HHS Public Access

Author manuscript

Am J Cardiol. Author manuscript; available in PMC 2025 January 01.

Published in final edited form as:

Am J Cardiol. 2024 January 01; 210: 183–187. doi:10.1016/j.amjcard.2023.09.115.

The Effect of Udenafil on Heart Rate and Blood Pressure in Adolescents with the Fontan Circulation

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Declarations of Interest:

Funding for this project was provided by the National Heart, Lung, and Blood Institute (HL135646, HL135665, HL135666, HL135678, HL135680, HL135682, HL135683, HL135685, HL135689, HL135691) and by Mezzion Pharma Co. Ltd. (Seoul, Republic of Korea). The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; the U.S. Department of Health and Human Services; or Mezzion Pharma Co. Ltd.

Clinical Trial Number: NCT0274115

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abstract

The FUEL trial showed that treatment with udenafil was associated with improved exercise performance at the ventilatory anaerobic threshold in children with Fontan physiology. However, it is not known how the initiation of PDE-5 inhibitor therapy affects heart rate and blood pressure in this population. These data may help inform patient selection and monitoring after initiation of udenafil therapy.The purpose of this study is to evaluate the effects of udenafil on vital signs in the cohort of patients enrolled in the FUEL Trial. This international, multicenter, randomized, double-blind, placebo-controlled trial of udenafil included adolescents with single ventricle congenital heart disease who had undergone Fontan palliation. Changes in vital signs [heart rate (HR), systolic (SBP) and diastolic blood pressure (DBP)] were compared both to subject baseline and between the treatment and the placebo groups. Additional exploratory analyses were performed to evaluate changes in vital signs for pre-specified subpopulations thought to be most sensitive to udenafil initiation.Baseline characteristics were similar between the treatment and placebo cohorts (n=200 for each). Both groups demonstrated a decrease in HR, SBP, and DBP two hours after drug/placebo administration, excepting SBP in the placebo group. There was an increase in SBP from baseline to after 6-minute walk test (6MW) in both treatment and placebo groups; and the treatment group showed an increase in HR (87.4±15.0 to 93.1±19.4 bpm, *p<0.01)* after exercise. When comparing changes from baseline to the 26-week study visit, small decreases were seen in the treatment group in both SBP (−1.9 ± 12.3 mmHg, *p=0.03)* and DBP (−3.0 ± 9.6 mmHg, *p<0.01)*. There were no clinically significant differences between treatment and placebo group in change in heart rate or blood pressure in the youngest age quartile, lightest weight quartile, or those on afterload reducing agents. In conclusion, initiation of treatment with udenafil in patients with Fontan circulation was not associated with clinically significant changes in vital signs, implying that for patients similar to those enrolled in the FUEL trial, udenafil can be started without the requirement for additional monitoring after initial administration.

Keywords

Single Ventricle; Fontan procedure; Phosphodiesterase 5 inhibitor

Introduction:

The development and refinement of surgical palliation for children with single ventricle congenital heart disease (SV-CHD), which culminates with the Fontan circulation, has allowed many children who once would have died in infancy or early childhood to survive to adulthood. Current studies estimate a worldwide population of up to 70–80,000 patients who have undergone the Fontan procedure[1]. However, while the Fontan may be life-prolonging, the lack of a sub-pulmonary ventricle creates an inefficient circulation characterized by elevated central venous pressure and an impaired ability to increase cardiac output in the setting of increased demand. Exercise capacity is limited across the Fontan cohort, with an association between the degree of impairment and the onset of symptomatic heart failure and death.[2–6].

Phosphodiesterase-5 (PDE-5) inhibitors in children with Fontan physiology may be beneficial, with studies demonstrating improvements in both exercise capacity and cardiac output[7–9]. More recently, the FUEL trial showed that treatment with udenafil was

associated with improved exercise performance at the ventilatory anaerobic threshold and an improvement in the myocardial performance index, findings which suggests that this medication may be of clinical benefit to certain children and adults living with Fontan physiology[10]. However, while the data from the FUEL trial were encouraging, a knowledge gap exists with respect to acute effect of udenafil on heart rate and blood pressure and thus the potential to initiate therapy in the outpatient setting. Given the systemic effect of PDE-5 inhibitors, and that some adult studies have shown an acute decrease in blood pressure after administration[17,18], understanding the effect of udenafil on the vital signs of children with the Fontan circulation is a critical step in understanding how to best use this therapy properly. Thus, the purpose of this study is to evaluate the effects of udenafil on heart rate and blood pressure in the cohort of subjects enrolled in the FUEL trial.

Methods

The FUEL trial was an international, multicenter, randomized, double-blind, placebo-controlled trial of udenafil, in addition to standard of care, in adolescents with SV-CHD who had undergone Fontan palliation. The trial was supported by the National Heart, Lung, and Blood Institute–funded Pediatric Heart Network in partnership with the industry sponsor, Mezzion Pharma Co Ltd, under a Special Protocol Assessment through the US Food and Drug Administration. Four-hundred subjects, ages 12–18 years, were enrolled and randomized in a double-blind manner and 1:1 ratio to either the udenafil treatment group or the placebo group using randomly permuted blocks and stratified by ventricular morphology. Eligibility criteria included weight ≥40kg, height ≥132 cm and not previously using a PDE-5 inhibitor. All 400 participants were included in the primary analysis of the FUEL trial. Imputation of the 26-week end point was performed for participants with missing data (11 randomly assigned to udenafil and 10 to placebo). Additional details with regards to the FUEL study procedures have been previously described[10,11].

This secondary analysis of the FUEL dataset focused on vital signs collected during the trial. These vital signs include systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR). Measurements of vital signs were performed at the following time points: baseline (<1 hour prior to the first dose), immediately before 6-minute walk (6MW) (approximately two hours after the first dose, selected to reflect the time of peak drug effect), immediately after 6MW, and at the week 26 (final) study visit. Changes in vital signs from baseline were assessed and compared between the treatment and the placebo groups. Additional exploratory analyses were performed to evaluate changes in vital signs for pre-specified subpopulations (reflecting biological sex, self-identified race, ventricular morphology, age, weight, and subjects using afterload reducing agents).

Summary descriptive statistics for vital signs are presented as mean ± standard deviation. Paired t-testing was used to compare changes in vital signs from baseline to pre-specified time points. Differences in the change in vital signs from baseline between the treatment and placebo groups were assessed using an analysis of covariance with fixed factors for ventricular morphology (LV versus RV or mixed) and treatment group with a continuous covariate of baseline value of the outcome. Additionally, vital signs changes were assessed and compared between treatment arms for pre-specified populations. Analyses were

performed for complete cases. In all analyses, a p-value <0.05 was accepted for statistical significance. No formal adjustment was made for multiple testing. Rather, based upon the principle in the American Statistical Association's Statement on p-values, we report the number of hypotheses explored during the study, all data collection decisions, all statistical analyses conducted, and all p-values computed. Analyses were performed with SAS enterprise Guide 8.3 (SAS Institute, Cary NC) software[12].

Results

The mean overall age was 15.5 years, the mean height 163.6 cm, and the mean weight 58.1kg[10]. The majority of the cohort were male and identified as Caucasian. Key baseline clinical and demographic characteristics of the 400 subjects in both the treatment and placebo groups are included in Table 1. Baseline characteristics were similar between the treatment and placebo cohorts. Subjects in the placebo group were slightly taller (165 cm vs 162 cm) and heavier (59.0 kg vs 57.1 kg). Each cohort had a similar distribution of right and left ventricular morphologies. Angiotensin converting enzyme inhibitors/Angiotensin receptor antagonists (ACEi/ARB) were the most frequently used cardiac medications followed by beta-blockers and diuretics.

Table 2 shows changes in HR, SBP, and DBP from baseline measurements at various timepoints for both treatment and placebo groups. Both groups demonstrated a statistically significant decrease in all measured vital signs two hours after drug/placebo administration. The decrease in SBP was statistically significant in the udenafil group but not in the placebo group. After 6MW there was a statistically significant increase in SBP for both groups when compared to baseline, and the treatment group showed an increase in HR (87.4±15.0 to 93.1±19.4 bpm, $p<0.01$). When comparing baseline to the 26-week study visit, changes were limited to small decreases in SBP (−1.9 ± 12.3mmHg, $p=0.03$) and DBP (−3.0 ± 9.6mmHg, $p<0.01$) in the treatment group. Importantly, all mean values remained within the normal range after initiation of udenafil. Furthermore, there were no serious adverse events related to changes in HR or BP in the udenafil group, nor did the udenafil group have an increased frequency of nonserious adverse events, such as dizziness, which would suggest clinically significant changes in vital signs[10].

When comparing the changes in vital signs between the treatment arms, the decrease in SBP from baseline to 120 minutes after drug/placebo administration was greater in treatment compared to placebo. The treatment group also had a greater change in HR from baseline to after 6MW. At the 26-week mark, the only statistically significant difference between the treatment and placebo cohorts was a marginally greater decrease in DBP in the treatment group.

Supplemental Tables 1–3 show vital sign changes as stratified by sub-populations. Changes in SBP from baseline compared to two hours after drug/placebo administration were slightly more pronounced in female and non-Caucasian subjects in the treatment group compared to placebo, and in female placebo subjects after 6MW. The lowest weight quartile in the treatment group had a slight decrease in SBP at the final study visit, while placebo did not. There were no clinically significant changes in DBP, though treatment subjects in the

older age quartiles, heavier weight quartiles, and on other afterload reducing agents, had a greater change in DBP from baseline to 26-week visit compared to placebo. Greater HR change from baseline to 120 minutes was observed in the placebo group in female subjects, Caucasian and non-Caucasian subjects, single right ventricle subjects and in those using afterload reducing medications. When comparing HR from baseline to after 6MW, patients in the treatment group had a significant increase regardless of biological sex, race or ventricular morphology. Older age quartiles, heavier weight quartiles, and afterload reducing agents also had a significant HR increase when compared to placebo. Importantly, there were no clinically significant differences between treatment and placebo changes in either SBP or DBP for subjects in the youngest age quartile, lowest weight quartile, or those on afterload reducing agents.

Discussion

To the best of our knowledge, this is the first study to evaluate the effect of udenafil on HR and BP in children with Fontan physiology, with several important findings. Udenafil caused a small but clinically insignificant decrease in SBP, DBP, and HR at 120 minutes after administration. HR increased in the treatment group after exercise relative to the placebo group, but there were no differences in change in SBP or DBP. Lastly, there were no notable or clinically significant acute vital sign changes in smaller patients or in patients already on an afterload reducing agent, the sub-populations considered most sensitive to the initiation of a phosphodiesterase type 5 (PDE-5) inhibitor.

Pulmonary vasodilators are thought to be an effective therapy for patients with Fontan physiology due to their ability to modulate pulmonary vascular resistance, and in turn, augment ventricular preload and ultimately cardiac output[13–16]. While PDE-5 inhibitors preferentially affect the pulmonary vasculature, there is also a systemic effect, and some adult studies have shown an acute decrease in blood pressure after administration[17,18]. These findings led to the inclusion of vital sign checks and provocative exercise testing at initiation of udenafil therapy[11]. Importantly, in the FUEL treatment cohort no substantial change was noted in any vital signs obtained 120 minutes after first dose, with SBP and DBP decreasing by < 5mmHg and HR by < 3bpm, and vital signs remained in the normal ranges for age. These small and clinically insignificant changes suggest that the initiation of udenafil in certain Fontan patients can take place as an outpatient, and without any specialized period of vital sign monitoring.

Similarly, no clinically significant difference was detected between the treatment and placebo groups when SBP and DBP were assessed after six-minute walk, lending further support to the contention that udenafil is a well-tolerated medication in patients with the Fontan circulation. While it is interesting that a small increase in heart rate was noted after exercise in the treatment group compared to no HR change in the placebo group, given the lack of change in blood pressure it is not clear if this difference has clinical significance.

The exploratory component of this analysis was designed to evaluate the effect of udenafil on patients thought to be at higher risk of having an adverse hemodynamic reaction upon its initiation, including smaller patients and those already on afterload reducing agents.

Some studies of PDE-5 inhibitors have suggested an exaggerated response in patients on other afterload reducing agents, with more pronounced changes in blood pressure[18]. This was not observed in the FUEL cohort, an important finding given the prevalent use of these medications in children and adolescents with Fontan physiology[19]. Similarly, the youngest and smallest patients in the cohort did not have clinically significant changes in vital signs with the introduction of udenafil. Importantly, the FUEL protocol did not specify that udenafil administration needed to be staggered with respect to other daily medications.

In children with Fontan physiology, cardiac output is inherently limited by preload, and the role of pulmonary vascular resistance is critical. Udenafil has been shown to have a meaningful impact on exercise performance in children with Fontan physiology, and the results of this study support its tolerability and suggest that it can be administered on an outpatient basis to patients with characteristics similar to those who met enrollment criteria for the FUEL trial.

Limitations

Despite the important results and implications presented in this paper, this study had several limitations. The analysis was limited to those enrolled in the original FUEL cohort and was therefore subject to potential selection bias. Children less than 40kg, those with severe ventricular dysfunction, and those with very low maximum oxygen consumption were not included, and it is unclear whether these results can be generalized to those groups. Hemodynamic variables, including pulmonary vascular resistance, were not measured and may have contributed to differential responses among subjects. The sub-group analyses were of exploratory nature, as the study was not powered for formal sub-group analyses. No formal adjustment was made for multiple testing and some of the findings might be due to chance. Had we adjusted for multiple testing, it would have biased our results to the null, making it less likely that vital sign differences between udenafil and placebo were detected. Lastly, this analysis was not designed to assess the long-term safety of udenafil; this will be evaluated in the long-term FUEL open-label extension trial.

Conclusions

Initiation of treatment with udenafil in patients with Fontan circulation was associated with small and clinically insignificant changes in HR and BP, implying that for patients similar to those enrolled in the FUEL trial, udenafil can be initiated in the outpatient setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

6MW	6-minute walk
ACEi	angiotensin converting enzyme inhibitors
ARB	angiotensin receptor antagonists

DBP	diastolic blood pressure
HR	heart rate
PDE-5	phosphodiesterase-5
SV-CHD	single ventricle congenital heart disease
SBP	systolic blood pressure

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Highlights

- Udenafil did not cause significant changes in vital signs in children with Fontan physiology
- Vital signs did not change in the smallest subjects or those on afterload reducing agents
- For patients like those in the FUEL trial udenafil can be started without additional monitoring

Table 1:

Demographic and Clinical Characteristics

	Udenafil (n=200)	Placebo (n=200)
Biological sex, n (%)		
Male	111 (56%)	128 (64%)
Female	89 (44%)	72 (36%)
Age (years), mean (SD)	15.4 (2.0)	15.6 (2.0)
Ventricular morphology, n (%)		
Left	94 (47%)	95 (48%)
Right	89 (44%)	87 (43%)
Other	17 (9%)	18 (9%)
Race, n (%)		
Caucasian	169 (84%)	155 (78%)
Asian	17 (9%)	21 (11%)
Black or African American	10 (5%)	13 (6%)
Other	4 (2%)	11 (5%)
Weight (kg), mean (SD)	57.1 (13.9)	59.0 (13.2)
Height (cm), mean (SD)	162(10)	165 (9)
BMI, mean (SD)	21.5 (3.9)	21.7 (4.2)
Concomitant medications, n (%)		
ACEi or ARB containing medications	121 (61%)	117 (59%)
Beta blockers	17 (9%)	24 (12%)
Diuretics	19 (10%)	14 (7%)

ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker

Table 2:

Baseline Vital Signs and Change in Vital Signs by Timepoint, Comparison between Treatment and Placebo

	Udenafil			Placebo			
	Measurement mean±SD (n)	Change from baseline mean±SD	p-value*	Measurement mean±SD (n)	Change from baseline mean±SD	p-value*	p-value**
Systolic blood pressure (mmHg)							
Baseline	112.3±12.6 (200)	-	-	113.3±12.7 (200)	-	-	
120 minutes	109.4±10.8 (200)	−3.0±14.2	<0.01	112.4±10.2 (200)	−0.9±13.4	0.33	<0.01
After 6-minute walk	117.8±13.6 (200)	5.5±15.8	<0.01	118.7±11.8 (199)	5.4±15.6	<0.01	0.59
26-week visit	110.4±11.9 (191)	−1.9±12.3	0.03	112.6±11.1 (195)	−0.5±11.8	0.59	0.07
Diastolic blood pressure (mmHg)							
Baseline	68.5±9.4 (200)	-	-	69.7±10.3 (200)	-		
120 minutes	64.1±9.2 (200)	−4.4±11.7	<0.01	65.7±9.7 (200)	−3.6±12.4	<0.01	0.10
After 6-minute walk	68.1±9.2 (200)	−0.4±11.0	0.60	68.8±9.1 (199)	−0.6±12.2	0.53	0.56
26-week visit	65.2±9.8 (191)	−3.0±9.6	<0.01	69.1±9.2 (195)	0.0±10.7	0.99	<0.01
Heart rate (bpm)							
Baseline	87.4±15.0 (200)	-	-	88.0±14.1 (200)	-	-	
120 minutes	85.1±15.9 (199)	−2.3±13.9	0.02	81.7±14.5 (200)	−6.3±13.6	<0.01	<0.01
After 6-minute walk	93.1±19.4 (200)	5.8±17.8	<0.01	87.3±18.8 (200)	−0.6±17.0	0.61	<0.01
26-week visit	86.8±15.4 (191)	−0.7±12.5	0.47	87.0±15.7 (195)	−0.7±12.4	0.41	0.99

*p-value from paired t-test comparing value at specified time point to baseline.

**p-value from ANCOVA with fixed factors for ventricular morphology (single left vs single right or mixed) and a continuous covariate of baseline value.