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Plasma milrinone concentrations during continuous hemodiafiltration : A case report

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Abstract

Milrinone enhances myocardial contraction and has vasodilating activity by inhibiting phosphodiesterase (PDE) in the myocardial cells, increasing cellular cAMP and inducing increased Ca^{2+} inflow[1,2]. Some patients with severe cardiac failure require continuous hemodiafiltration (CHDF) due to complicated renal failure. We report a case in which CHDF was performed during the administration of milrinone after open heart surgery and the plasma concentration of the drug was measured.

Key word : Plasma milrinone concentration, Renal dysfunction, Continuous hemodiafiltration

Case presentation

The patient was a 41-year-old woman, (height; 151 cm, weight; 34kg) and she was diagnosed as mitral stenosis and regurgitation with tricuspid insufficiency. The SLE was pointed out at the age of 24 years and it progressed from lupus nephritis to chronic renal failure at the age of 32 years, resulting in introduction of homodialysis three times a week. The patient had cardiac failure at the age of 35 years, at which time valvular disease was diagnosed but the patient refused surgical treatment until the aggravation of lassitude on exertion at aged 41.

At the time of admission blood pressure was 110/60 mmHg and pulse rate of 90/min. BUN was 47 mg/dl, serum creatinine (Cr) was 5.57 mg/dl, AST was 37 U/l and ALT was 28 U/l. There was no marked abnormality in respiratory functions.

The surgical procedure was mitral valve replacement and tricuspid annuloplasty and the operation lasted 5 hr and 5 min and anesthesia was maintained for 6 hr and 40 min.

When she was trasfered to the ICU under artificial ventilation dopamine and dobutamine were administered at 10 μg/kg/min, respectively tagether with isosorbide nitrate at 1 μg/kg/min, blood pressure was 80/40 mmHg, heart rate was 80/min, pulmonary arterial pressure was 54/27 mmHg, right atrial pressure was 4 mmHg and cardiac index was 4.1 l/min/m^2.

The administration of milrinone was started at 0.05 μ/kg/min at 3 hours after weaning from extracorporeal circulation. Continuous hemodiafiltration (CHDF) was started in the ICU and continued for 24 hours. Twenty-four hour after the drug administration dialysis membrane for CHDF was replaced, the drug administration was resumed at 0.1 μ/kg/min of milrinone, again. To measure the concentration of milrinone, 0.5 ml of patient's plasma was mixed with 50 μl of 0.01 N hydrochloric acid and 2 ml of 1 M ammonium acetate, stirred and eluated with methanol using Sep Pak C18. The eluate was dried to solid at 50℃ under N_2 stream. The sample was measured by the high-performance liquid chromatographic fluorometry (HPLC-UV)[3]. The effective plasma concentration of milrinone was between 100 and 200 ng/ml.

Continuous hemodiafiltration (apperatus, TR-520, Toray Co., Osaka) was used and a polymethyl methacrylate (PMMA) hollow fibrous membrane

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(HEMOFEEL-CH 1.0L, Toray Co., Osaka) was supplied. The blood pump was operated at 100 ml/min using Sublood B® solution and the parenteral fluid and dialysate pumps were operated at 600 ml/hr, respectively. Eluation from CHDF was eliminated at 80 ml/hr and nafamostat mesilate was administered at 30 mg/hr as an anticoagulant during CHDF.

In the profile of plasma milrinone concentrations, a constant concentration was maintained around three hr when the drug was administered at 0.05 μg/kg/min but an increasing tendency was shown thereafter. The blood concentration after 24-hr withdrawal was below the assay sensitivity (< 5 μg/mℓ). When the drug administration was resumed at 0.1 μg/kg/min, a constant concentration was reached around one hr after the start but a sharp increase was observed at around 6 hr and the concentration was almost doubled after 24 hr. However, the plasma concentration started to

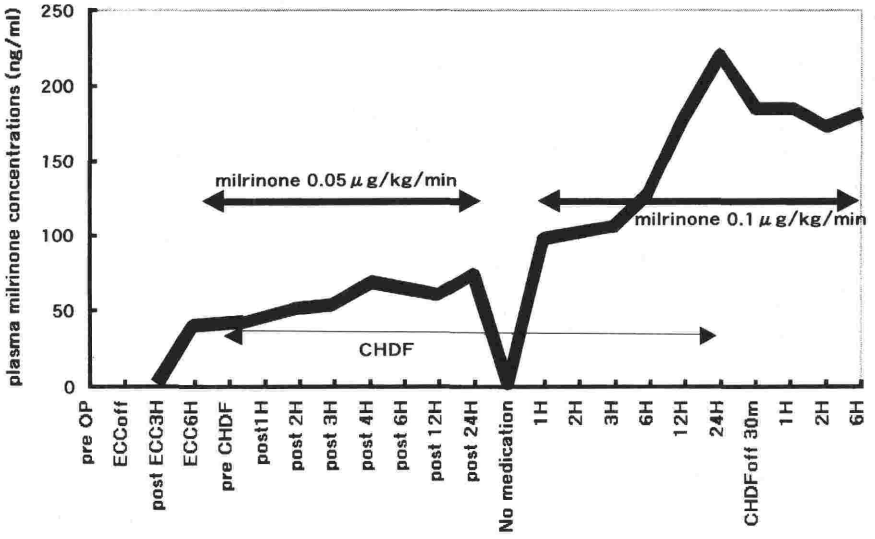

Fig 1 Time coures in plasma milrinone concentrations

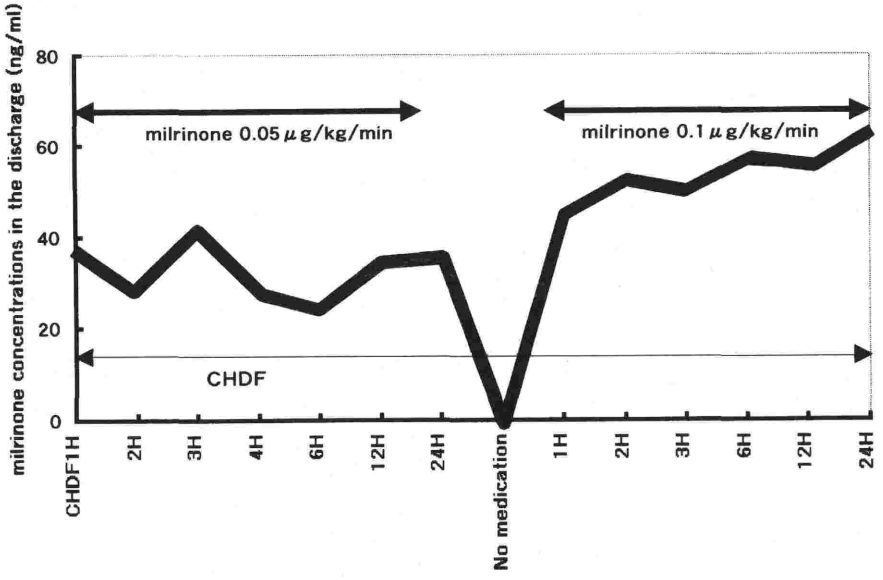

Fig 2 Time coures in milrinone concentrations in the eluation from CHDF
CHDF : continuous hemodiafiltration

slightly decrease after the discontinuation of CHDF. (Fig 1)

The milrinone concentration in the eluation from CHDF was between 20 and 40 ng/mℓ during the drug administration at 0.05 μg/kg/min. The final plasma concentration during 24-hr drug withdrawal was below the assay sensitivity and the concentration was between 50 and 70 ng/mℓ during the drug administration at 0.1 μg/kg/min. (Fig. 2)

Discussion

Milrinone hardly metabolizes in the body and is excreted through urine unchanged. As this is passed through the urinary tract unchanged it may hinder renal functions with a reduction in dose required if renal functions are getting worse[4~7]. While the half-life of milrinone is between 40 and 50 min with normal renal functions, it is prolonged if renal function is impaired and the blood concentration increases cumulatively even if the dose is reduced.

In the present case, we investigated the pharmacokinetics of milrinone when CHDF was introduced after open heart surgery in a patient undergoing dialysis three times a week before operation. At both 0.05 and 0.1 μg/kg/min of milrinone, the blood concentration showed a sharply increasing tendency from the 6 hour after the start of administration indicating that it would be extremely difficult to maintain the blood concentration of the therapeutic range.

The plasma protein binding rate of milrinone is generally 76.7 to 95.8% and the drug is present in plasma mostly in the form bound with albumin. Thus, milrinone exists in the plasma having the molecular weight of 66,200 since the molecular weight of milrinone is 211.22 and that of albumin is 66,000.

The PMMA membrane used as the dialysis membrane (HEMOFEEL-CH 1.0L) in the present study shows an albumin elimination rate of 90% and above; the sieving coefficient (SC) is 10% or less and the values in the filtration experiment in bovine blood and in clinical studies were several % or below. Thus, the SC value of albumin-bound milrinone through the PMMA membrane becomes several % or below due to the large molecular weight and the drug is accumulated in the plasma cumulatively with time, which increases the concentrations. Moreover, as the volume of the distribution of milrinone is 12.4 to 16.7 l[8], it is readily distributed to tissues rather than to blood and the tissue concentration increases because CHDF cannot eliminate the drug in the tissues.

In our case, the plasma milrinone concentration showed a slight decreasing tendency after the discontinuation of CHDF, which might have been due to the dilution of the drug in the plasma due to the increase in the amount of water in the body after discontinuation of CHDF. Howeve a further large scale study is required to confirm this theory.

In concluslon, we found that when milrinone was administered continuously for a long time during CHDF, a dose reduction should be required.

Reference

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