Intravenous Administration of Nifekalant Hydrochloride for the Prevention of Ischemia-Induced Ventricular Tachyarrhythmia in Patients With Renal Failure Undergoing Hemodialysis

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Nifekalant hydrochloride (NIF) is a novel class III antiarrhythmic agent that is administered intravenously and selectively blocks the rapid component of the delayed rectifier K⁺ current! The most significant adverse effect of NIF is QT-interval prolongation with torsades de pointes, which may be dose-related. Because excretion in the urine is an important pathway for its elimination, NIF must be administered cautiously in patients with renal failure. We report 3 patients undergoing hemodialysis (HD) for whom NIF administered at a relatively low dose effectively prevented ischemia-induced ventricular tachyarrhythmia.

Case Reports

Case 1
A 69-year-old man with diabetic nephropathy was hospitalized because of congestive heart failure following acute anterior myocardial infarction. The left ventricular ejection fraction was severely depressed to 33% and the ST segment remained elevated in the V1–5 leads. During HD, ventricular tachyarrhythmias were frequently observed and difficult to terminate by direct-counter shock and to prevent with conventional medical therapy. Thus, we administered NIF intravenously, at a loading dose of 0.1 mg/kg body weight (BW) and a maintenance dose of 0.2 mg/kg BW/h, which were much lower doses than previously reported (ie, loading dose: 0.30 mg/kg BW; maintenance dose: 0.60 mg/kg BW/h)!. The ventricular tachyarrhythmias were effectively suppressed by NIF, and the corrected QT interval (QTc) was extended from 0.46 s to 0.57 s as the baseline. Percutaneous coronary intervention was performed on the 75% residual stenosis of the mid-segment of the left anterior descending artery.

Case 2
A 78-year-old man undergoing HD because of diabetic nephropathy was referred for assessment of unstable angina pectoris and ST segment depression that remained symptomatic in the V3–5 leads. He also had the complication of sustained ventricular tachycardia, which appeared to be of the incessant form. Intravenous administration of NIF was effective in preventing the ventricular tachycardia at a loading dose of 0.1 mg/kg BW and a maintenance dose of 0.15 mg/kg BW/h, and increased the QTc from 0.45 s as the baseline to 0.48 s. Coronary angiography revealed 90% stenosis in the proximal segment of the left anterior descending artery and 75% stenosis in mid-segment of the left circumflex artery, and a hypoplastic right coronary artery. The left ventricular ejection fraction was 42%. The patient underwent coronary artery bypass grafting as revascularization therapy.

Case 3
A 77-year-old man with chronic glomerulosclerosis undergoing HD had undergone coronary artery bypass grafting 14 years earlier. Only the graft of the left internal thoracic artery to the posterolateral branch was patent and the left ventricular ejection fraction was severely depressed to 21%. He was hospitalized because of acute dyspnea and chest discomfort. Because of high fever, the heart rate increased and then sustained ventricular tachycardia, which was frequently accompanied by hemodynamic collapse (Fig 1A,B). To prevent this life-threatening tachyarrhythmia, NIF was administered intravenously at a loading dose of 0.2 mg/kg BW and a maintenance dose of 0.20 mg/kg BW/h with the prolongation of the QTc (Fig 1C). However, torsade de pointes was newly induced when the QTc exceeded 0.60 s (Fig 1D) and therefore the dosage of NIF was decreased.
was decreased to 0.15 mg/kg BW/h, minimizing the induction of proarrhythmic adverse events. Coronary angiography revealed the patency of the graft to the posterolateral branch, progression of the left main trunk lesion to 75% stenosis and total occlusion of the right coronary artery, for which the left anterior descending artery was the source of collateral circulation. Coronary artery stenting was performed successfully on the left main trunk lesion protected by the bypass graft.

We also measured the plasma NIF concentration by high-performance liquid chromatography and it did not change significantly before or after HD (Fig 1E,F). In this patient with chronic renal failure, even a relatively low dosage was sufficient to obtain a therapeutic concentration (≈0.5 μg/ml). Fig 2 shows the relationship between the plasma concentration of NIF and the QTc during continuous infusion of NIF at 0.15 mg/kg BW/h.

**Discussion**

Cardiovascular mortality is high in patients with chronic renal failure, which may be related in part to ventricular arrhythmias. Myocardial ischemia is a potential contributing factor, in association with the rapid changes in the concentrations of electrolytes and in pH that occur during HD. Therefore, antiarrhythmic treatment is very important in patients with renal failure and ischemic heart disease, but because renal failure modifies the pharmacokinetics and pharmacodynamics of drugs, the dosages need to be adjusted.

Nifekalant hydrochloride is a pure K⁺ channel blocker that does not have a β-adrenergic inhibiting effect. This unique class III antiarrhythmic agent is a useful emergency intravenous treatment that effectively suppresses refractory ventricular tachyarrhythmias in patients with myocardial ischemia and infarction, in which the K⁺ channels play a key role. Although the kidney is one of the important pathways of elimination of NIF, there is limited information on using NIF in patients with chronic renal failure undergoing HD.

Regarding the pharmacokinetics of NIF, only the unchanged form is active. Its half-life is 1.5 h and the volume of distribution is 0.14 L/kg. The urinary excretion ratio for the unchanged form is approximately 30%. The remaining NIF undergoes glucuronate conjugation in the liver, which may be affected by hemodynamics.

In the present study, taking into account the impaired left ventricular function and the interruption to renal excretion, we administered NIF at dosages that were one-half of those previously used in patients with normal renal function and stable hemodynamics. As shown in case 3, continuous infusion of NIF at 0.15 mg/kg BW/h achieved a therapeutic concentration, in the plasma (≈0.5 μg/ml), comparable with administration of 0.25 mg/kg BW/h reported previously in a patient without renal failure. We also noted that the NIF concentration did not change significantly before or after HD, even under continuous infusion. Because NIF binds strongly to protein (86–96%, unpublished data), it may not be dialysed.

A serious complication of NIF is torsade de pointes, which was transiently induced in case 3 when the QTc extended beyond 0.60 s. However, it was not associated with an elevated blood concentration of NIF, indicating that the dose range for the safe use of NIF may be narrow in patients with renal failure. Therefore, it is important to monitor the QTc in these particular patients and to use a low starting dose in order to minimize the induction of proarrhythmic adverse events.

In conclusion, NIF is an effective emergency intravenous treatment for patients with renal failure undergoing HD. Administration even at relatively low doses achieves a therapeutic concentration sufficient for the prevention of ischemia-induced ventricular tachyarrhythmias.

**References**


