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Research paper

Bioavailability of dronedarone tablets administered with or without food in healthy participants

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ABSTRACT

Study objective: There is inadequate awareness of the effect of food on the bioavailability of dronedarone. We report results from two phase 1 studies assessing the effect of food on dronedarone's bioavailability.
Design, setting and participants: Study 1; single-center, open-label, randomized study in healthy adults (males and females). Study 2; single-center, open-label, randomized study in healthy males.
Interventions: Study 1; a single 400-mg oral dose of dronedarone (marketed formulation) in fed (high-fat [47.4 g] meal) and fasted states. Study 2; a single 800-mg oral dose of dronedarone (two 400-mg tablets) after fat-rich (37.3 g) and low-fat (5.3 g) meals, and after fasting.
Main outcome measures: Pharmacokinetic parameters including maximum plasma concentration (C_{max}) and area under the curve from time 0 to last measurable time (AUC_{last}) were assessed for dronedarone and its active N-debutyl metabolite.
Results: Twenty-six participants were included in Study 1 and nine in Study 2. In Study 1, administration of 400 mg dronedarone with a high-fat meal vs. fasted state resulted in 2.8-fold and 2.0-fold increases in C_{max} and AUC_{last}, respectively. In Study 2, administration of 800 mg dronedarone with a fat-rich or low-fat meal vs. fasted state resulted in 4.6-fold and 3.2-fold increases in C_{max}, respectively, and 3.1-fold and 2.3-fold increases, respectively, in AUC_{last}. Results for the N-debutyl metabolite were similar to dronedarone. No adverse events were considered related to dronedarone.
Conclusion: With food, the bioavailability of dronedarone is markedly increased. In clinical practice, dronedarone should be administered with a complete meal to maximize drug absorption.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with substantial morbidity and mortality [1–3]. Although management of AF is multifaceted, antiarrhythmic drugs (AADs) are the most commonly used rhythm control strategy [4]. The bioavailability of orally administered therapies depends on factors related to absorption and to presystemic first-pass metabolism [5]. Food can influence the bioavailability of orally administered therapies, as it may affect tablet disintegration, drug dissolution, or drug transit in the gastrointestinal tract. In addition, drug metabolism can be affected [6]. The bioavailability of several AADs has been shown to be affected by food. For example, when administered with food, amiodarone absorption is significantly increased [7]; in contrast, sotalol absorption is decreased by 20% [8]. Taken without food, the absolute bioavailability of dronedarone is approximately 4% due to incomplete absorption and presystemic first-pass metabolism [9]. However, the bioavailability of dronedarone can increase to up to 15% when taken with a high-fat meal (overall absorption being >70% under fed conditions) [9]. As such, the United States Food and Drug Administration (FDA)-approved dosing instructions for dronedarone are that a 400-mg tablet should be taken twice daily with morning and evening meals, as per the dosing regimens used in the dronedarone pivotal clinical trials [9–12].

Dronedarone is indicated to reduce the risk of hospitalization for AF

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in people in sinus rhythm who have a history of paroxysmal or persistent AF [9]. Recent communications, including medical information requests from clinicians who prescribe dronedarone, have indicated there is a lack of awareness regarding the effect of food on the bioavailability of dronedarone and, particularly, of the need for dronedarone to be taken with food (Sanofi; data on file). In part, this may be due to many clinicians and patients not always being familiar with the information within package inserts supplied with medications [13]. In a survey of patients ($n = 307$) in the New York City metropolitan area, 29.7% indicated that they seldom or never read the information supplied with their medication [14]. In addition, some previous publications that have commented on the need for dronedarone to be taken with food have emphasized the food effect with a high-fat meal only [15,16]. However, when dronedarone is administered with a low-fat meal, compared with a high-fat meal, the difference in the effect on dronedarone bioavailability is minimal. Some clinicians incorrectly believe that the only reason dronedarone should be administered with food is to reduce the likelihood of gastrointestinal adverse effects. However, administration of dronedarone without food may result in subtherapeutic concentrations and suboptimal efficacy; therefore, it is important for clinicians to understand how food improves the bioavailability of dronedarone.

Here, we present the findings of two previously unpublished phase 1 studies that will allow the clinician to better understand the magnitude of the food interaction with dronedarone to ensure the drug will be administered appropriately to maximize its bioavailability. The primary objective of each was to assess the effect of administration with food on the bioavailability of dronedarone compared with administration under the fasted state. The secondary objective of each was to assess the tolerability of dronedarone under fasted and fed states.

2. Methods

Study 1 (400 mg dronedarone) was a phase 1, single-center, open-label, randomized, 2-sequence, 2-treatment by 2-period crossover study performed in healthy male and female participants (18–45 years of age). For full inclusion and exclusion criteria, please see Supplemental Material Table S1. The study took place between July 15 and September 18, 2009, and was approved by an independent ethics committee.

Study 2 (800 mg dronedarone) was a phase 1, single-center, open-label, randomized, 3-sequence, 3-treatment by 3-period crossover study conducted in healthy male White participants (18–40 years of age). For full inclusion and exclusion criteria, please see Supplemental Material Table S2. The study took place between April 23 and June 9, 1997, and was approved by the Ethics Committee of the Bayerische Landesärztekammer, Munich, Germany, before enrollment of any participants.

Both studies complied with the recommendations of the 18th World Health Congress (Helsinki, 1964) as amended at the 29th Congress (Tokyo, 1975), the 35th Congress (Venice, 1983), and the 41st World Medical Assembly (Hong Kong, 1989). All participants provided written informed consent.

In Study 1 (400 mg dronedarone), each participant was randomly allocated to 1 of 2 treatment sequences. In Sequence 1 (fasted/high-fat meal), 400 mg dronedarone (marketed formulation containing 10% poloxamer 407 [synthetic polymer poloxamer-based polymeric compound that acts as a surfactant assisting with tablet dissolution]) was administered under the fasted state for Period 1 and the fed (high-fat meal) state for Period 2. In Sequence 2 (high-fat meal/fasted), dronedarone (400 mg) was administered under the fed (high-fat meal) state for Period 1 and the fasted state for Period 2. The randomization list assigning participants to Sequence 1 or 2 was stratified by sex. Each participant underwent screening from 2 to 21 days prior to the first administration of dronedarone. Periods 1 and 2 lasted for 5 days each, and there was a washout period of at least 7 days between periods. Participants attended an end-of-study visit 7–10 days after the last administration of dronedarone. Plasma samples were collected as per the methodology described in the assessment section. Each participant received a single 400-mg oral dose of dronedarone with 240 mL of non-carbonated water. The fed state comprised a high-fat meal (consistent with FDA guidance for assessing food effect) containing 2 eggs fried in butter, 2 slices of toasted white bread, 2 strips of bacon, 10 g of butter, 113 g of hash browns, 250 mL of whole milk, and 1 tablespoon of jelly, providing a total of 47.4 g fat (total meal of 814.9 cal of which 425.7 cal were from fat), which was consumed 30 min before administration of dronedarone. For participants randomized to the fasted state, water intake was restricted until 1 h after administration of dronedarone and food intake was restricted until at least 4 h after administration of dronedarone. All participants received a standardized lunch and dinner at 1 pm and 8 pm, respectively. Water intake had to be at least 1500 mL for each 24-h period.

In Study 2 (800 mg dronedarone; two 400-mg tablets containing 10% poloxamer 407), participants were randomized to each treatment sequence according to a Latin square design (3 participants for each sequence). In Sequence 1 (fasted/low-fat/fat-rich), dronedarone (800 mg) was administered under the fasted state for Period 1, with a low-fat meal for Period 2, and with a fat-rich meal for Period 3. In Sequence 2 (low-fat/fat-rich/fasted), dronedarone (800 mg) was administered with a low-fat meal for Period 1, with a fat-rich meal for Period 2, and in the fasted state for Period 3. In Sequence 3 (fat-rich/fasted/low-fat), dronedarone (800 mg) was administered with a fat-rich meal for Period 1, in the fasted state for Period 2, and with a low-fat meal for Period 3. Each sequence was administered over a study period of 4 days with a washout period of at least 7 days between study periods. Each participant underwent screening 1–14 days prior to the first administration of dronedarone. On Day 1, dronedarone was administered according to the randomization schedule (fat-rich meal, low-fat meal, or fasted state). Plasma samples were collected as per the methodology described in the assessment section. Each participant received a single 800-mg oral dose of dronedarone, given as two 400-mg tablets containing 10% poloxamer 407, administered with 200 mL of non-carbonated water, under different states as follows: (1) with a fat-rich meal: 2 eggs (scrambled), 2 slices of toasted white bread, 2 strips of bacon, 1 teaspoon of butter, 113 g of hash browns, 226 g of whole milk, and 1 tablespoon of jelly, providing a total of 37.3 g fat (total meal of 718.1 cal of which 335.7 cal were from fat); (2) with a low-fat meal: 120 g of yogurt, 2 rolls, 40 g of honey, 25 g of jam, 5 g of margarine, 2 cups of decaffeinated coffee, providing a total of 5.32 g fat (total meal of 511.6 cal of which 49.5 cal were from fat); or (3) under the fasted state: no food. Both meals were given 30 min before administration of dronedarone.

Blood samples for determination of plasma concentrations of dronedarone and its active N-debutyl metabolite were collected up to 96 and 48 h post administration for Studies 1 and 2, respectively (Supplemental Material Table S3). In both studies, concentrations of dronedarone and its active N-debutyl metabolite were determined using a validated liquid chromatographic-tandem mass spectrometric methodology. The limit of quantification (LOQ; the lowest analyte concentration that could be quantified with a stated accuracy and precision) was 0.5 ng/mL for both the parent compound and its metabolite.

The following pharmacokinetic parameters were determined by non-compartmental analysis: lag time (T_{lag}; the interval between administration and the sampling time preceding the first concentration above the LOQ), maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the plasma concentration curve extrapolated to infinity (AUC_{0-inf}; Study 1 only), area under the plasma concentration vs. time curve calculated using the trapezoidal method from time zero to the time of the last observed concentration above the LOQ (AUC_{last}), and terminal half-life ($T_{1/2z}$; Study 1 only).

Adverse events (AEs) were recorded throughout both studies including during washout periods. AEs were coded according to the World Health Organization Adverse Reactions Terminology (WHO-ART) and were assigned according to system organ class. Investigators specified the dates of onset, severity, corrective therapies given (if any),

outcomes, and their opinion as to whether AEs were related to the study drug.

For both studies, continuous demographic variables (age, weight, and height) were summarized using mean, standard deviation (SD), minimum, maximum, and number of available observations. Pharmacokinetic parameters determined by non-compartmental analysis were summarized by calculating the mean, SD, median, coefficient of variation (CV%), and minimum and maximum for each food regimen. For the calculation of mean plasma concentrations and pharmacokinetic parameters, values below the LOQ were set as zero.

In Study 1 (400 mg dronedarone), pharmacokinetic parameters were determined separately (PKDMS Version 2.0 with WinNonlin Professional, version 4.0.1) for each food state using descriptive statistics. C_{max}, AUC_{0-inf}, AUC_{last}, and $T_{1/2z}$ values were log-transformed and analyzed using a linear mixed effects model using SAS Proc Mixed® with fixed terms for sequence, period, food state, and sex, and with an unstructured R matrix of food variances and covariance for participant within sequence-by-sex blocks. C_{max}, AUC_{0-inf}, AUC_{last}, and $T_{1/2z}$ estimates and 90% confidence intervals (CIs) for the fed (high-fat meal) vs. fasted state geometric mean ratios were obtained by computing the estimate and 90% CIs for the difference in means within the linear mixed effects model framework, and then converting to a ratio using the anti-log transformation. All analyses were performed using SAS (version 9.1).

In Study 2 (800 mg dronedarone), pharmacokinetic parameters (C_{max}, T_{max}, and AUC_{last}) were determined by non-compartmental analysis using in-house–developed software running on a VAX-VMS computer (RDB Digital Database, version 4). Estimation of $T_{1/2z}$ and AUC_{0-inf} was not possible because plasma samples were collected for 48 h only. Food regimens were compared by analysis of variance (ANOVA) using a model that included terms for sequence, participant-within-sequence, period, food regimen, and carryover (to assess potential residual drug effects from previous treatment sequences). If the carryover effect was not significant ($P > 0.05$), the ANOVA was repeated without that term. Parameters showing evidence of an overall food effect ($P < 0.05$) were tested for pairwise food regimen differences. For AUC_{last} and C_{max}, the magnitude of food regimen differences was assessed by calculation of relative ratios with 90% and 95% CIs within the ANOVA context, then using the anti-log transformation. All statistical tests were 2-tailed, with the alpha level fixed at 0.05. No adjustment for multiple testing was performed. All analyses were performed using SAS (version 6.09).

3. Results

In Study 1 (400 mg dronedarone), a total of 26 participants were included (Table 1). One participant discontinued the study due to an AE that occurred after receiving dronedarone under the fed (high-fat meal) state and did not receive dronedarone in the fasted state. In Study 2 (800 mg dronedarone), nine participants were included (Table 1). None withdrew or discontinued the study.

Table 1
Baseline demographic characteristics.

Characteristic	Study 1 (400 mg dronedarone) ($N = 26$)	Study 2 (800 mg dronedarone) ($N = 9$)
Age (years)		
Mean (SD)	27.9 (6.7)	31.1 (6.5)
Min, max	20.0, 44.0	24.0, 39.0
Male, n (%)	15 (57.7)	9 (100)
Race, n (%)		
White	23 (88.5)	9 (100)
Black	3 (11.5)	0
Height (cm)		
Mean (SD)	171.8 (9.6)	181.9 (3.6)
Min, max	153.0, 183.0	177.0, 188.0
Weight (kg)		
Mean (SD)	68.6 (11.8)	77.5 (6.7)
Min, max	49.0, 93.0	68.5, 88.5
BMI (kg/m^2)		
Mean (SD)	23.2 (3.3)	–
Min, max	18.8, 29.9	–

Abbreviations: BMI = body mass index; max = maximum; min = minimum; SD = standard deviation.

In Study 1 (400 mg dronedarone), plasma concentrations of dronedarone were increased at all timepoints after administration with a high-fat meal compared with administration in the fasted state (Fig. 1A). Results for the active N-debutyl metabolite were similar to those for dronedarone, although concentrations were lower than with dronedarone (Fig. 1B). Plasma concentrations for dronedarone were quantifiable up to 96 h and 72 h in the fed (high-fat meal) and fasted states, respectively, and those for the N-debutyl metabolite were quantifiable for up to 96 h in both the fed (high-fat meal) and fasted states. All dronedarone and N-debutyl metabolite concentrations observed from 3 to 48 h after administration were above the LOQ. The total variability in dronedarone pharmacokinetic parameters was moderate (CV: 45–48%) in the fed (high-fat meal) state and moderate-to-high in the fasted state (CV: 28–92%) (Table 2). The median T_{max} and T_{lag} for dronedarone were 3.0 h and 0.5 h, respectively, in both the fed (high-fat meal) and fasted states (Table 2). The total variability in N-debutyl metabolite pharmacokinetic parameters was moderate (CV: <57%) in both states, though lower in the fed (high-fat meal) compared with fasted state (Table 2). Median T_{max} and T_{lag} values for the N-debutyl metabolite were 4.0 h and 0.5 h, respectively, in both the fed (high-fat meal) and fasted states. An increase in dronedarone bioavailability was observed in the fed (high-fat meal) vs. the fasted state, with 2.8-fold (90% CI 2.0–3.8), 2.0-fold (90% CI 1.6–2.4), and 1.8-fold (90% CI 1.5–2.2) greater C_{max}, AUC_{last}, and AUC_{0-inf} values, respectively (Table 3). Dronedarone $T_{1/2z}$ remained constant with (16.7 h) and without (13.8 h) food (the 90% CI of $T_{1/2z}$ ratio containing 1). An increase in N-debutyl metabolite exposure was observed after a high-fat meal compared with the fasted state, with 2.3-fold (90% CI 1.9–2.8), 1.8-fold (90% CI 1.6–2.0), and 1.6-fold (90% CI 1.4–1.8) greater C_{max}, AUC_{last}, and AUC_{0-inf} values, respectively (Table 3). The N-debutyl metabolite $T_{1/2z}$ also remained relatively constant regardless of whether it was administered with (17.1 h) or without (18.6 h) food (the 90% CI of $T_{1/2z}$ ratio containing 1).

In Study 2 (800 mg dronedarone), the plasma concentration of dronedarone after administration with a fat-rich or a low-fat meal was increased at all timepoints compared with administration in the fasted state (Fig. 1C). Plasma concentrations of dronedarone and its active N-debutyl metabolite were quantifiable up to 48 h after administration (the last sampling time) in all states. The peak concentration was higher after administration of dronedarone with a fat-rich vs. a low-fat meal; however, after approximately 5 h, the plasma concentration curves were nearly superimposable (Fig. 1C). The results for the active N-debutyl metabolite were comparable with those of dronedarone, although concentrations were lower overall (Fig. 1D). All dronedarone and N-debutyl metabolite concentrations observed from 2 to 48 h after administration were above the LOQ. The total variability in dronedarone pharmacokinetic parameters was moderate (CV: 21–50%) in all states. The median T_{max} and T_{lag} for dronedarone were 5.0 h and 0.0 h, respectively, in both the fed (fat-rich and low-fat) and fasted states (Table 2). The total variability in N-debutyl metabolite pharmacokinetic parameters was moderate (CV: <40%) in all states (Table 2). The median T_{max} for the N-debutyl metabolite was 5.0, 6.0, and 5.0 h in the fat-rich, low-fat, and fasted states, respectively. The median T_{lag} for the N-debutyl metabolite was 0 h in all states. Geometric mean values revealed 4.6-fold (95% CI 3.3–6.4) and 3.2-fold (95% CI 2.3–4.4) increases in C_{max} after administration with a fat-rich or low-fat meal, respectively, compared with administration in the fasted state. Administration of dronedarone with a fat-rich meal only slightly increased C_{max} (1.5-fold [95% CI 1.1–2.0]) compared with administration with a low-fat meal (Table 3). Mean (SD) AUC_{last} values for dronedarone after administration with either a fat-rich (1274 [330] ng.h/mL) or a low-fat meal (976 [252] ng.h/mL) were both higher than after administration in the fasted state (416 [107]

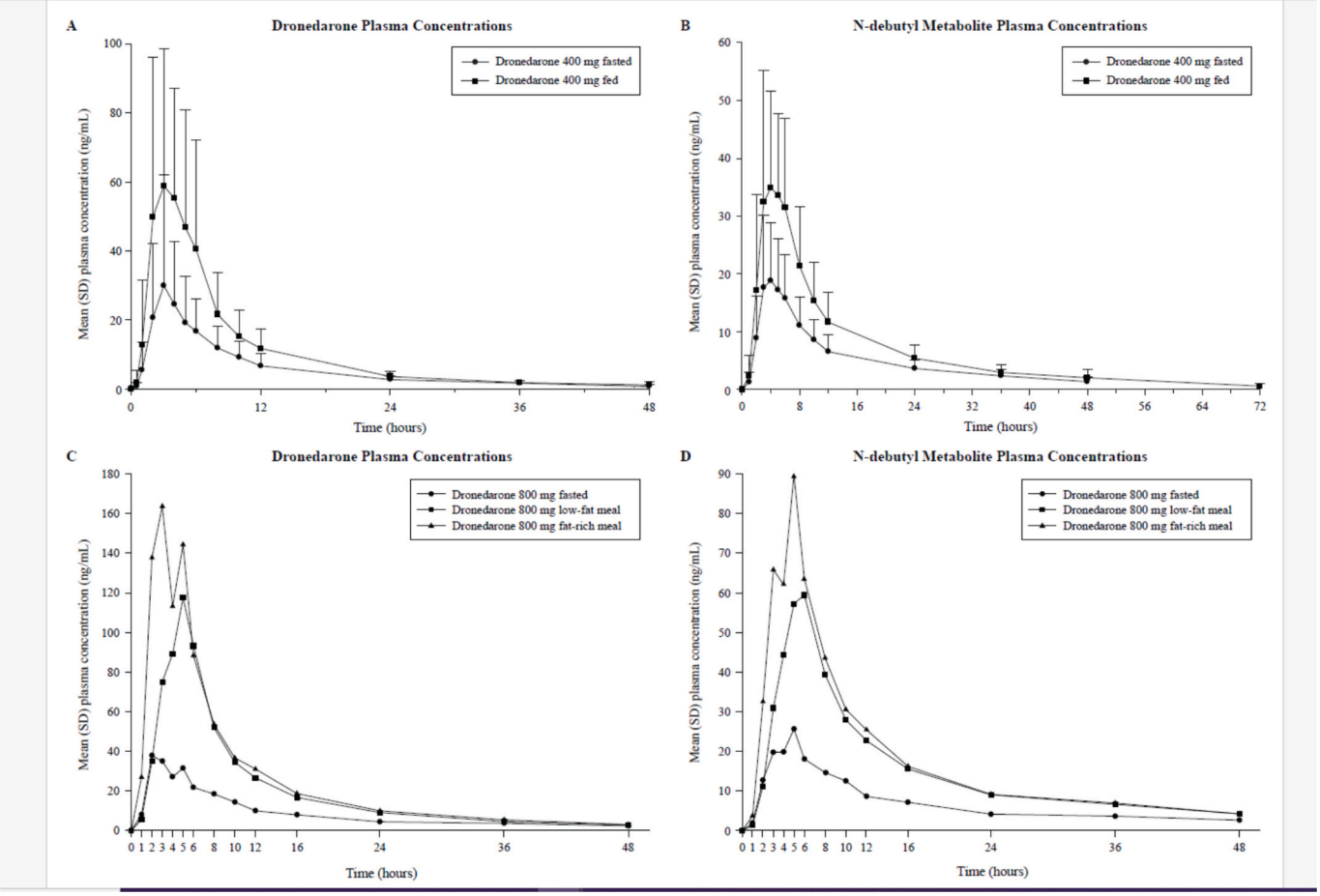

Fig. 1. Mean plasma concentration vs. time curves for dronedarone and the active N-debutyl metabolite administered at 400 mg (A and B) and administered at 800 mg (C and D) under different meal states.

ng.h/mL; Table 2). Geometric means showed 3.1-fold (95% CI 2.6–3.6) and 2.3-fold (95% CI 2.0–2.8) increases in AUC_{last} after administration of dronedarone with a fat-rich or low-fat meal, respectively, compared with administration in the fasted state. Administration of dronedarone with a fat-rich meal only slightly increased AUC_{last} (1.3-fold [95% CI 1.1–1.5]) compared with administration after a low-fat meal (Table 3). The results for the active N-debutyl metabolite were comparable with those of dronedarone (Tables 2 and 3). As no carryover effect for dronedarone or the active N-debutyl metabolite was observed, the ANOVA was performed without considering a carryover effect. The results showed a significant treatment effect with food on dronedarone C_{max} and AUC_{last} ($P = 0.0001$), but not T_{max} ($P = 0.1568$). For the active N-debutyl metabolite, a significant treatment effect with food was observed for C_{max} ($P = 0.0001$), AUC_{last} ($P = 0.0001$), and T_{max} ($P = 0.0056$).

In Study 1 (400 mg dronedarone), no severe or serious treatment-emergent adverse events (TEAEs) were reported. One participant discontinued the study due to a TEAE after receiving dronedarone in the fed (high-fat meal) state (eosinophil count increased). Five of the 26 participants experienced TEAEs, 2 in the fed (high-fat meal) state ($n = 1$ each for orthostatic hypotension and eosinophil count increased) and 3 in the fasted state (n = 1 each for hypoglycemia, anxiety, dizziness postural, headache, abdominal pain, vomiting, asthenia, and malaise). No prolonged QTc values and no delta QTc >60 ms were reported.

In Study 2 (800 mg dronedarone), 3 participants reported AEs; the relationship to dronedarone was unknown. One participant reported diarrhea, which occurred only during the fat-rich meal period and was mild in intensity; no corrective treatment was provided, and the participant fully recovered. A second participant reported 2 episodes of non-sustained asymptomatic ventricular tachycardia, which were mild, lasted only a few seconds, and resolved spontaneously. A third participant had a serious AE (fracture of the left calcaneus) due to an accident. There were no discontinuations and no deaths.

4. Discussion

These analyses represent the results of two previously unpublished studies conducted to assess the effect of food on dronedarone bioavailability and the formation of its active N-debutyl metabolite. These data support the FDA-approved label recommendation for dronedarone to be taken with food. Due to first-pass metabolism and incomplete absorption, the absolute bioavailability of dronedarone is low when administered in the fasting state [9,17]. The bioavailability of dronedarone after a single 400-mg or 800-mg dose increased significantly with food. In the 800-mg dose study, the high-fat meal only slightly increased the bioavailability of dronedarone compared with a low-fat meal. Although the N-debutyl metabolite is less pharmacologically active than dronedarone, the clinical effects of the metabolite are likely to be clinically significant. These data highlight the importance of administering dronedarone with food to maximize drug availability, a critical aspect of dronedarone administration that almost certainly has clinical ramifications.

The FDA-approved label recommendation for dronedarone to be taken with food is based on the results of the phase 1, single 800-mg dose study (Study 2), in addition to the multiple clinical trials performed during the development of dronedarone that used the 800-mg daily dose

Table 2
Dronedarone pharmacokinetics.

	Study 1 (400 mg dronedarone)			
	Dronedarone		Active N-debutyl metabolite	
Parameters	Fasted (n = 25)	Fat-rich meal (n = 26)	Fasted (*n* = 25)	Fat-rich meal (n = 26)
C_{max} (ng/mL)				
Mean (SD)	34.0 (31.4)	84.3 (40.7)	21.7 (12.4)	47.3 (18.0)
Geometric mean	25.8	70.4	18.9	43.0
CV%	92	48	57	38
T_{max} (h)				
Median (min, max)	3.0 (2.0, 6.0)	3.0 (2.0, 6.0)	4.0 (3.0, 6.0)	4.0 (3.0, 6.0)
T_{lag}				
Median (min, max)	0.5 (0.0, 1.0)	0.5 (0.0, 2.0)	0.5 (0.5, 1.0)	0.5 (0.0, 2.0)
AUC_{last} (ng.h/mL)				
Mean (SD)	273 (154)	523 (233)	272 (125)	464 (169)
Geometric mean	236	461	244	429
CV%	56	45	46	37
AUC_{0-inf} (ng.h/mL)				
Mean (SD)	289 (157)	534 (243)	312 (119)	477 (167)
Geometric mean	252	472	291	445
CV%	54[a]	45[b]	38[c]	35[b]
$T_{1/2z}$				
Mean (SD)	13.8 (3.9)	16.7 (7.9)	18.6 (5.7)	17.1 (4.0)
Geometric mean	13.3	15.2	17.9	16.6
CV%	28[a]	47[b]	31[a]	24[b]

	Study 2 (800 mg dronedarone)					
	Dronedarone (n = 9)			Active N-debutyl metabolite (*n* = 9)		
Parameters	Fasted	Low-fat meal	Fat-rich meal	Fasted	Low-fat meal	Fat-rich meal
C_{max} (ng/mL)						
Mean (SD)	42.9 (21.5)	128 (50.3)	192 (90.9)	26.43 (9.5)	63.0 (17.3)	98.7 (39.7)
Median	40.0	121	173	27.3	69.4	81.6
CV%	50	39	47	36	28	40
T_{max} (h)						
Mean (SD)	3.7 (1.6)	4.7 (1.0)	3.9 (1.4)	4.6 (0.9)	5.6 (0.5)	4.6 (0.9)
Median	5.0	5.0	5.0	5.0	6.0	5.0
CV%	43	21	35	19	9	19
T_{lag}						
Median (min, max)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)
AUC_{last} (ng.h/mL)						
Mean (SD)	416 (107)	976 (252)	1274 (330)	329 (83.9)	724 (171)	869 (221)
Median	416	965	1180	345	733	812
CV%	26	26	26	25	24	25

Abbreviations: AUC_{0-inf} = area under the plasma concentration extrapolated to infinity; AUC_{last} = area under the plasma concentration vs. time curve calculated using the trapezoidal method from time zero to the time of the last observed concentration above the limit of quantification; C_{max} = maximum plasma concentration observed; CV% = coefficient of variation; SD = standard deviation; $T_{1/2z}$ = terminal half-life; T_{lag} = lag time, interval between administration time and the sampling time preceding the first concentration above the limit of quantification; T_{max} = time to reach C_{max}.

[a] n = 24.

[b] n = 25.

[c] n = 22.

given as 400 mg twice a day [9–12]. The label states that dosing is "one tablet of 400 mg twice a day with morning and evening meals" [9]. At the request of Health Canada, the 400-mg dose study (Study 1) was performed in 2009, the results of which confirmed the food-effect observations from the 800-mg dose study. The magnitude of the food effect was higher in the 800-mg study due to the differences in dose between the 2 studies. This is because as the dose of dronedarone is increased, its limited absorption due to low solubility is more apparent; therefore, the food effect would be expected to be greater at the higher dose due to increased solubility with food.

An important consideration for these findings is that in the 800-mg dose study (Study 2) there was only a slight difference in the bioavailability of dronedarone when administered with a low-fat meal compared with a fat-rich meal. The primary difference in dronedarone exposure is accounted for during the first 5 h after administration, during which the peak plasma concentration was observably higher after administration with a fat-rich meal compared with a low-fat meal. After this timepoint, the plasma concentration curves for both meal types overlap. This may explain the 31% increase in AUC_{last} that was observed when comparing administration with a fat-rich vs. a low-fat meal. Since the timing of dronedarone ingestion relative to a meal is an important determinant of exposure, one of the most important recommendations for the prescribing clinician is to emphasize that dronedarone should be taken with a substantial meal (with no need to recommend a high-fat option) and not on an empty stomach.

As dronedarone is a biopharmaceutical classification system class II drug (low solubility and high permeability), the primary mechanism of increased absorption is likely due to an increase in drug solubilization with food. Recent studies have suggested the amount of free drug available in the plasma may be affected by lipoprotein binding of dronedarone associated with a high-calorie intake [18,19]. However, we did not study these mechanisms for this report.

Effects of food on bioavailability are common with many AADs. These are summarized in Table 4 [9,20–24]. It is important for clinicians to be familiar with the effect of food on all agents and to not associate the effects of food with just one AAD. Neither should they assume that the

Table 3
Fed vs. fasted ratios and 90% CIs for dronedarone dosed at 400 mg and geometric mean of the relative ratios and 95% CIs of C_{max} and AUC_{last} of dronedarone dosed at 800 mg.

	Study 1 (400 mg dronedarone)	
	Dronedarone (n = 25)	Active N-debutyl metabolite (*n* = 25)
	Estimate of high-fat meal/fasted ratio (90% CI)	Estimate of high-fat meal/fasted ratio (90% CI)
C_{max} (ng/mL)	2.8 (2.0–3.8)	2.3 (1.9–2.8)
AUC_{last} (ng.h/mL)	2.0 (1.6–2.4)	1.8 (1.6–2.0)
AUC_{0-inf} (ng.h/mL)	1.8 (1.5–2.2)	1.6 (1.4–1.8)
$T_{1/2z}$	1.1 (1.0–1.3)	1.0 (0.9–1.0)

	Study 2 (800 mg dronedarone)					
	Dronedarone (n = 9)			Active N-debutyl metabolite (n = 9)		
	Low-fat meal:fasted (95% CI)	Fat-rich meal:fasted (95% CI)	Fat-rich meal:low-fat meal (95% CI)	Low-fat meal/fasted (95% CI)	Fat-rich meal/fasted (95% CI)	Fat-rich meal/low-fat meal (95% CI)
C_{max} (ng/mL)	3.2 (2.3–4.4)	4.6 (3.3–6.4)	1.5 (1.1–2.0)	2.4 (2.0–3.1)	3.7 (3.0–4.6)	1.5 (1.2–1.9)
AUC_{last} (ng.h/mL)	2.3 (2.0–2.8)	3.1 (2.6–3.6)	1.3 (1.1–1.5)	2.2 (2.0–2.5)	2.7 (2.4–2.9)	1.2 (1.1–1.3)

Abbreviations: AUC_{0-inf} = area under the plasma concentration vs. time curve extrapolated to infinity; AUC_{last} = area under the plasma concentration vs. time curve calculated using the trapezoidal method from time zero to the time of the last observed concentration above the limit of quantification; CIs = confidence intervals; C_{max} = maximum plasma concentration observed; $T_{1/2z}$ = terminal half-life.

Table 4
Summary of food effects on antiarrhythmic drugs.

AAD	Effects	Dosing recommendations
Vaughan–Williams class I-IV		
Amiodarone [20]	Food increases exposure and rate of absorption Grapefruit juice increases exposure by inhibiting drug metabolism	To be taken with/without meals Avoid grapefruit juice
Dronedarone [9]	4-fold increase in bioavailability with food Grapefruit juice increases exposure by 3-fold by inhibiting drug metabolism	To be taken with meals Avoid grapefruit juice
Vaughan–Williams class IC		
Flecainide [21]	No food effect Milk may reduce the absorption in children and infants	To be taken with/without meals A reduction in flecainide dosage should be considered when milk is removed from the diet of infants
Propafenone [22]	No food effect Grapefruit juice increases exposure by inhibiting drug metabolism	To be taken with/without meals Avoid grapefruit juice
Vaughan–Williams class III		
Dofetilide [23]	Unaffected by food Grapefruit juice increases exposure by inhibiting drug metabolism	To be taken with/without meals Caution with grapefruit juice
Sotalol [24]	20% reduction in absorption with food vs. fasting	To be taken with/without meals

Abbreviation: AAD = antiarrhythmic drug.

food effects are the same within or across AAD classes. Dronedarone has antiarrhythmic properties belonging to all four Vaughan–Williams classes, similar to amiodarone. In addition to dronedarone and amiodarone, the bioavailability of which are both affected by food, sotalol, a class III antiarrhythmic agent, is affected by food [7,8,24]. Administration of amiodarone with food increases both exposure and rate of absorption [7]; however, administration with food reduces the bioavailability of sotalol by 20% compared with administration without food [8,24].

In addition to effects on drug bioavailability, certain foods, for example, grapefruit juice, can inhibit the activity of CYP3A4, which is the primary route for metabolism for dronedarone and amiodarone. Therefore, it is recommended to avoid grapefruit juice with these AADs (Table 4).

Few AEs were observed in these studies, and the only serious AE reported was due to an accident unrelated to the study. In the 800-mg dose study, 1 participant had 2 episodes of asymptomatic non-sustained ventricular tachycardia; however, as the first episode occurred 6 days after drug administration, these episodes were not considered related to dronedarone.

For Study 2 (800-mg dose), the difference in dosing compared with Study 1 occurred in part due to the study being conducted prior to the determination of the final dosing for dronedarone, and before the dose-ranging study (The Dronedarone Atrial FibrillatioN study after Electrical Cardioversion [DAFNE]), which definitively established improved tolerance for the 400-mg twice-daily dosing regimen vs. the 800-mg once-daily regimen [12]. In Study 2, sampling for pharmacokinetic parameters was conducted for 48 h; therefore, $T_{1/2z}$ was not able to be estimated and not reported and the AUC_{0-inf} could not be extrapolated to infinity. The studies described in this manuscript were designed to assess the effect of food on the bioavailability of dronedarone to guide dronedarone dosing recommendations, and as such, the pharmacokinetic parameters investigated focused on measures of dronedarone exposure. While other factors to describe the dronedarone food interaction could

also have been investigated, for example, protein binding, they were not included in these study designs. This approach focusing on exposure data permits the delivery of a clear and concise message for clinicians regarding the need to administer dronedarone with a meal. Additionally, both Study 1 and Study 2 were conducted in young healthy adults in which the majority of participants were male (69%) or White (90%). In clinical practice, people often have comorbid states, and as such, receive multiple concomitant medications that may affect the bioavailability of dronedarone. Therefore, the population in this study may not be representative of all population groups receiving dronedarone. However, dronedarone was administered with food in the pivotal phase 3 clinical trials conducted in representative populations of patients with AF, such as EURIDIS and ADONIS, and ATHENA [10,11], which demonstrated the clinical efficacy and safety of dronedarone and led to FDA approval and labeling indications.

In the fasted state, dronedarone absorption is not complete and undergoes considerable presystemic, first-pass metabolism, resulting in low absolute bioavailability. When administered with food, the absorption of dronedarone and therefore its bioavailability is significantly increased compared with administration in the fasted state, resulting in significantly higher plasma concentrations of dronedarone and its N-debutyl metabolite. In clinical practice, it is important clinicians advise their patients that to achieve maximum efficacy, dronedarone needs to be taken with a substantial meal (rather than just a light snack), although it should be noted that it is not crucial that the meal has a high-fat content. Administration without food or failure to take dronedarone with a substantial meal may result in reduced plasma concentrations of dronedarone, thereby potentially reducing its clinical effectiveness.

CRediT authorship contribution statement

Gerald V. Naccarelli: Writing – review & editing, Conceptualization. **David S. McKindley:** Writing – review & editing, Conceptualization. **Jason Rashkin:** Writing – review & editing, Conceptualization. **Celine Ollier:** Writing – review & editing, Visualization, Data curation, Conceptualization. **James A. Reiffel:** Writing – review & editing, Conceptualization.

Declaration of competing interest

GVN is a consultant for Sanofi, Acesion Pharma, Milestone, InCarda Therapeutics, and GlaxoSmithKline. DSM, JR, and CO are employees and stockholders of Sanofi. JAR is an investigator for Johnson & Johnson, InCarda Therapeutics, Amarin Corporation, and Sanofi; a consultant for Acesion Pharma and Sanofi.

Data availability

Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient level data will be anonymized, and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/.

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Ethical statement

Both studies complied with the recommendations of the 18th World Health Congress (Helsinki, 1964) as amended at the 29th Congress (Tokyo, 1975), the 35th Congress (Venice, 1983), and the 41st World Medical Assembly (Hong Kong, 1989). All participants provided written informed consent. Study 1 took place between July 15 and September 18, 2009, and was approved by an independent ethics committee. Study 2 took place between April 23 and June 9, 1997, and was approved by the Ethics Committee of the Bayerische Landesärztekammer, Munich, Germany, before enrollment of any participants.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2024.100423.

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