New Drug Overview
Diclegis® (doxylamine succinate/pyridoxine hydrochloride)

- **Overview/Summary:** Diclegis® (doxylamine succinate/pyridoxine hydrochloride) is a fixed dose combination drug product of doxylamine succinate, an antihistamine, and pyridoxine hydrochloride, a vitamin B6 analog. The agent is Food and Drug Administration (FDA)-approved for the treatment of nausea and vomiting of pregnancy (NVP) in women who do not respond to conservative management. It should be noted that the agent has not been studied in hyperemesis gravidarum.[1] The combination of doxylamine and pyridoxine was previously available in the United States under the brand name Bendectin®. However this product was removed from the market in 1983 due to law suits alleging teratogenicity, although scientific evidence supports the safety and efficacy of the medication. A meta-analysis of controlled studies on outcome of pregnancies exposed to Bendectin® reported no increase in the incidence of birth defects.[2]

  Doxylamine competes with histamine for H1-receptor sites and blocks the chemoreceptor trigger zone thereby decreasing nausea and vomiting. Antihistamine agents also work indirectly on the vestibular system by decreasing stimulation of the vomiting center. Hypotheses to explain the antiemetic effects of pyridoxine include prevention/treatment of vitamin B6 deficiency, intrinsic antinausea properties, and/or synergy with the antinausea properties of antihistamine.[1-3]

  Nausea with or without vomiting is common in early pregnancy and affects 70 to 85% of pregnant women.[2,4] Severe vomiting resulting in dehydration and weight loss is termed hyperemesis gravidarum and occurs infrequently. The treatment goals in patient with NVP are to reduce symptoms through changes in diet/environment and by medication, to correct consequences or complications of nausea and vomiting such as dehydration and to minimize the fetal effects of NVP treatment.[2]

Table 1. Dosing and Administration[1]

Generic Name	Adult Dose	Pediatric Dose	Availability
doxylamine succinate/ pyridoxine hydrochloride	Nausea and Vomiting of Pregnancy: Delayed-release tablet: Initial, two tablets QHS on day one; if symptoms persist into day two increase dose to one tablet QAM and two tablets QHS on day three; if symptoms continue increase to a maximum of four tablets per day with one in the morning, one in the mid-afternoon and two QHS	Safety and efficacy in children have not been established.	Delayed-release tablet: 10 mg/10 mg

NSAID=nonsteroidal anti-inflammatory drug

Evidence-based Medicine

- FDA-approval of Diclegis® (doxylamine succinate/pyridoxine hydrochloride) was based on one double-blind, randomized, multi-center, placebo-controlled study that evaluated the safety and efficacy of the agent in pregnant adult women in the gestational age range of 7 to 14 weeks with nausea and vomiting. Patients (N=298) were randomized to 14 days of placebo or two tablets daily at bedtime and up to a maximum dose of four tablets of doxylamine succinate/pyridoxine hydrochloride.[5] Doxylamine succinate/pyridoxine hydrochloride treatment resulted in a statistically significant improvement in both the symptom and quality of life domains of the Pregnancy Unique-Quantification of Emesis (PUQE) score. There was a 4.8 point mean decrease from baseline in the symptom domain PUQE score at day 15 in the doxylamine succinate/pyridoxine hydrochloride group compared to 3.9 point decrease in the placebo group. For quality of life, there was also a 2.8 point mean increase from baseline in the score at day 15 in the Diclegis® (doxylamine succinate/pyridoxine hydrochloride) group compared to a 1.8 point decrease in the placebo group.[5]

- A second study compared a five-day course of low-dose ondansetron to low-dose doxylamine succinate/pyridoxine hydrochloride. The study concluded that ondansetron provided a statistically significant reduction in the nausea and vomiting (P=0.019 and P=0.049, respectively). There were no difference between groups for the side effects of sedation or constipation (P=0.707 and P=0.412, respectively).[6]

Key Points within the Medication Class

- According to Obstetrician-Gynecologists Clinical Management Guideline for Nausea and Vomiting of Pregnancy[4]
  - Mild cases of nausea and vomiting may be resolved with lifestyle and dietary changes such as eating frequent small meals or avoiding spicy or fatty foods.
  - First-line pharmacotherapy with pyridoxine or in combination with doxylamine.
  - If initial therapy with pyridoxine monotherapy fails and if this is inadequate for symptom control then the addition of doxylamine is recommended.
  - For patients who fail this combination, promethazine or dimenhydrinate can be substituted for doxylamine. After this point, if the patient is still experiencing nausea and vomiting, options include metoclopramide, trimethobenzamide, methylprednisolone or ondansetron.

- Other Key Facts:
  - Only FDA-approved agent for the treatment of nausea and vomiting of pregnancy.
  - Initial dosing allows for once daily dosing.

References

1. Diclegis® [package insert]. Bryn Mawr (PA): Duchesnay USA, Inc; 2013 Sep.
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New Drug Review
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Overview/Summary

Diclegis® (doxylamine succinate/pyridoxine hydrochloride) is a fixed dose combination drug product of doxylamine succinate, an antihistamine, and pyridoxine hydrochloride, a vitamin B6 analog. The agent is Food and Drug Administration (FDA)-approved for the treatment of nausea and vomiting of pregnancy (NVP) in women who do not respond to conservative management. It should be noted that the agent has not been studied in hyperemesis gravidarum.[1] The combination of doxylamine and pyridoxine was previously available in the United States under the brand name Bendectin®. However this product was removed from the market in 1983 due to law suits alleging teratogenicity, although scientific evidence supports the safety and efficacy of the medication. A meta-analysis of controlled studies on outcome of pregnancies exposed to Bendectin® reported no increase in the incidence of birth defects.[2]

Doxylamine competes with histamine for H1-receptor sites and blocks the chemoreceptor trigger zone thereby decreasing nausea and vomiting. Antihistamine agents also work indirectly on the vestibular system by decreasing stimulation of the vomiting center. Hypotheses to explain the antiemetic effects of pyridoxine include prevention/treatment of vitamin B6 deficiency, intrinsic antinausea properties, and/or synergy with the antinausea properties of antihistamine.[1-3]

Nausea with or without vomiting is common in early pregnancy and affects 70 to 85% of pregnant women.[2,4] Severe vomiting resulting in dehydration and weight loss is termed hyperemesis gravidarum and occurs infrequently. The treatment goals in patient with NVP are to reduce symptoms through changes in diet/environment and by medication, to correct consequences or complications of nausea and vomiting such as dehydration and to minimize the fetal effects of NVP treatment.[2] According to the Obstetrician-Gynecologists Clinical Management Guideline for Nausea and Vomiting of Pregnancy, mild cases of nausea and vomiting may be resolved with lifestyle and dietary changes such as eating frequent small meals or avoiding spicy or fatty foods. For more severe cases, safe and effective treatments are available. The guideline recommends the use of monotherapy with pyridoxine or in combination with doxylamine as safe and effective and that these treatment options should be considered as first-line pharmacotherapy. A treatment algorithm provided in the guideline indicates initial therapy with pyridoxine monotherapy and if this is inadequate for symptom control then the addition of doxylamine is recommended. For patients who fail this combination, promethazine or dimenhydrinate can be substituted for doxylamine. After this point, if the patient is still experiencing nausea and vomiting, options include metoclopramide, trimethobenzamide, methylprednisolone or ondansetron.[4]

Indications

Diclegis® is indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

Pharmacokinetics

Table 1. Pharmacokinetics[1]

Generic Name	T_{max} (hours)	Excretion	Serum Half-Life (hours)
Doxylamine succinate	7.8	Urine	12.5
Pyridoxine hydrochloride	5.6	Urine	0.5

Clinical Trials

FDA-approval of Diclegis® (doxylamine succinate/pyridoxine hydrochloride) was based on one double-blind, randomized, multi-center, placebo-controlled study that evaluated the safety and efficacy of the agent in pregnant adult women in the gestational age range of 7 to 14 weeks with nausea and vomiting. Patients (N=298) were randomized to 14 days of placebo or two tablets daily at bedtime and up to a maximum dose of four tablets of Diclegis® (doxylamine succinate/pyridoxine hydrochloride).[5]

The primary efficacy endpoint was the change from baseline to day-15 in the symptom domain and the quality of life (QOL) domain of the Pregnancy Unique-Quantification of Emesis (PUQE) score. The symptom domain score incorporates the number of daily vomiting episodes, number of daily heaves, and length of daily nausea in hours, for an overall score of symptoms from 3 (no symptoms) to 15 (most severe). The QOL domain score incorporates patient's report of their present well-being from zero (worst possible) to 10 (best possible). [5]

Treatment with Diclegis® (doxylamine succinate/pyridoxine hydrochloride) resulted in a statistically significant improvement in both the symptom and QOL domains of the PUQE score. There was a 4.8 point mean decrease from baseline in the symptom domain PUQE score at day 15 in the Diclegis® (doxylamine succinate/pyridoxine hydrochloride) group compared to 3.9 point decrease in the placebo group. For QOL, there was also a 2.8 point mean increase from baseline in the score at day 15 in the Diclegis® (doxylamine succinate/pyridoxine hydrochloride) group compared to a 1.8 point decrease in the placebo group.[5]

Secondary endpoints included the day-by-day area under the curve for change in PUQE from baseline, time loss from employment and the number of women in each arm who continued with blinded compassionate use of their medication. The number of patients who reported concurrent use of alternate therapy for nausea and vomiting were also recorded. Finally safety was examined. [5]

The mean area under the curve of the change in PUQE from baseline was significantly larger with Diclegis® (doxylamine succinate/pyridoxine hydrochloride) than with placebo. There was also a trend toward more time lost from employment in the placebo group (2.37 days) compared to the Diclegis® (doxylamine succinate/pyridoxine hydrochloride) group (0.92); however, this difference was not statistically significant.[5]

At the end of the 15 day trial, a significantly higher percentage of patients in the Diclegis® (doxylamine succinate/pyridoxine hydrochloride) group (48.9%) compared to in the placebo group (32.8%) requested to continue compassionate use of their medication. Significantly more patients receiving placebo (36%) requested alternate therapies for nausea and vomiting compared to the Diclegis® (doxylamine succinate/pyridoxine hydrochloride) group (23.7%).[5]

For the Diclegis® (doxylamine succinate/pyridoxine hydrochloride) group and placebo group, respectively, the most common treatment emergent adverse events included somnolence (14.5% vs 2%), dry mouth (3.0% vs 0.8%), hypersensitivity (0.8% vs 0%), dizziness (6.0% vs 6.4%), headache (13.0% vs 16.0%), and loss of consciousness (0% vs 0.8%).[5]

A second study compared a five-day course of low-dose ondansetron to low-dose doxylamine/pyridoxine. The study concluded that ondansetron provided a statistically significant reduction in the nausea and vomiting (P=0.019 and P=0.049, respectively). There were no difference between groups for the side effects of sedation or constipation (P=0.707 and P=0.412, respectively).[6]

Table 2. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Koren et al[5] Doxylamine succinate/pyridoxine hydrochloride, two tablets QHS, up to a maximum dose of four tablets per day vs placebo	DB, MC, PC, RCT Pregnant women ≥ 18 years of age in the gestational age range of 7 to 14 weeks with NVP and a PUQE score ≥ 6 and had not responded to conservative management consisting of dietary/lifestyle advice	N=298 15 days	Primary: Change from baseline to day-15 in symptom and QOL domain PUQE scores Secondary: Day-by-day area under the curve for change in PUQE from baseline, time loss from employment, number of women in each arm who continued with blinded compassionate use of their medication, number of patients who reported concurrent use of alternate therapy for NVP, safety	Primary: There was a 4.8 point mean decrease from baseline in the symptom domain PUQE score at day-15 in the doxylamine succinate/pyridoxine hydrochloride group compared to 3.9 point decrease in the placebo group (P=0.006). There was a 2.8 point mean increase from baseline in QOL domain PUQE score at day 15 in the doxylamine succinate/pyridoxine hydrochloride group compared to 1.8 point decrease in the placebo group (P=0.005). Secondary: The mean area under the curve of the change in PUQE from baseline as measured day-by-day was significantly larger in the doxylamine succinate/pyridoxine hydrochloride combination group compared (61.5) to placebo (53.5) with the difference being statistically significant ((P<0.001). There was a trend toward more time lost from employment in the placebo group (2.37 days) compared to the doxylamine succinate/pyridoxine hydrochloride combination group compared (0.92); however, it should be noted that this difference was no statistically significant (P=0.06). At the end of the 15-day trial, 48.9% of patients in the doxylamine succinate/pyridoxine hydrochloride combination group compared to 32.8% in the placebo group requested to continue compassionate use of their medication (P=0.009). Significantly more women receiving placebo (36%), requested alternate therapies for NVP compared to the doxylamine succinate/pyridoxine hydrochloride combination group (23.7%). The difference was statistically significant (P=0.04). For the doxylamine succinate/pyridoxine hydrochloride combination group and placebo group respectively the most common treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				emergent adverse events included somnolence (14.5% vs 2%; P=0.54), dry mouth (3.0% vs 0.8%; P=0.37), hypersensitivity (0.8% vs 0%; P>0.99), dizziness (6.0% vs 6.4%; P=0.94), headache (13.0% vs 16.0%; P=0.51), and loss of consciousness (0% vs 0.8%; P=0.49).
Oliveira et al[6] Ondansetron 4 mg every eight hours for five days vs pyridoxine/doxylamine 25/12.5 mg every eight hours for five days	AC, DB,DD, PC, RCT Women 18 years of age or older with nausea with or without vomiting and less than 16 weeks of gestation	N=36 5 days	Primary: Reduction in nausea on the VAS Secondary: Reduction in vomiting and the proportion of patients reporting sedation or constipation while using either study regimen.	Primary: There was a statistically significant difference for reduction in nausea in the ondansetron group compared with the pyridoxine/doxylamine group (median 51 mm [interquartile range 37 to 64] compared with 20 mm [interquartile range 8 to 51]; P=0.019). In the ondansetron group, 12 out of the 13 patients had a clinically significant reduction in nausea from baseline (defined as a 25-mm or greater reduction in nausea on the VAS); however, in the pyridoxine/doxylamine group, only 7 out of 17 patients had a clinically significant reduction from baseline. There was a statically significant difference in the reduction of nausea from baseline in favor of ondansetron (P=0.007). Secondary: The ondansetron group reported less vomiting on the VAS as compared with the pyridoxine/doxylamine group (median 41 [interquartile range 17 to 57] compared with 17 [interquartile range -4 to 38]; P=0.049). In the ondansetron group, 10 out of the 13 patients had a reduction in emesis on the VAS; however, in the pyridoxine/doxylamine group, only 6 out of 17 patients had a reduction in emesis (P=0.033). There was no difference between groups for sedation or constipation (P=0.707 and P=0.412, respectively).

Drug regimen abbreviations:, QHS=every night at bedtime
Study abbreviations: DB=double-blind, MC=multicenter, PC=placebo-controlled, PUQE= Pregnancy Unique-Quantification of Emesis, RCT=randomized controlled trial, QOL=quality of life, VAS=visual analog scales

Special Populations

Table 3. Special Populations[1]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Doxylamine succinate/pyridoxine hydrochloride	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	No dosage adjustment required..	A	Yes (Women should not breastfeed while using the agent)

Adverse Drug Events

Table 4. Adverse Drug Events[1]

Adverse Event	doxylamine succinate/ pyridoxine hydrochloride	
	doxylamine succinate/ pyridoxine hydrochloride N (%), N=133	placebo N (%), N=128
Somnolence	19 (14.3)	15 (11.7)

Contraindications

Table 5. Contraindications[1]

Contraindication	doxylamine succinate/ pyridoxine hydrochloride
Concurrent use of a monoamine oxidase inhibitor as they intensify and prolong the adverse effects of the agent.	a
Known hypersensitivity to doxylamine succinate other ethanolamine derivative antihistamines, pyridoxine hydrochloride or any inactive ingredients in the formulation.	a

CNS=central nervous system

Warnings/Precautions

Table 6. Warnings and Precautions[3,5]

Contraindication	doxylamine succinate/ pyridoxine hydrochloride
Activities Requiring Mental Alertness; avoid activities that require mental alertness unless cleared by a healthcare provider. Avoid use with other CNS depressants or alcohol.	a
Concomitant Medical Conditions; due to anticholinergic effects, use caution in patients with: asthma, increased intraocular pressure, narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction and urinary bladder-neck obstruction.	a

CNS=central nervous system

Drug Interactions

Table 7. Drug Interactions[3,5]

Generic Name	Interacting Medication or Disease	Potential Result
doxylamine succinate/ pyridoxine hydrochloride	Monoamine oxidase inhibitors (MAOIs)	Concurrent use is contraindicated as MAOIs can prolong and intensify the anticholinergic effects of the doxylamine succinate component.

Dosage and Administration

Table 8. Dosing and Administration[1]

Generic Name	Adult Dose	Pediatric Dose	Availability
doxylamine succinate/ pyridoxine hydrochloride	Nausea and Vomiting of Pregnancy: Delayed-release tablet: Initial, two tablets QHS on day one; if symptoms persist into day two increase dose to one tablet QAM and two tablets QHS on day three; if symptoms continue increase to a maximum of four tablets per day with one in the morning, one in the mid-afternoon and two QHS	Safety and efficacy in children have not been established.	Delayed-release tablet: 10 mg/10 mg

QAM=every morning, QHS= every night at bedtime

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
Clinical Management Guidelines For Obstetrician-Gynecologists **ACOG Practice Bulletin: Nausea and Vomiting of Pregnancy (2004)**[4]	· Nausea and vomiting of pregnancy (NVP) is a common condition that affects 70 to 85% of pregnant women. · The incidence of hyperemesis gravidarum is 0.5% to 2% of pregnancies. · Mild cases of NVP may be resolved with lifestyle and dietary changes and sage and effective treatments are available for more severe cases. · Symptoms of NVP manifest before week 9 of gestation in virtually all women. Non-Pharmacological Therapies: · It is reasonable for women with NVP in a previous pregnancy to take a multivitamin at the time of the next conception. · Common recommendation to alleviate initial signs and symptoms of NVP include rest and avoidance of sensory stimuli that may provoke symptoms. · Frequent, small meals, avoiding spicy or fatty foods, eliminating pills containing iron, and eating dry bland or dry foods are also recommended. · It should be noted however that there is little published evidence regarding the efficacy of dietary changes for prevention or treatment of NVP. Pharmacological Therapies: · Despite the fact that the combination of doxylamine and pyridoxine is no longer commercially available in the US it remains among first-line therapies. · Treatment with either pyridoxine or combination pyridoxine plus doxylamine are both recommended as first-line treatment options based on good and consistent scientific evidence (Level A). · The treatment algorithm indicates that initial pharmacologic therapy consists of monotherapy pyridoxine followed by the addition of doxylamine

Clinical Guideline	Recommendations
	if systems persist. · In patients with consistent symptoms promethazine or dimenhydrinate should be added. · After this if symptoms still persist options include the addition of any of the following: o Metoclopramide o Promethazine o Trimethobenzamide · For patients who continue to be refractory options include: o Methylprednisolone o Ondansetron

Conclusions

Diclegis® (doxylamine succinate/pyridoxine hydrochloride) is a fixed dose combination drug product of doxylamine succinate, and pyridoxine hydrochloride, a vitamin B6 analog. The agent is indicated for the treatment of nausea and vomiting of pregnancy in women who do not responds to conservative management.[1] The combination of these agents was previous available in the United States under the name brand Bendectin®.[2]

In the clinical study that evaluated the use of Diclegis® (doxylamine succinate/pyridoxine hydrochloride) compared to placebo the agent was found to be effective and well tolerated in relieving the symptoms of NVP.[5] Doxylamine/pyridoxine was shown to be less effective at reducing nausea and vomiting in pregnancy when compared with ondansetron; however, only the low doses were study for a short duration of time.[6]

The clinical consensus guideline on nausea and vomiting of pregnancy from the American College of Obstetricians and Gynecologists recommend pyridoxine alone or in combination with doxylamine as first line pharmacologic therapy.[4]

References

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