Thieme

Nausea and Vomiting of Pregnancy and its Management with the Dual-Release Formulation of Doxylamine and Pyridoxine

Management von Übelkeit und Erbrechen in der Schwangerschaft mit der Wirkstoffkombination von Doxylamin und Pyridoxin mit dualer Freisetzung

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ABSTRACT

Nausea and vomiting of pregnancy (NVP) is among the most common conditions that pregnant women encounter in the early stages of pregnancy. It can affect up to 85 % of pregnant women, thus representing a significant public health concern. NVP results in substantial negative physical, emotional, and financial consequences. Despite its prevalence, the pathogenesis remains elusive. Few guidelines have been published; however, several interventions exist for the symptomatic treatment of NVP.

The aim of this review is to provide an overview of modern treatment strategies of NVP with a special focus on the recently approved dual-release formulation of the doxylamine and pyridoxine combination. This combination was approved by the Food and Drug Administration (FDA) in November 2016 for the treatment of NVP when conservative management fails, and it has been introduced to the American market in April 2018.

The maximum plasma concentration (T_{max}) of doxylamine and pyridoxal-5-phosphate is reached 3.5 h and 15 h, respectively, after administration of one tablet twice daily, or 4.5 h and 9 h, respectively, when one tablet is administered just once daily.

In addition, the delayed-release combination allows sufficient levels of doxylamine and the active metabolite pyridoxal-5-phosphate in the systemic circulation, providing symptoms relief in the subsequent morning.

Hence, the dual-release formulation can improve the quality of life of pregnant women suffering from NVP. Additionally, large epidemiological trials have shown no increased risk of adverse effects to newborns, demonstrating that its use is not teratogenic.

ZUSAMMENFASSUNG

Übelkeit und Erbrechen in der Schwangerschaft (Nausea and Vomiting of Pregnancy, NVP) gehören zu den häufigsten Schwangerschaftsbeschwerden, mit denen schwangere Frauen in der Frühschwangerschaft zu kämpfen haben. Bis zu 85 % aller schwangeren Frauen können davon betroffen sein; diese Beschwerden stellen somit ein wichtiges Gesundheitsproblem dar. NVP kann beträchtliche negative physische, emotionelle und finanzielle Konsequenzen haben. Trotz der weiten Verbreitung von NVP ist die Pathogenese immer noch unklar. Bislang wurden nur wenige Leitlinien dazu veröffentlicht; es gibt aber mehrere Interventionen zur Behandlung der Symptome von NVP.

Ziel dieser Übersichtsarbeit war es, einen Überblick der modernen Strategien zur Behandlung von NVP zu geben, mit einem besonderen Schwerpunkt auf die kürzlich zugelassene duale Wirkstoffkombination von Doxylamin und Pyridoxin. Diese Wirkstoffkombination wurde im November 2016 von der US-amerikanischen Zulassungsbehörde FDA (Food and Drug Administration) zur Behandlung von NVP bei Versagen von konservativen Managementstrategien zugelassen und kam im April 2018 auf den US-amerikanischen Markt.

Die maximale Plasmakonzentration (T_{max}) von Doxylamin und Pyridoxin stellt sich ca. 3,5 bzw. 15 Stunden nach Einnahme einer Tablette, die 2-mal am Tag verabreicht wird, ein und 4,5 bzw. 9 h Stunden nach Einnahme einer Tablette, wenn nur 1 Tablette am Tag eingenommen wird.

Die Verzögerung bei der Freisetzung der Wirkstoffe bedeutet, dass der Blutspiegel von Doxylamin und dem aktiven Metaboliten Pyridoxal-5-Phosphat in der systemischen Zirkulation ausreicht, um eine Symptomlinderung auch am nächsten Morgen zu gewährleisten.

Diese Wirkstoffkombination mit dualer Freisetzung kann folglich die Lebensqualität von schwangeren Frauen, die unter NVP leiden, verbessern. Hinzu kommt, dass große epidemiologische Studien kein erhöhtes Risiko für negative Auswirkungen auf Neugeborene feststellen konnten; dies zeigt, dass diese Wirkstoffkombination nicht teratogen ist.

Introduction

Epidemiology

Nausea and Vomiting of Pregnancy (NVP) represents one of the most common conditions encountered during pregnancy [1]. The symptoms of NVP include nausea, retching and/or vomiting [2]. A survey including 1000 women revealed that up to 85% of pregnant women experience nausea and 52% vomiting [3]. Notably, up to 70% of these women face nausea episodes and 40% experience vomiting on a daily base [3]. Another study revealed that one out of two pregnant women suffers from NVP, highlighting the considerable burden of this disease [2]. In one third of women, NVP manifests within four weeks after the last menstrual period, and within six weeks in three quarters of cases [3].

NVP affects women worldwide. A meta-analysis summarized global rates of NVP and showed that NVP rates varied from 35 % to 91 % with an average of 69 % [4]. The study also revealed that 32.7% of pregnant women experience nausea without vomiting and that NVP persists into the third trimester in up to 23.5% of pregnancies overall. Additionally, the severity of NVP was categorized as mild in 40% of cases, moderate in 46%, and severe in 14% of cases [4]. Although NVP affects most pregnant women, many of them are hesitant to discuss their symptoms with their health care professional (HCP). According to the National Voice of Pregnancy survey, out of the 621 respondents, 24% never mentioned their NVP symptoms to their HCP, while 37% admitted waiting until their first prenatal visit between weeks 6 to 10. Notably, 51% waited even longer until a later visit [5]. Women with moderate or severe symptoms were more likely to inform their HCP about their NVP. When asked about the reasons for not informing their HCP, most stated that the experienced symptoms were a natural part of pregnancy, and thus did not require attention (53%), or they simply did not desire treatment with drugs (9%). Among those who did inform their HCP about their NVP, 41% sought suggestions on how to alleviate the problem, 23% wanted a prescription to manage the symptoms, and 24% hoped for reassurance. These findings emphasize the role of the physicians and the importance of psychosocial support for pregnant women [5].

The term “morning sickness” has been coined and is associated with NVP; however, it is important to note that most women experience symptoms of NVP not just in the morning but also in the afternoon and during daytime [3, 6]. This was demonstrated in a study with 160 pregnant women, where 74% reported NVP symptoms [6]. Of these women, only 1.8% suffered from “morning sicknesses” while 80% experienced NVP symptoms throughout the day [6]. Hence, the term “morning sickness” is not appropriate and it would be more accurate to refer to this symptom complex as “episodic daytime pregnancy sickness” [2, 6].

Etiology and predisposing factors for the development of NVP

NVP usually occurs during the first half of the pregnancy, with symptoms typically starting during the 4 th and 6 th week and peaking around week 10 [6, 7]. In most pregnant women, NVP resolves by week 20 [2, 8, 9]. However, in about 10% of pregnant women, symptoms persist during the entire pregnancy [4, 6, 7, 10].

The underlying pathophysiology of NVP has not been understood yet but is thought to be multifactorial. A combination of genetic, endocrine, and gastrointestinal factors has been discussed, including family or personal history, increased placental mass, estrogen and progesterone level, growth/differentiation factor 15 (GDF15), thyroid hormone, serotonin, and infection with Helicobacter pylori (in hyperemesis gravidarum) [1, 11, 12]. One of the most common theories for the development of NVP includes the presence and the respective levels of human chorionic gonadotropin (hCG) [13]. hCG is crucial for the synchronization of fetal and

endometrial development and is a marker for placental function throughout the entire pregnancy [13, 14]. It has been shown that the temporal occurrence of NVP correlates with hCG levels [14]. Increased progesterone and estrogen levels, as well as anxiety or stress and the number of previous pregnancies or multiple pregnancies also seem to have an impact on NVP [1, 11, 12].

NVP is more common in Western countries and urban populations and less frequent in Africans, Native Americans, Inuit, and most Asian populations [15, 16]. Further data from the Collaborative Perinatal Project identified NVP to be more prevalent among younger women, primigravidas, women with less than 12 years of education, non-smokers, and obese women [17]. Besides, a one-year population survey of 1000 pregnant women revealed that, compared to older women (> 32 years), young women (15–22 years) were less likely to feel nauseated but more likely to experience vomiting [3]. Additionally, there has been an association between women suffering from NVP and their mothers having also gone through NVP during their pregnancies [3]. Several other factors have been discussed as predisposing factors for the development of NVP, including multiple pregnancies, previous pregnancy experiences with mild or severe nausea and vomiting, a family history of NVP, a history of motion sickness or migraines, and being pregnant with a female fetus. Interestingly, some studies have even suggested that the presence of NVP may be associated with favorable pregnancy outcomes like lower rates of miscarriages, stillbirths, preterm births, and birth defects [10, 18]. However, despite various theories and speculations, there are currently no clear findings regarding the exact causes of NVP.

Diagnosis of NVP

The clinical diagnosis of NVP is typically achieved through an elimination process of differential diagnoses, such as gastrointestinal illnesses [19]. NVP can be categorized based on its intensity into mild, moderate, or severe, depending on the number of episodes involving nausea and/or vomiting. In general, there is no widely accepted approach for measuring the severity of symptoms in women experiencing NVP. However, the most used and well-known scoring system is the Motherisk Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score [20, 21, 22]. This validated score quantifies the severity of NVP based on three physical symptoms experienced in the past 24 hours: nausea, vomiting, and retching. Each symptom is assigned a score of 1 to 5 points based on its frequency and intensity, with a maximum total score of 15 points. Mild NVP is defined as a score of < 6 points, while severe NVP is categorized as a score of ≥ 13 points.

Other assessment tools used to measure the severity of NVP include the Rhodes Index of nausea, vomiting and retching (RINVR) [23, 24, 25]. Additionally, the McGill Nausea Questionnaire can be deployed to measure nausea only [6, 26]. Furthermore, the Nausea and Vomiting in Pregnancy Instrument (NVPI) comprises three questions that inquire about nausea, retching, and vomiting over the past 7 days. Each symptom can be scored between 0 (no symptoms) and 5 points (worst possible symptoms), resulting in a maximum total score of 15 points [27, 28]. A score of ≥ 8 indicates severe symptoms. Finally, symptoms may also be evaluated with a visual analogue scale (VAS) ranging from 0 (no symptoms) to 10 (very severe symptoms) [29].

▶**Table 1** Comparison between Nausea and Vomiting of Pregnancy and Hyperemesis gravidarum (adapted from [12]).

Nausea and Vomiting of Pregnancy	Hyperemesis gravidarum
Minimal weight loss	Weight loss > 5 %
Adequate nutrient intake on most days	Inadequate nutrient intake for days/weeks
Nausea and vomiting are unpleasant; nevertheless, only minor restriction of most essential activities	Nausea and vomiting cause misery and limit daily activities, including selfcare
Symptoms can be addressed through dietary/lifestyle changes	Medical care (medication; intravenous therapy; nutrition support) is required
Symptoms improve significantly from the 14 th week of pregnancy onwards	Symptoms may improve, but may persist until the end of the pregnancy
Family obligations can usually be taken care of, especially from the 14 th week of pregnancy	Family obligations over weeks and months are very difficult or impossible to handle

Hyperemesis gravidarum: the most severe form of NVP

The most severe form of NVP is referred to as Hyperemesis gravidarum (HG). This condition affects approximately 0.3–1.0 % of pregnant women, making it much less common than NVP [1, 11]. A meta-analysis revealed that the prevalence of HG is around 1.1%, with a range of 0.3% to 3.6% [4]. HG is more frequently diagnosed in pregnant women from India, Pakistan, Asian, New Zealand populations compared to European, American Indian, and Inuit populations [29, 30]. It is important to note that there is no widely accepted definition to distinguish when NVP progresses to HG. HG is characterized by severe and persistent vomiting, dehydration, ketosis (due to acute starvation), electrolyte imbalance, nutritional deficiencies such as vitamin and mineral deficiencies and weight loss (usually defined as > 5% of pre-pregnancy weight) [1, 11]. The severity of HG symptoms can also result in major psychosocial burden leading to depression, anxiety, and even pregnancy termination [11, 30]. Both the mother and child are at risk of harm due to the lack of adequate fluids and nutrients caused by constant vomiting [1, 11]. A comparison between HG and NVP can be found in ▶**Table 1**. It was found that women who have experienced HG in their first pregnancy have a notably high risk of recurrence in subsequent pregnancies [31]. Furthermore, HG is one of the most common reasons for seeking medical attention during the first trimester of pregnancy, and the second most common cause for hospitalization during pregnancy, after preterm labor [11]. In severe cases other NVP medications may be necessary under medical supervision. Thus, it is advisable to initiate early treatment for symptoms of morning sickness and NVP to

▶**Table 2** Overview of guideline recommendations of pharmacological treatment of Nausea and Vomiting of Pregnancy (adapted from [10, 11, 38, 41]).

	Indication for NVP	SOGC [38] (2016)	ACOG [11] (2018)	APGO [10] (2015)	RCOG [41] (2016)
Doxylamine/Pyridoxine	Yes	1st line	1st line	1st line	1st line
Dimenhydrinate	No	2nd line	2nd line	2nd line	1st line
Promethazine	No	3rd line	2nd line	2nd line	1st line
Chlorpromazine	No	3rd line	4th line	3rd line	1st line
Metoclopramide	No	3rd line	3rd line	3rd line	2nd line
Prochlorperazine	No	3rd line	2nd line	3rd line	1st line
Ondansetron	No	4th line	3rd line	3rd line	2nd line

prevent the condition from progressing to HG [32]. Currently, there is no drug available with an indication for effective treatment of HG.

Impact of NVP

Most women (55%) perceive their nausea during pregnancy to be of moderate intensity, while only a small percentage (1%) rate their symptoms as severe [31]. Nevertheless, several studies have shown that NVP significantly affect the quality of life and well-being of pregnant women. NVP can have a major impact on the woman's physical and mental health requiring hospitalization for rehydration and treatment [5, 32]. This, in turn, will affect their daily life, including work commitments [7, 33]. Furthermore, NVP may influence the willingness of women to conceive again [33]. It is estimated that 30 to 40% of pregnant women experience limitations in participating fully in family and social activities due to NVP [5, 23, 34, 35, 36]. A survey of 621 pregnant women revealed that NVP has strongly affected their eating behavior, pleasure, diet, and sleep [5]. The severity of NVP symptoms is directly related to the negative impact on sleep and quality of life (both physical and mental) [37]. Besides, social activities, intimacy with the partner and caregiving responsibilities may also be influenced by NVP [5].

The huge impact of NVP on pregnant women's lives is well documented by a study investigating factors associated with elective termination of pregnancy among 3201 Canadian and American women experiencing NVP [35]. Results of this study showed that 108 women chose to terminate their pregnancy due to NVP, and an additional 413 women considered termination as an option. These results are consistent with a Scandinavian cross-sectional study, which reported that over 25% of women with NVP considered terminating their pregnancy due to NVP severity [33]. Additionally, a prospective study with 160 women revealed that the severity of nausea experienced during NVP is comparable to that experienced during chemotherapy [6]. Hence, NVP represents a significant public health concern, with adverse physical, emotional, and financial consequences.

Treatment of NVP

Effective treatment for NVP is crucial due to its significant impact on pregnant women's lives. Further, it is decisive to administer treatment without delay, as delayed intervention can lead to difficulties in managing symptoms [11]. Early treatment of NVP symptoms is recommended to prevent progressing to HG and to avoid complications, such as hospitalizations [11].

In women with mild NVP, lifestyle and dietary modifications may effectively alleviate symptoms [11, 12, 38]. However, there are presently no randomized controlled trials available that evaluate the impact of diet and lifestyle changes on NVP. Currently available studies primarily focus on the personal experiences of women using conservative treatment methods. If NVP symptoms persist or if women suffer from moderate to severe NVP, women are advised to consult their physician and consider pharmacologic treatments [38]. Although various classes of antiemetic drugs have shown efficacy in treating nausea and vomiting associated with chemotherapy, motion sickness, gastrointestinal conditions or cyclic vomiting, data regarding their maternal and fetal safety during pregnancy remain sparse [39, 40]. Until now, there have been few published guidelines and treatment algorithms for NVP. The recommendations of the American College of Obstetricians and Gynecologists (ACOG) [11], the Association of Professors of Gynecology and Obstetrics (APGO) [10], the Royal College of Obstetricians and Gynaecologists (RCOG) [41] and the Society of Obstetricians and Gynaecologists of Canada (SOGC) [38] only provide guidance of low evidence [10, 11, 12, 38, 41, 42, 43, 44] (▶ **Table 2**).

Management of NVP with the doxylamine and pyridoxine combination

Several H1 receptor antagonists, such as doxylamine, have demonstrated safety and efficacy in treating NVP [45, 46, 47, 48]. These drugs act by interfering with the vestibular nausea pathway, which eventually disrupts signal transduction in the vomiting center [49]. Additionally, pyridoxine (vitamin B_6) has been shown to be effective in treating NVP, supported by several trials [48, 50, 51]. Also, although data is limited, a Cochrane systematic review supports the efficacy of pyridoxine [52]. A study has demonstrated

that up to 200 mg of pyridoxine intake per day is not teratogenic or fetotoxic [38, 53].

While the antiemetic effect of doxylamine is well established, it is believed that the pyridoxine's metabolite, pyridoxal-5-phosphate, is the most bioactive form [50]. Both doxylamine and pyridoxal-5-phosphate are considered safe for use during pregnancy according to the Embryotox database, which is a valuable source for selecting the appropriate treatment for NVP in Germany [53]. This database, operated by the Pharmacovigilance and Advisory Center for Embryonic Toxicology of the Charité – Universitätsmedizin in Berlin, provides independent information on drug tolerability during pregnancy and breastfeeding. Since 1988, this publicly funded institute has been offering independent information on drugs tolerability during pregnancy and breastfeeding based on relevant study results from journals and the current state of discussion among relevant professional societies [53].

Treatment with the doxylamine and pyridoxine combination has been found to significantly improve symptoms in women with NPV [47]. Extensive research, including two meta-analyses involving over 168000 patients and 18000 exposures, demonstrated that this combination therapy of 10 mg doxylamine and 10 mg pyridoxine is safe and effective without increased risk of harmful fetal effects [43, 47, 54]. Thus, based on data acquired in a phase III double-blind, randomized, placebo-controlled study, the FDA approved the delayed-release doxylamine/pyridoxine formulation, Diclegis, in April 2013 [47]. This delayed-release formulation contains 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride.

Initially, this combination drug comprised of 10 mg doxylamine succinate, 10 mg pyridoxine hydrochloride, and 10 mg dicyclomine hydrochloride [55, 56]. Introduced as Bendectin in 1956 in the USA, it was widely used until 1983 when its manufacturer voluntarily removed it from the market, not due to safety or efficacy concerns as clarified by the FDA in 1999 but rather due to increased liability cost [57]. Following the removal of Bendectin from the American market, no reduction in malformation rates of newborns was reported, but the hospitalization rates of women with NVP doubled, according to data from government authorities such as National Center for Health Statistics, Centers for Disease Control and Prevention (CDC) and FDA [57], illustrating that Bendectin had no teratogenic effects. An eight-way study in 1976, showed that dicyclomine had no independent antiemetic effect when combined with doxylamine and pyridoxine [51]. As a result, Bendectin was reformulated to contain only 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride [55, 56, 58, 59].

Notably, all currently available combinations of doxylamine and pyridoxine are not indicated for the treatment of HG or the prevention of it. Nevertheless, early treatment of symptoms associated with morning sickness as common during pregnancy is recommended to prevent progression to HG [60].

Clinical effectiveness of the delayed-release doxylamine and pyridoxine combination

The clinical effectiveness of this delayed-release combination (marketed as Bonjesta has been consistently documented in various randomized, controlled trials and open, controlled post-marketing studies [56, 57, 58, 59, 60]. The most pivotal gold-standard study by Koren et al. included 256 pregnant women with NVP for whom conservative management has failed and who were randomized to obtain a delayed-release form of 10 mg doxylamine combined with 10 mg pyridoxine or placebo for 14 days. On day 15, significantly larger improvements regarding symptoms of NVP as well as global assessment of well-being could be observed in the study group compared to placebo. This data demonstrates that the combination is effective and well-tolerated [47].

The recommended dosage for the delayed-release form of the medication suggests taking two tablets in the evening prior to bedtime. If symptoms persist, an additional tablet containing 10 mg doxylamine and 10 mg pyridoxine should be taken in the morning starting from day 3. If symptoms continue, another tablet should be administered in the afternoon from day 4 onwards, resulting in an intake of 4 tablets per day to reach the maximum dosage [2].

Interestingly, a study by Boskovic et al. involving 68 pregnant women revealed that significant underdosing was prevalent in women with NVP who were using the delayed-release formulation [61]. In this study, despite suffering from moderate to severe NVP (based on PUQE score), most women (50 out of 68) were only receiving two tablets a day of the delayed-release formulation. However, after doubling the dose to an average of four tablets per day, a significant decrease in the duration of nausea (from 4 to 3 hours, $p < 0.001$), frequency of vomiting (from an average of 1.6 to 1.3 per day, $p = 0.02$), and overall PUQE score (from an average of 7.5 to 6.1, $p < 0.001$) was observed. Importantly, most of these improvements occurred within 3 days of the dose increase, highlighting the urgency of a higher dosage per tablet [61].

Furthermore, one apparent limitation of the delayed-release combination of doxylamine and pyridoxine is that it takes 6 to 8 hours after administration to exert its antiemetic effect. Consequently, symptom improvement may be delayed, which might require the use of an immediate release medication. This emphasizes the necessity for a formulation of the doxylamine/pyridoxine combination with a faster onset of action.

Formulation and dose of a dual-release system: the key to immediate and long-lasting relief of symptoms

To address the limitations of the delayed-release formulation, the FDA approved a dual-release combination of doxylamine and pyridoxine in November 2016, consisting of a rapid release phase followed by a delayed-release phase, for the treatment of NVP when conservative management fails, hence, overcoming the time delay in action of the delayed-release formulation. This new formulation was introduced to the American market in April 2018. Its approval was based on the same results of clinical and pharmacological studies that involved the delayed-release formulation, along with three clinical pharmacology studies that presented the pharmacokinetic of the dual-release tablets versus the delayed-release tablets [62, 63]. This new dual-release formulation of doxylamine and pyridoxine represents a significant step forward in improving the treatment of women with NVP.

The dual-release combination of doxylamine and pyridoxine is composed of a multilayer, extended-release tablet consisting of an

enteric-coated core containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, and an immediate-release coating of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, delivering a total of 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride. The new formulation offers a rapid relief of NVP symptoms and a sustained therapeutic effect, controlling nausea and vomiting symptoms that occur in the morning, during the day into the night. The 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, from the multiple immediate release layers, are sequentially and rapidly delivered when the tablet is taken, followed by 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride approximately 6 to 8 hours later. The immediate-release coating along with the delayed-release enteric-coated core make a prolonged-release drug with continuous pharmacotherapeutic effect [62].

The reasons for the reformulation of the delayed-release combination of doxylamine and pyridoxine originated from various clinical perspectives, including [63]:

1. The combination of a fast-acting form of doxylamine/pyridoxine with the delayed-release form results in an immediate antiemetic effect that was not obtainable with the delayed-release combination. This innovative approach provides rapid relief from nausea and vomiting, addressing one of the limitations of the previous formulation.
2. The new formulation has reduced optimal dosing frequency from three times daily (morning, noon, and evening) to twice daily (morning and evening), improving adherence among women during the challenging days of NVP and making it more convenient and easier to follow the prescribed dosage regimen.
3. The median maximum plasma concentration of doxylamine and pyridoxal-5-phosphate is reached 3.5 h and 15 h, respectively (T_{max}), after administration of one tablet twice daily, or 4.5 h and 9 h, respectively, when one tablet is administered just once daily.

The effective plasma levels of 37 ng/ml for doxylamine and 12 ng/ml for pyridoxal-5-phosphate are reached 1 h after dosing, conferring an immediate relief of symptoms.

Pharmacokinetics of the dual-release formulation

Additionally, the delayed-release component of the formulation ensures sufficient concentrations of doxylamine and the active metabolite pyridoxal-5-phosphate in the systemic circulation at the time of awakening (about 8 am), effectively improving morning NVP symptoms. This contrasts with the previous delayed-release system, where the morning dose may not provide adequately rapid therapeutic levels compared to the new dual-release combination. The improved pharmacokinetics of the new formulation offer faster and more effective symptom relief for women experiencing NVP.

Because the dual-release combination contains twice the concentration of both doxylamine and pyridoxine found in the delayed-release formulation, the recommended maximum daily dose is reduced from four delayed-release tablets to two dual-release tablets per day, maintaining an equal maximum daily dose for both formulations. Consequently, this reduction in pill burden, coupled with the simplified intake regimen, can potentially improve patient adherence. A secondary analysis of a double-blind randomized controlled study carried out with the delayed-release formulation of doxylamine/pyridoxine showed that the average number of tablets taken per day was negatively associated with treatment adherence [64]. This is of clinical importance for pregnant women experiencing NVP, as they may find it challenging to swallow multiple tablets while needing to eat small meals frequently. Additionally, by reducing the pill burden, patient adherence can be increased, contributing to a sustained therapeutic effect of the dual-release combination.

A multiple-dose, crossover clinical study compared the dual-release tablet (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) administered twice daily for 11 days to the delayed-release tablet (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) administered three times daily (1 tablet in the morning, 1 tablet in the afternoon and 2 tablets at bedtime) [62]. In summary, the dual-release formulation showed a more rapid T_{max}, even after reaching steady state, when compared to the delayed-release formulation. Specifically, on day 1, the mean plasma concentration of both ingredients was reached 1 h after dosing with blood concentrations of 37 ng/ml and 12 ng/ml for doxylamine and pyridoxal-5-phosphate. On day 11, the mean T_{max} of doxylamine in the dual-release formulation was 3.5 h, compared to 21 h with the delayed-release formulation. This difference can be explained by the immediate-release portion found in the coating of the dual-release combination, which quickly releases both active ingredients.

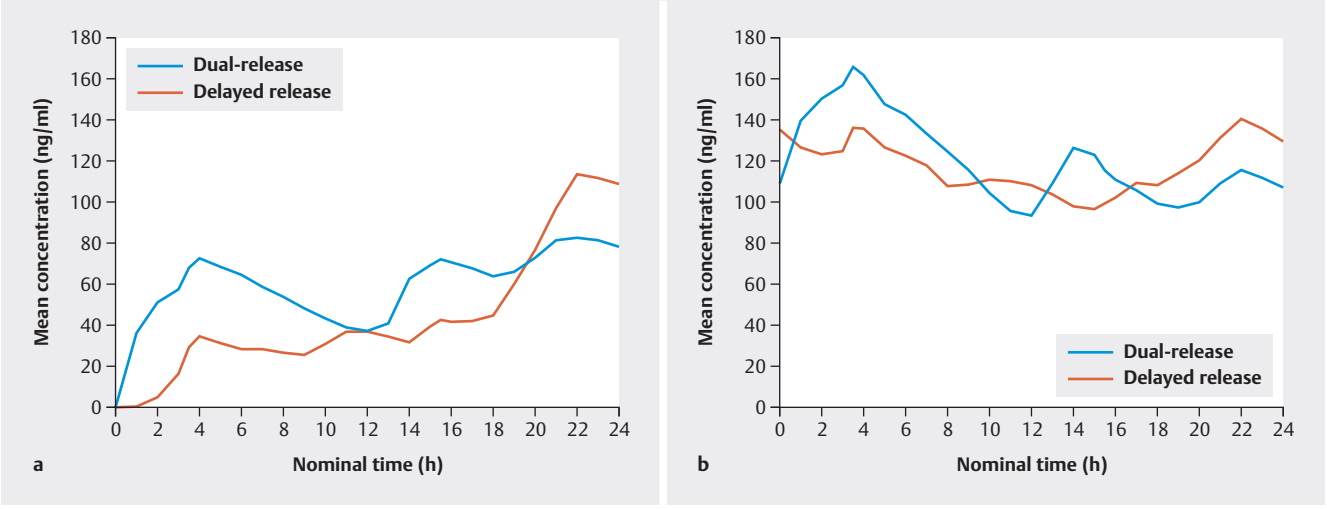
▶ **Fig. 1** and ▶ **Fig. 2** illustrate the course of doxylamine and pyridoxal-5-phosphate plasma levels on day 1 and day 11. The data demonstrate the equivalence of plasma values of the immediate-release proportion of the dual-release tablet and the delayed-release form at day 1 after 12 hours (▶ **Fig. 1a** and ▶ **Fig. 2a**) and display the levels after steady state on day 11 (▶ **Fig. 1b** and ▶ **Fig. 2b**). A significant difference between the dual-release and the delayed-
release formulation is evident.

Conclusions

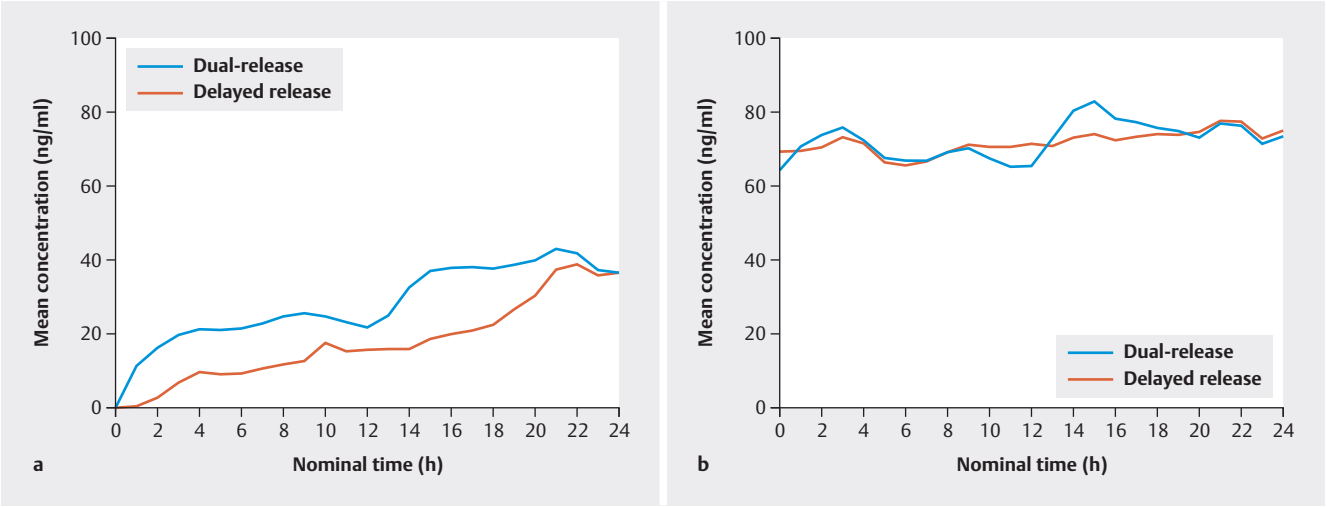
Nausea and vomiting of pregnancy (NVP) is among the most common conditions that pregnant women encounter in the early stages of pregnancy. It can affect up to 85 % of pregnant women, thus representing a significant public health concern. NVP results in substantial negative physical, emotional, and financial consequences. Despite its prevalence, the pathogenesis remains elusive. Few guidelines have been published; however, several interventions exist for the symptomatic treatment of NVP.

Several H1 receptor antagonists, such as doxylamine, have demonstrated safety and efficacy in treating NVP [45, 46, 47, 48]. These drugs act by interfering with the vestibular nausea pathway, which eventually disrupts signal transduction in the vomiting center [49]. Additionally, pyridoxine (vitamin B_6) has been shown to be effective in treating NVP, supported by several trials.

The dual-release formulation described in this work is characterized by the unique combination of both immediate and



▶ **Fig. 1** Time profile of mean (± SD) plasma concentrations of Doxylamine on day 1 (**a**) and day 11 (**b**).



▶ **Fig. 2** Time profile of mean (± SD) plasma concentrations of Pyridoxal-5-phosphate on day 1 (**a**) and day 11 (**b**).

delayed-release action of doxylamine and pyridoxine. This dual feature allows for an immediate effect at bedtime and ensures sustained control of NVP symptoms throughout the day.

In summary, the dual-release combination offers several advantages over traditional formulations. Firstly, it provides a more rapid onset of action, offering faster relief to pregnant women experiencing NVP. Secondly, it reduces the pill burden together for patients since it combines the effects of both immediate and delayed-release components in a single tablet. This could potentially lead to increased patient adherence to the treatment regimen. Thirdly, the dual-release formulation results in lower variability in effective plasma concentrations which contributes to a more consistent and reliable therapeutic response. Finally, it minimizes absorption delay caused by food intake, allowing for more predictable and consistent symptom control.

In conclusion, the introduction of the dual-release formulation of doxylamine and pyridoxine represents a significant advancement in the treatment of women with NVP. By providing both immediate and sustained relief from symptoms, this formulation can greatly improve the quality of life of pregnant women suffering from NVP, offering them an effective and convenient treatment option [63].

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Contributors' Statement

All authors contributed to the conception and design. Material preparation and data collection were performed by TS and JE. The first draft of the manuscript was written by TS, JE and PAR. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

Pedro-Antonio Regidor is an employee of Exeltis Healthcare. Johanna Eiblwieser and Theresa Steeb are employees of Exeltis Germany. The remaining authors have received advisory board honoraria from Exeltis Germany GmbH and state nor further conflict of interest.

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