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ORIGINAL ARTICLE

Clevidipine for severe hypertension in patients with renal dysfunction: A VELOCITY trial analysis

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Abstract

Introduction. Acute and severe hypertension is common, especially in patients with renal dysfunction (RD). Clevidipine is a rapidly acting ($t^{1}/_{2}$~1 min) intravenous (IV) dihydropyridine calcium-channel blocker metabolized by blood and tissue esterases and may be useful in patients with RD. The purpose of this analysis was to assess the safety and efficacy of clevidipine in patients with RD. *Methods*. VELOCITY, a multicenter open-label study of severe hypertension, enrolled 126 patients with persistent systolic blood pressure (SBP) >180 mmHg. Investigators pre-specified a SBP initial target range (ITR) for each patient to be achieved within 30 min. Blood pressure monitoring was by cuff. Clevidipine was infused via peripheral IV at 2 mg/h for at least 3 min, then doubled every 3 min as needed to a maximum of 32 mg/h (non-weight-based treat-to-target protocol). Per protocol, clevidipine was continued for at least 18 h (96 h maximum). RD was diagnosed and reported as an end-organ injury by the investigator and was defined as requiring dialysis or an initial creatinine >2.0 mg/dl. Primary endpoints were the percentage of patients within the ITR by 30 min and the percentage below the ITR after 3 min of clevidipine infusion. *Results*. Of the 24 patients with moderate to severe RD, most (13/24) were dialysis dependent. Forty-six percent were male, with mean age 51±14 years; 63% were black and 96% had a hypertension history. Median time to achieve the ITR was 8.5 min. Almost 90% of patients reached the ITR in 30 min without evidence of overshoot and were maintained on clevidipine through 18 h. Most patients (88%) transitioned to oral antihypertensive therapy within 6 h of clevidipine termination. *Conclusions*. This report is the first demonstrating that clevidipine is safe and effective in RD complicated by severe hypertension. Prolonged infusion maintained blood pressure within a target range and allowed successful transition to oral therapy.

Key Words: *Calcium-channel blocker, clevidipine, hypertension, intravenous antihypertensive agent, renal insufficiency*

Introduction

Approximately 72 million people in the USA suffer hypertension and it is estimated that 1–2% of patients with hypertension will at some point develop a hypertensive crisis. The Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) identifies patients with a systolic blood pressure (SBP) >180 mmHg or a diastolic blood pressure (DBP) >120 mmHg as having a "hypertensive crisis" (1). Hypertensive crisis is further defined as "hypertensive emergencies" (i.e. severe elevations with evidence of impending or progressive end-organ dysfunction such as renal dysfunction, RD) that requires immediate blood pressure (BP) reduction to prevent or limit end-organ damage, or "hypertensive urgencies" (i.e. severe elevations in BP without end-organ dysfunction). Patients with "severe" or "accelerated" hypertension (i.e. an SBP>179 mmHg or a DBP>109 mmHg and have a recent significant increase in BP with evidence of target organ damage) should also be treated as hypertensive crisis patients.

The pathophysiology of acute severe hypertension, although not completely understood, is thought to be related to abrupt increases in systemic vascular resistance related to humoral vasoconstrictors and

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can develop *de novo,* or can complicate already existing essential hypertension. The goal of intervention in a hypertensive crisis is to reduce BP safely. The appropriate therapeutic approach to each patient will depend on their clinical presentation.

The optimal treatment options of each patient type, especially those with RD, have yet to be clearly elucidated. Since diuretics are less effective in patients with RD, vasodilators are commonly used for acute BP control. Limited clinical data are available to help guide physicians as to which vasodilator is most safe and effective in the setting of RD. As these patients often present with numerous comorbidities, and their acuity may be exacerbated by severe hypertension, many intravenous (IV) antihypertensives are either contraindicated or challenging to use in the patient with RD. The ideal treatment modality remains to be determined; nonetheless, some recommendations on the management of severely hypertensive patients with RD, largely based on clinical experience, have been made and suggest dihydropyridine calcium-channel blockers may be appropriate first-line agents (2). Clevidipine is the latest-generation dihydropyridine calcium-channel blocker with characteristics of arterial selectivity, rapid onset and offset of action, and high clearance (3–6). Clevidipine reduces BP by exerting an arterial-specific, vascular-selective vasodilating effect with no associated negative inotropic effects (7–9). Unlike other drugs of the dihydropyridine family, such as nifedipine, a key characteristic of clevidipine is its arterial selectivity. In hemodynamic studies, clevidipine has been shown to increase both stroke volume and cardiac output with minimal effect on heart rate (9). Clevidipine is an afterload reducer and does not affect central venous pressure. Clevidipine has an approximate half-life of 1 min and is metabolized by blood and tissue esterases independent of renal and hepatic function. Steady state is rapidly achieved with a small volume of distribution (7). It has been shown to achieve target BP within 5–6 min in over 90% of cardiac surgery patients (3,10). In animal models, clevidipine has been also shown to protect against ischemia/reperfusion injury of myocardial ischemia and to maintain renal function and splanchnic blood flow (11–13). Moreover, in head-to-head clinical trials, it was found to offer improved BP control compared with nitroglycerin, sodium nitroprusside (SNP) at pre-specified BP target ranges and nicardipine at narrower BP target ranges during major surgery (14).

With a renally independent metabolic pathway that generates no toxic metabolites, clevidipine may be useful for patients presenting with severely elevated BP with concomitant RD. This subgroup analysis of the VELOCITY trial (15) was performed to assess safety and efficacy of clevidipine for the treatment of severe hypertension in patients presenting with RD.

Methods

The eValuation of the Effect of uLtra-shOrt-acting Clevidipine In the Treatment of patients with severe hYpertension (VELOCITY) trial (15) was an open-label, single-arm study of clevidipine in patients aged ≥18 years presenting to the emergency department or intensive care unit with severe hypertension, defined as SBP>180 mmHg and/or DBP>115 mmHg (assessed twice at least 15 min apart at baseline). All BP monitoring was done by cuff sphygmomanometry. The diagnosis of RD was determined by the physician after the review of all available clinical and laboratory data. RD was reported as an end-organ injury defined as being dialysis dependent or having an initial creatinine >2.0 mg/dl (baseline creatinine clearance ≤50 ml/min, derived from serum creatinine by the Cockcroft–Gault equation:

$$\text{Men: creatinine clearance} = [(140-\text{age}) \times \text{weight}]/(72 \times \text{serum creatinine});$$

$$\text{Women: creatinine clearance} = [(140-\text{age}) \times \text{weight}]/(72 \times \text{serum creatinine}) \times 0.85).$$

The primary endpoints of the study were the percentage of patients within the initial target range (ITR), set by the treating physician for each individual patient, at 30 min (efficacy), and the percentage of patients below the ITR after 3 min of starting clevidipine infusion (safety). Times to achieving the ITR, mean decrease in SBP at 18 h, and incidence of adverse events (AEs) related to clevidipine were assessed as well.

Clevidipine (0.5 mg/ml in a 20% lipid emulsion vehicle) was administered by IV infusion. Using a non-weight-based, treat-to-target protocol, clevidipine was initiated at a dosage of 2 mg/h and titrated as needed in doubling increments every 3 min to a maximum of 32 mg/h, during 30 min, and then continued for a total duration of ≥18 h to ≤96 h. If ITR was achieved during the first 30 min, clevidipine was maintained at that dose to keep SBP within the ITR, or titrated as needed to keep SBP within the ITR. After the first 30 min, the SBP target range could be altered at the discretion of the attending physician and additional dose adjustments made to achieve the new BP target. If ITR was not achieved, alternative IV antihypertensive agents were permitted with or without stopping clevidipine.

The VELOCITY trial was conducted in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. The study was approved by the institutional review board at each participating institution. The VELOCITY trial was performed under IND 65,114 and was registered at clinicaltrials.gov under the identifier NCT00369837. Written informed consent was obtained from all patients before

enrollment. The VELOCITY trial was a randomized, open-label, prospective, single-arm study conducted at 14 medical centers in the USA between August 2006 and February 2007.

Results

One hundred and twenty-six patients in the VELOCITY trial received clevidipine infusion (i.e. the safety population), and of these, 24 (19%) had RD and 13 (54% of all RD) were dialysis dependent. Patients with RD were severely hypertensive with a median baseline SBP of 210 and DBP of 120 mmHg. The median upper ITR was 180 mmHg therefore requiring an approximate 15% reduction from baseline BP in the first 30 min to achieve the primary efficacy endpoint. There were no significant differences between non-dialysis-dependent and dialysis-dependent patients. Baseline characteristics, medical history and pre-specified ITR of patients with RD in the safety population are described in Table I.

Similarly, of the 117 VELOCITY patients with SBP above their pre-specified target range at clevidipine initiation (modified intent-to-treat population), 22 (18.8%) had RD, of whom 12 (54.5%) were dialysis dependent, most were diabetic and over a third had a history of cardiac disease. During the initial 30 min of clevidipine infusion, the overall median infusion rate was 6 mg/h and the overall maximum median infusion rate was 12 mg/h. Twenty-one of the 22 (95.5%) received clevidipine infusion for at least 18 h. BP response to clevidipine initiation was similar between the RD population and the non-RD cohort (Figure 1). Also similar to the overall patient cohort, approximately 90% of patients with RD (regardless of dialysis dependency) achieved the pre-specified SBP ITR within 30 min. During clevidipine infusion, mean SBP decreased 7.0 mmHg (3.5%) at 3 min and 54.0 mmHg (25.6%) at 30 min (Table II). SBP was reduced steadily during the first 30 min regardless of the RD status. No patients with RD had SBP below ITR within 3 min of initiating clevidipine infusion.

At 18 h of clevidipine infusion, the median infusion rate for patients with RD was 11 mg/h with a range of 1–32 mg/h. The mean decrease in SBP from baseline was 53.8 mmHg (25.3%). Clevidipine infusion was maintained for 18 h without incident and maintained SBP to target levels. In the safety population, 21 of 24 (87.5%) patients successfully transitioned to oral antihypertensive therapy within 6 h of clevidipine cessation; one patient discontinued clevidipine without needing transition to oral agents and two patients with a protocol deviation discontinued clevidipine after $<$18 h.

There was a modest 14% increase in heart rate, representative of a typical physiological response to rapid BP reduction, and no patient required cessation of clevidipine as a consequence. In the safety population, 12/24 patients with RD had at least one AE, with most being assessed by investigators as unrelated to clevidipine. Headache, pain in extremity and hypokalemia each occurred in two patients. Two patients (8.3%) had AEs assessed by investigators as related to clevidipine; one patient had increased BP after clevidipine infusion had been stopped and one patient had hyperlipidemia and renal insufficiency. Two patients had AEs leading to discontinuation of clevidipine infusion, one for hypotension and one for increased triglyceride levels. Upon further examination of these patients, the hypotension was recorded after administration of an oral antihypertensive agent, where clevidipine infusion was stopped just prior to the 18 h and was assessed as unrelated to clevidipine

Table I. Baseline characteristics, medical history and pre-specified initial target range (safety population patients with renal dysfunction).

Statistic	All RD patients, $n = 24$	Non–dialysis-dependent patients,[a] $n = 10$	Dialysis-dependent patients, $n = 13$
Age, years, mean (SD)	51.3 (14.3)	49.2 (16.5)	51.8 (12.7)
Female, *n* (%)	13 (54.2)	5 (50.0)	8 (61.5)
Weight, kg, mean (SD)	83.1 (37.6)	99.9 (48.6)	67.8 (19.5)
BMI, kg/m^2, mean (SD)	29.4 (10.7)	33.4 (13.8)	25.4 (5.8)
African American, *n* (%)	15 (62.5)	7 (70.0)	8 (61.5)
Hispanic, *n* (%)	5 (20.8)	0 (0.0)	5 (38.5)
White, *n* (%)	3 (12.5)	2 (20.0)	0 (0.0)
Asian, *n* (%)	1 (4.2)	1 (10.0)	0 (0.0)
SBP (mmHg), median (range)	209.5 (167–243)	210.5 (183–241)	209.0 (167–243)
DBP (mmHg), median (range)	119.5 (72–148)	124.5 (77–140)	119.0 (84–148)
ITR (high, low), median (range)	180.0 (150–220)	182.5 (160–210)	180.0 (150–220)
	150.0 (120–180)	160.0 (120–180)	140.0 (120–180)
MI, *n* (%)	3 (12.5)	1 (0.1)	2 (15.4)
CAD, *n* (%)	9 (37.5)	3 (30.0)	5 (38.5)
CHF, *n* (%)	9 (37.5)	2 (20.0)	7 (53.8)
Diabetes, *n* (%)	13 (54.2)	8 (80.0)	4 (30.8)

[a]Dialysis status of 1 patient is unknown. RD, renal dysfunction; SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ITR, initial target range; MI, myocardial infarction; CAD, coronary artery disease; CHF, congestive heart failure.

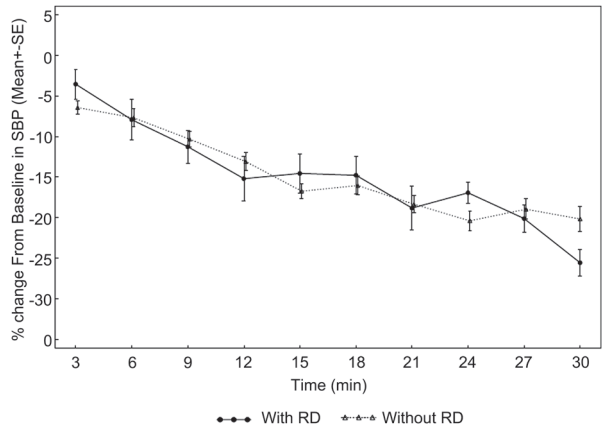

Figure 1. Mean percentage change in systolic blood pressure over time during clevidipine infusion for VELOCITY patients with and without renal dysfunction, showing similar decrease for both groups (modified intent-to-treat population).

infusion. Increased triglyceride levels in the second patient were confounded as the blood sample was taken from the same catheter as the IV infusion of clevidipine. The catheter was not flushed and these laboratory results were likely related to cross contamination with the lipid emulsion. Serious AEs were recorded for two patients and were assessed as unlikely related and unrelated to clevidipine.

Discussion

In this subset analysis of the VELOCITY trial, clevidipine rapidly and effectively lowered BP, was not associated with excessive or precipitous drops in BP and had similar results in patients with or without RD. This is the first report to demonstrate the effects of clevidipine in severely hypertensive patients with moderate to severe RD, with or without dialysis (16,17). Targeted BP control was rapidly achieved in 8.5 min and was maintained for the specified 18 h duration after which most patients effectively transitioned to oral therapy. Patients were administered clevidipine using a non-weight-based treat-to-target infusion protocol and were monitored by BP cuff. Typical infusion rates to maintain BP control were 6–12 mg/h, representing a fluid infusion volume of 12–24 ml/h.

The management of the patient with RD, especially those requiring dialysis, with associated acute severe hypertension can be challenging. These patients typically have long-standing chronic hypertension, fluid overload, underlying comorbidities including cardiac disease and diabetes, and resistance to antihypertensive therapy often requiring multiple agents to achieve the desired therapeutic response. Moreover, because of the complicated and compromised nature of the patient's renal status, many therapies to control these hypertensive episodes are not suitable because of the potential for serious or fatal AEs. This is especially the case with the commonly used IV agent SNP. One molecule of SNP contains 44% cyanide by weight and is released non-enzymatically upon infusion. Cyanide is metabolized in the liver to the less toxic thiocyanate (18,19), which is then excreted largely through the kidneys. Cyanide removal, therefore, requires adequate liver and renal function. Considering the potential for severe toxicity with SNP, this drug should not be used in patients with evidence of compromised renal function (20). Clevidipine is rapidly metabolized by blood and tissue esterases, allowing for metabolism that is independent of the kidney and making it a safe alternative to SNP. In this study, the majority of patients with RD (87.5%) were able to be treated with clevidipine monotherapy alone, while only 8.3% of clevidipine-treated patients with RD required treatment with more than 1 IV antihypertensive agent (Table III). Likewise, 84.3% of patients without RD were able to be treated with clevidipine monotherapy alone, while only 8.7% required treatment with more than 1 IV antihypertensive agent (Table III).

In this high-risk subpopulation, most AEs were assessed as unrelated to clevidipine treatment. This supports the relative safety of this product. The results of this subgroup analysis in patients with RD are also consistent with the primary results of the overall VELOCITY trial (15). Similarly, in other

Table II. Efficacy results in patients with renal dysfunction from the modified intent-to-treat population.

	All patients	Patients without RD	Patients with RD
	$n = 117$	$n = 95$	$n = 22$
Time to first reaching SBP ITR after CLV initiation, min; median (95% CI)	10.9 (9.0–15.0)	11.1 (9–15)	8.5 (7–17)
Patients who reached their ITR within 30 min of CLV initiation, *n* (%)	104 (88.9)	85 (89.5)	19 (86.4)
	$n = 112$	$n = 91$	$n = 21$
Patients who reached their SBP ITR within 30 min of CLV initiation (excluding patients with ITR protocol deviations[a]), *n* (%)	101 (90.2)	82 (90.1)	19 (90.5)
	$n = 110$	$n = 89$	$n = 21$
Mean decrease in SBP at 3 min of CLV infusion, mmHg; mean (%)	11.8 (5.9)	12.9 (6.4)	7.0 (3.5)
	$n = 48$	$n = 40$	$n = 8$
Mean decrease in SBP at 30 min of CLV infusion, mmHg; mean (%)	44.8 (21.1)	42.9 (20.2)	54.0 (25.6)

[a]ITR protocol deviation, ITR that was pre-specified to be too narrow (<20 mmHg) or too wide (>40 mmHg) per protocol. RD, renal dysfunction; SBP, systolic blood pressure; ITR, initial target range; CLV, clevidipine; 95% CI, 95% confidence interval.

Table III. Summary of intravenous antihypertensive medications.

	Patients with RD	Patients without RD	Total
Total sample size (safety population)	24	102	126
Received ≥1 IV antihypertensive(s) with CLV	2 (8.3)	9 (8.8)	11 (8.7)
Received ≥1 IV antihypertensive(s) without CLV	1 (4.2)	7 (6.9)	8 (6.3)
Received monotherapy of CLV	21 (87.5)	86 (84.3)	107 (84.9)

studies, clevidipine has been shown to be a safe and tolerable drug with almost no reported adverse effects in Phase III trials with a combined enrollment exceeding 1800 patients. The cardiac surgery ESCAPE-1 and ESCAPE-2 trials demonstrated that the most notable adverse effect from clevidipine was an increase in heart rate, which was relatively small and of minimal clinical significance (3,10). In ECLIPSE, another cardiac surgery trial, there were no differences in death or adverse outcomes at the time of hospital discharge or Day 7 among any of the treatment groups (clevidipine, nitroglycerine, SNP and nicardipine) (14). Finally, the VELOCITY trial reported no drug-related serious AEs and no episodes of rebound hypertension in patients with acute and severe hypertension (15). Clevidipine has been shown to be a safe and effective treatment across all pivotal studies for patients with acute and severe hypertension and those requiring pre-, intra- and post-operative management of BP (3,10,14,15).

Limitations

VELOCITY was an open-label, multicenter, uncontrolled study designed to demonstrate the safety and efficacy of clevidipine. Concomitant IV antihypertensive therapy was allowed at any time if needed for safety or lack of efficacy; hence, each patient essentially served as their own control. The definition for severe hypertension used in this study (SBP>180 mmHg and/or DBP>115 mmHg) was developed according to clinical experience, as there is no universally accepted definition for severe hypertension (21,22). While the results of this subgroup analysis suggest that clevidipine is safe, well tolerated, and efficacious for patients with RD, the relatively small number of patients and lack of control prevents broad-based conclusions from being drawn. Additional prospective studies and a larger clinical experience will be required to substantiate the safety and efficacy of clevidipine further in patients with compromised renal function.

Conclusions

The results of this subgroup analysis of the VELOCITY trial suggest that clevidipine is well tolerated and effective in the treatment of patients with acute severe hypertension with compromised renal function.

Competing interests

W.F.P. has received honoraria for lectures from Abbott, Biosite, Otsuka Pharmaceuticals, Ortho Clinical Diagnostics, PDL Pharmaceuticals, Scios, Inc. and The Medicines Company. He has served as a consultant for Abbott, Beckman-Coulter, Inc., Biosite, Inovise Medical, Inc., Inverness Medical Innovations, Inc., Otsuka Pharmaceuticals, Ortho Clinical Diagnostics and The Medicines Company, Heartscape Technologies, Inc.; and he has received support in the form of research grants from Abbott, BAS, Biosite, Brahms, PCT, CHF Solutions, Heartscape Technologies, Inc., Inovise Medical, Inverness Medical Innovations, Inc., PDL Pharmaceuticals, and The Medicines Company.

JV has received honoraria for lectures from PDL Pharmaceuticals, Eli Lilly & Company, and The Medicines Company, and has served as a consultant for EKR Pharmaceuticals and The Medicines Company.

Authors' contributions

W.F.P., J.V., R.E., L.D. and C.V.P. participated in experimental investigations. W.F.P. and J.V drafted the manuscript. All authors read and approved the final manuscript.

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References

1. National High Blood Pressure Education Program. The Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, MD: US National Heart, Lung, and Blood Institute; 2004 [cited 2007 July 8]. Report No.: 04-5230. Available from: http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf.

2. Herzog E, Frankenberger O, Aziz E, Bangalore S, Balaram S, Nasrallah EJ, et al. A novel pathway for the management of hypertension for hospitalized patients. Crit Pathw Cardiol. 2007;6:150–160.
3. Levy JH, Mancao MY, Gitter R, Kereiakes DJ, Grigore AM, Aronson S, et al. Clevidipine effectively and rapidly controls blood pressure preoperatively in cardiac surgery patients: The results of the randomized, placebo-controlled efficacy study of clevidipine assessing its preoperative antihypertensive effect in cardiac surgery – 1. Anesth Analg. 2007;105: 918–925.
4. Kieler-Jensen N, Jolin-Mellgård A, Nordlander M, Ricksten SE. Coronary and systemic hemodynamic effects of clevidipine, an ultra-short-acting calcium antagonist, for treatment of hypertension after cardiac surgery. Acta Anaesthesiol Scand. 2000;44:186–193.
5. Ericsson H, Fakt C, Jolin-Mellgård A, Nordlander M, Sohtell L, Sunzel M, et al. Clinical and pharmacokinetic results with a new ultrashort-acting calcium antagonist, clevidipine, following gradually increasing intravenous doses to healthy volunteers. Br J Clin Pharmacol. 1999;47: 531–538.
6. Rodriguez G, Varon J. Clevidipine: A unique agent for the critical care practitioner. Critical Care Shock. 2006;9:37–41.
7. Nordlander M, Sjöquist PO, Ericsson H, Rydén L. Pharmacodynamic, pharmacokinetic and clinical effects of clevidipine, an ultrashort-acting calcium antagonist for rapid blood pressure control. Cardiovasc Drug Rev. 2004; 22:227–250.
8. Ericsson H, Bredberg U, Eriksson U, Jolin-Mellgård A, Nordlander M, Regårdh CG. Pharmacokinetics and arteriovenous differences in clevidipine concentration following a short- and a long-term intravenous infusion in healthy volunteers. Anesthesiology. 2000;92:993–1001.
9. Kieler-Jensen N, Jolin-Mellgård A, Nordlander M, Ricksten SE. Coronary and systemic hemodynamic effects of clevidipine, an ultra-short-acting calcium antagonist, for treatment of hypertension after coronary artery surgery. Acta Anaesthesiol Scand. 2000;44:186–193.
10. Singla N, Warltier DC, Gandhi SD, Lumb PD, Sladen RN, Aronson S, et al. Treatment of acute postoperative hypertension in cardiac surgery patients: An efficacy study of clevidipine assessing its postoperative antihypertensive effect in cardiac surgery-2 (ESCAPE-2), a randomized, double-blind, placebo-controlled trial. Anesth Analg. 2008;107: 59–67.
11. Segawa D, Sjöquist PO, Wang QD, Gonon A, Nordlander M, Rydén L. Calcium antagonist protects the myocardium from reperfusion injury by interfering with mechanisms directly related to reperfusion: An experimental study with the ultrashort-acting calcium antagonist clevidipine. J Cardiovasc Pharmacol. 2000;36:338–343.
12. Segawa D, Sjöquist PO, Wang QD, Gonon A, Rydén L. Time-dependent cardioprotection with calcium antagonism and experimental studies with clevidipine in ischemic-reperfused pig hearts: Part II. J Cardiovasc Pharmacol. 2002; 40:339–345.
13. Stephens CT, Jandhyala BS. Effects of fenoldopam, a dopamine D-1 agonist, and clevidipine, a calcium channel antagonist, in acute renal failure in anesthetized rats. Clin Exp Hypertens. 2002;24:301–313.
14. Aronson S, Dyke CM, Stierer KA, Levy JH, Cheung AT, Lumb PD, et al. The ECLIPSE trials: Comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. Anesth Analg. 2008;107:1110–1021.
15. Pollack CV, Varon J, Garrison NA, Ebrahimi R, Dunbar L, Peacock WF. Clevidipine, an intravenous dihydropyridine calcium channel blocker, is safe and effective for the treatment of patients with acute severe hypertension. Ann Emerg Med. 2009;53:329–338.
16. US Food and Drug Administration. Guidance for industry: Pharmacokinetics in patients with impaired renal functions – Study design, data analysis, and impact on dosing and labeling. Rockville, MD: US Department of Health and Human Services; 1998 [cited 2007 July 8]. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory%20Information/Guidances/UCM072127.pdf.
17. US Food and Drug Administration. Guidance for industry: Pharmacokinetics in patients with impaired hepatic function: Study design, data analysis, and impact on dosing and labeling. Rockville, MD: US Department of Health and Human Services; 2003 [cited 2007 July 8]. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf.
18. Pasch T, Schulz V, Hoppelshauser G. Nitroprusside-induced formation of cyanide and its detoxication with thiosulfate during deliberate hypotension. J Cardiovasc Pharmacol. 1983; 5:77–85.
19. Hall VA, Guest JM. Sodium nitroprusside-induced cyanide intoxication and prevention with sodium thiosulfate prophylaxis. Am J Crit Care. 1992;1:19–25.
20. Robin ED, McCauley R. Nitroprusside-related cyanide poisoning. Time (long past due) for urgent, effective interventions. Chest. 1992;102:1842–1845.
21. Varon J, Marik PE. Clinical review: The management of hypertensive crises. Crit Care. 2003;7:374–384.
22. Gilmore RM, Miller SJ, Stead LG. Severe hypertension in the emergency department patient. Emerg Med Clin North Am. 2005;23:1141–1158.