Letter to the Editor

Antihypertensive Bridge Therapy by Continuous Drug Infusion With an Elastomeric Pump in Device-Resistant Hypertension

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To the Editor:

Over recent years, invasive hypertension treatments have led to a new clinical condition, called device-resistant hypertension (DRH).1 DRH is defined as blood pressure (BP) >140/90 mm Hg, with at least 3 antihypertensives at maximal doses, including a diuretic;2 without BP decrease after the invasive treatments. These patients are not infrequent and are obliged to visit several hypertension units for managing their BP. We have observed a significant BP decrease only by using intravenous drugs recommended for emergencies.2,3 Thus, we refined a protocol to perform a chronic intravenous antihypertensive infusion in patients with DRH via an elastomeric pump and a peripherally inserted central catheter (PICC).

After exclusion of several intravenous drugs for contraindications, urapidil was selected as the drug of choice. Here, we present the case of the first treated patient with DRH.

The Case

The patient is a 45-year-old male. He was hypertensive and undergoing treatment since 2009. He was overweight (body mass index, 29.6), a smoker and dyslipidaemic. In 2012, he underwent percutaneous transluminal coronary angioplasty plus stenting for unstable angina and underwent a further new percutaneous transluminal coronary angioplasty in 2013. The same year, he was admitted to the Hypertension Unit of the University of Pisa for uncontrolled hypertension (office BP, 240/150 mm Hg and day-time ambulatory BP monitoring 200/102 mm Hg). Secondary causes of hypertension were ruled out. After several drug changes, the patient was treated with furosemide 50 mg/d, metoprolol 100 mg/d, spironolactone 50 mg/d, ramipril 10 mg/d, and amlodipine 10 mg/d without BP control. In March 2014, he underwent radiofrequency renal denervation without complications, but no significant BP reduction. Seven months later, he underwent baroreflex-activating therapy with office systolic BP reduction of ≈9 to 7 mm Hg. In January 2015, when he was visited at our Hypertension unit for the first time, his therapy consisted of 5 drug classes plus baroreflex-activating therapy. Office BP values were 210/150 mm Hg, 24-hour ambulatory BP monitoring was 181/123 mm Hg. He was having continuous headache. Serum and urine therapeutic drug monitoring excluded malingering.4 Biochemical and instrumental evaluation showed severe cardiac and renal target organ damage. We unsuccessfully modified his oral therapy as follows: telmisartan 80 mg/d, furosemide 75 mg/d, spironolactone 50 mg/d, nicardipine 60 mg/d, bisoprolol 10 mg/d, and minoxidil 10 mg/d. Thus, we started an intravenous infusion of urapidil at a dose of 6 mg/h to 10 mg/h that gave significant headache relief and a perception of well-being during the following days. After obtaining the patient’s informed consent, we operated and performed a long-term intravenous antihypertensive treatment. First, the stability of urapidil in an elastomeric pump for a 10-day period was investigated and confirmed in the Laboratory of Clinical Pharmacology and Pharmacogenetics of our Department.

Then, a PICC was inserted in the basilic vein using ultrasound guidance. Twenty-three vials of urapidil solution 50 mg/10 mL plus 45 mL of sodium chloride (NaCl 0.9%) were inserted in an elastomeric pump for large infusions with flux regulation Autoselector 275 mL (with an infusion rate ranging from 0.5 to 7 mL/h), to obtain an urapidil concentration of 4 mg/mL. The patient began the urapidil infusion at a rate of 8 mg/h (2 mL/h for a 5-day infusion) and, he was dismissed with the usual and above described antihypertensive oral treatment. The infusion was renewed every 5 days in the outpatient clinic together with PICC medications. Therapeutic drug monitoring of oral antihypertensive drugs was serially repeated and malingering excluded.

The 24-hour ambulatory BP monitoring values before and after 3 months are shown in Figure. The infusion has been maintained for 6 months. During this period, the patient was not hospitalized for hypertensive emergencies, but for a PICC infection that required a new PICC placement.

In agreement with the patient, we have planned a second renal denervation and the urapidil infusion via elastomeric pump will be continued until an alternative solution is established.

Comment

The real number of patients with DRH is difficult to ascertain, but even if rare they are present in all hypertension units and represent a challenge for the “what next” scenario. The use of continuous long-term intravenous infusion of antihypertensives provides a temporary resolution to this dilemma. We also propose this approach when oral antihypertensive intake is unviable in the midterm because of mouth, or neck, or extensive gut surgery, when transdermal administration is insufficient and patients may be treated as outpatients. The ideal characteristics of an antihypertensive drug suitable for chronic intravenous infusion are good tolerance, body weight independent dosing to reduce the amount of drug loaded in the elastomeric pump, no local side effects, chemical stability in solution for several days, no tachyphylaxis, and potential association with the majority of oral antihypertensive drugs.

Urapidil has several of these characteristics. It has complex pharmacodynamics: α1-blocker and weak β1-blocker, it interacts with the serotonin receptor and, it is a central depressor of sympathetic tone.5,6 Urapidil shows few contraindications and can be stored at doses sufficient for at least 5 days in an elastomeric pump, that generally cannot exceed a volume of >300 mL, and it is compatible with high concentrations in solution.

It is available as a 50 mg/10 mL solution for intravenous use. In our experience, it generally acts at a dose of 8 mg/h at a concentration of 4 mg/mL, without interfering with other oral antihypertensives. Among other available intravenous hypertensive drugs, nitroglycerin...
and sodium nitroprusside are not recommended because of serious side effects: risk of thiocyanate intoxication for nitroprusside; headache, methemoglobinemia for nitroglycerin, that is also characterized by fast tachyphylaxis.

Esmolol is a short-acting ß-L-blocker, available as 100 mg/10 mL, has an acceptable chemical stability of 7 days in solution. Its dosing is body weight dependent, thus a 576 mL of solution/d is required to obtain a concentration of at least 50 μg/kg per minute in patients undergoing nephron sparing surgery. Fenoldopam mesylate is a selective agonist of dopaminergic-1 receptors, located mainly in the renal and in the splanchnic arteries, it has been successfully used in elastomeric pumps at the doses of 0.1 μg/kg per minute in patients undergoing nephron sparing surgery. Fenoldopam has a good tolerability, it can generally be combined with several oral antihypertensive drugs, but there are no pharmacological studies that demonstrate its stability for >72 hours. Nicardipine, is a calcium channel blocker used in hypertensive emergencies, is available as 100 mg in 20 mL vials. The maximal drug concentration in solution is 1 mg/mL and an efficacious effect can be obtained at doses of <50 mg/h, unsuitable for elastomic pump. The angiotensin-converting enzyme inhibitor, enalaprilat, has no indications for continuous infusion. Fenoldopam mesylate is a selective agonist of dopaminergic-1 receptors, located mainly in the renal and in the splanchnic arteries, it has been successfully used in elastomeric pumps at the doses of 0.1 μg/kg per minute in patients undergoing nephron sparing surgery. Fenoldopam has a good tolerability, it can generally be combined with several oral antihypertensive drugs, but there are no pharmacological studies that demonstrate its stability for >72 hours. Furthermore, it is an expensive drug. Nicardipine, is chemically stable in solution for 7 days, is supplied in 25 mg/25 mL vials and each vial should be diluted in 240 mL of sodium chloride (0.9%) or dextrose 5% to avoid risks of venous thrombosis and phlebitis. The requirement for its high dilution does not allow an infusion of >0.2 mg/h (2 mL/h) in elastomeric pumps. Clevidipine butyrate is an ultra short-acting, third-generation calcium channel blocker. It is insoluble in water and, thus, formulated as a 20% phospholipid emulsion.

An elastomeric infusion pump with a regulation system is recommended, it allows the preparation of a standard drug solution with the possibility of modifying the infusion speed at each follow-up. PICC in peripheral vein is the most tolerable option for the patient, who wishes to live a normal life. Our patient underwent this therapy for 6 months with a good improvement in quality of life, even if he need periodical medications and drug renewal.

In conclusion, this approach may represent a bridge therapy for the temporary reduction of BP in patients with symptomatic and severe DRH who are awaiting an alternative therapeutic solution. In the meantime, urapidil elastomic pump infusion allows an acceptable quality of life outside the hospital.

**Disclosures**

None.

**References**


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