A Case Analysis of Antihypertensive Treatment in a Patient Undergoing CRRT with Comorbid Coronary Heart Disease

Shuang Zhao*

Tianjin Xiqing Hospital, Tianjin, 300380, China
**Corresponding author: zhaos321@163.com*

Abstract: *Continuous Renal Replacement Therapy (CRRT) refers to a set of extracorporeal blood purification techniques, encompassing all treatment modalities that continuously and slowly remove fluids and solutes. Conventional CRRT should be administered continuously for over 24 hours, although the treatment duration can be flexibly adjusted in clinical practice based on patient needs. Its mechanism involves removing excess fluid from the body through ultrafiltration, eliminating small and medium molecular solutes via convection, and clearing inflammatory mediators through adsorption. The objectives of CRRT extend beyond merely replacing impaired renal function; in recent years, its application has expanded to the emergency management of common critical illnesses, making it one of the most vital supportive therapies in the treatment of various critical conditions[1]. However, CRRT may reduce effective drug concentrations in the body, thereby affecting treatment efficacy and patient prognosis. Therefore, investigating the impact of CRRT on drug clearance in critically ill patients holds significant importance for ensuring clinical drug safety, rational drug application, and reducing adverse drug reactions. This article analyzes the appropriateness of the antihypertensive regimen for this patient by exploring the factors influencing drug clearance during CRRT treatment, along with corresponding drug dosage adjustments, in consideration of the patient's individual characteristics.*

Keywords: *CRRT, Antihypertensive Regimen, Factors Influencing Drug Clearance, Drug Dosage Adjustment*

1. Medical History Summary:

The patient is a 54-year-old male admitted due to "intermittent chest pain for 5 years, aggravated for 1 day."

Present Illness: In September 2016, the patient experienced chest tightness and pain without obvious cause, accompanied by back discomfort and a cold sensation in the left arm. The episodes lasted several minutes and could resolve spontaneously, occurring more frequently at night. Administration of Su-Xiao-Jiu-Xin Wan (a traditional Chinese medicine for angina) did not result in significant improvement. Coronary angiography performed at that time revealed: no significant abnormality in the Left Main (LM) coronary artery; a long lesion in the proximal segment of the Left Anterior Descending (LAD) artery with the narrowest point showing 60% stenosis, and 60%-70% stenosis observed in the proximal-to-mid segment; no significant abnormality in the Left Circumflex (LCX) artery; an ulcer-like projection in the proximal segment of the Right Coronary Artery (RCA), with irregularities in the mid and distal segments, and irregularity at the origin of the Posterior Descending Artery (PDA) with proximal 80% stenosis. He was discharged on regular oral medications. The aforementioned symptoms occurred intermittently thereafter.

In December 2021, during a hospitalization in the Nephrology Department of our hospital, the patient again experienced the aforementioned symptoms without obvious cause, with episodes lasting from several minutes to one hour. He was subsequently transferred to our department for further evaluation. A repeat coronary angiography showed: right-dominant coronary distribution; no stenosis in the Left Main trunk; 70% stenosis in the proximal segment of the LAD, 50-60% stenosis in the mid segment, with collateral formation from the distal LAD toward the RCA; 50% stenosis in the proximal segment of the LCX; 70% stenosis in the proximal segment of the RCA, with total occlusion distal to the mid segment. Upon discharge, he was prescribed regular oral medications: "Clopidogrel Bisulfate Tablets 75mg QD, Atorvastatin Calcium Tablets 20mg QN, Arotinolol Hydrochloride 10mg BID."

Despite this regimen, the symptoms continued to occur intermittently.

One day prior to admission, the patient experienced sudden onset of chest pain accompanied by profuse sweating during dialysis. An electrocardiogram (ECG) showed atrial fibrillation with a heart rate around 145 beats per minute. Oral administration of Metoprolol Tartrate Tablets and Isosorbide Dinitrate provided no sustained relief of symptoms, leading to hospital admission. After treatment with Cedilanid (Lanatoside C) and intravenous amiodarone infusion, the atrial fibrillation converted to sinus rhythm. The patient's chest pain lasted for over one hour before subsiding. A follow-up ECG then showed ST-segment elevation in leads II, III, and aVF. Laboratory tests revealed an elevated high-sensitivity troponin level of 8703 pg/ml. Cardiac ultrasound indicated: left ventricular enlargement (end-diastolic diameter 53mm) and reduced pulsation amplitude in the basal segment of the left ventricular inferior wall. He was admitted to the Cardiology Department for further diagnosis and treatment.

Since the onset of the illness, the patient's mental state has been fair, his appetite has been poor, his bowel movements are normal, his daily urine output is approximately 500ml, and his body weight has shown no significant change.

1.1 Admission Diagnoses:

(1) Coronary Heart Disease→Acute Inferior Wall Myocardial Infarction→Killip Class I→Arrhythmia→Paroxysmal Atrial Fibrillation

(2) Chronic Renal Failure Uremic Stage→Continuous Hemodialysis Status→Renal Anemia

(3) Type 2 Diabetes Mellitus→Diabetic Retinopathy

(4) Hypertension Stage 3 (Very High Risk)

(5) Old Cerebral Infarction

1.2 Treatment Course

After admission, the patient underwent the relevant laboratory tests and examinations. The medical team provided nursing care for acute myocardial infarction and initiated treatment including antiplatelet aggregation, lipid regulation and plaque stabilization, heart rate reduction, coronary vasodilation, gastric protection, and anti-arrhythmia therapy. Given the patient's abnormal renal function in the uremic stage, the Nephrology Department was promptly consulted to perform bedside hemofiltration. The patient's condition was closely monitored, and the treatment plan was adjusted according to changes in his clinical status.

1.3 The patient's initial treatment medications were as follows:

Action	Drug Name	Dosage and Administration
Blood Pressure Control Heart Failure Improvement	Arotinolol Hydrochloride Tablets	10.0mg PO BID
	Sacubitril Valsartan Sodium Tablets	50.0mg PO BID
Antiplatelet	Indobufen Tablets	0.1g PO BID
	Clopidogrel Bisulfate Tablets	75.0mg PO QD
Lipid Regulation and Plaque Stabilization	Atorvastatin Calcium Tablets	20.0mg PO QN
Blood Glucose Reduction	Acarbose Tablets	50.0mg PO TID
	Levemir (Penfill) Insulin Detemir Injection	10IU IH QN
	NovoRapid (Penfill) Insulin Aspart Injection	10IU IH TID

Coronary Vasodilation	Isosorbide Mononitrate Sustained-Release Tablets	60.0mg PO BID
Microvascular Dilation	Pancreatic Kininogenase Enteric-coated Tablets	120.0IU PO TID
Anticoagulation	Nadroparin Calcium for Injection	3075.0IU IH BID
Gastroprotection	Pantoprazole Sodium Enteric-coated Capsules	40.0mg PO QD
Protein Supplementation	Compound α-Ketoacid Tablets	4tablets PO BID

On the fourth day after admission (D4), the patient's blood pressure remained inadequately controlled. The antihypertensive regimen was therefore adjusted from Arotinolol Tablets 10.0mg PO BID plus Sacubitril Valsartan Sodium Tablets 50.0mg PO BID to Arotinolol Tablets 15.0mg PO BID plus Sacubitril Valsartan Sodium Tablets 50.0mg PO BID. On D8, the regimen was further adjusted from Arotinolol Tablets 15.0mg PO BID plus Sacubitril Valsartan Sodium Tablets 50.0mg PO BID to Arotinolol Tablets 15.0mg PO BID plus Sacubitril Valsartan Sodium Tablets 150.0mg PO BID. On D9, the regimen was changed from Arotinolol Tablets 15.0mg PO BID plus Sacubitril Valsartan Sodium Tablets 150.0mg PO BID to Arotinolol Tablets 15.0mg PO BID plus Sacubitril Valsartan Sodium Tablets 150.0mg PO BID plus Levamlodipine Besylate Tablets 2.5mg PO BID plus Spironolactone Tablets 20.0mg PO QD. On D11, the regimen was adjusted from Arotinolol Tablets 15.0mg PO BID plus Sacubitril Valsartan Sodium Tablets 150.0mg PO BID plus Levamlodipine Besylate Tablets 2.5mg PO BID plus Spironolactone Tablets 20.0mg PO QD to Arotinolol Tablets 15.0mg PO BID plus Sacubitril Valsartan Sodium Tablets 200.0mg PO BID plus Levamlodipine Besylate Tablets 2.5mg PO BID plus Spironolactone Tablets 20.0mg PO QD. After 25 days of standardized treatment, the patient's condition stabilized without significant discomfort, and he was deemed suitable for discharge.

2. Analysis and Discussion

2.1 Factors Influencing Drug Clearance during CRRT Treatment

The factors influencing drug clearance during CRRT treatment primarily encompass two aspects: the characteristics of the CRRT system and the properties of the drugs themselves. Firstly, the characteristics of the CRRT system include the CRRT modality and the CRRT system parameters. CRRT modalities include Slow Continuous Ultrafiltration (SCUF), Continuous Veno-Venous Hemofiltration (CVVH), Continuous Veno-Venous Hemodialysis (CVVHD), and Continuous Veno-Venous Hemodiafiltration (CVVHDF), each suitable for filtering solutes of different molecular weights. CRRT system parameters, such as blood flow rate, dialysate flow rate, replacement fluid rate, ultrafiltration rate, total effluent flow rate, hemofilter membrane material, and filter surface area, all exert a certain influence on drug clearance[2].

Secondly, the inherent properties of the drugs themselves also impact their clearance rate. These include:

2.1.1 Drug Molecular Weight

The molecular weight of most chemical drugs is generally less than 500 Da (with a few exceptions having larger molecular weights, such as vancomycin at 1448 Da). Drugs within this range can be cleared by the dialysis membrane used in CRRT. The clearance rate tends to be higher for drugs with smaller molecular weights.

2.1.2 Drug Protein Binding Rate

Drugs in their free (unbound) state are more readily cleared by CRRT. Drugs with a high protein binding rate are difficult to clear through CRRT. When the protein binding rate exceeds 90%, the amount of drug cleared by dialysis becomes negligible. For critically ill patients, albumin levels are often below normal. This can lead to increased concentrations of the non-protein-bound fraction of a drug, thereby enhancing its elimination by CRRT.

2.1.3 Apparent Volume of Distribution of Drugs

The apparent volume of distribution (Vd) reflects the extent of a drug's distribution into body tissues. A higher Vd indicates a greater proportion of the drug is distributed into the tissues, resulting in

a correspondingly lower proportion of the drug within the vascular compartment that is available for elimination via endogenous or exogenous pathways. Drugs with a Vd < 1 L/kg are more readily cleared by CRRT compared to drugs with a Vd > 2 L/kg.

2.1.4 Drug Elimination Pathways

For drugs primarily eliminated through the kidneys, dosage adjustments, often an increase, may be necessary during CRRT. Furthermore, for patients undergoing CRRT who still possess some residual renal function, drug dosages may require further adjustment. Generally, dosage adjustments are not needed for drugs that are primarily eliminated through hepatic metabolism.

2.1.5 Drug Charge

Negatively charged drugs are more readily cleared, while positively charged drugs are more difficult to clear.

2.1.6 Effluent Flow Rate and Blood Flow Rate

Both factors are directly proportional to drug clearance.

2.1.7 Type of Dialysis Membrane

Certain membranes (such as AN69, PAN, etc.) have adsorptive properties for drugs, thereby increasing clearance[3].

2.2 Dosage Adjustment of Drugs during CRRT Treatment

Dosage adjustments for drugs during CRRT treatment encompass the administration of a loading dose, determination of the maintenance dose, and therapeutic drug monitoring.

2.2.1 Administration of a Loading Dose

The purpose of a loading dose is to achieve the target serum concentration after the first dose; therefore, changes in drug clearance do not affect the prescribed loading dose (see formula). The loading dose is directly proportional to the Vd. Typically, no adjustment to the loading dose is required during CRRT[4].

$$F=(AUC_{po}\times D_{iv})/(AUC_{iv}\times D_{po}), \qquad (1)$$

Note: F represents bioavailability; AUCpo is the AUC following oral administration; AUCiv is the AUC following intravenous administration; Dpo is the oral administration dose; Div is the intravenous administration dose.

$$C\,max=\frac{Dose\times F}{Vd}. \qquad (2)$$

Note: The Volume of Distribution (Vd) is a parameter relating the concentration of a drug in plasma to the total amount of drug in the body. It is quantified in liters per kilogram of body weight and primarily depends on the distribution and binding of the drug to extravascular tissues compared to plasma proteins.

$$LD\ (\mathrm{mg})=\frac{\text{target concentration}\ \left(\mathrm{mg/L}\right)\times Vd\ (\mathrm{L})}{F}.$$

(Equation 1)

Note: LD stands for loading dose; F represents bioavailability; Vd denotes the volume of distribution[5].

2.2.2 Determination of the Maintenance Dose

For continuous intravenous infusion, the maintenance dose is calculated as: Maintenance Dose = Drug Clearance × Target Concentration. Therefore, the maintenance dose depends on the drug's clearance rate. For oral administration, the maintenance dose is adjusted using the formula: Maintenance Dose = (CLcrrt / F) × Target Concentration, where CLcrrt represents the clearance rate of the drug during CRRT[6].

$$MD\,(\mathrm{mg/h}) = \mathrm{clearance}(\mathrm{L/h}) \times \mathrm{target\ concentration}\,(\mathrm{mg/L}).$$

(Equation 2)

Note: MD stands for Maintenance Dose.

2.2.3 For Intermittent Dosing

Intermittent Dose = Maintenance Dose × Dosing Interval Time.

$$MD\ (\mathrm{mg/dose}) = MD\,(\mathrm{mg/h}) \times \mathrm{dosing\ interval}\,(\mathrm{h/dose}).$$

(Equation 3)

2.2.4 Therapeutic Drug Monitoring

Therapeutic drug monitoring is essential, particularly for medications with a narrow therapeutic window or significant adverse effects, to help avoid drug-related complications.

During CRRT treatment, in addition to applying pharmacokinetic and pharmacodynamic principles for dosing, it is necessary to monitor post-administration drug plasma concentrations or clinical responses. This monitoring may include tracking specific signs or symptoms, such as laboratory results (e.g., activated partial thromboplastin time[aPTT] or anti-Xa levels) and vital sign parameters (e.g., heart rate or blood pressure).

2.3 Analysis of the Rationality of the Antihypertensive Regimen in This Patient

The adjustment of oral antihypertensive drugs during CRRT treatment generally refers to the medication recommendations for patients undergoing hemodialysis[6]. This follows the workflow for hypertension control recommended in the Standard Operating Procedures for Blood Purification[1].

2.3.1 Assessing the Clinical Type of Hypertension in Hemodialysis Patients

For hemodialysis patients with comorbid hypertension, a comprehensive assessment should be conducted over a cycle of three dialysis days and intervening non-dialysis days. This involves monitoring the patient's blood pressure on both non-dialysis and dialysis days, specifically before, during, and after dialysis sessions. Plotting the patient's blood pressure fluctuation curve based on these measurements helps to clarify the clinical type of hypertension.

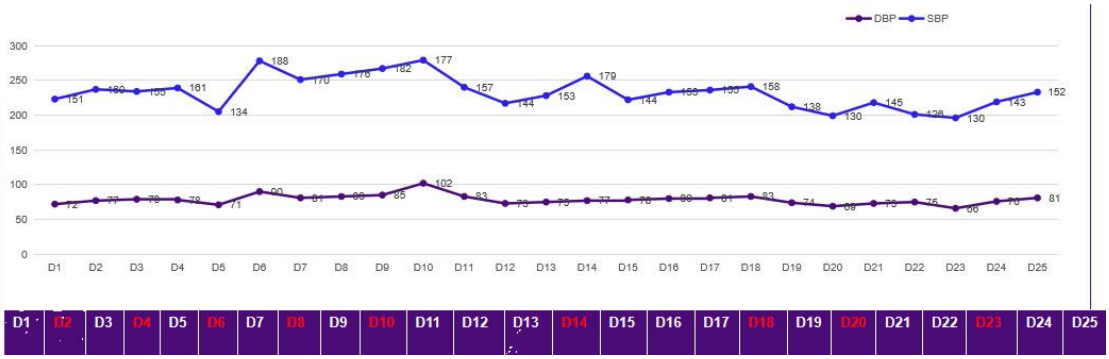

Figure 2. Changes in the Patient's Blood Pressure During Hospitalization

As shown in Figure 2, analysis of the patient's blood pressure changes during hospitalization indicates that the clinical type is "High-Rise-High-High Type": the patient presented with hypertension before dialysis; blood pressure gradually increased during dialysis alongside rising ultrafiltration volume; blood pressure decreased somewhat after dialysis; and hypertension persisted during the interdialysis period.

2.3.2 Control of Interdialytic Fluid Volume and Achievement of Target Dry Weight

The patient's dry weight was within the target range.

2.3.3 Selection of Antihypertensive Regimen

For the "High-Rise-High-High Type": On the basis of dry weight control, administer ACE inhibitors

(such as benazepril or fosinopril), ARBs, and/or α- and β-blockers, which are not easily cleared by dialysis, to inhibit the patient's renin-angiotensin system or sympathetic nerve reactivity. Calcium channel blockers can be added if the efficacy is suboptimal. The patient's final antihypertensive regimen was "Arotinolol Tablets + Sacubitril Valsartan Tablets + Levamlodipine Besylate Tablets + Spironolactone Tablets". Consultation of the spironolactone drug labeling indicates that it is "not routinely recommended for patients on intermittent hemodialysis or peritoneal dialysis; however, two small-scale trials have demonstrated the safety of spironolactone in patients with end-stage renal disease on dialysis, suggesting a maximum daily dose of 25mg". In summary, based on the aforementioned domestic and international research and standard operating procedures[1], the selection of antihypertensive drug classes for this patient was rational.

2.3.4 Clarify the Impact of Hemodialysis on the Metabolism of Antihypertensive Drugs

This is based on the recommendations in the Standard Operating Procedures for Blood Purification[1] regarding the clearance effects of commonly used antihypertensive drugs and the need for post-dialysis supplementation. The patient's final antihypertensive regimen consisted of "Arotinolol Tablets, Sacubitril Valsartan Tablets, Levamlodipine Besylate Tablets, and Spironolactone Tablets". Among these, arotinolol, sacubitril/valsartan, and levamlodipine are not cleared by hemodialysis, and thus do not require supplementation after dialysis. According to the drug labeling for spironolactone, its plasma protein binding rate is greater than 90%. Consequently, it is also not cleared by hemodialysis, and no post-dialysis dose supplementation is necessary.

2.3.5 Achieving Blood Pressure Control Targets and Dynamic Adjustment of the Antihypertensive Treatment Plan

According to the recommendations in the Standard Operating Procedures for Blood Purification[1], the target for blood pressure control in hemodialysis patients is a pre-dialysis blood pressure measured in the clinic of less than 140/90 mmHg for patients under 60 years old, and less than 160/90 mmHg for patients aged 60 and above (including pharmacotherapy). As this patient is 54 years old, the target for his hemodialysis blood pressure control is a pre-dialysis clinic blood pressure of less than 140/90 mmHg.

As shown in Figure 2, through the dynamic adjustment of the antihypertensive regimen (including the types and dosages of medications), the pre-dialysis blood pressure measured in the clinic was consistently maintained around 140/90 mmHg. Therefore, the patient's final antihypertensive regimen is rational.

2.3.6 Monitoring Adverse Effects of Antihypertensive Drugs

The adverse effects of antihypertensive drugs requiring particular attention in this patient include: monitoring for peripheral angioedema and its potential impact on the assessment of the patient's dry weight when using Levamlodipine Besylate Tablets; vigilance for the occurrence of hyperkalemia with valsartan-containing medications; and attention to the negative inotropic effects, bradycardia, and conduction block associated with Arotinolol Tablets.

3. Summary

For patients undergoing CRRT treatment, the dosages of many medications require adjustment based on the relevant influencing factors. However, there is currently no unified standard for the specific adjustment methods, particularly regarding the magnitude of dose changes. By referencing relevant international studies and analyzing the selection of antihypertensive drug types and dosages in the context of the patient's specific condition, this case provides a basis for rational drug use in such patients during CRRT.

References

[1] Standard Operating Procedures for Blood Purification (2021 Edition).
[2]Thompson Ashley,Li Fanny,Gross A Kendall,Considerations for Medication Management and Anticoagulation During Continuous Renal Replacement Therapy.AACN Adv Crit Care, 2017, 28: 51-63.
[3] Ding Xiaoqiang. Clinical Standards for Continuous Renal Replacement Therapy. People's Medical Publishing House. 2016.

[4]Roberts Darren M,Sevastos Jacob,Carland Jane E et al. Clinical Pharmacokinetics in Kidney Disease: Application to Rational Design of Dosing Regimens..Clin J Am Soc Nephrol, 2018, 13: 1254-1263.
[5]Lea-Henry TN, Carland JE, Stocker SL, Sevastos J, Roberts DM. Clinical Pharmacokinetics in Kidney Disease: Fundamental Principles. Clin J Am Soc Nephrol. 2018;13(7):1085-1095.
[6] Chen Qi, Li Yuehong. Precision Adjustment of Drug Dosage in Continuous Renal Replacement Therapy. Journal of Clinical Internal Medicine, 2017, 34(4): 233-235.