Intensive Care Med (1997) 23: 885–888

BRIEF REPORT

M.M. Hirschl
M. Binder
A. Bur
H. Herkner
M. Müllner
C. Woisetschläger
A.N. Laggner

Safety and efficacy of urapidil and sodium nitroprusside in the treatment of hypertensive emergencies

Received: 21 November 1996
Accepted: 14 May 1997

M.M. Hirschl (✉) · A. Bur · H. Herkner · M. Müllner · C. Woisetschläger · A.N. Laggner
Department of Emergency Medicine, New General Hospital, Waehringer Guertel 18–20, A-1090 Vienna, Austria
FAX: + 43–40400–1965 or 3953

M. Binder
Department of Dermatology, New General Hospital, Waehringer Guertel 18–20, A-1090 Vienna, Austria

Abstract *Objective*: To assess the safety and efficacy of urapidil compared to sodium nitroprusside in the treatment of hypertensive emergencies.
Design: randomized, prospective clinical study.
Setting: Emergency department in a 2000-bed inner city hospital.
Patients: Eighty-one patients with hypertensive emergencies defined as elevation of systolic blood pressure above 200 mmHg and/or diastolic blood pressure above 110 mmHg plus evidence of end-organ damage were included in the study protocol. The efficacy of therapy was defined as 1) blood pressure reduction below 180/95 mmHg within 90 min and 2) no re-elevation of blood pressure during a 4-h follow-up period in primary responders. The safety of both drugs was defined as the number of minor and major side effects during treatment.
Interventions: Patients received either sodium nitroprusside ($n = 35$; continuous intravenous administration with a starting dose of 0.5 μg/kg per min; increase in increments of 0.5 μg/kg per min every 15 min until response to treatment or a maximum of 3 μg/kg per min) or urapidil ($n = 46$; intravenous bolus; starting dose: 12.5 mg; repetitive administration of 12.5 mg every 15 min until response or a maximum dose of 75 mg).
Measurements and results: Blood pressure was measured every 2.5 min by using a non-invasive oscillometric blood pressure measurement unit. Response to treatment within 90 min was observed in 75 (93%) patients (urapidil: $n = 41$ [89%]; nitroprusside: $n = 34$ [97%]; $p = 0.18$). During the follow-up period 8/34 (24%) patients in the nitroprusside group and 1/41 (2%) patients in the urapidil group exhibited blood pressure re-elevation. Major side effects were observed in seven patients receiving nitroprusside and two patients in the urapidil group ($p = 0.04$).
Conclusion: Urapidil is equally effective, compared to sodium nitroprusside, in the treatment of hypertensive emergencies. Due to a smaller number of adverse events, urapidil is a reasonable alternative to nitroprusside in the treatment of hypertensive emergencies.

Key words Hypertensive emergencies · Urapidil · Sodium nitroprusside

Introduction

Hypertensive emergencies constitute conditions that are associated with acute complications of the heart, the brain, the great vessels or the kidneys [1]. As immediate reduction of blood pressure is required to limit end-organ damage, parenteral therapy is preferred [2]. Most commonly, sodium nitroprusside or urapidil are recommended in this clinical setting [3].

Until now no prospective clinical study has compared the safety and efficacy of these drugs in hypertensive emergencies. We, therefore, undertook a study to evaluate the response rate and the number of adverse events of both drugs in patients with hypertensive emergencies.

Methods

This randomized and prospectively designed study was conducted in the Emergency Department of the General Hospital in Vienna between January and August 1996. The study was approved by the local ethical committee. Eighty-one patients (39 males; 42 females; mean age: 60 years; range 26–60) with hypertensive emergencies, defined as systolic blood pressure (SBP) above 200 mmHg and/or diastolic blood pressure (DBP) above 110 mmHg plus evidence of end-organ damage, i.e. hypertensive encephalopathy, stroke, acute congestive heart failure, angina pectoris or aortic dissection, were included. Exclusion criteria were age over 80 years, evidence of acute or chronic renal failure, known pheochromocytoma, a history of organ transplantation, pregnancy or lactation. Complete physical examination, electrocardiogram and laboratory evaluations to determine serum creatinine, serum urea nitrogen, creatine kinase, creatine kinase MB and electrolyte levels were performed. Heart rate was monitored continuously and BP was measured every 2.5 min automatically by means of a non-invasive BP measurement unit (Hewlett Packard Component Monitoring System). After these primary examinations the patients were randomized either to urapidil ($n = 46$) or to sodium nitroprusside ($n = 35$). The baseline characteristics of the patients were similar in the two treatment groups (Table 1). The dose regimens of urapidil and sodium nitroprusside are shown in Fig. 1. Adjunctive therapy included 40 mg furosemide intravenously and 5 mg morphine subcutaneously for patients with acute congestive heart failure, 100 mg aspirin and 1000 IU/h heparin for patients with angina pectoris and 5–10 mg morphine for patients with aortic dissection. Morphine was administered subcutaneously, as i.v. morphine may lead to a rapid depression of respiratory function, which may be deleterious especially in emergencies with hypoxemia, i.e acute pulmonary edema.

Response to treatment was defined as a reduction of SBP below 180 mmHg and DBP below 95 mmHg within 90 min after the start of treatment. Primary responders to treatment were observed for 4 h (follow-up period) to detect re-elevation of BP, i.e. increase of SBP above 185 mmHg and/or DBP > 100 mmHg. In the follow-up period BP was measured every 15 min until 4 h after the start of treatment. During the follow-up, nitroprusside infusion was maintained for 30 min and then tapered down by 1.0 µg per kg/min every 10 min until cessation. Patients randomized to urapidil did not receive any further antihypertensive medication.

Primary study endpoints were the percentage of responders within 90 min after the start of therapy, the number of primary responders with a re-elevation of BP and the percentage of adverse events in each group. Major adverse events were reduction of BP by more than 50% of the initial value and/or heart rate more than 120 beats/min or more than 50 beats/min and aggravation of clinical symptoms, requiring immediate therapeutic interventions by the emergency physician, i.e. volume substitution, administration of inotropic agents or antiarrhythmica. Minor adverse events included symptoms described by the patient without any significant changes in BP or heart rate. Secondary endpoints included the extent of BP reduction, the time to achieve BP control and the cumulative dose of each drug.

Base-line characteristics measured on a nominal scale were compared by chi-square procedures; continuous measurments were compared by one-factor analysis of variance.

When serial changes in the continuous blood pressure data were compared within a group or between groups, analysis of variance for repeated measurements was used. Statistical tests were two-sided, with an alpha error of 0.05.

Table 1 Clinical characteristics of patients randomized either to urapidil or to sodium nitroprusside

	Sodium nitroprusside	Urapidil	p
Number of patients	35	46	
Age (years)	58 (14.9)	62 (12.9)	0.16
Gender (male/female)	17/18	22/24	0.87
SBP (mm Hg) on admission	211 (14.2)	215 (12.4)	0.48
DBP (mm Hg) on admission	109 (13.9)	107 (16.2)	0.51
Heart rate (beats/min) on admission	92.3 (12.0)	93.8 (8.5)	0.49
Angina pectoris	15 (43%)	11 (24%)	0.07
Neurological emergencies	15 (43%)	22 (48%)	0.66
Acute congestive heart failure	2 (6%)	7 (15%)	0.18
Aortic dissection	3 (9%)	6 (13%)	0.53

Results

Primary response to treatment was observed in 34 (97%) nitroprusside patients and in 41 (89%) urapidil patients ($p = 0.18$). SBP was lowered at an average of 65 mmHg in the nitroprusside group and of 48 mmHg in the urapidil group ($p < 0.01$; Fig. 2). DBP decreased at an average of 30 mmHg in the nitroprusside group and 24 mmHg in the urapidil group ($p < 0.01$; Fig. 2). Within 90 min a significant trend of heart rate reduction was observed in both treatment groups (nitroprusside: -8.2 ± 2.4 beats/min, $p < 0.01$; urapidil: -9.2 ± 3.2 beats/min, $p < 0.01$). Response to treatment within 15 min was observed in 49% of the nitroprusside patients and in 20% of the urapidil patients ($p = 0.001$). Within 30 min the proportion of responders given nitroprusside compared to those given urapidil was 69% to 48% ($p = 0.07$).

In 1/41 (2%) urapidil patients and in 8/34 (24%) nitroprusside patients a BP re-elevation was noted within

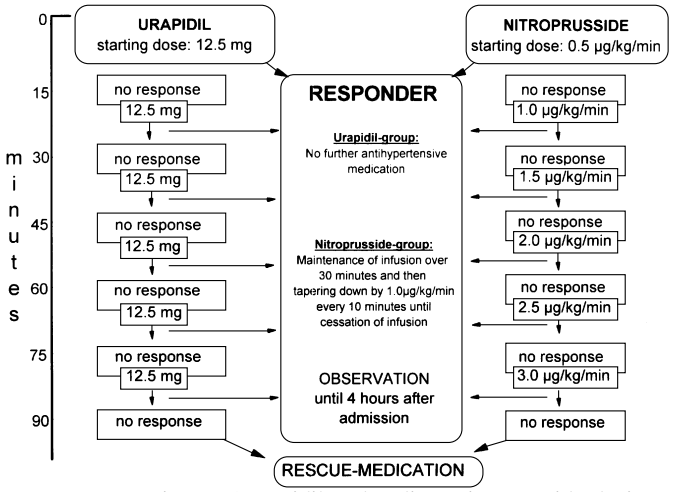

Fig. 1 Dose regimen of urapidil and sodium nitroprusside during the first 90 min after admission and in responders until 4 h after admission.

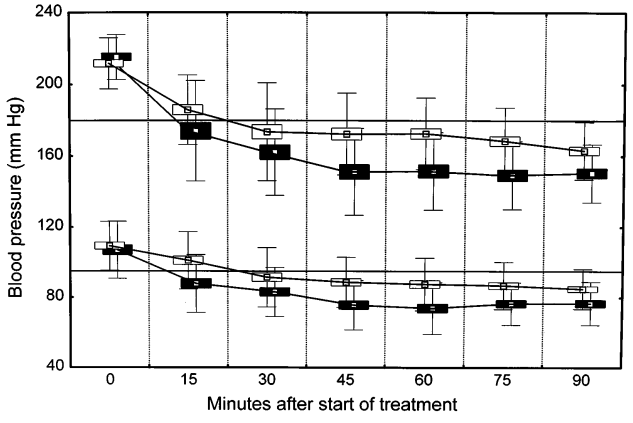

Fig. 2 Line graph shows the blood pressure within 90 min after the administration of urapidil or sodium nitroprusside. Systolic and diastolic blood pressures are given as mean and standard deviation (SD) and standard error (SE). *Solid line* indicates the target blood pressure for systolic and diastolic blood pressures (180 mmHg and 95 mmHg); *open boxes* indicate the urapidil group and *dark boxes* the sodium nitroprusside group

4 h after admission ($p = 0.02$). The mean re-elevation of SBP and DBP in patients receiving urapidil was 2.8 mmHg (SD 4.5) and 1.8 mmHg (SD 4.0) and in patients receiving sodium nitroprusside 9.7 mmHg (SD 19.5) and 3.4 mmHg (SD 9.5) (SBP: $p = 0.0002$; DBP: $p = 0.003$). In the urapidil group two (4%) major (1 hypotension, 1 bradycardia) and three (7%) minor adverse events (2 orthostatic dysregulation, 1 vertigo) were noted. In the nitroprusside group seven (20%) major (all hypotension) and one (3%) minor adverse event (flush) were observed. The overall rate of adverse events was not statistically significant between urapidil and nitroprusside (5 vs 8; $p = 0.11$). The frequency of major adverse events was significantly higher in the nitroprusside group (7 vs 2; $p = 0.04$).

The lowest dose of sodium nitroprusside was sufficient in two (6%) patients, the second and third steps of escalating dose was necessary in 28 (80%) patients. Higher dosages up to 3.0 µg/kg per min were needed in less than 15% of the patients. In 26 (57%) patients response was achieved using 12.5 or 25 mg urapidil. Higher doses (37.5–62.5 mg) were used in 32% of the patients. In 5 of 11 patients receiving 75 mg urapidil no sufficient blood pressure control was achieved.

Discussion

In this study, the primary response to treatment was higher in patients treated with sodium nitroprusside compared to those treated with urapidil (89% vs 97%). However, analyzing the course of blood pressure during the 4 h follow-up period eight nitroprusside-patients, but only one urapidil patient, exhibited a re-elevation of BP after cessation of infusion. Thus, the number of patients with stable blood pressure conditions 4 h after admission did not differ significantly between the two treatment groups (86% versus 74%).

The short duration of the nitroprusside infusion may be, in part, responsible for the high percentage of patients with BP re-elevation. However, accumulation of thiocyanates has been reported even 180 min after the start of sodium nitroprusside infusion [4–7]. Additionally, Patel et al. demonstrated that toxicity developed over a wide range of nitroprusside doses suggesting that the development of cyanide toxicity remained unpredictable [8]. Despite the capability of sodium thiosulfate to prevent thiocyanate accumulation, signs of thiocyanate toxicity persisted in some postoperative patients even after the administration of sodium thiosulfate [8]. We, therefore, decided to limit sodium nitroprusside infusion to a maximum of 2.5 h and a maximum dose of 3.0 µg/kg per min, to avoid any complications associated with thiocyanate toxicity.

The time required to achieve blood pressure control was significantly shorter in the nitroprusside group compared to the urapidil group. Within 45 min 85% of all nitroprusside patients, but only 57% of all urapidil patients, had achieved goal of treatment. In patients with aortic dissection rapid blood pressure control may provide a therapeutic advantage, as the determinants for the propagation of the dissecting hematoma are the steepness of the pulse wave and the blood pressure. A rapid lowering of blood pressure, as achieved with nitroprusside, therefore, reduce the forces on the dissecting aortic wall and may prevent further dissection or even rupture. In contrast, such a rapid decline of BP may be harmful in patients with pre-existing atherosclerotic le-

sions, as hypoperfusion of the brain or myocardium may occur.

The recommendations concerning the ideal dose include a wide range, e.g. 0.3–8.0 μg/kg per min for sodium nitroprusside, 12.5–75 mg for urapidil [2, 9]. Eighty percent of all patients responded to 1.0 or 1.5 μg/kg per min nitroprusside, indicating that doses below 1.0 μg/kg per min are rather ineffective. Therefore, the recommended dose of 0.3 μg/kg per min should be reevaluated in a future dose-finding study. In the urapidil group, 57 % of all patients responded to 12.5–25 mg. A further increase of the dose was associated with a very low rate of response to treatment, indicating that higher initial doses also may be without any effect in non-responders. Therefore, an initial dose of 12.5 or 25 mg urapidil seems the appropriate dose to achieve blood pressure control without a high risk of severe hypotension.

Adverse effects were observed more frequently in patients receiving sodium nitroprusside compared to those receiving urapidil (23 % vs 11 %). All major complications in the sodium nitroprusside group were severe hypotensive episodes, which required therapeutic intervention by the emergency physician. The reasons for these severe adverse effects were the short time taken to achieve blood pressure control and the more pronounced BP reduction. The percentage of hypotension due to sodium nitroprusside is in line with previous data demonstrating a rate between 12.5 and 20 % in patients treated with sodium nitroprusside [10]. We, therefore, do not assume that non-invasive blood pressure measurement is responsible for the high percentage of hypotensive episodes. The chosen time interval of 2.5 min seems short enough to detect any changes of blood pressure even in the nitroprusside group, as drug effects occur 1–2 min after dose adjustment.

In conclusion, urapidil is equally effective compared to sodium nitroprusside in the treatment of hypertensive emergencies. The drug may be more suitable for patients with pre-existing cerebrovascular or cardiovascular diseases, as the risk of hypoperfusion is rather low in patients receiving urapidil. Due to a smaller number of adverse events, urapidil is a reasonable alternative to nitroprusside in the treatment of hypertensive emergencies.

References

1. Kaplan NM (1994) Management of hypertensive emergencies. Lancet 344: 1335–1138
2. The Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (1993) Arch Intern Med 153: 154–183
3. Hirschl MM (1995) Guidelines for the drug treatment of hypertensive crises. Drugs 50: 991–1000
4. Aitken D, West D, Smith F, Poznanski W, Cowan J, Hurtig J, Peterson E, Benoit B (1977) Cyanide toxicity following nitroprusside induced hypotension. Can Anaesth Soc J 24: 651–660
5. Cetnarowski AB, Conti DR (1986) Nitroprusside toxicity and low-dose infusion. Ann Intern Med 6: 895–896
6. Robin ED, McCauley R (1992) Nitroprusside-related cyanide poisoning. Time (long past due. for urgent, effective interventions. Chest 102: 1842–1845
7. Nightingale SL (1991) New labeling for sodium nitroprusside emphasizes risk of cyanide toxicity (FDA Bulletin). JAMA 265: 847
8. Patel CB, Laboy V, Venus B, Mathru M, Wier D (1986) Use of sodium nitroprusside in post-coronary bypass surgery. A plea for conservativism. Chest 89: 663–667
9. Michel D (1990) Recognizing and treating hypertensive crises. Etiology-recommendations for therapy by the German Hypertension League. Fortschr Med 108: 18–21
10. Panacek EA, Bednarczyk EM, Dunbar LM, Foulke GE, Holcslaw TL, for the Fenoldapam Study Group (1995) Randomized prospective trial of fenoldapam vs sodium nitroprusside in the treatment of acute severe hypertension. Acad Emerg Med 2: 959–965