrochloride (10 mg each) was introduced into the market in the 1950's to treat nausea and vomiting of pregnancy (NVP).[1]

These two components exhibited synergistic antinauseant effects. The rationale for the delayed-release combination was based on evening administration of two tablets, when NVP symptoms tend to be minimal, in order to achieve effective antiemetic levels in the morning, when symptoms are typically maximal.[2,3,4] This agent, marketed originally as Bendectin was used at its peak during the 1970s, by as many as 30% of pregnant American women.[5]

In 1983 Bendectin was removed from the market by its manufacturer due to litigations and despite mounting evidence of its fetal safety.[6] It

must be emphasized that Bendectin was never banned from sale in any country. In Canada this drug combination has been manufactured as Diclectin® (Duchesnay Inc.) since 1978.[7]

Because of its invention 50 years ago, before present regulatory standards were implemented, there have never been pharmacokinetic studies of the doxylamine-pyridoxine delayed-release combination published, and the nature of its absorption never documented pharmacokinetically. The current pharmacokinetic work was performed on Diclectin® tablets consisting of an acrylic based coating formula. This formulation allows for a delayed-release action, however, once reaching the small intestine a rapid absorption would occur.

In humans, doxylamine is biotransformed in the liver by N-dealkylation. Pyridoxine is primarily metabolised in the liver following a complex metabolic process with formation of the biologically active metabolites pyridoxal, pyridoxal 5'phosphate, pyridoxamine and pyridoxamine 5'phosphate.

The objective of the present study was to describe the pharmacokinetics of doxylamine-pyridoxine (Diclectin®) and their metabolites pyridoxal, and pyridoxal 5'phosphate, and to compare it to immediately released oral solutions of each of its two ingredients.

METHODS

Study Design

This was a single center, randomized, single dose, open-label, 2-way crossover study to compare the rate and extent of absorption of the delayed-release combination of doxylamine succinate-and pyridoxine hydrochloride administered as 2 × 10 mg-10 mg delayed-release tablets, vs. 20 mL × 10 mg/10 mL oral solutions (for a total dose of 20 mg of doxylamine succinate and 20 mg pyridoxine hydrochloride), under fasting conditions. Treatment periods were separated by a washout period of at least 28 days. Two tablets of Diclectin® were used because this is the recommended evening dose schedule of the medication. No higher doses of the drug are currently recommended. Although the study was open-label in nature, the randomization code was not available to the analytical facility (MDS Pharma Services, Blainville, Quebec).

Study Population

The study protocol was approved by the Ethics Review Committee. All clinical work was conducted in compliance with Good Clinical Practice Rules (GCP) (ICH E6). All subjects signed an informed consent prior to initiation of study procedures. Participating healthy non pregnant women ranged in age from 18 to 42 years, and their body mass indices ranged between 19.1 and 28.1 kg/m^2. It was deemed important to focus on women of reproductive age, because the only indication for the medication is nausea and vomiting of pregnancy and it is conceivable that the pharmacokinetics in men or in older women may differ considerably. Subject screening procedures included informed consent, medical history, demographic data (including sex, age, body weight (kg), height (cm) and BMI (kg/m2), medication history, physical examination, vital signs (blood pressure, respiratory rate, heart rate, and oral temperature), 12-lead ECG, clinical laboratory tests such as hematology, biochemistry, urinalysis, HIV and hepatitis C (HCV) antibodies, and hepatitis B antigen (HB_sAg), urine drug screen, alcohol breath test, and serum pregnancy test.

Women were randomised to receive first either two tablets of doxylamine succinate-pyridoxine hydrochloride (Diclectin®); 2×10 mg-10 mg delayed-release tablets, or oral solution of doxylamine succinate + pyridoxine hydrochloride from reconstituted powder (20 mL as 10 mg/10 mL, for a total dose of 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) with 240 mL of water. In the second study period, each woman received the other formulation. Subjects were served a controlled meal not less than 8 hours post-dose and standard meals at appropriate time thereafter, in each period. Subjects received identical meals in each period.

With the exception of the fluid administered at the time of dosing, water was not permitted from 1 hour before dosing to 1 hour after dosing, but was permitted ad libitum at all other times. All blood samples were drawn into blood collection tubes (1×10 mL) containing EDTA approximately 24 and 12 hours pre-dose, within 30 minutes pre-dose and 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 10.0, 12.0, 24.0, 48.0, 72.0, and 120.0 hours post-dose blood draws. The intense sampling in

the first few hours aimed at capturing in great detail the absorption phase, as the delayed absorption is the typical characteristic and purported advantage of Diclectin®. Samples were collected via a dead-volume intravenous catheter (when possible) and via direct venipuncture otherwise. Each subject completing this study did not exceed 614 mL. Blood samples were cooled in an ice bath and were centrifuged at 3,000 rpm for 10 minutes at proximately 4°C before plasma samples were transferred to a -80°C (-65°C to -85°C) freezer, pending shipment to the analytical facility.

Doxylamine, pyridoxine, and pyridoxal were measured in plasma using a validated LC/MS/MS method while pyridoxal 5' –phosphate was measured in plasma using a validated liquid chromatography with UV detector method. The standard curve ranges used for the analysis of plasma samples were from 1.00 ng/mL to 150 ng/mL for doxylamine and pyridoxine, from 15.0 ng/mL to 150 ng/mL for pyridoxal, and from 14.8 ng/mL to 196 ng/mL for pyridoxal 5' –phosphate.

The following pharmacokinetic values were calculated by standard non-compartmental methods for doxylamine, pyridoxine, pyridoxal, and pyridoxal 5'phosphate: $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, K_{el}, $T_{1/2el}$, and $F_{rel.}$

Using general linear models procedures in SAS®, we compared T_{max}, K_{el}, $T_{1/2el}$, and on ln-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and C_{max}, for the delayed-release vs. oral solution data, using WinNonlin Software. Factors incorporated in the model included: sequence, subject (sequence), period and treatment. Ratio of means (T/R) calculated using least-squares means from ANOVA of the ln-transformed data are present for these parameters.

RESULTS

Eighteen women of childbearing age completed the study, while an additional 4 did not complete the cross-over due to personal inability to commit the time and were not included in the analysis. During the study, no serious or significant adverse events were reported. For two subjects, the elimination rate constant could not be estimated properly due to an insufficient number of detectable concentrations in the terminal elimination phase as the last points were still exhibiting absorption. In two cases the concentration of pyridoxine, pyridoxal and pyridoxal 5' phosphate could not be used due to error in internal standards.

For doxylamine, pyridoxine, and pyridoxal the time-to peak (T_{max}) values were respectively 3 times, 6 times, and 4 times longer for the tablet formulation than for the oral solution ($P<0.0001$ for all). For pyridoxal 5' –phosphate, the T_{max} values were similar at approximately 8 hours. Consistently, the two drugs given in oral solutions were more rapidly absorbed than those given in Diclectin® tablets (Tables 1-4). Comparative bioavailability revealed similar extent of absorption for the Diclectin® tablets and oral solutions (Tables 1-4).

TABLE 1 Doxylamine Pharmacokinetic Values

PK parameter Geometric CI	Delayed-release tablets (mean ± SD)	Oral solution (mean ± SD)	Ratio[1]	90%
AUC_{0-t} (ng.h/mL)	1678.19 ± 548.62	1616.85 ± 458.79	103.27%	97.63% to 109.23%
AUC_{0-inf} (ng.h/mL)	1728.89 ± 571.19	1659.51 ± 469.57	103.53%	97.96% to 109.42%
C_{max} (ng/mL)	90.4 ± 13.1	98.7 ± 18.1	--	--
T_{max} (h)	6.10 ± 1.77*	2.04 ± 0.85*	--	--
K_{el} (h^{-1})	0.0630 ± 0.0159	0.0614 ± 0.0142	--	--
$T_{1/2el}$ (h)	11.76 ± 3.40	11.91 ± 3.03	--	--
F_{rel} (%)	104.51 ± 14.69	--	--	--

* P<0.0001
[1]Ratios between the two formulations based on least-square means

TABLE 2 Pyridoxine Pharmacokinetic Values

PK parameter Geometric CI	Delayed-release tablets (mean ± SD)	Oral solution (mean ± SD)	Ratio[1]	90%
AUC_{0-t} (ng.h/mL)	51.41 ± 23.22	64.95 ± 26.94	78.28%	66.94% to 91.55%
AUC_{0-inf} (ng.h/mL)	59.34 ± 22.35	66.37 ± 26.36	89.93%	79.33% to 101.96%
C_{max} (ng/mL)	50.7 ± 31.0	96.5 ± 46.7	--	--
T_{max} (h)	3.81 ± 1.20*	0.618 ± 0.179*	--	--
K_{el} (h^{-1})	2.4205 ± 0.9363	2.8223 ± 0.7059	--	--
$T_{1/2el}$ (h)	0.34 ± 0.15	0.26 ± 0.07	--	--
F_{rel} (%)	92.49 ± 21.71	--	--	--

* P<0.0001
[1]Ratios between the two formulations based on least-square means

TABLE 3 Pyridoxal Pharmacokinetic Values

PK parameter Geometric CI	Delayed-release tablets (mean ± SD)	Oral solution (mean ± SD)	Ratio[1]	90%
AUC_{0-t} (ng.h/mL)	124.02 ± 46.70	149.72 ± 50.18	80.57%	73.31% to 88.56%
AUC_{0-inf} (ng.h/mL)	175.86 ± 60.87	88.53 ± 66.49	91.53%	79.39% to 105.52%
C_{max} (ng/mL)	62.3 ± 19.1	82.8 ± 21.2	--	--
T_{max} (h)	4.84 ± 1.44*	1.15 ± 0.26*	--	--
K_{el} (h^{-1})	0.5989 ± 0.3002	0.6146 ± 0.1825	--	--
$T_{1/2el}$ (h)	1.51 ± 0.85	1.27 ± 0.59	--	--
F_{rel} (%)	96.11 ± 30.74	--	--	--

* P<0.0001
[1]Ratios between the two formulations based on least-square means

TABLE 4 Pyridoxal 5'-phosphate Pharmacokinetic Values

PK parameter Geometric CI	Delayed-release tablets (mean ± SD)	Oral solution (mean ± SD)	Ratio[1]	90%
AUC_{0-t} (ng.h/mL)	1678.90 ± 1238.14	1600.38 ± 1285.66	105.15%	88.73% to 124.61%
AUC_{0-inf} (ng.h/mL)	3094.17 ± 988.39	3451.65 ± 2130.13	102.45%	81.90% to 128.14%
C_{max} (ng/mL)	42.9 ± 17.5	41.6 ± 14.5	--	--
T_{max} (h)	8.59 ± 2.77	7.64 ± 3.88	--	--
K_{el} (h^{-1})	0.0150 ± 0.0066	0.0154 ± 0.0081	--	--
$T_{1/2el}$ (h)	55.64 ± 24.55	59.05 ± 31.77	--	--
F_{rel} (%)	109.58 ± 43.25	--	--	--

[1]Ratios between the two formulations based on least-square means

DISCUSSION

The objective of this study was to compare the rate and extent of absorption of Diclectin® delayed-release tablets versus a combination of oral solutions of doxylamine succinate and pyridoxine hydrochloride under fasting conditions. The study products were administered using a randomized, two-way crossover fasting study design. Each healthy woman received both treatments after a supervised fast of at least 8 hours, in accordance with the randomization schedule, with a washout period of 28 days between doses.

Our data show that Diclectin® delayed-release tablets are fully absorbed for both the doxylamine and pyridoxine components when compared to an equal dose administered as an oral solution of these medications. Importantly, our study documents for the first time the delayed-release characteristics of Diclectin®, achieving Tm several hours after administration, whereas the equivalent aqueous solution of these medications achieve peak plasma concentrations in less than one hour. The combination of delayed absorption and a similar extent of absorption to regular doxylamine and pyridoxine, well explains pharmacokinetically the delayed efficacy of the drug taken in the evening and exerting its effect in the morning

If the symptoms of retching, nausea and vomiting of pregnancy extend beyond the noon hours, a third delayed-release tablet taken in the morning can be expected to achieve its peak plasma concentrations in the early afternoon. A similar dose can be taken at noon, targeting peak levels if needed in the early evening.[2] The effectiveness and safety of Bendectin and Diclectin® have been documented in a large number of studies.[8-10]

It is noteworthy that it took a drug combination used by millions of pregnant women worldwide for a common condition over 50 years to be characterized pharmacokinetically in corroborating its clinical efficacy profile.

In summary, this study documents the delayed-release characteristics of Diclectin®, corroborating its pharmacodynamic antiemetic effect.[2] Future studies should focus on correlating the pharmacokinetics and antiemetic/antinauseant pharmacodynamics of doxylamine succinate and the active pyridoxine hydrochloride metabolites including pyridoxal, pyridoxal 5'phosphate, pyridoxamine and pyridoxamine 5'phosphate.

Conflict of Interest Statement

GK has been served as a paid consultant for Duchesnay Inc. - the manufacturer of Diclectin®.

Funding Support / Disclosures

Funding was supported by Duchesnay Inc., Canadian Institutes for Health Research grant, and by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation.

Acknowledgement

GK is holder of the Ivey Chair in Molecular Toxicology, Department of Medicine, University of Western Ontario, Canada.

REFERENCES

1. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Engl J Med 1998 April 6; 338(16):1128-37.
2. Levichek Z, Atanackovic G, Oepkes D, Maltepe C, Einarson A, Magee L, Koren G. Nausea and vomiting of pregnancy. Evidence-based treatment algorithm. Can Fam Physician 2002 Feb; 48:267-8, 277.
3. Magee LA, Mazzotta P, Koren G. Evidence-based view of safety and effectiveness of pharmacologic therapy for nausea and vomiting of pregnancy (NVP). Am J Obstet Gynecol. 2002 May; 186(5):S256-61.
4. Bishai R, Mazzotta P, Atanackovic G, Levichek Z, Pole M, Magee LA, Koren G. Critical appraisal of drug therapy for nausea and vomiting of pregnancy: II. Efficacy and safety of diclectin (doxylmaine-B6). Can J Clin Pharmacol. 2000 Autumn; 7(3):138-43.
5. Brent RL. Bendectin: review of the medical literature of a comprehensively studied human nonteratogen and the most prevalent tortogen-litigen. Reprod Toxicol. 1995;39337-49.
6. Brent R. Bendectin and birth defects: hopefully, the final chapter. Birth Defects Res A Clin Mol Teratol. 2003 Feb; 67(2):79-87.
7. Ornstein M, Einarson A, Koren G. Bendectin/diclectin for morning sickness; a Canadian follow-up of an American tragedy Reprod Toxicol. 1995 Jan-Feb; 9(1):1-6.
8. Boskovic R, Einarson A, Maltepe C, Wolpin J, Koren G. Diclectin therapy for nausea and

vomiting of pregnancy: effects of optimal dosing. J Obstet Gynaecol Can. 2003 Oct; 25(10):830-3.

9. Koren G, Maltepe C. Pre-emptive therapy for severe nausea and vomiting of pregnancy and hyperemesis gravidarum. J Obstet Gynaecol. 2004 Aug; 24(5):530-3.
10. Atanackovic G, Navioz Y, Moretti ME, Koren G. The safety of higher than standard dose of doxylamine-pyridoxine (Diclectin) for nausea and vomiting of pregnancy. J Clin Pharmacol. 2001 Aug; 41(8):842-5.