Midodrine for ICU patients suffering from refractory hypotension

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Abstract - Hypotension is a common clinical problem in the intensive care unit, and intravenous inotropic or vasopressor therapy is often necessary. In dialysis-dependent patients the process of tapering the dose of intravenous inotropics can be complicated by refractory hypotension. The two cases described in this report outline the successful introduction of midodrine, an oral α1-receptor agonist, in two patients suffering from refractory hypotension.

Keywords - midodrine, hypotension, intensive care, inotropic therapy

Introduction
Persistent hypotension is a common problem in intensive care unit (ICU) treatment. Hypotension is caused either by a low systemic vascular resistance (sepsis, spinal shock, vasodilatory medication), low stroke volume (hypovolaemia, adrenal insufficiency, tachyarrhythmia, tamponade, high PEEP, pulmonary embolism, right and left sided heart failure, valvular dysfunction) or low heart rate. Chronic hypotension and inotropic dependency is less common. Treatment can be challenging when blood pressure remains low due to continuous or intermittent haemodialysis.

This report covers two hypotensive patients who are both suffering from renal insufficiency with concurrent heart disease. In addition, the introduction of midodrine therapy is discussed.

Case A
A 60-year-old man was referred to the department of internal medicine because of a six-month history of fatigue and recurrent infections. His medical history was positive for chronic obstructive pulmonary disease and he was not taking any medication. After bone marrow examination, the diagnosis of multiple myeloma, stage la according to the Durie-Salmon staging system, was made. During induction chemotherapy and autologous stem cell transplantation the patient gained weight and developed shortness of breath. Transthoracic echocardiography (E/A < 1; Deceleration time > 220 msec; E' 6.4 cm/sec; E/E' 13.8) and cardiac MRI (Figure 1 and http://www.nvic.nl/njcc.php) demonstrated severe hypertrophy of the left and right ventricles as well as a hypertrophic interatrial septum, causing diastolic dysfunction with delayed relaxation. The late enhancement pattern was highly suggestive of cardiac amyloidosis. Furthermore, the patient developed severe renal insufficiency that required the start of intermittent haemodialysis which was complicated by severe hypotension. The patient was transferred to the ICU and treatment with norepinephrine and continuous venovenous haemofiltration (CVVH) was started. After 3 weeks a peritoneal dialysis (PD) catheter was implanted and PD was started. Despite the discontinuation of CVVH the patient remained dependent on intravenous vasopressor therapy. Oral ibopamine was added to the medication but the patient developed ventricular tachycardia within 24 hours. Following this the patient was started on oral caffeine, which was soon discontinued due to side effects. Finally, we decided to introduce oral midodrine which was started at a low dose of 2.5 mg three times daily (tid). After more than 60 days, the patient was weaned off norepinephrine and discharged from the ICU using midodrine 10 mg tid.

Case B
A 76-year-old man was admitted to the ICU following aortic valve replacement. He had a medical history of coronary surgery (1978), redo-coronary surgery (1991), severe aortic valve calcification and stenosis, reduced left ventricular function, and renal failure due to familial polycystic kidney disease. Intermittent haemodialysis was started in May 2008. One day post-surgery CVVH was initiated. However, profound hypotension associated with CVVH therapy forced us to start intravenous norepinephrine which was later replaced by dopamine as the patient experienced severe peripheral vasoconstriction. After 2 weeks the dopamine treatment was tapered. However, the patient’s systolic blood pressure dropped below 55-60 mm Hg. Intravenous inotropic treatment was reintroduced. Three days later, midodrine 2.5 mg tid was initiated and the patient was weaned from inotropic support. CVVH therapy was terminated and after 33 days in the ICU the patient was discharged. The final invasive blood pressure before discharge was 124/69 mm Hg.
Discussion

Common causes of hypotension in patients in the ICU are sepsis, the use of vasodilatory medication, and adrenal insufficiency. Both patients in this report did not use antihypertensive or vasodilatory medication. Furthermore, infection was ruled out as a possible cause of hypotension and the blood pressure of both patients did not react to treatment with hydrocortisone.

Cardiac involvement is frequent in systemic amyloidosis, often leading to diastolic dysfunction and restrictive cardiomyopathy [1]. In addition, amyloidosis may induce dysfunction of the autonomic nervous system. In case report A, we present a patient suspected of cardiac amyloidosis who simultaneously suffered from end stage renal failure, initially leading to CVVH and later to PD. Both amyloidosis and haemodialysis have been associated with hypotension. In this particular case, ultrafiltration induced plasma depletion, probably causing inadequate filling of a hypertrophic heart muscle, which when combined with an impaired compensatory increase in sympathetic tone led to severe hypotension [2]. In order to induce appropriate vasoconstriction norepinephrine was started. After unsuccessful oral treatment with the dopamine agonist ibopamine and the adenosine receptor antagonist caffeine, this patient (A) was treated with midodrine. Norepinephrine was successfully discontinued. In case B, the pathophysiological mechanism underlying the patient’s low blood pressure also involved diastolic dysfunction. However, in this patient hypertrophy and impaired relaxation of the left ventricle were caused by severe aortic stenosis. Furthermore, his left ventricular systolic function was impaired.

Instead of using sympathicomimetic amines in the initial stage of stabilization, treatment with the phosphodiesterase III inhibitor enoximone could have been effective for this patient. Given the underlying pathophysiological considerations, the α-sympathomimetic properties of norepinephrine were preferred over the vasodilatory effects of enoximone in patient A [3]. Theoretically, the calcium sensitizer levosimendan could become an alternative therapy for similar patients in the future. It appears to be more beneficial and it has also proved to be energetically less disadvantageous for the myocardium than existing inotropic agents [4]. Both enoximone and levosimendan could potentially have been effective in the stabilization of patient B as his left ventricular function was impaired. After stabilization, patient B was treated with low-dose midodrine and he was able to resume intermittent dialysis after a post-operative interval of CVVH.

Midodrine is a selective α1-receptor agonist and is a prodrug of 1-(2’5’-dimethoxyphenyl)-2-aminoethanol (DMAE) that combines glycine by a peptide bond. After oral administration, the bioavailability of midodrine is reported to be approximately 100%, whereas that of DMAE is approximately 50%. The metabolite increases peripheral resistance by inducing constriction of both arterial and venous capacitance vessels and it prevents venous pooling of the blood thus increasing blood pressure. Its action is identical to that of other α1-adrenoceptor stimulators, such as phenylephrine. Peak levels of the active metabolite in serum are achieved in 1 hour and its half-life is approximately 3 hours. In patients with end stage renal disease, the half-life will be prolonged three times. Importantly, haemodialysis effectively removes both the prodrug and active metabolite [5]. In patients with a normal renal function the usual starting dose is 2.5 mg tid. The dose can be gradually increased up to 10 mg tid. In a previous report, the pharmacokinetic characteristics of the prodrug and its active metabolite in a dialysis patient approximated those reported for patients with normal renal function [6]. This seems to
suggest that similar dosing schedules could be used for patients on dialysis. In patients with end stage renal disease who are not on dialysis, the dose is not yet clear and great care should be taken when midodrine is administered in these patients. Several side effects have been reported, such as scalp paraesthesias, heartburn, flushing, headache, urinary retention, supine hypertension, neck soreness and weakness. However, please note that none of our patients experienced any of these side effects.

Midodrine is known to increase glomerular pressure and has been used therapeutically to reverse endogenous vasodilators that result in low glomerular pressure in hepatorenal syndrome [7]. Furthermore, midodrine has been prescribed for the treatment of neurogenic orthostatic hypotension in patients with spinal cord injury, for patients with neurocardiogenic syncope, for the treatment of hypotension associated with carotid artery stenting, and for several other indications [8]. Although still under investigation, midodrine has also been studied in the treatment of dialysis induced hypotension [9,10]. Unfortunately, these studies were small and not always randomized. While there are no known studies in patients on peritoneal dialysis, trials in patients on haemodialysis have shown that midodrine is safe and can be useful in the treatment of symptomatic dialysis-related hypotension [11]. To our knowledge no studies have been published that describe the use of midodrine as a replacement therapy for intravenous inotropic or vasopressive agents.

Conclusion

In these case reports, we have described the successful introduction of midodrine as an oral alternative for low-dose intravenous inotropic or vasopressive therapy in patients in the intensive care unit.

References