

THE IMPACT OF URAPIDIL USE IN HYPERTENSION PREHOSPITAL EMERGENCY INTERVENTION

GABRIELA PRODAN (PURA)^{1,3}, DANIEL-CORNELIU LEUCUȚA^{2*}, GABRIEL MARC¹, HORIA SIMU³, CRISTINA NASTASĂ¹, OVIDIU ONIGA¹

¹Department of Pharmaceutical Chemistry, "Iuliu Hațieganu" University of Medicine and Pharmacy, 41 Victor Babeș Street, RO-400012, Cluj-Napoca, Romania

²Department of Medical Informatics and Biostatistics, "Iuliu Hațieganu" University of Medicine and Pharmacy, 6 Louis Pasteur Street, RO-400012, Cluj-Napoca, Romania

³Department of Ambulance Emergency Service, 55 Horea Street, RO-400202, Cluj-Napoca, Romania

*corresponding author: dleucuta@umfcluj.ro

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Abstract

The aim of this study was to determine if urapidil, used as a first-line emergency antihypertensive agent represents, in prehospital interventions, a superior choice if it is administered after other antihypertensive drugs. The paper presents the results of a retrospective study, based on the medical records of 100 interventions of the Cluj County Ambulance Service, Romania, for patients with hypertensive crisis. There have been identified significant differences on both intervention time and time duration until blood pressure normalizes, for the patients that received urapidil was administered as a first-line antihypertensive, compared to the patients for that received urapidil after other antihypertensive drugs. These preliminary results can support the use of urapidil as a first-choice antihypertensive agent in prehospital emergency treatment, in hypertensive outbreak.

Rezumat

Scopul acestei lucrări a fost de a stabili dacă urapidilul, ca antihipertensiv de urgență, de primă linie reprezintă, în intervențiile pre-spitalicești, o alegere superioară administrării sale ulterior altor antihipertensive. Lucrarea prezintă rezultatele unui studiu retrospectiv realizat pe baza fișelor medicale din 100 de intervenții ale echipajelor medicale ale Serviciului Județean de Ambulanță Cluj, România la pacienți în criză hipertensivă. Au fost identificate diferențe semnificative în privința duratei intervenției și a duratei până la normalizarea valorilor tensionale, în cazul pacienților cărora li s-a administrat urapidilul de primă intenție, comparativ cu cei cărora li s-a administrat după alte antihipertensive. Aceste rezultate preliminare ar putea susține utilizarea urapidilului ca antihipertensiv de primă alegere în intervenția din pre-spitalicească, de urgență, în puseul hipertensiv.

Keywords: urapidil, hypertension, prehospital emergency

Introduction

Hypertension represents a major public health problem, being the most common cardiovascular disease in the adult population, which affects over five million people in Romania [4, 7]. High blood pressure is defined as persistently systolic and diastolic blood pressure over 180/100 mmHg values. Many therapeutic agents can be used for the pharmacologic management of hypertension, in lowering the blood pressure. However, in special situations, when the blood pressure values sharply increase and major complications may occur, intravenous antihypertensive drugs are used to achieve a rapid and intense blood pressure decrease to a safe level. Urapidil can be administered intravenously in hypertensive emergencies, when used by a medical team in the prehospital setting [1, 2, 5-8, 10, 11]. This drug is a α -1 postsynaptic adrenergic receptor blocker and an α -2 presynaptic adrenergic receptor agonist, being used to treat severe high

blood pressure in emergency cases, with potential organ damage, which imminently threatens life. Urapidil is a pyrimidinedione compound, used as hydrochloride [3, 9].

In general, urapidil is administered in situations when other antihypertensive drugs of parenteral use fail consistently and sustainably to reduce blood pressure to normal levels. Therapeutic guidelines from other countries, for the management and treatment of pre-hospital hypertensive urgency, recommend several treatment lines, without a consensus on choice of first-line medication [13].

The purpose of this study was to evaluate the efficacy of urapidil in the reduction of the intervention time in prehospital emergency hypertensive crisis, when supplied by a medical team in a prehospital setting, right from the beginning of the intervention and not only as a medication following other antihypertensive drugs. Urapidil has been introduced in the medical kit of the ambulances from Romania in 2004. When

this study was performed, it was not frequently used in the prehospital hypertensive crisis.

Materials and Methods

Data were collected by studying the medical records, filled by the medical crews of ambulances, during interventions in patients with hypertensive crisis, after 112 emergency phone calls. The patients were treated, in the chronological order of the request of the Ambulance Service. From October 2015 until October 2016, 2377 emergency interventions regarding hypertensive crises were registered. In 111 interventions, urapidil was used, alone or together with other anti-hypertensive drugs. 11 patients were not included in the presented study, because they were suffering from some comorbidities (respiratory assistance, kidney transplant, aortic stenosis), or pregnancy or lactation were involved, and the protocol for the therapeutic intervention required some changes of the usual one. The criteria for the inclusion of the patients in the study was the presence of the hypertensive crisis, with systolic blood pressure (SBP) > 180 mmHg and/or diastolic blood pressure (DBP) > 100 mmHg and the use of urapidil to lower blood pressure. The patients were treated with 25 mg captopril s.l. (sublingual), 1.25 mg enalapril i.v., 20 mg furosemid i.v., and 12.5 mg urapidil i.v., from the Cluj Ambulance Emergency Service emergency kit.

Statistical analysis

Qualitative data were described numerically and by percentages and counts. Continuous data were described as medians and the first and third quartiles (skewed data). Qualitative data comparisons between independent groups were made with chi-square test. Continuous data comparisons between independent groups were made with the Wilcoxon rank-sum test. The relationship between the administration of the drugs and the total intervention time (in minutes)

was evaluated using linear regression. Variables included in the univariate and multivariate analyses: SBP (systolic blood pressure) on arrival (mmHg), number of doses of captopril 25 mg s.l., enalapril 1.25 mg i.v., furosemid 20 mg i.v., urapidil 12.5 mg i.v. and if any drugs were taken before urapidil. Normality of residuals, heteroskedasticity, and multicollinearity were checked as regression diagnostics. For all analyses, a 0.05 level of significance was used and the two tailed p values were computed. All analyses were performed with R environment for statistical computing and graphics, version 3.2.3 [12].

Results and Discussion

The group consisted of 100 subjects with a mean age of 68.5 ± 12.7 years, ranging between 40 and 94 years. Their main characteristics, along with the blood pressure evolution during the interventions to lower their blood pressure, are presented in Table I. The same table presents the differences between those who received urapidil from the beginning or later, after other blood pressure active drugs. The number of the female patients was higher than that of the male patients, but their distribution was similar between the compared groups. Also, the systolic, diastolic, mean blood pressures, on arrival, on departure and their differences, were comparable between the groups.

We found statistically significant differences between the total time, the time from the first blood pressure measurement until the first urapidil administration, and the percentage of time when urapidil was used compared to the whole duration of care, in respect of the two groups – those who received urapidil as the first drug having clinically significant lower values compared to those who received urapidil after other blood pressure drugs.

Table I

The comparison between the group who received urapidil as the first drug and the group who received urapidil after previous interventions to lower the blood pressure

Parameters	All subjects	Drugs before urapidil (n = 65)	Urapidil as the first drug (n = 35)	p
Age (years), median (IQR)	68.5 (60 - 78)	70 (61 - 80)	65 (57.5 - 76)	0.085
Gender (f/m), n (%)	63 (63)/ 37(37)	39 (60)/ 26(40)	24 (68.57)/ 11(31.43)	0.397
SBP on arrival (mmHg), median (IQR)	209 (193.75 - 225)	209 (194 - 225)	207 (191.5 - 223)	0.598
DBP on arrival (mmHg), median (IQR)	115 (101.75 - 131.25)	115 (105 - 132)	118 (101.5 - 127)	0.931
MBP on arrival (mmHg), median (IQR)	162.5 (150 - 177.75)	163 (150 - 179.5)	160 (150 - 174.5)	0.715
SBP final (mmHg), median (IQR)	159 (150 - 172.5)	160 (152 - 174)	157 (147 - 170.5)	0.253
DBP final (mmHg), median (IQR)	90 (83 - 99)	90 (83 - 99)	90 (80.5 - 96.5)	0.52

Parameters	All subjects	Drugs before urapidil (n = 65)	Urapidil as the first drug (n = 35)	p
MBP final (mmHg), median (IQR)	125 (117.5 - 134.12)	127 (119.5 - 134.5)	122 (116.5 - 133.5)	0.223
SBP difference (mmHg), median (IQR)	45.5 (33.75 - 65.25)	44 (34 - 68)	49 (32 - 62.5)	0.905
DBP difference (mmHg), median (IQR)	25 (14 - 36)	26 (14 - 36)	24 (16 - 32.5)	0.891
MBP difference (mmHg), median (IQR)	34.5 (24.88 - 51.62)	35 (22.5 - 54)	34 (27.25 - 49.5)	1
Total time (min), median (IQR)	50 (35.75 - 59.25)	53 (40 - 64)	37 (26.5 - 51)	< 0.001
Time from the first BP measure until the urapidil administration (min), median (IQR)	12.5 (5 - 25)	22 (13 - 30)	3 (2 - 5)	< 0.001

IQR – interquartile range; SBP – systolic blood pressure; DBP – diastolic blood pressure; MBP – mean blood pressure; BP – blood pressure; n – number of patients

Following these findings, we performed simple and multiple linear regressions to assess the relation between the total intervention time (minutes), as dependent variable, and age, gender, the systolic blood pressure measured on arrival, the drugs administrated (captopril, enalapril, furosemid, urapidil) and if urapidil

was taken as a first drug. The results are presented in Table II. The multiple linear regression model was adjusted for all these variables and the model was statistically significant ($p < 0.001$), with an adjusted determination coefficient of 0.22.

Table II

Simple and multiple linear regression of the total intervention time (min), adjusted for all the variables in the model

Characteristics	Simple linear regression			Multiple linear regression		
	B	(95% CI)	p	B	(95% CI)	p
Age (years)	0.09	(-0.19 - 0.37)	0.529	0.24	(-0.04 - 0.53)	0.097
Gender (m vs. f)	1.56	(-5.75 - 8.86)	0.673	-1.15	(-8.7 - 6.41)	0.764
SBP on arrival (mmHg)	-0.14	(-0.32 - 0.05)	0.143	0.04	(-0.13 - 0.22)	0.624
Captopril 25 mg s.l.	-0.72	(-7.35 - 5.9)	0.829	4.51	(-1.75 - 10.77)	0.156
Enalapril 1.25 mg i.v.	0.6	(-6.29 - 7.49)	0.863	5.77	(-0.64 - 12.19)	0.077
Furosemid 20 mg i.v.	4.08	(-0.34 - 8.49)	0.07	6.37	(2.57 - 10.17)	0.001
Urapidil 12.5 mg i.v.	7.91	(3.71 - 12.1)	0.001	4.18	(0.17 - 8.19)	0.041
Drugs before Urapidil (yes vs. no)	14	(3.71 - 24.3)	0.008	14.02	(6.9 - 21.14)	0.001

B – unstandardized regression coefficient; CI – confidence interval; P – probability

The unadjusted coefficients were statistically significant for all drugs taken before urapidil. The variable indicating if drugs were taken before urapidil had a statistically significant coefficient, with a high clinical value of 14 minutes longer compared to those taking urapidil first. From the adjusted coefficients regarding the drugs given, only for urapidil the data remained statistically significant. In respect to our study variable of interest - if drugs were taken before urapidil - the coefficient was statistically significant and clinically important. The situation of drug administrations to help lowering the blood pressure of the patients is presented in Table III.

Our study managed to show a statistically significant and clinically important shortage of the intervention

time if urapidil was administered from the beginning, compared to its administration after other drugs. The groups that were compared, those who received urapidil first and those who received it after other blood pressure lowering drugs, were comparable in respect of the initial, final and reduction in systolic, diastolic and mean blood pressures. There was a non-statistically significant difference in respect of age, but close to statistical significance level between these groups. We used multiple linear regression to adjust this difference, as well for the administration of the other blood pressure lowering drugs, and for the initial systolic blood pressure.

Table III

Number of antihypertensive drug administrations during the intervention to lower the blood pressure

Drug	Number of drug administrations:number of patients
Captopril 25 mg s.l.	0:68; 1:27; 2:5
Enalapril 1.25 mg i.v.	0:74; 1:21; 2:5
Furosemid 20 mg i.v.	0:56; 1:28; 2:15; 6:1
Urapidil 12.5 mg i.v.	1:31; 2:56; 3:5; 4:7; 6:1

Limitations. Because this study is an observational one, causal interferences are not allowed. Although we have adjusted the shortage of the intervention time for several important variables, this might be influenced by other subject characteristics that were not taken into account.

Implications. The reduction of the intervention time for the high blood pressure events, by using urapidil as the first drug administered can be clearly of major importance, since the intervention team can handle more interventions *per day*, and thus helping more people. Plus, the cost of urapidil is rather small and, in consequence, its impact on the health care budget is negligible. Further randomized clinical studies are needed to bring new evidences to our finding.

Conclusions

Our study found a statistically significant and clinically important shortage of the intervention time if urapidil was administered from the beginning, compared to its administration after other drugs.

The results of this study are in favour of a more frequent use of urapidil as a first-line drug in pre-hospital emergency interventions, in hypertensive crisis, due to its efficacy which develops at a short period of time from the administration and due to its safety profile which is known to be very good.

The direct beneficiary of these results is the patient in hypertensive crisis, who can receive emergency assistance offered by the medical crew, in a much shorter intervention time. These results can be used in developing new long-term strategies in public health.

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