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Clevidipine for hypertensive emergency

O uso de clevidipina em emergência hipertensiva

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ABSTRACT

Hypertensive emergency, is the most severe presentation of arterial hypertension, having high morbidity-mortality. Clevidipine is a calcium channel blocker. Its pharmacokinetics is favorable to use for hypertensive emergencies, rendering this drug a promising alternative to the restricted therapeutic armamentarium available both in the emergency room and intensive care unit. In this review we describe the pharmacodynamics, pharmacokinetics and clinical trials evaluating Clevidipine in emergency situations, comparing this drug to other traditionally used drugs in this condition.

Keywords: Antihypertensive agents/therapeutic use; Antihypertensive agents/pharmacology; Calcium channel blockers/therapeutic use; Emergencies; Hypertension/drug therapy

INTRODUCTION

Hypertensive emergency encompasses several conditions where the arterial blood pressure increases fast and aggressively, jeopardizing vital organs such as the brain, heart and kidney, among others integrity.[1,2] In the vast majority of times, the subject with hypertensive emergency has chronic hypertension, either unknown and/or not appropriately treated.[1,3] Population based surveys in some Brazilian cities have shown high blood pressure (≥ 140/90 mm Hg) prevalence to be between 22.3% and 43.9%.[4] Chronic hypertension has high morbidity and mortality, mainly due to complications such as heart failure, the main hospital admission cause, among other high-cost cardiovascular diseases. The risk factors for hypertensive emergency include inappropriate high blood pressure control, poor compliance to therapy, secondary hypertension, alcoholism, use of illicit drugs, black race, smoking, ageing, among others.[2,5,6] The main hypertensive emergencies involve acute pulmonary edema with left ventricle failure (36.8%), acute myocardial infarction/unstable angina (24.5%/12%), hypertensive encephalopathy (16.3%), intracerebral hemorrhage, eclampsy/pre-eclampsy (4.5%), acute aortal dissection (2%), rapidly progressing renal failure, pheochromocytoma, illicit drugs overdose, among others.[1,2] In addition, malignant hypertension is historically defined as a picture involving encephalopathy and nephropathy with papillary edema, being end-stage renal failure the common end to this condition, and the therapy identical to other emergencies.[1] The hypertensive emergency therapy should be gi-

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ven according to target organ involved, and requires intensive care due to its severity and also because is life-threatening.[3,7] Additionally, the blood pressure lowering should take place both gradually and quickly (from minutes to hours) to values up to 25% below the mean blood pressure levels in order to prevent ischemia in renal, brain and coronary territories.[2,3,7]

On the initial hypertensive emergency approach, measures concomitant to immediate pharmacologic therapy are generally prescribed: pulse oxymetry and appropriate oxygen therapy, laboratory tests, continued electrocardiogram monitoring, invasive blood pressure monitoring, 12-lead electrocardiogram, bed chest X-ray, urinary output monitoring, and admission to the intensive care unit (ICU).[2]

Drugs for effectively treating hypertensive emergencies are few, being Sodium Nitroprussiade the most relevant among them.[2,3,8,9] This drug has a potent and fast effect on hypertension control, acting directly on the vascular smooth muscle, both arterial and venous, thus reducing both pre- and after-load. Sodium Nitroprussiade reacts with Cysteine to form Nitrocysteine, which activates Guanylate Cyclase and stimulates Cyclic Guanosine Monophosphate formation, which relaxes the vascular smooth muscle.[8,9] However, this drug has some inconveniences, among them active and toxic metabolites (Cyanide and Thiocyanide), trending to intoxication.[10] Thyocyanide intoxication is more common, and may happen when Sodium Nitroprussiade is given in high doses for long times, and in renal failure patients. Its first feature is metabolic acidosis, which is joined by mental confusion, hyperreflexia, trembling and seizures.[10]

Nitroglycerin is another option for this type of hypertensive condition, having lower hypotensive power, and is mainly reserved for cases secondary to myocardial ischemia (myocardial infarction or unstable angina) and acute pulmonary edema.[3,7] This is a direct acting venous dilator which reduces the preload. Intravenous Hydralazine, an arterial vasodilator, is used in pre-eclampsy and eclampsy cases, and is contraindicated for myocardial ischemia and aortal dissection cases due to its tachycardizing effects.[7] Beta-blockers have a relevant role in acute aortal dissection cases, associated to Sodium Nitroprussiade and in alpha-agonists associated pheochromocytoma cases, among others.[7]

Clevidipine is a recently discovered and studied drug. Belongs to the calcium channel blockers class, having fast onset of action, vascular selectivity, short half-life, needing no dose adjustments in renal or liver failure patients, thus being a promising drug for hypertensive emergency.[11-13]

CLEVIDIPINE PHARMACOLOGY

Pharmacodynamics

Clevidipine is a member of the calcium channel blockers group, belongs to the Dihydropiridines family, featuring peculiar characteristics.[12,14] This drug has an extra ester-connection in its body, allowing rapid serum esterases hydrolysis, with no active metabolites, thus without need of dose changes in both renal and liver disease patients.[14] Clevidipine has no interaction with P450 cytochrome enzymes, being thus free of significant drug interactions. Clevidipine is selective to arteries, only acting on mean to small gauge arteries, thus reducing peripheral vascular resistance, with none or negligible venous circulation effect.[13,14] It only acts reducing after-load, causing no venous dilation, thus being free of effects on the systolic volume, cardiac output and heart rate, rendering it a drug safer than others, specially in heart disease patients.

Pharmacokinetics

Clevidipine is structurally similar to other dihydropiridines, with an inactive carboxylic acid metabolite released to the blood stream and extravascular tissues, primarily excreted by urine and feces.[13,14] It is given by intravenous continuous infusion, with fast effect reversion following infusion discontinuation.[13,14] Additionally this drug is selective for arteries, has fast onset of action,[14] and a very short half-life (± 1 minute), high blood clearance (after discontinuation the effect stops in up to 15 minutes), low distribution volume, thus allowing its dose to be titrated to appropriate pressure effect (fast onset of action and also fast clearance).[13,14]

Clevidipine should be started with 1-2 mg/hour continued infusion. The dose may be doubled after 90 seconds of the infusion start. It should be progressively increased every 5-10 minutes according to the target. The maximal dose for adult and elderly patients is 32 mg/hour. Because of the drug formulation, with lipid vehicle, no more than 1000 mL (21 mg/hour in average) should be infused in 24 hours due to lipid overload and the bottle should be replaced every 4 hours due to the lipid vehicle. Additionally, the drug may be given peripherally, allowing easy access. No dilution is needed, an important feature in patients who can't afford additional volume.[15]

CLINICAL TRIALS

Clevidipine was initially tested in the ESCAPE 1 (Efficacy Study of Clevidipine Assessing its Preoperative Antihypertensive Effect in Cardiac Surgery), a randomized, double-blind, placebo-controlled trial in patients undergoing heart surgery (total 105 subjects). The study has shown a > 15% blood pressure reduction versus placebo (82.7% * 7.5%; P<0.0001).[16]

In the ESCAPE 2 (Efficacy Study of Clevidipine Assessing its Postoperative Antihypertensive Effect Surgery-2), a double-blind, placebo-controlled trial where the Clevidipine safety and efficacy in hypertensive patients following heart surgery were evaluated. Clevidipine has shown better performance on hypertension therapy (91.8% * 20.4% in the placebo group; P < 0.0001), with onset of action about 2 minutes after the infusion, blood pressure lowering of 5.7 mm Hg versus 0.1 mm Hg with placebo (P<0.0001), and was proven to be a safe and effective drug on rapid control of surgical hypertensive emergency surgical patients.[17]

In the VELOCITY (Evaluation of the Ultra-Short-Acting Clevidipine in the treatment of patients with severe hypertension) trial, a multicenter, open label, quasi-trial, the Clevidipine safety and systemic blood pressure control were evaluated. This study involved 126 hypertension patients either in the emergency department or intensive care unit, showing fast and effective control, with a 6% blood pressure reduction in the first 3 minutes, and a total 15% reduction after 9.5 minutes.[18] Also a good response with prolonged time drug infusion was shown, with a 27% blood pressure reduction after 18 hours administration. Additionally, the study subgroups analysis evidenced safety for administration to patients with renal and heart failure.[18] In the renal disease subgroup, 24 patients with moderate to severe renal dysfunction (> 50% in hemodyalisis) with similar blood pressure control (both in magnitude and effectiveness) versus non-renal disease patients.[18] The VELOCITY trial has shown little drug side effects, including rebound hypertension.[18]

The ECLIPSE, a multicenter, randomized, non-blinded trial conducted in patients with peri-operative hypertension evaluated 1512 patients undergoing heart surgery divided into three distinct groups: Clevidipine versus Nicardipine, Clevidipine versus Nitroglycerin, or Clevidipine versus Sodium Nitroprussiade. The primary endpoint was the 30 days rates of infarction, death and renal dysfunction, and the secondary endpoint was the observed blood pressure control and its maintenance. In all cases Clevidipine had superior blood pressure control, with almost half of the pressure levels variation in the Clevidipine group (3.8 * 7.8 mm Hg * min/h). Compared to each drug alone, Clevidipine has also shown better results: 4.14 * 8.87 mm Hg * min/h (versus Nitroglycerin), 4.37 * 10.5 mm Hg * min/h (versus Sodium Nitroprussiade),[19] with more variability and "instability" observed with the other drugs versus Clevidipine. Only when compared to Nicardipine no statistical difference was observed for both pre- and post-operative periods regarding pressure fluctuations (1.76 * 1.69 mm Hg * min/h).[19] The ECLIPSE trial, corroborating the results in other trials (ESCAPE 1 and 2 and VELOCITY) has shown Clevidipine to be safe and effective for acute hypertension therapy, with reduced pressure fluctuations versus Nitroglycerin and Sodium Nitroprussiate, the drugs most used in Brazil for rapid pressure control.[19] In the ECLIPSE trial, Clevidipine not only was superior for the pressure control versus Sodium Nitroprussiade, but also reduced the 30 days mortality versus this drug (4.7 * 1.7%).[20] However, after controlling for potential confounding biases in a multiple logistic regression model, this difference disappeared.

CONCLUSION

Clevidipine is a promising drug for hypertensive emergency therapy, with a fast onset of action, few side effects, added to easy administration. The ESCAPE 1 and 2, ECLIPSE and VELOCITY trials have shown Clevidipine to be a safe and effective drug for hypertensive emergency therapy. The ECLIPSE trial, the largest available trial, has shown Clevidipine superiority over the most used among us drugs (Sodium Nitroprussiade and Nitroglycerin) for pressure levels control. It should, however, be kept in mind that, although this trial had a large population, had as limitation that the primary endpoint was not reached, just the secondary, and additionally was a non-blinded trial. It also should be highlighted that the studies were mostly conducted in pre- and post-heart surgery patients, with one single open study (no placebo control) in clinical patients. Controlled, randomized and larger subjects numbers studies are warranted to allow concluding that this drug is effectively applicable for all hypertensive emergency presentations.

RESUMO

A emergência hipertensiva, forma mais grave de manifestação da hipertensão arterial, é uma entidade clínica prevalente com alta morbimortalidade associada. A clevidipina é uma droga pertencente ao grupo dos bloqueadores dos canais de cálcio. Suas características farmacocinéticas favorecem seu uso em emergências hipertensivas tornando-se uma alternativa promissora ao restrito arsenal terapêutico disponível em salas de emergências e unidades de tratamento intensivo. Nesta revisão, descrevemos aspectos de farmacodinâmica, farmacocinética e estudos clínicos que avaliaram a clevidipina no contexto da emergência hipertensiva, comparando-a com medicamentos tradicionalmente utilizados nesta situação.

Descritores: Anti-hipertensivos/uso terapêutico**;** Anti-hipertensivos/farmacologia; Bloqueadores dos canais de cálcio/uso terapêutico; Emergências; Hipertensão/quimioterapia

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