

# Droxidopa is a safe and effective treatment for dialysis-induced hypotension: a double-blind, randomized, placebo controlled phase II study.

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## Introduction:

Intradialytic hypotension (IDH) is a common and serious complication that can cause cramping, nausea and/or loss of consciousness. It can also result in the disruption of, or discontinuation of, the dialysis session. When clinical measures are not sufficient to reduce the incidence or severity of IDH, there is a medical need to provide a safe and effective therapy. IDH has been associated with a decreased secretion of norepinephrine which may represent an over-taxation of the autonomic nervous system responding to repeated dialysis-induced volume depletion events. This autonomic "deficit" may ultimately lead to diminished vascular reactivity which is manifested as symptomatic low blood pressure (BP) during hemodialysis (HD). Droxidopa is a synthetic amino acid which is enzymatically converted into "natural" norepinephrine. It is orally bioavailable and has been shown in a number of Japanese clinical trials to be of benefit in the reduction of symptoms associated with IDH, and has been approved for that indication in Japan since 2001. Prior to the present study no trials have been performed with droxidopa in IDH in the USA where dialysis sessions are typically of shorter duration and may therefore be associated with more severe/frequent IDH.

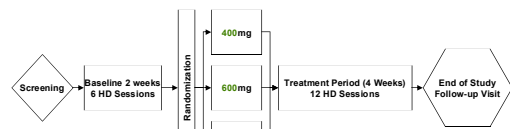
## Methods:

This was a randomized, double-blind, placebo-controlled, parallel-group study, planned to be completed in approximately 75 patients. Inclusion was based on a history of end-stage renal disease (ESRD), a requirement for maintenance HD sessions of at least 3 hours in duration at least 3 times a week, a history consistent with IDH present for at least 1 month, and a symptomatic IDH demonstrated in at least 3 out of 6 HD sessions during baseline (defined as a decrease in systolic BP by ≥20 mm Hg or a decrease in MAP by 10 mm Hg associated with symptoms that include abdominal discomfort; yawning; sighing; nausea; vomiting; muscle cramps; restlessness; dizziness or fainting; and anxiety). Following a one week screening and two week baseline period, eligible patients were randomized (1:1:1) to double-blind treatment with 400 mg of Droxidopa, 600 mg of Droxidopa, or placebo, administered orally approximately one hour prior to each dialysis session over four weeks. During the treatment period, patients underwent the following evaluations: BP and HR measurements pre-, during and after each HD session, hypotension-induced interventions and symptom assessment during each HD, weight measurement pre- and post-dialysis and daily HD-associated symptom assessments. Fatigue assessment utilizing the MFI-20 questionnaire was completed at the end of the 2nd and 4th treatment weeks. Safety was assessed by the frequency of adverse events, vital signs and changes in concomitant medications at each visit, as well as changes from baseline values for routine clinical laboratory parameters (haematology, chemistry, and urinalysis), 12-lead electrocardiogram (ECG). Safety follow-up for changes in adverse events continued up to 30 days following the last study treatment.

## Key Endpoints:

- Change in average mean arterial blood pressure from baseline to that observed during treatment
- Change in mean nadir systolic and diastolic blood pressure
- Number of interventions caused by IDH
- Hypotension symptoms
  - During sessions
  - Daily symptoms (associated with dialysis)
- Fatigue
- Safety of Droxidopa was evaluated based on the occurrence of treatment-emergent adverse events (TEAE) and evaluation of changes from baseline in BP, HR, ECG, and laboratory findings to study end.

## Overall Study Design

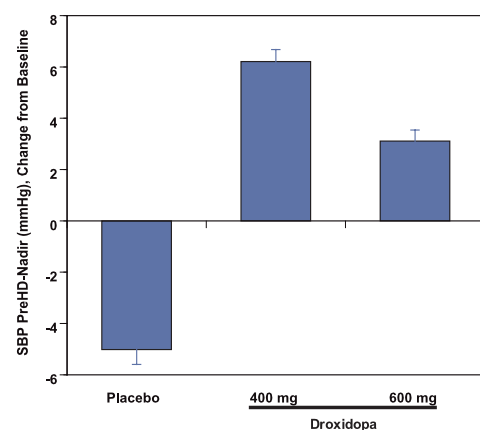


**Table 1: Patient Demographics**

Parameter	Placebo (23)	400 mg (30)	600 mg (32)	Total (85)
Age (yr.) Mean (std)	60.2 (16.0)	60.3 (12.7)	59.7 (15.0)	60.0 (14.3)
Race - N (%)				
• African American	11 (47.8%)	19 (63.3%)	15 (46.9%)	46 (54.1%)
• Caucasian	11 (47.8%)	8 (26.7%)	16 (50.0%)	35 (41.2%)
• Other	0 (0.0%)	3 (10.3%)	1 (3.0%)	4 (4.7%)
Gender - N (%)				
• Male	9 (39.1%)	14 (46.7%)	15 (46.9%)	38 (44.7%)
• Female	14 (60.9%)	16 (53.3%)	17 (53.1%)	47 (55.3%)
Duration of Disease				
ESRD (yr) Mean (std)	5.1 (3.75)	7.0 (5.06)	4.0 (4.69)	5.4 (4.72)
IDH (mo) Mean (std)	24 (36.43)	15.9 (19.85)	12.6 (14.52)	17.1 (24.21)
HD (yr) Mean (std)	4.9 (3.64)	6.2 (4.71)	4.0 (4.62)	5.0 (4.46)

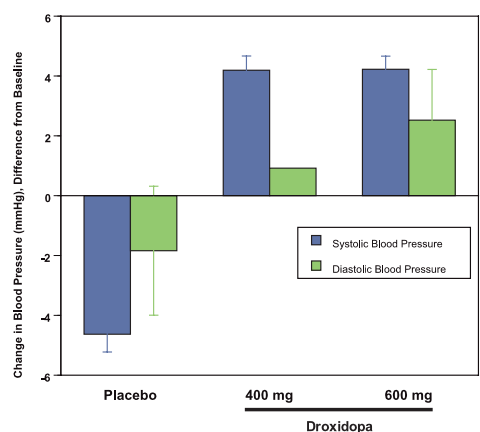
## Results:

In the patients treated with 400 and 600mg Droxidopa there was a statistically significant improvement in the severity of the drop in blood pressure to the nadir during dialysis (8.25 mmHg, P=0.03). At the end of the dialysis treatment both the 400mg (7.80 mmHg, p=0.025) and 600mg (9.16 mmHg, p=0.022) treatment groups experienced an improvement in the severity in the drop in BP. Both doses of Droxidopa reduced the number of treatment interventions for IDH. There was a significant reduction in the number of early terminations of the dialysis session due to IDH. Of the 23 patients on placebo, 7 (30.4%) required the discontinuation of at least one of their dialysis sessions during the double-blind portion of the trial, unchanged from the baseline incidence of dialysis termination. This compared to 3 (10.0%) of the 30 patients receiving 400mg of Droxidopa, a 50% decrease in early terminations and 1 (3.1%) of the 32 patients receiving 600mg of Droxidopa, an 87.5% decrease from baseline (p=0.008). Droxidopa treatment was well tolerated; the majority of reported adverse events (AEs) were listed as mild and not related to treatment. Possibly related AEs were reported for 2 patients in each of the treatment groups respectively. There was one on study death in the placebo group which was listed as being of unknown but unrelated cause; there were no other serious AEs.



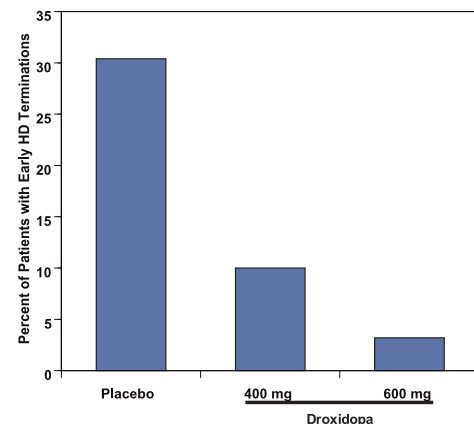
**Figure 1: Droxidopa induced a significant improvement in change of SBP from pre-dialysis to nadir during dialysis**

An exploratory analysis of the change in the magnitude (severity) of the drop in SBP from pre-dialysis to nadir intradialytic values showed significant improvement in patients taking Droxidopa (-3.11 mmHg, p=0.03 for Droxidopa 600mg and -6.21mmHg, p=0.004 for Droxidopa 400mg), compared to placebo (+5.02 mmHg).



**Figure 2: Droxidopa induced a significant improvement in change of SBP from pre-dialysis to post-dialysis**

To evaluate the efficacy of Droxidopa in improving blood pressure immediately following dialysis, the study compared the mean change from pre-dialysis BP to BP five minutes post-dialysis. Both Droxidopa treatment groups demonstrated a significant mean improvement in post- vs. pre-dialytic SBP (4.8 mmHg for the 600mg group; p=0.022 and 3.4 mmHg for the 400mg group; p=0.022), compared to placebo (-4.4 mmHg) and a trend towards improvement in post- vs pre-dialytic DBP (2.5 mmHg for the 600mg group; p=0.056 and 0.9 mmHg for the 400 mg group; p=0.15) compared to placebo (-1.8 mmHg).



**Figure 3: Treatment with Droxidopa significantly decreased the incidence of early termination of hemodialysis due to hypotension**

Both doses of Droxidopa showed an improvement in the overall number of patients requiring treatment interventions during dialysis including early termination of dialysis sessions. Of the 23 patients on placebo, 7 (30.4%) required the termination of at least one of their dialysis sessions as a result of symptoms associated with IDH (unchanged from baseline). This compares to 3 (10%) of the 30 patients receiving Droxidopa 400mg, for whom dialysis sessions were stopped, a 50% decrease in HD terminations from baseline. Only 1 (3.1%) of the 31 patients receiving Droxidopa 600mg had dialysis sessions interrupted as a result of IDH, an 87.5% decrease from baseline. This finding was statistically significant (p=0.008) and appeared to be dose-dependent.

**Table 2: Safety of pre-dialysis treatment with Droxidopa**

Parameter	Placebo (23)	400 mg (30)	600 mg (32)
% Patients with AE	60.9 %	82.8 %	81.3 %
% Patients with Serious AE	26.1 %	10.3 %	15.6 %
% Patients with AEs possibly or definitely related	8.7 %	6.0 %	6.5 %
% Patients with hypertension	4.3 %	0%	3.2 %

A total of 273 adverse events were reported by 64 patients during the study; 102 AEs by 25 patients in the Droxidopa 600mg group, 99 AEs by 25 patients in the Droxidopa 400mg group and 72 AEs by 14 patients in the placebo group. The percentage of patients with at least one adverse event was higher in the active groups compared to placebo (81% and 83% vs. 61%, respectively), but the percentage of patients with AEs assessed as treatment-related by the investigators was similar in the three groups (<7% in both Droxidopa groups vs. 9% in placebo group). The majority of the AEs (73%, 70% and 82%, respectively) were mild to moderate in intensity and the percentage of patients with at least one severe AE was not greater with Droxidopa 600mg (29%) than in the placebo group (30%).

## Conclusions:

This exploratory phase II study indicates droxidopa taken 1 hour prior to dialysis results in stable hemodynamics during dialysis, reduced need for IDH interventions, and decreased incidence of early termination of dialysis sessions. In conclusion, Droxidopa is a safe and effective treatment for IDH.

## Abstract:

**Droxidopa is a safe and effective treatment for dialysis-induced hypotension: a double-blind, randomized, placebo controlled phase II study.**

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**Background:** Intradialytic hypotension (IDH) is a common and serious complication that can cause cramping, nausea and/or loss of consciousness. It can also result in the disruption of, or discontinuation of, the dialysis session. When clinical measures are not sufficient to reduce the incidence or severity of IDH, there is a medical need to provide a safe and effective therapy. IDH has been associated with a decreased secretion of norepinephrine which may represent an over-taxation of the autonomic nervous system responding to repeated dialysis-induced volume depletion events. This autonomic "deficit" may ultimately lead to diminished vascular reactivity which is manifested as symptomatic low blood pressure (BP) during hemodialysis (HD). Droxidopa is a synthetic amino acid which is enzymatically converted into "natural" norepinephrine. It is orally bioavailable and has been shown in a number of Japanese clinical trials to be of benefit in the reduction of symptoms associated with IDH, and has been approved for that indication in Japan since 2001. Prior to the present study no trials have been performed with droxidopa in IDH in the USA where dialysis sessions are typically of shorter duration and may therefore be associated with more severe/frequent IDH.

**Methods:** This exploratory clinical trial was designed to evaluate the efficacy and safety of four weeks of treatment with either 400mg or 600mg droxidopa or matching placebo. The study enrolled 85 patients confirmed to have symptomatic IDH during a 2 week baseline evaluation period. Study outcomes that were assessed included mean arterial blood pressure during dialysis, nadir blood pressure and end of dialysis blood pressure (5 minutes post dialysis) as well as the advent of IDH symptoms and IDH-induced treatment interventions.

**Results:** In the patients treated with 600mg Droxidopa there was a statistically significant improvement in the severity of the drop in blood pressure to the nadir during dialysis (8.25 mmHg, P=0.03). At the end of the dialysis treatment both the 400mg (7.80 mmHg, p=0.025) and 600mg (9.16 mmHg, p=0.022) treatment groups experienced an improvement in the severity in the drop in BP. Both doses of Droxidopa reduced the number of treatment interventions for IDH. There was a significant reduction in the number of early terminations of the dialysis session due to IDH. Of the 23 patients on placebo, 7 (30.4%) required the discontinuation of at least one of their dialysis sessions during the double-blind portion of the trial, unchanged from the baseline incidence of dialysis termination. This compared to 3 (10.0%) of the 30 patients receiving 400mg of Droxidopa, a 50% decrease in early terminations and 1 (3.1%) of the 32 patients receiving 600mg of Droxidopa, an 87.5% decrease from baseline (p=0.008). Droxidopa treatment was well tolerated; the majority of reported adverse events (AEs) were listed as mild and not related to treatment. Possibly related AEs were reported for 2 patients in each of the treatment groups respectively. There was one on study death in the placebo group which was listed as being of unknown but unrelated cause; there were no other serious AEs.

**Conclusion:** This exploratory phase II study indicates droxidopa taken 1 hour prior to dialysis results in stable hemodynamics during dialysis, reduced need for IDH interventions, and decreased incidence of early termination of dialysis sessions. In conclusion, Droxidopa is a safe and effective treatment for IDH.