

Clevidipine, an Intravenous Dihydropyridine Calcium Channel Blocker, Is Safe and Effective for the Treatment of Patients With Acute Severe Hypertension

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Study objective: We assess the safety and efficacy of intravenous clevidipine for treating patients with acute severe increase in blood pressure by using prespecified, non-weight-based titration dosing, with continuous maintenance infusion for 18 hours or longer.

Methods: Prospective, open-label, single-arm evaluation of patients aged 18 years or older and presenting in the emergency department or ICU with severe hypertension (systolic blood pressure >180 mm Hg and/or diastolic blood pressure >115 mm Hg) and treated with clevidipine to achieve a predetermined, patient-specific systolic blood pressure target range. Clevidipine was initiated at 2 mg per hour and titrated as needed in doubling increments every 3 minutes to a maximum of 32 mg per hour, during 30 minutes, and then continued for a total duration of 18 to 96 hours.

Results: Study patients commonly presented with both acute hypertension and end-organ injury; 81% (102/126) had demonstrable end-organ injury at baseline. Within 30 minutes of starting clevidipine, 88.9% (104/117) of patients achieved target range. Median time to target range was 10.9 minutes. No concomitant intravenous antihypertensives were needed in 92.3% (108/117) of patients receiving 18 hours or more of clevidipine infusion. Clevidipine was well tolerated with successful transition to oral antihypertensive therapy after infusion to a defined blood pressure target in 91.3% (115/126) of patients.

Conclusion: Clevidipine, dosed in a non-weight-based manner, was safe and effective in a cohort of patients with severe hypertension at a starting dose of 2 mg per hour, followed by simple titration during 18 hours or more of continuous infusion. Patients were effectively managed via simple blood pressure cuff monitoring throughout. [Ann Emerg Med. 2009;53:329-338.]

0196-0644/\$-see front matter

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doi:10.1016/j.annemergmed.2008.04.025

INTRODUCTION

Hypertensive emergencies are estimated to occur in 1% to 2% of all patients with hypertension at some point in their lives, with the reported prevalence of high blood pressure in the United States continuing to increase and now at 73 million individuals.¹⁻³ In the emergency department (ED), prompt and appropriate management of acute, severe hypertension may be needed to prevent permanent end-organ damage.^{3,4} The goal of rapid blood pressure reduction must be balanced against the need for a controlled, predictable response to therapy, to avoid hypoperfusion and ischemia. For severely hypertensive patients without evidence of end-organ injury or other indications for parenteral treatment, management with oral antihypertensives, followed by observation and confirmed follow-up care, may be

most beneficial.³⁻⁶ Patients with severe hypertension who have end-organ injury or comorbidities requiring intensive blood pressure control, or who cannot safely take oral medications, are treated with intravenous antihypertensives and continuous blood pressure monitoring.³⁻⁷

The choice of intravenous antihypertensive in critical care settings appears to vary widely.^{8,9} According to preliminary findings from an ongoing patient registry (n=982), which assessed antihypertensives given as an intravenous bolus or continuous infusion, labetalol is most often selected as the initial intravenous antihypertensive, accounting for 32% of patients with acute severe hypertension, followed by metoprolol, nitroglycerin, and hydralazine at 16%, 15%, and 15%, respectively; nicardipine and sodium nitroprusside were

Editor's Capsule Summary

What is already known on this topic

Most intravenous agents used to acutely lower blood pressure have problems with safety characteristics, and some require continuous direct arterial monitoring during use.

What question this study addressed

This study examined the safety and efficacy of intravenous clevidipine, an investigational drug, in an open-label convenience sample of 126 patients with severe hypertension.

What this study adds to our knowledge

Blood pressure was quickly decreased in most patients to target range using a non-weight-based dosing of intravenous clevidipine. Further titration of blood pressure by continuous infusion was safely achieved with simple blood pressure cuff monitoring.

How this might change clinical practice

Further experience will be required before this investigational agent is considered for routine clinical practice.

administered at rates of 8% and 6%, respectively.⁸ Preliminary data from a national survey (n=234 responses) of acute hypertension management suggest that intermittent intravenous labetalol is most often administered initially for patients without stroke (21%), followed by nicardipine (20%) and sodium nitroprusside (19%), whereas nicardipine is most often administered initially for patients with acute hemorrhagic stroke (35%), followed by intermittent intravenous labetalol (21%) and sodium nitroprusside (16%).⁹ These initial agents are commonly combined with other, subsequent intravenous antihypertensives.^{8,9} Currently available intravenous antihypertensive agents have less-than-ideal therapeutic efficacy or safety characteristics, such as contraindications with common comorbidities, drug interactions and toxicity, slow onset or offset of effect, unpredictable effects with risk of precipitous hypotension, development of tolerance, and adverse cardiac effects. ED use may be further complicated because some intravenous antihypertensives require special handling or monitoring with an arterial line.^{3,4,6,7,10,11}

Clevidipine is an arterially selective dihydropyridine calcium channel blocker with a half-life of approximately 1 minute.¹²⁻¹⁴ It demonstrates rapid onset and offset of blood pressure-decreasing effect,¹⁵⁻¹⁷ allowing for responsive titration and a decreased risk of overshoot hypotension. Additionally, because clevidipine undergoes metabolism by ubiquitous plasma esterases, its elimination is independent of the liver and kidney,

providing an increased margin of safety in the ED. Finally, this metabolic degradation pathway may provide a lower potential for drug-drug interactions and is attractive for use when patient characterization is not always well determined before therapy is begun.¹⁴

The evaluation of the effect of ultra-short-acting clevidipine in the treatment of patients with severe hypertension (VELOCITY) trial was performed as an open-label, single-arm study to assess the safety and efficacy of intravenous clevidipine when initiated at a non-weight-based dose of 2 mg per hour for patients with acute severe hypertension with or without end-organ injury. We hypothesized that intravenous clevidipine could be administered to patients with severe hypertension to provide rapid, predictable blood pressure control, as shown by the percentage of patients reaching target blood pressure within 30 minutes, the time to reaching target blood pressure, and the percentage of patients experiencing blood pressure below the lower limit of the target range within 3 minutes. We also hypothesized that intravenous clevidipine could be administered for a prolonged period (≥ 18 hours) with good tolerance and safety.

MATERIALS AND METHODS

Study Design

This was a prospective, multicenter, open-label, single-arm study evaluating the safety and efficacy of intravenous clevidipine for patients who present to the ED or the ICU with severe hypertension.

Setting

The study was conducted at 12 study sites in the United States. Study institutions were academic (8) and community (4) tertiary care centers located in urban areas on the East and West Coasts, in the Midwest, and in the Southwest.

Selection of Participants and Interventions

The study protocol and written informed consent form were reviewed and approved by the institutional review board at each participating institution. All patients provided written informed consent before initiation of any study-related procedures. Patients presenting to the ED or the ICU with persistent severe hypertension were evaluated by physician investigators for study eligibility and evidence of end-organ damage. Study sites enrolled qualified, consenting patients in the order of presentation. Patients were eligible for inclusion in the study if they were aged 18 years or older and had persistent severe hypertension, defined as systolic blood pressure greater than 180 mm Hg and/or diastolic blood pressure greater than 115 mm Hg, assessed on 2 successive readings at least 15 minutes apart. Patients were excluded if systolic blood pressure was less than or equal to 180 mm Hg and diastolic blood pressure was less than or equal to 115 mm Hg, or if they met any of the following criteria: likely to be intolerant of at least 18 hours of intravenous antihypertensive therapy; known or suspected aortic dissection;

known liver failure or cirrhosis; acute hypertension precipitated by the use or withdrawal from alcohol, illicit drugs, or by intentional overdose; positive pregnancy test result; intolerance or allergy to calcium channel blockers, soybean oil, or egg lecithin; receipt of any antihypertensive drug within 2 hours before enrollment; or participation in a drug or device research study in the previous 30 days. Eligible patients were assessed for acute or chronic end-organ injury, although the presence of such injury was not an inclusion requirement. For purposes of study assessment, end-organ injury was defined as evidence of at least 1 of the following: hypertensive changes on funduscopy, left ventricular hypertrophy observed on an ECG, acute congestive heart failure, renal dysfunction, proteinuria or hematuria, acute focal neurologic signs, or positive troponin or creatine kinase MB band results or ischemic ECG changes with symptoms of acute coronary syndrome. All eligible patients received clevidipine infusion and were treated in the ED, the ED observation unit, the ICU or the coronary care unit, per institutional practice.

After each patient was enrolled, a patient-specific systolic blood pressure target range, with a range of 20–40 mm Hg from upper to lower limit, was predetermined and recorded into an interactive voice response system. The target range was selected per treating physician discretion, according to the patient's presenting condition, baseline blood pressure, and presence of comorbidities. Clevidipine, supplied as a 20% oil-in-water emulsion for infusion (0.5 mg/mL in 50-mL glass bottles), was then administered through a peripheral or central vein with a volumetric or syringe pump at an initial rate of 2 mg per hour for at least 3 minutes. Clevidipine could be titrated to higher infusion rates during the next 30 minutes by doubling the dose every 3 minutes until the systolic blood pressure reached the predetermined target range or to a maximum of 32 mg per hour. Downward titration was also permitted. If the patient's systolic blood pressure reached the target range within the initial 30-minute treatment period, clevidipine was continued for a prespecified duration of at least 18 hours and up to 96 hours, with dosing adjustments as needed to maintain desired blood pressure. After the initial 30-minute treatment period, the target range could be altered as needed for the desired long-term systolic blood pressure reduction. If target range was not achieved during the initial 30 minutes, the use of additional intravenous antihypertensive agents was permitted per institutional practice, with or without continuing clevidipine.

All investigators, study staff, and pharmacists were familiarized with clevidipine and the conduct of the study through documented training sessions. To standardize clinical procedures, a meeting for investigators was held before enrollment of the first patient. All study sites received a full study initiation visit by study monitors before enrollment of the first patient, and ongoing training was provided.

Transition to oral antihypertensive treatment as selected by the investigator was allowed as soon as 18 hours, but no longer than 96 hours after clevidipine was started. Per protocol, the

administration of oral therapy was to begin approximately 1 hour before stopping clevidipine infusion, but was not to occur before the 18-hour time point. At any time during this transition to oral agents, the clevidipine infusion rate could be down-titrated or terminated to achieve the desired blood pressure. If blood pressure rose too high after stopping clevidipine infusion, additional oral antihypertensive therapy was administered or the clevidipine infusion was restarted (at 2.0 mg/hour and titrated as necessary) and maintained until successful transition to oral therapy was achieved. Successful transition to oral therapy was defined as transition with systolic blood pressure remaining within the applicable (last identified) target range at 6 hours after stopping clevidipine.

Methods of Measurement and Data Collection and Processing

Patient assessments were obtained during screening, treatment, and follow-up. Screening occurred before clevidipine administration and included baseline medical history as obtained from patient interview and physical examination, medication history, at least 2 blood pressure measurements confirming severe hypertension per study criteria, a urine pregnancy test if applicable, and blood samples for hematology and other baseline laboratory assessments. Urinalysis, funduscopy, 12-lead ECG, and chest radiography were performed to evaluate potential end-organ injury.

After the initiation of clevidipine infusion, blood pressure and pulse rate were assessed after the first 3 minutes and repeated before and 3 minutes after each dose titration. Blood pressures were determined by manual or automatic sphygmomanometry and pulse rates by continuous ECG monitor. After systolic blood pressure within the target range was achieved, cuff pressure and pulse rate were measured every 15 minutes during the next 2 hours and then hourly until clevidipine was transitioned to oral therapy. During transition to an oral antihypertensive agent, blood pressure and pulse rate were assessed every 15 minutes until 30 minutes after the clevidipine infusion was stopped and then at least hourly until clevidipine had been stopped for 6 hours. Blood samples were obtained from all patients for blood chemistry, hematology, and lipid panel every 24 hours after clevidipine initiation and 6 hours after stopping infusion. Concomitant medications were recorded and adverse events assessed from clevidipine initiation until 6 hours after stopping infusion. The severity of an adverse event and its relationship to study drug were assessed by the physician investigator at the study site. Patients remained hospitalized in the ICU, coronary care unit, or ED for at least 6 hours after clevidipine infusion cessation. Seven days after clevidipine initiation, patients were contacted by telephone by trained, qualified study personnel to determine whether any serious adverse events had occurred after clevidipine treatment.

Outcome Measures and Primary Data Analysis

The primary outcome measures of the study were the percentage of patients in whom systolic blood pressure

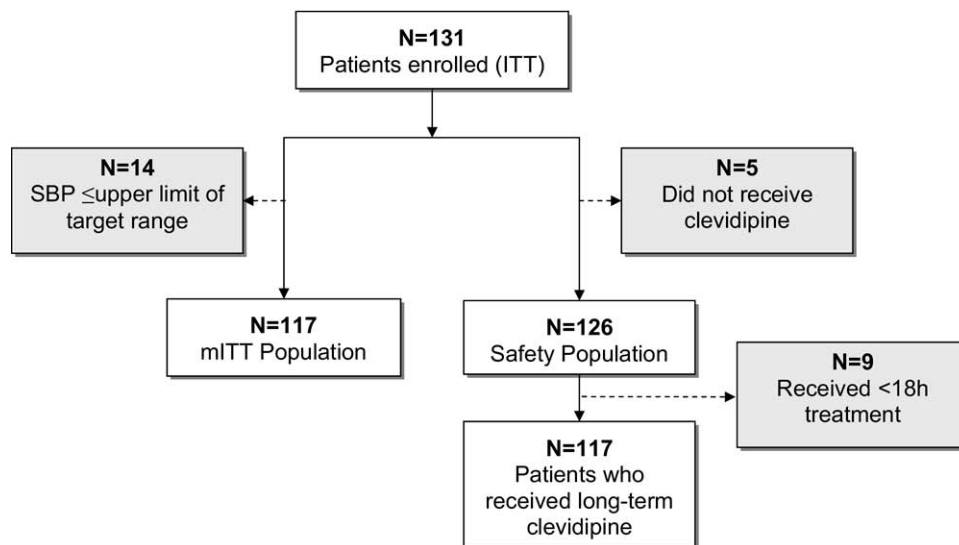


Figure 1. Disposition of patients in the trial. *ITT*, Intention to treat; *mITT*, modified intention to treat.

decreased *below* the lower limit of the initial target range within 3 minutes of initiating infusion (safety) and the percentage of patients in whom systolic blood pressure decreased to *within* the initial target range within 30 minutes of initiating infusion (efficacy). Secondary outcome measures included change in pulse rate during the initial 30-minute treatment period, the clevidipine dose used, the proportion of patients successfully transitioned to oral antihypertensive therapy, and time to achievement of target range within the initial 30-minute treatment period.

The intention-to-treat population consisted of all enrolled patients. As blood pressure may be volatile, at times decreasing below the minimum criterion for severe hypertension in some patients, and evaluating an antihypertensive agent in this group cannot be performed, efficacy was evaluated only in those patients whose systolic blood pressure was above their prespecified target range at clevidipine initiation (modified intention-to-treat population). Because the safety of an antihypertensive can be evaluated only in patients who actually received the drug, the safety evaluation was performed only in patients who received clevidipine, regardless of infusion duration (safety population). Because the risk of an adverse event may be time-dependent, an analysis was also performed on “long-term” clevidipine patients, defined as those receiving clevidipine for 18 hours or longer as a continuous infusion (with no more than 1 infusion interruption for >1 minute, lasting up to ≤15 minutes).

Patients were to be enrolled at 10 to 20 centers until approximately 100 patients had been treated continuously with clevidipine for at least 18 hours, including at least 50 patients with acute or chronic end-organ injury. This sample size was determined by clinical judgment without formal power calculation. No formal statistical hypothesis testing was included as part of study design. Descriptive statistics were

calculated. Kaplan-Meier curves for time to attainment of initial systolic blood pressure range were provided by end-organ status for all modified intention-to-treat patients. The last observation before the start of clevidipine infusion was used as baseline. If repeated or unscheduled assessments resulted in several values that could be used in a summary, the first nonmissing value was used for generating summary statistics. Mean clevidipine infusion rate for each patient was derived as the time-weighted average of infusion rates.

RESULTS

Characteristics of Study Subjects

A total of 131 patients were enrolled between September 2006 and January 2007, constituting the intention-to-treat population. Fourteen of these patients did not have baseline systolic blood pressure above the prespecified target range before clevidipine administration and were excluded to form the 117-patient modified intention-to-treat efficacy population. The safety population consisted of 126 patients, after exclusion of 5 patients who did not receive clevidipine. Of these, 108 (85.7%) patients initially received clevidipine in the ED; the remainder initially received drug in an ICU setting. Among all patients in the safety population, there were 117 (92.9%) who met the definition of having received long-term clevidipine (Figure 1).

Demographic and baseline characteristics were similar for the intention-to-treat population and the efficacy and safety populations. Demographic and baseline characteristics and medical history of the safety population are presented (Tables 1 and 2). Overall, most patients were black. Patients with and without end-organ injury in the safety population had similar demographic characteristics and baseline blood pressure. Patients commonly presented with a combination of severe hypertension and end-organ injury (81%). The most prevalent end-organ injury was left ventricular hypertrophy, followed by

Table 1. Demographic and baseline characteristics (safety population).

Parameter	Statistic	Patients With End-Organ Injury (N=102)	Patients Without End-Organ Injury (N=24)	All Patients (N=126)
Age, y	Mean (SD)	53.7 (14.5)	52.5 (18.2)	53.5 (15.2)
Sex				
Female	No. (%)	49 (48.0)	16 (66.7)	65 (51.6)
Male	No. (%)	53 (52.0)	8 (33.3)	61 (48.4)
Weight, kg	Mean (SD)	84.9 (25.2)*	92.5 (21.5)	86.4 (24.6) [†]
Height, cm	Mean (SD)	169.6 (10.8)*	168.9 (11.3)	169.5 (10.9) [†]
BMI, kg/m ²	Mean (SD)	29.4 (7.5)*	32.6 (7.6)	30.0 (7.6) [†]
Race/ethnicity				
American Indian or Alaskan Native	No. (%)	0	0	0
Asian	No. (%)	1 (1.0)	0	1 (0.8)
Black	No. (%)	80 (78.4)	17 (70.8)	97 (77.0)
Hispanic or Latino	No. (%)	7 (6.9)	1 (4.2)	8 (6.3)
White	No. (%)	14 (13.7)	6 (25.0)	20 (15.9)
Baseline BP, mm Hg				
Systolic	Mean (SD)	203.1 (22.8)	197.7 (16.5)	202.1 (21.8)
Diastolic	Mean (SD)	112.5 (21.1)	104.4 (19.4)	111.0 (21.0)
Initial SBP target range, mm Hg				
Bottom of range	Mean (SD)	142.5 (20.7)	144.6 (17.4)	142.9 (20.1)
Top of range	Mean (SD)	174.3 (20.0)	176.3 (19.1)	174.7 (19.8)

BMI, Body mass index; BP, blood pressure; SBP, systolic blood pressure.

*N=101 patients with end-organ injury having data for weight, height, and BMI.

[†]N=125 total patients having data for weight, height, and BMI.

retinal changes and renal dysfunction; because of the small number of patients in the study overall, we did not separately analyze the even smaller groups by affected organ, but the incidence of each is listed in Table 3.

Although clevidipine may be administered through a central venous catheter, 96.8% of patients received their infusion by a peripheral vein. A volumetric pump was used for most patients. Clevidipine was initially administered at an infusion rate of 2 mg per hour. Total exposure to clevidipine was similar for patients with or without end-organ injury in the safety population (Table 4) and in the long-term cohort. Among all patients who achieved their initial systolic blood pressure target range within or past the 30-minute period (n=112), the average mean infusion rate was 5.71 ± 4.9 mg per hour. The average maximum infusion rate was 10.9 ± 10.9 mg per hour.

Most patients (114/126; 90.5%) in the safety population were treated with clevidipine monotherapy, without the need for concomitant intravenous antihypertensives. The use of concomitant intravenous antihypertensive therapy was similar in patients with (8.8%) and without (8.3%) end-organ damage. In the long-term cohort, 108 of 117 (92.3%) patients were treated without concomitant intravenous antihypertensives.

All patients in the safety population were monitored with a blood pressure cuff. One patient received an arterial line after blood pressure was initially monitored using a cuff subsequent to starting and titrating clevidipine infusion.

The systolic blood pressure decreased below the lower limit of the prespecified initial target range in 2 of 126 (1.6%) patients in the safety population within 3 minutes after the start of clevidipine infusion at 2 mg per hour. Both of these patients

continued clevidipine infusion beyond 18 hours and did not experience any adverse events. One patient had been assigned an initial target range of 195 to 205 mm Hg systolic (narrower than the minimum 20 mm Hg protocol-specified target range) and had a decrease in systolic blood pressure from 239 mm Hg to 180 mm Hg at 3 minutes postinfusion start before continuing clevidipine for 30 hours. The other patient had a decrease in systolic blood pressure from 192 mm Hg to 156 mm Hg, 4 mm Hg below the prespecified lower limit of 160 mm Hg, at 2 minutes postinfusion but was asymptomatic and continued receiving clevidipine for 19 hours.

Within 30 minutes of starting clevidipine infusion, 104 of 117 (88.9%) patients in the modified intention-to-treat (efficacy) population achieved systolic blood pressure within the prespecified target range. Five modified intention-to-treat patients had an initial prespecified target range that was too narrow (<20 mm Hg) or too wide (>40 mm Hg) per protocol criteria. If the protocol violation patients were excluded from the analysis, the rate of patients achieving prespecified target range during the initial 30-minute treatment period would be 90.2% (101/112). According to Kaplan-Meier analysis, the probability of achieving the prespecified systolic blood pressure target range by 30 minutes (all modified intention-to-treat patients) was estimated as 91.4% (Figure 2).

Among modified intention-to-treat patients, systolic blood pressure decreased to within the initial target range in a median time of 10.9 minutes (95% confidence interval 9.0 to 15.0 minutes). Only 3 of 117 patients did not reach systolic blood pressure target range (initial or revised) during or after the initial 30-minute treatment period. The median percentage decrease in

Table 2. Medical history (safety population).

Parameter	Patients With End-Organ Injury (N=102), No. (%)	Patients Without End-Organ Injury (N=24), No. (%)	All Patients (N=126), No. (%)
Myocardial infarction	5 (4.9)	1 (4.2)	6 (4.8)
History of renal disease			
Total	32 (31.4)	0	32 (25.4)
Dialysis-dependent	14 (13.7)	0	14 (11.1)
Non-dialysis-dependent	18 (17.6)	0	18 (14.3)
Coronary artery disease	30 (29.4)	5 (20.8)	35 (27.8)
Hypertension	99 (97.1)	23 (95.8)	122 (96.8)
Previous hospitalization for hypertension	35 (34.3)	4 (16.7)	39 (31.0)
Congestive heart failure	21 (20.6)	1 (4.2)	22 (17.5)
Dyslipidemia	34 (33.3)	12 (50.0)	46 (36.5)
Cigarette smoker			
Current	41 (40.2)	8 (33.3)	49 (38.9)
Former	23 (22.5)	3 (12.5)	26 (20.6)
Diabetes			
Total	32 (31.4)	7 (29.2)	39 (31.0)
Insulin-dependent	13 (12.7)	2 (8.3)	15 (11.9)
Non-insulin-dependent	19 (18.6)	5 (20.8)	24 (19.0)
Transient ischemic attack	8 (7.8)	1 (4.2)	9 (7.1)
Stroke			
Total	14 (13.7)	0	14 (11.1)
Hemorrhagic	8 (7.8)	0	8 (6.3)
Ischemic	6 (5.9)	0	6 (4.8)
Angina pectoris			
Total	16 (15.7)	1 (4.2)	17 (13.5)
Stable	12 (11.8)	0	12 (9.5)
Unstable	4 (3.9)	1 (4.2)	5 (4.0)
Peripheral vascular disease	10 (9.8)	2 (8.3)	12 (9.5)
Previous atrial fibrillation	4 (3.9)	2 (8.3)	6 (4.8)
Previous atrial flutter	4 (3.9)	0	4 (3.2)
Chronic obstructive pulmonary disease	11 (10.8)	0	11 (8.7)

Table 3. Presence of end-organ injury (safety population).

Parameter	All Patients (N=126), No. (%)
Did not have end-organ injury	24 (19.0)
Had end-organ injury	102 (81.0)
Brain	
Acute focal neurologic signs	10 (7.9)
Eye	
Retinal changes consistent with hypertension	27 (21.4)
Heart	
Acute congestive heart failure	19 (15.1)
Ischemic ECG changes	4 (3.2)
Left ventricular hypertrophy (total)	64 (50.8)
Left ventricular hypertrophy alone (without concurrent end-organ injuries)	26/64 (40.6)
Positive CK-MB result	0
Positive troponin result	2 (1.6)
Unstable angina	2 (1.6)
Kidney	
Hematuria	6 (4.8)
Proteinuria	18 (14.3)
Renal dysfunction	24 (19.0)

systolic blood pressure necessary to achieve the upper limit of the initial target range was calculated as 14.2%. The median time for patients to achieve a 15% reduction in systolic blood pressure was 9.5 minutes (post hoc analysis). Systolic blood pressure decreased by a mean of 5.9% in the first 3 minutes of clevidipine infusion and gradually decreased during the 30-minute titration period, with a mean decrease of 21.1% at 30 minutes (Figure 3).

Further blood pressure lowering and dose titration of clevidipine infusion was allowed after the 30-minute initial titration phase per physician discretion. Patients were then maintained at the desired blood pressure for a protocol-specified minimum of 18 hours postinfusion initiation. By 18 hours, systolic blood pressure had been reduced by a mean of 26% from baseline (Figure 4). At 15-minute points during the first 2 hours of clevidipine infusion (after the first 30 minutes), systolic blood pressure was within the applicable target range for 63% to 76% of patients. At hourly points after the initial 2 hours to 24 hours of infusion, systolic blood pressure was within the target range for 57% to 80% of patients. Analysis of the change in systolic blood pressure among patients receiving clevidipine titration up to 32 mg per hour showed that further systolic blood pressure decreases occur at doses up to this level.

Table 4. Clevidipine administration (safety population).

Parameter	Statistic	Patients With End-Organ Injury (N=102)	Patients Without End-Organ Injury (N=24)	All Patients (N=126)
Mode of administration, No. (%)				
Peripheral vein		99 (97.1)	23 (95.8)	122 (96.8)
Central vein		3 (2.9)	1 (4.2)	4 (3.2)
Type of pump used, No. (%)				
Syringe		2 (2.0)	0	2 (1.6)
Volumetric		100 (98.0)	24 (100.0)	124 (98.4)
Overall maximum infusion rate (mg/h)				
Mean (SD)		17.4 (10.8)	18.1 (11.3)	17.5 (10.9)
Median (min, max)		16.0 (2, 32)	16.0 (3, 32)	16.0 (2, 32)
Overall mean infusion rate (mg/h)				
Mean (SD)		9.51 (6.8)	9.59 (8.4)	9.52 (7.1)
Median (min, max)		7.93 (1.0, 31.6)	5.43 (1.3, 27.4)	7.88 (1.0, 31.6)
Overall median infusion rate (mg/h)				
Mean (SD)		7.46 (5.0)	7.55 (5.3)	7.48 (5.0)
Median (min, max)		7.25 (1.5, 25.0)	5.50 (2.0, 22.0)	7.00 (1.5, 25.0)
Overall infusion duration (min)				
Mean (SD)		1,294.1* (422.0)	1,198.0 [†] (269.2)	1,275.8 [‡] (398.3)
Median (min, max)		1,243.5 (7, 3,582)	1,197.0 (98, 1,615)	1,239.5 (7, 3,582)
Total dose infused (mg)				
Mean (SD)		208.42 (161.8)	196.86 (198.2)	206.22 (168.5)
Median (min, max)		176.37 (0.4, 731.8)	101.24 (24.0, 676.9)	168.17 (0.4, 731.8)

Min, Minimum; Max, maximum.

*Equivalent to 21.6 hours.

[†]Equivalent to 20.0 hours.

[‡]Equivalent to 21.3 hours.

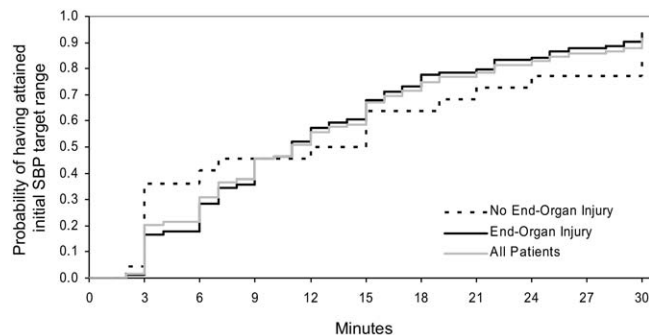


Figure 2. Kaplan-Meier curves demonstrating probability of attaining initial systolic blood pressure target range within 30 minutes (modified intention-to-treat population: patients with or without end-organ injury, and all patients).

Successful transition to oral antihypertensive therapy, defined as transition with systolic blood pressure remaining within the last identified target range at 6 hours after discontinuing clevidipine infusion, occurred in 91.3% (115/126) of patients. Of the 11 patients remaining, 3 were transitioned from clevidipine but with inadequate blood pressure control despite treatment with multiple oral antihypertensive agents, 2 had critical medical conditions preventing the use of oral agents (both later died), 1 discontinued clevidipine without the need for oral antihypertensive therapy, and 5 discontinued clevidipine before reaching the 18-hour point. Of the 118 patients eligible for transition to oral therapy, 115 patients

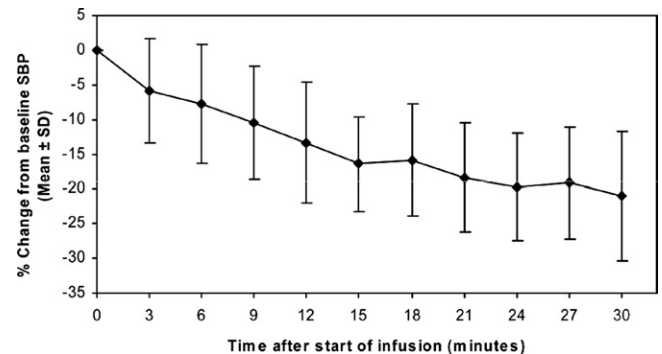


Figure 3. Mean percentage change in systolic blood pressure from baseline during first 30 minutes of clevidipine infusion (initial systolic blood pressure target range titration period, modified intention-to-treat population).

(97.5%) did so within 6 hours. The most commonly administered oral antihypertensive medications were imidazoline receptor agonists (41/126; 33%), angiotensin-converting enzyme inhibitors (36/126; 29%), dihydropyridine derivatives (30/126; 24%), and β -blocking agents (26/126; 21%).

In the safety population, pulse rate changes were not clinically meaningful during the first 3 minutes of clevidipine infusion. Median pulse rate was 79 beats/min at baseline and was 82 beats/min at 3 minutes. For safety patients, median

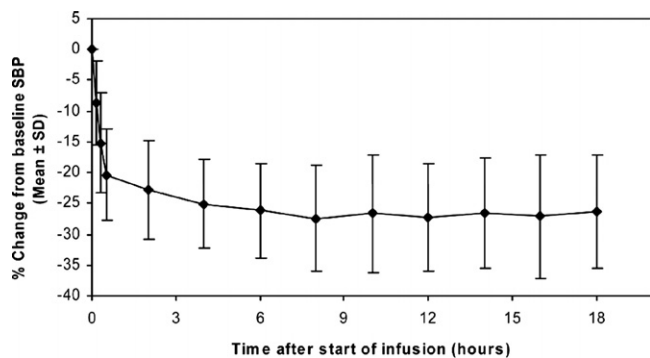


Figure 4. Mean percentage change in systolic blood pressure from baseline during 18 hours of clevidipine infusion (modified intention-to-treat population).

increases from baseline pulse rate were 3 beats/min (3.5%) at 6 minutes, 5 beats/min (6.5%) at 9 minutes, 9 beats/min (8.5%) at 12 minutes, and 9.5 beats/min (10.3%) at 15 minutes. After 15 minutes, median percentage increase from baseline pulse rate did not exceed 13.2% (10 bpm) at any point during the first 30-minute period. Median change in pulse rate continued to remain stable during 18 hours of continuous clevidipine infusion. One patient discontinued clevidipine because of increased pulse rate, which increased from a baseline of 89 beats/min to 142 beats/min at 7 minutes after the start of infusion.

In the safety population, 39.7% of patients experienced at least 1 adverse event after clevidipine initiation, and 8.7% of patients experienced at least 1 serious adverse event. Headache was the most frequently reported adverse event, with an overall incidence of 6.3% (8/126), followed by nausea (4.8%; 6/126), chest discomfort (3.2%; 4/126), and vomiting (3.2%; 4/126). Patients in the safety population most often had adverse events categorized by the investigator as mild (13.5%) or moderate (17.5%) in severity, as opposed to severe (8.7%). Safety patients most often had adverse events assessed by the investigator as unrelated to clevidipine (30.2%) versus related (9.5%). Two of 126 patients complained of pruritus at the infusion site. The frequency of adverse events, severity, and possible relationship to clevidipine were similar in the long-term cohort. There were 3 deaths during the study. All were assessed as unrelated to clevidipine and none occurred during clevidipine infusion.

Serious adverse events from clevidipine initiation to 7 days later were reported in 11 of 126 (8.7%) safety population patients. In one patient, chest discomfort was assessed as possibly related to treatment; all other serious adverse events were assessed as unrelated or unlikely to be related to clevidipine.

Overall, no clinically significant changes were observed in hematology or biochemical laboratory test results. According to serum creatinine levels, clevidipine was not associated with an increased risk of renal injury in patients with preexisting renal disease. Because clevidipine is delivered in a lipid-rich vehicle, serum triglyceride levels were followed, and the median

percentage change in concentration was zero. Post hoc analyses were conducted to evaluate the relationship of triglyceride levels to total lipid dose exposure. There was no relationship observed when triglyceride concentrations at baseline and 6 hours postinfusion were examined according to the total clevidipine dose received (Pearson's correlation coefficient = -0.0269). One patient discontinued clevidipine because of increased triglyceride concentration (818 mg/dL) after 24 hours of infusion; the concentration before clevidipine was initiated was within the normal range (116 mg/dL). However, the results from this patient are confounded because the blood sample for triglyceride measurement was drawn from the unflushed clevidipine infusion intravenous cannula. No other clinically significant changes in laboratory characteristics were observed and no other adverse events occurred in this patient.

LIMITATIONS

The VELOCITY trial was performed as an open-label uncontrolled study. However, it was designed to permit the use of concomitant intravenous antihypertensive therapy at any time if needed; thus, each patient effectively served as his or her own control. The definition for severe hypertension used in this study (systolic blood pressure >180 mm Hg and/or diastolic blood pressure >115 mm Hg) was developed according to clinical experience. No universally accepted definition exists for severe hypertension.^{18,19} The patient population studied represented a mixture of hypertensive urgencies and emergencies. It is possible, therefore, that the patients without acute end-organ injury would not all have received intravenous antihypertensive therapy in routine clinical practice but would have been treated with oral antihypertensive agents.

DISCUSSION

Clevidipine is a unique medication with many characteristics suggesting an appropriate role in the ED. It has an effective half-life of about 1 minute,¹²⁻¹⁴ with a rapid onset of action and linear dose response.^{12,13,16,20,21} Furthermore, it is rapidly metabolized by blood esterases to inactive metabolites, without dependence on kidney or liver function. These pharmacologic characteristics account for its rapid offset and easy titratability with predictable blood pressure effect and may contribute to a lack of toxicity and low risk of drug-drug interactions.^{15-17,22} The combination of ultrashort half-life, salutary safety profile, and non-weight-based dosing is of value in the ED when hemodynamic stability is uncertain, underlying pathology undefined, and accurate patient weight unknown. Finally, these pharmacologic characteristics appear to be maintained even after long-term continuous infusion (72 hours) with no evidence of tachyphylaxis, drug accumulation, or rebound hypertension on discontinuation.²¹

VELOCITY was designed to evaluate the safety and efficacy of continuous clevidipine infusion in patients with severe hypertension. A minimum treatment period of 18 hours was chosen to increase our understanding of clevidipine as

prolonged therapy. Patients who required continuation of intravenous antihypertensive therapy beyond 18 hours were admitted to the appropriate hospital department and followed. Patients who did not need further intravenous therapy had their clevidipine infusion discontinued, with transition to oral antihypertensive therapy as considered necessary by the physician investigator, and were discharged after 6 hours of follow-up without admission to the hospital. The definition of severe hypertension was prespecified as systolic blood pressure greater than 180 mm Hg and/or diastolic blood pressure greater than 115 mm Hg, according to the authors' clinical experience and with reference to current guidelines.⁵

The effects demonstrated in VELOCITY are consistent with previous dose-finding and dose-response studies in small populations of hypertensive patients.^{15,16} The use of non-weight-based dosing of clevidipine, followed by simple titration and monitoring by blood pressure cuff, was shown to be a safe and effective means of rapidly reducing severely increased blood pressure and controlling blood pressure for 18 hours or longer. More than 92% of patients in the long-term cohort were treated without the need for additional intravenous antihypertensive medications. The ability to titrate clevidipine with the use of a blood pressure cuff also suggests superiority over other agents that result in such labile blood pressure that an arterial line is required for monitoring.

The use of clevidipine was not limited by unwanted effects such as excessive reflex tachycardia. Small median increases from baseline pulse rate were observed during the first 15 minutes but were relatively stable afterward. Median percentage change in pulse rate continued to remain stable during 18 hours of clevidipine continuous infusion. One patient discontinued clevidipine because of increased pulse rate.

The VELOCITY trial evaluated the use of clevidipine in the ED and ICU. With the notable exception of specific pathologies with well-defined hypertension treatment pathways (aortic dissection, pregnancy, and drug abuse/withdrawal) or disease states that are readily apparent to the emergency physician (severe hepatic disease), this study allowed the enrollment of a large segment of patients who presented to the ED with hypertensive emergencies. The liberal entry criteria suggest that these results may be generalizable to many patients presenting to the ED and requiring intravenous antihypertensive therapy.

Just as important is that enrollment could occur immediately on arrival because, with the exception of the disease states noted above, there were no inclusion or exclusion criteria preventing immediate therapy. This is important in the ED, where acute severe hypertension often requires immediate therapy and also may occur in patients with such compromised presentations that obtaining an accurate medical history is impossible.

Blacks represent a population in which hypertension is common and severe and often results in serious sequelae.⁷ An important feature of VELOCITY was the 77% prevalence of black patients. Few previous studies appear in the emergency medicine literature that address the treatment of hypertensive

blacks in the ED, and in VELOCITY there was no disparity in treatment effect by race.

The results of the present study suggest that the initial non-weight-based dose of 2 mg per hour is appropriate in the ED setting. The titration schedule evaluated in this study demonstrated rapid and precise blood pressure decreases, with approximately 90% of patients reaching their systolic blood pressure target by 30 minutes, without precipitous and uncontrolled decreases in blood pressure. Furthermore, these findings were persistent for a minimum of 18 hours, and during this time less than 2% of patients had blood pressure below their target range. Thus, systolic blood pressure was controlled in most patients for hours beyond the initial 30-minute titration period. Mean change in systolic blood pressure remained relatively steady throughout the drug infusion period (up to 60 hours), without increasing doses of clevidipine. The appropriateness of the clevidipine dose range in the study was validated by the observation that systolic blood pressure decreases occurred at doses titrated up to 32 mg per hour, the maximum allowed per protocol. The risk of excessive blood pressure reduction remains an important consideration for hypertensive emergency patients treated with currently approved agents.²³⁻²⁵

Analysis of the VELOCITY data with a 15% systolic blood pressure decrease, common to other hypertension studies, showed that the median time to achieve this reduction was 9.5 minutes. The Efficacy Study of Clevidipine Assessing its Pre/Postoperative Antihypertensive Effect in Cardiac Surgery (ESCAPE)-1 and -2 studies, which evaluated clevidipine compared with placebo in pre- and postoperative cardiac surgery patients, demonstrated a 15% reduction in systolic blood pressure median time of 5 to 6 minutes,^{20,26} which is consistent with the findings of the present study.

Transition from clevidipine to oral antihypertensive therapy was successful and generally predictable. Among patients eligible for transition to oral therapy, 97.5% (115/118) were successfully transitioned to a defined blood pressure goal within 6 hours of stopping intravenous clevidipine infusion. The short time required for control of hypertension, blood pressure assessment by cuff, and effective transition to oral therapy may allow for observation unit admission instead of hospitalization in selected patients.

This study demonstrated that intravenous clevidipine, at a non-weight-based starting dose of 2 mg per hour, followed by titration and prolonged (≥ 18 hours) continuous infusion, is safe with simple blood pressure cuff monitoring and effective for controlling blood pressure in patients with severe hypertension requiring urgent treatment.

Supervising editor: Rita K. Cydulka, MD, MS

Author contributions: All authors contributed to the development of the study protocol, enrolled patients, and participated in data analysis and drafting of the article. CP and FP take responsibility for the paper as a whole.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article, that might create any potential conflict of interest. See the Manuscript Submission Agreement in this issue for examples of specific conflicts covered by this statement. Funding for this study was provided by The Medicines Company, Parsippany, NJ. Drs. Pollack, Varon, and Peacock have served as consultants for The Medicines Company.

Publication dates: Received for publication January 11, 2008. Revisions received March 5, 2008, and March 11, 2008. Accepted for publication April 7, 2008. Available online June 5, 2008.

Presented as a poster at the American College of Emergency Physicians 2007 *Scientific Assembly*, October 2007, Seattle, WA.

Reprints not available from the authors.

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