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Treatment of milrinone-associated tachycardia with β -blockers

Purpose: To describe a case of milrinone-associated tachycardia that was successfully treated with two β -blockers.

Clinical features: A 74-yr-old male patient underwent elective abdominal aortic aneurysm repair under combined epidural/general anaesthesia. He had a history of alcohol abuse, controlled hypertension and ischaemic heart disease. Postoperatively, the patient had persistent sinus tachycardia that was initially unsuccessfully treated with metoprolol. Subsequently, the patient's blood pressure and cardiac index decreased with an associated increase in pulmonary artery pressure. Analysis of the ST-segment revealed no evidence of myocardial ischaemia or infarction. These haemodynamic changes were treated with milrinone which exacerbated the baseline tachycardia without adverse blood pressure response. The subsequent administration of β -blockers (esmolol and metoprolol) was successful in controlling the heart rate response to milrinone without adversely affecting the patient's haemodynamic profile.

Conclusion: This report demonstrates the efficacy of esmolol and metoprolol for the treatment of milrinone-associated tachycardia, without compromising the haemodynamic effects of milrinone.

Objectif : Rapporter un cas de tachycardie causée par la milrinone contrôlée avec deux β -bloquants.

Éléments cliniques : Un homme de 74 ans a subi une réparation non urgente d'un anévrisme abdominal sous anesthésie épidurale combinée à une anesthésie générale. Il avait des antécédents d'alcoolisme, d'hypertension sous contrôle et d'insuffisance coronaire. En postopératoire, il présentait une tachycardie sinusale persistante traitée initialement avec du métoprolol. Par la suite, sa pression artérielle et son index cardiaque ont diminué simultanément avec une augmentation de la pression artérielle pulmonaire. L'analyse du segment ST ne révélait pas d'ischémie myocardique ni d'infarctus. Ces désordres hémodynamiques ont été traités avec de la milrinone qui a exagéré la tachycardie initiale sans affecter la pression artérielle. L'administration subséquente de β -bloquants (esmolol et métoprolol) a réussi à contrôler la réponse cardiaque à la milrinone sans détérioration du profil hémodynamique.

Conclusion : Cette observation démontre l'efficacité de l'esmolol et du métoprolol dans le traitement de la tachycardie associée à la milrinone, sans en atténuer les effets hémodynamiques.

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MILRINONE is a bipyridine phosphodiesterase (PDE) III inhibitor that is used to treat low cardiac output syndromes.¹⁻³ It exerts positive inotropic effects on the heart and has potent vasodilatory properties.⁴⁻⁶ Despite increases in myocardial contractility, milrinone causes little if any increase in myocardial oxygen consumption (MVO_2).⁷ However, this favourable effect on MVO_2 may be negated by increases in heart rate (HR) that sometimes accompany its administration.⁸ Accordingly, tachycardia, in association with milrinone therapy, may become a limiting factor in the administration of the drug unless this adverse effect is treated.

We describe the use of two selective β -adrenoceptor blockers to treat milrinone-exacerbated tachycardia in a postoperative patient who underwent elective abdominal aortic aneurysm repair. This is the first reported case describing the use of β -adrenergic blocking drugs to treat this adverse effect of milrinone administration.

Case report

A 74-yr-old, 75-kg man was admitted to the intensive care unit (ICU) for postoperative care following elective abdominal aortic aneurysm repair under combined T12-L1 epidural/general anaesthesia. He had a history of myocardial infarction 15 yr previously, paroxysmal atrial fibrillation (AF), hypertension, and alcohol abuse. There was no history of angina, congestive heart failure or thyroid dysfunction. The patient's blood pressure was controlled with terazosin preoperatively. The intraoperative course was uneventful except for a pre-induction AF with a ventricular rate of 110–140 beats·min⁻¹, for which 0.5 mg digoxin *iv* was given.

On arrival to the ICU, the trachea was intubated and the lungs ventilated. Analgesia was provided with an epidural mixture of 10 μ g·ml⁻¹ hydromorphone and bupivacaine 0.1% at 10 ml·hr⁻¹. Initial haemodynamic data with a haemoglobin of 105 g·L⁻¹ were as follows: HR 120 beats·min⁻¹ (AF rhythm), BP 100/55 mmHg, pulmonary artery pressure (PAP) 41/25 mmHg, CVP 14 mmHg, PAOP 21 mmHg, stroke volume (SV) 34 ml, cardiac index (CI) 2.2 L·min⁻¹·m⁻², systemic vascular resistance (SVR) 975 dyne·s·cm⁻⁵, SvO_2 of 71% and SaO_2 of 98% breathing O_2 50%. The patient was given thiamine and multivitamins and was started on 2 mg·hr⁻¹ lorazepam infusion to prevent alcohol withdrawal symptoms. Ringer's lactate was infused at 250 ml·hr⁻¹ and digitalisation was continued in the postoperative period.

On the first postoperative day, sedation was continued to prevent alcohol withdrawal, the lungs continued to be mechanically ventilated and urine output was >0.5 ml·kg⁻¹·hr⁻¹. Arterial blood gases and acid base status

were normal. Haemodynamically, the patient was in sinus rhythm with a rate of 130 beats·min⁻¹, BP was 125/65 mmHg, PAP 48/33 mmHg, PAOP 19 mmHg, CI 2.4 L·min⁻¹·m⁻² and SvO_2 of 76%. An attempt was made to control HR by β -adrenoceptor blockade. However, the BP decreased to 110/70 mmHg following 1 mg metoprolol *iv* with no change in HR. The addition of ethanol 10% at 25 ml·hr⁻¹ to treat possible alcohol withdrawal-related tachycardia was unsuccessful in slowing HR.

Seven hours later, the patient continued to be in sinus rhythm but systolic BP decreased to 90 mmHg, PAP increased to 50/33 mmHg, while HR remained unchanged. This was accompanied by decreased CI to 1.7 L·min⁻¹·m⁻² and a low urine output, while the CVP remained at 15 mmHg and the PAOP at 22 mmHg. These haemodynamic changes were not associated with ECG or biochemical evidence of acute myocardial ischaemia/infarction. A bolus infusion of 4 mg milrinone was started to run over 30 min. Milrinone was stopped after 2 mg had been infused due to an increase in HR to 145 beats·min⁻¹ despite improvement in BP and maintenance of PAOP at 20 mmHg. To rule out the possibility of breakthrough pain and anxiety, boluses of morphine and midazolam *iv* were administered without any change in HR. Esmolol 30 mg *iv* was then given with a good haemodynamic response. A few minutes later, the HR returned to baseline at 130 beats·min⁻¹. The remaining 2 mg milrinone bolus was then infused over 15 min, but again the HR increased. Metoprolol was then administered in 1 mg *iv* increments to a total of 5 mg with resultant decrease in HR to 85 beats·min⁻¹. An infusion of milrinone was then commenced at 0.5 μ g·kg⁻¹·min⁻¹ to maintain CI at 2.5 L·min⁻¹·m⁻². The target CI was achieved with no increase in HR, and the patient's urine output improved. Metoprolol infusion was also started at 2 mg·hr⁻¹ with a favourable haemodynamic response. A day later, the patient was switched to oral metoprolol, and milrinone was weaned off and substituted by oral captopril. The CI remained >2.5 L·min⁻¹·m⁻² until the time of discharge from ICU. Nine days later, the patient was discharged from hospital.

Discussion

Milrinone exerts its haemodynamic effects via a non- β -receptor mediated mechanism of action. Accordingly, milrinone may have an advantage, compared with dobutamine, when β -receptors are down-regulated as may occur in patients with congestive heart failure.⁹ Despite the lack of β -receptors stimulation, tachycardia in association with milrinone administration occurs in up to 10% of patients.⁸ This adverse effect may be attributed to vasodilation and decreased systemic vascular resistance as a secondary effect of milrinone, or it

may result from a direct effect of milrinone on the heart. Although the vasodilatory effects are beneficial in patients with heart failure,¹⁰ the tachycardia may be counterproductive due to increased MVO_2 and a shortened diastolic time which in turn has the potential to compromise myocardial perfusion and lead to progressive myocardial ischemia.

In this case report, the patient had persistent postoperative sinus tachycardia which was treated with metoprolol, in order to prevent tachycardia-induced myocardial ischaemia/infarction. Mangano *et al.* have recently demonstrated the efficacy of perioperative β -blockade in reducing postoperative cardiac morbidity and mortality, for up to two years following non-cardiac surgery, in patients with coronary artery disease.¹¹

In this patient, initial β -blockade with metoprolol was unsuccessful, and the persistent tachycardia may have induced myocardial ischaemia which was not detected by ST-segment analysis. This would explain the observed decline in BP and CI and the increase in PAP. Nitroglycerin treatment was avoided because of the low BP, and administration of catecholamines for low CI was dismissed because of their propensity to increase HR. Milrinone, on the other hand, was chosen because of its favourable inotropic and lusitropic properties, and its lack of effect on MVO_2 compared with dobutamine.^{4,7} Although its administration resulted in increased CI and BP, milrinone also exacerbated the patient's tachycardia. The latter was unlikely to be due to vasodilatation as reflected by improvement in BP and maintenance of adequate filling pressures. Furthermore, the recurrence of sinus tachycardia following reinstitution of the drug infusion supports the hypothesis that milrinone was responsible for exacerbating the patient's tachycardia. The exact mechanism of this adverse effect, however, remains unknown. Other causes of increased heart rate such as pain, anxiety, anaemia, and alcohol withdrawal were unlikely in this patient since he was receiving epidural hydromorphone and bupivacaine in conjunction with *iv* infusions of lorazepam and ethanol. In addition, supplements of morphine and midazolam *iv* were ineffective in treating the tachycardia.

Since the CI had improved, the most appropriate therapy to prevent ischaemia and other adverse cardiovascular events was to control the HR. Because milrinone functions independently of β -receptors, administration of β -blockers is justifiable. Conversely, there is a theoretical concern that intracellular cAMP levels may decrease in response to β -receptor blockade which may attenuate the haemodynamic effects of PDE III inhibition due to decreased levels of the substrate. This hypothesis, however, has not been sub-

stantiated by the work of Travill *et al* who demonstrated the preservation of the inotropic and haemodynamic effects of milrinone during β -adrenergic blockade.¹² In addition, Redahan and Karski described the successful use of amrinone to treat esmolol-induced myocardial depression in a patient with thyroid storm.¹³

The short duration of action of esmolol, in the event of unwanted haemodynamic response, influenced its selection for HR control. Following the favourable response to esmolol, metoprolol was infused successfully to achieve adequate heart rate control at a lower drug cost. Milrinone was continued to maintain adequate CI for organ perfusion, and to counteract the negative inotropic effect of β -adrenergic blockade. In addition, milrinone-induced vasodilation was targeted to unload the left ventricle and thus decrease MVO_2 .

In view of the history of previous myocardial infarction and alcohol abuse, the patient could have had unrecognised preoperative myocardial dysfunction which was exacerbated by the stress of surgery, intraoperative aortic cross-clamping, and postoperative fluids shift. Therefore, the observed baseline sinus tachycardia may have been a compensatory mechanism to maintain adequate cardiac output, and hence was the initial failure of metoprolol to control the HR. The initial decrease in BP following the administration of 1 mg metoprolol *iv* was likely due to unmasking of the negative inotropism of β -adrenergic antagonists in the presence of impaired myocardial contractility. The improved inotropic state of the heart in response to milrinone bolus administration counterbalanced the negative inotropic effects of subsequent doses of β -adrenergic blockers, and also accounted for their effectiveness in controlling HR and improving the patient's haemodynamic profile.

In conclusion, this case report demonstrated the efficacy of two β -adrenergic blocking drugs for treatment of milrinone-associated tachycardia, without compromising the haemodynamic effects of milrinone. Patients who require β -adrenoceptor blockade and positive inotropic support may benefit from this combination since the combined administration of β -blockers and catecholamines would in most circumstances appear to be counterproductive.¹⁴

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