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Cholestasis due to biliary obstruction can cause cardiogenic shock with bradycardia by delaying the elimination of arotinolol

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SUMMARY

Cardiogenic shock with bradycardia due to beta-blockers is well-documented; however, this condition in association with arotinolol is unreported. We present a case of cardiogenic shock resulting from delayed arotinolol clearance caused by bile duct obstruction. A man in his 60s presented to our hospital with jaundice. We suspected acute obstructive suppurative cholangitis; however, the patient did not exhibit fever or abdominal symptoms. Based on the physical examination results, we concluded the patient was in cardiogenic shock as a consequence of delayed arotinolol elimination. We attempted to maintain organ perfusion using norepinephrine and dopamine, with minimal response. On initiating isoproterenol, the heart rate stabilised. After tapering off isoproterenol, endoscopic retrograde cholangiopancreatography (ERCP) was performed. Subsequent serum arotinolol level measurement revealed a significant reduction in the elimination half-life before and after ERCP. In cases of cardiogenic shock associated with arotinolol, presumably eliminated via the bile duct, it is crucial to consider potential delayed elimination and to appropriately time ERCP.

BACKGROUND

Beta-blockers are commonly used for chronic heart failure, particularly in cases of heart failure with reduced ejection fractions. In these cases, beta-blockers can reduce cardiovascular events and related mortality.[1]

Arotinolol, similar to carvedilol, is a beta-blocker that decreases heart rate, increases coronary blood flow, and reduces myocardial oxygen consumption.[2] In Japan, it is also used to treat hypertension and essential tremors.[3] However, beta-blockers can cause bradycardia as a side effect, which may lead to syncope and the development of bradycardia, renal failure, atrioventricular blockade, shock and hyperkalaemia (BRASH) syndrome. This syndrome includes circulatory failure, renal dysfunction, and electrolyte abnormalities.[4 5] Arotinolol is only available in Japan, China, and Korea, and reports on its metabolic pathways remain limited.[6] Additionally, there are no reports regarding its adverse events.

Several studies have suggested that cholestasis resulting from biliary obstruction can lead to delayed metabolism of sedatives and neuromuscular blocking agents.[7 8] Furthermore, no previous have documented the prolonged effects of beta-blockers in cases of obstructive jaundice, highlighting a gap in knowledge, including regarding changes in serum drug levels.

Here, we describe a case of cardiogenic shock with bradycardia due to bile duct obstruction, which delayed the elimination of arotinolol. Furthermore, we identified the haemodynamic impact of elevated arotinolol levels by measuring the drug's serum levels.

CASE PRESENTATION

The patient, a man in his 60s, had been experiencing fatigue for 1 week prior to presentation. Due to significant dizziness, he visited his primary care physician, where jaundice was noted, and he was referred to our hospital for further evaluation. He had a medical history of hypertension and schizophrenia. His medications included arotinolol (20 mg), amlodipine besylate (10 mg), olanzapine (20 mg), brotizolam (0.25 mg) and epinastine hydrochloride (10 mg). He had no history of smoking or alcohol consumption and lived alone without immediate family. No significant familial medical history was noted. On examination, he was alert, with a temperature of 36.1°C, blood pressure of 75/50 mm Hg, pulse rate of 46 beats per minute, respiratory rate of 14 breaths per minute and oxygen saturation of 95% on room air. Conjunctival jaundice was present, with no cardiac murmurs and a regular pulse. There was no spontaneous pain or tenderness on abdominal examination. His limbs were cold peripherally, with a capillary refill time exceeding 3 s.

INVESTIGATIONS

He presented with a marked elevation of direct bilirubin levels, indicating severe hyperbilirubinaemia, along with a significant elevation of biliary enzyme levels. Additionally, renal dysfunction and coagulation abnormalities were evident. The laboratory findings are presented in table 1.

On electrocardiography, there was evidence of sinus bradycardia (figure 1), and abdominal CT without intravenous contrast revealed severe dilation of the biliary tract, extending from the common bile duct to the intrahepatic bile ducts (figure 2).

DIFFERENTIAL DIAGNOSIS

Initially, acute obstructive suppurative cholangitis (AOSC) with septic shock was considered as part of the differential diagnosis due to the presence of shock, as indicated by the vital signs, accompanied by obstructive jaundice. However, the absence of

Table 1 Tabulation of laboratory parameters

Laboratory parameters	Results	Units
White cell count	7.8×10^9	/L
Haemoglobin	104	g/L
Platelets	26.1×10^9	/L
Prothrombin time	20.5	s
Activated partial thromboplastin time	65.4	s
Total serum proteins	66	g/L
Serum albumin	24	g/L
Blood urea nitrogen	22.1	mmol/L
Creatinine	297.02	µmol/L
Total bilirubin	813.10	µmol/L
Direct bilirubin	627.91	µmol/L
Indirect bilirubin	185.19	µmol/L
Sodium	138	mmol/L
Potassium	2.7	mmol/L
Chloride	98	mmol/L
Phosphate	1.71	µmol/L
Magnesium	1.19	µmol/L
Creatine kinase	384	IU/L
Aspartate aminotransferase	147	IU/L
Alanine aminotransferase	57	IU/L
Lactate dehydrogenase	454	IU/L
Alkaline phosphatase	466	IU/L
Gamma-glutamyl transferase	853	IU/L
Cholinesterase	168	IU/L
C reactive protein	47.8	mg/L

a history of fever or abdominal symptoms did not support this diagnosis. Most notably, the presence of sinus bradycardia and cold limbs on physical examination suggested cardiogenic or hypovolaemic shock rather than distributive shock, based on the haemodynamic assessment.

A transthoracic echocardiogram revealed that the left ventricular outflow tract (LVOT) velocity time integral was 28.7 cm, with an LVOT diameter of 1.8 cm. Due to the bradycardia (heart rate: 40 beats per minute), the estimated cardiac was 2.9 L/min. Considering a body weight of 70 kg and a body surface area of 1.85 m^2, the cardiac index was reduced to 1.6 L/min/m^2. Despite the reduced cardiac output, the stroke volume was 73 mL.

Based on the physical examination and ultrasound findings, it was determined that the patient was experiencing cardiogenic shock due to bradycardia rather than the distributive shock

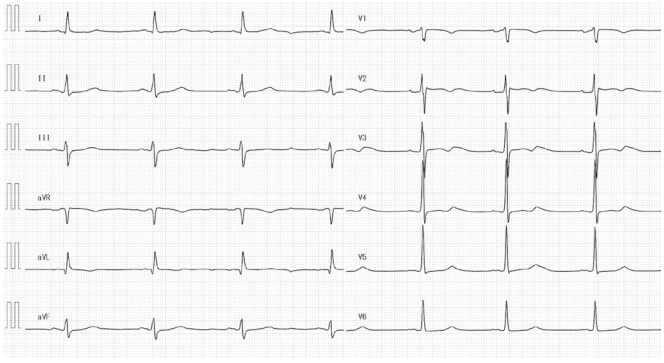

Figure 1 Electrocardiography on admission. Regular rhythm at a rate of 43 beats per minute. Each QRS complex is preceded by a normal P wave and a normal P wave axis.

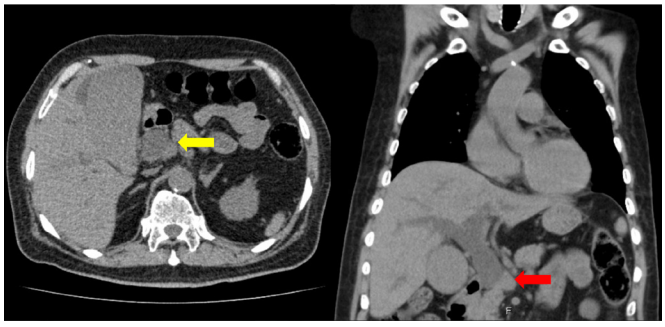

Figure 2 Abdominal CT without intravenous contrast. A man in his 60s presented with jaundice. A CT scan without intravenous contrast was performed. Axial and coronal images from the abdominal CT revealed dilation of the common bile duct (yellow arrow) and an abrupt narrowing of the distal bile duct (red arrow).

typically associated with septic shock. Therefore, the final diagnosis was not AOSC but rather cardiogenic shock with bradycardia, resulting from the delayed elimination of arotinolol.

The possibility of BRASH syndrome was also considered; however, the absence of atrioventricular blockage and hyperkalaemia made this diagnosis unlikely.

TREATMENT

Considering the possibility of hypovolaemic shock, fluid resuscitation was performed; however, the response was minimal. Vasopressors were used to manage the cardiogenic shock associated with bradycardia. Initially, norepinephrine (also known as noradrenaline) was introduced to maintain the mean arterial pressure, and dopamine was added due to its anticipated positive inotropic effect. Despite high-dose vasopressor therapy, his haemodynamics remained unstable. Concurrently, administration of atropine and glucagon was attempted without success.

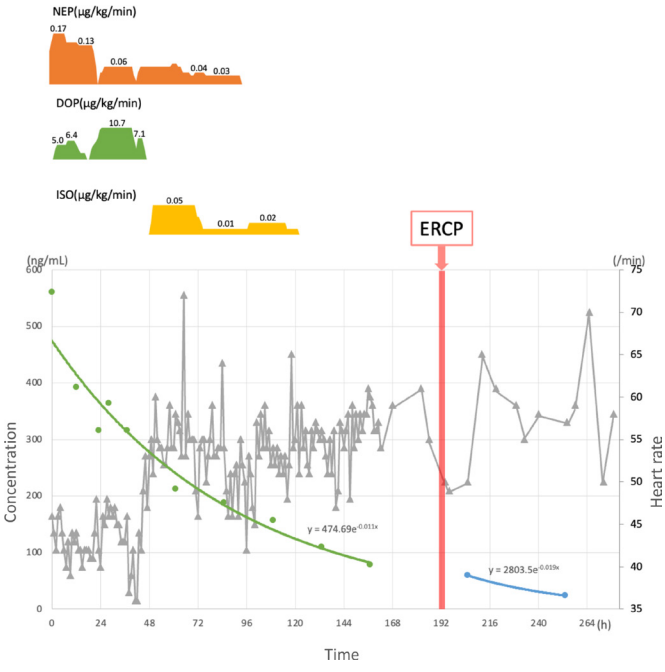

Figure 3 Time course of serum arotinolol levels, heart rate and vasopressor administration. DOP, dopamine; ERCP, endoscopic retrograde cholangiopancreatography; ISO, isoproterenol; NEP, norepinephrine.

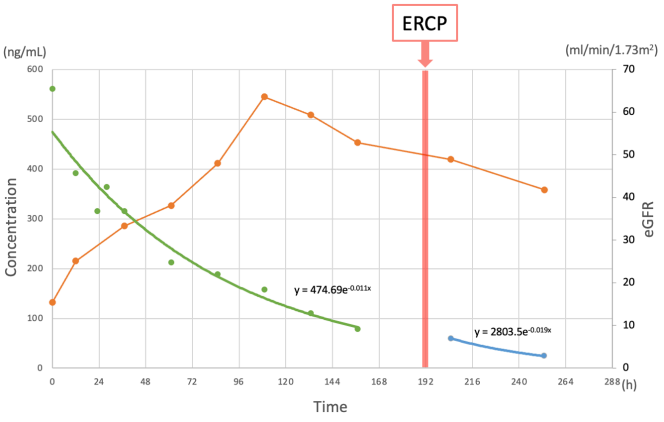

Figure 4 Time course of serum arotinolol levels and estimated glomerular filtration rate. eGFR, estimated glomerular filtration rate; ERCP, endoscopic retrograde cholangiopancreatography.

On day 3, isoproterenol (also known as isoprenaline) administration was initiated, leading to a prompt increase in heart rate, and the patient gradually stabilised. Vasopressors were discontinued by day seven (figure 3). On day 5, endoscopic ultrasonography (EUS) was performed, and intravenous contrast-enhanced abdominal CT imaging on day 8 was suggestive of bile duct obstruction, likely due to distal bile duct cancer. Subsequently, endoscopic retrograde cholangiopancreatography (ERCP) was performed on day 9.

OUTCOME AND FOLLOW-UP

After undergoing ERCP, the patient's haemodynamics remained stable. Cytological results raised suspicion of distal bile duct cancer. Following treatment for catheter-related bloodstream infection and retrograde cholangitis with *Klebsiella pneumoniae* bacteremia, subtotal stomach-preserving pancreaticoduodenectomy was performed on day 73 for suspected distal bile duct cancer (cT2N1M0, cStage IIb).

Histopathological findings from the surgical specimen confirmed the final diagnosis of pancreatic head carcinoma (pT3pN1acM0, pStage IIb). The patient's activities of daily living improved to the point that stair climbing was possible. However, due to the influence of pre-existing schizophrenia, the patient was transferred to another hospital on postoperative day 46 instead of being discharged home.

Subsequently, it was found that his serum arotinolol level was markedly elevated at 560.5 ng/mL. Although there was a gradual decrease in serum levels prior to ERCP, the elimination half-life was prolonged to 63.0 hours, indicating delayed elimination. Conversely, following ERCP, the elimination half-life was shortened to 36.4 hours (figure 3 and online supplemental figure 1). Considering the clinical course, the primary condition was presumed to be circulatory failure due to the delayed elimination of arotinolol.

DISCUSSION

Arotinolol was developed as a novel antihypertensive drug that has demonstrates a beta-blocking effect two to five times greater than that of propranolol, with approximately one-eighth of its alpha-blocking effect and a prolonged duration of action. In Japan, it was included under insurance coverage in 1985 and is now used in Japan, China, and Korea.

In this case, the patient experienced delayed arotinolol elimination due to biliary obstruction, leading to cardiogenic shock accompanied by bradycardia. A reduction in the elimination half-life was observed following ERCP. The administration of isoproterenol played a pivotal role in stabilising the patient's circulation while managing bradycardia. This highlights the importance of determining the optimal timing for ERCP in such clinical scenarios. Previous studies have demonstrated that beta-blockers can induce bradycardia severe enough to necessitate the discontinuation of oral medication, as evidenced by a 0.6% incidence in the Cardiac Insufficiency Bisoprolol Study (bisoprolol), 0.8% in the MERIT-HF study (metoprolol), and 0.9% in the COPERNICUS study (carvedilol).[9–11] Commonly reported adverse effects include fatigue, dizziness, nausea, and constipation, with some individuals also reporting sexual dysfunction and erectile dysfunction.[12] In Japan, the prescribing information notes a 1.24% incidence of bradycardia.[6] Nevertheless, no adverse events, including bradycardia, have been associated with arotinolol, the implicated drug in this case, likely due to its limited market presence. Given the severe bradycardia and associated organ dysfunction, including renal dysfunction and coagulation disorders, this case is considered serious. Arotinolol is primarily metabolised by hepatic esterases, and animal studies indicate that most of the drug is eliminated through the faeces. Furthermore, although bile elimination rates in rats are approximately 20%, with about 30% of this undergoing enterohepatic circulation and being reabsorbtion, the metabolic pathways in humans remain poorly understood.[13] The therapeutically effective blood level of arotinolol is considered to be 20 ng/mL. In healthy adults, a single oral dose of 10 mg results in a peak blood level of 117 ng/mL approximately 2 hours post administration. Conversely, older adult individuals (average age, 75.7 years) have shown peak blood levels up to 220 ng/mL with the same dosage,[14] a value assumed to present the upper limit of normal in this demographic. Serum arotinolol levels were determined using high-performance liquid chromatography coupled with ultraviolet spectroscopy. No accumulation was noted with repeated administration; however, initial blood sampling in this patient revealed an abnormally high level of 560.5 ng/mL. Notably, the reported elimination half-life is 7.2 hours,[15] but in this case, it was significantly prolonged to 69.3 hours prior to ERCP, indicating a severe delay in elimination. Following ERCP, the elimination half-life was significantly reduced to 36.4 hours, supporting the inference that the metabolic delay was associated with biliary obstruction. Although the elimination half-life remained prolonged compared to previous studies even post-ERCP, this discrepancy may be attributed to those studies primarily involving healthy adults without accounting for variables such as hepatic esterase levels, which were not assessed in this instance. Furthermore, in this case, we were limited to measuring blood levels at only two points following ERCP. Had more data points been available, a more precise determination of the elimination half-life could have been achieved.

Regarding haemodialysis for beta-blocker intoxication, it has been shown that most beta-blockers are not dialysable.[16] Similarly, arotinolol has been reported to maintain good antihypertensive effects in patients undergoing maintenance dialysis, indicating that dialysis has little impact on serum levels.[17] In this case, the patient initially presented with acute kidney injury, which rapidly improved with the use of vasopressors to maintain haemodynamics. Consequently, the improvement in the estimated glomerular filtration rate did not contribute to the reduction of arotinolol blood levels, suggesting that biliary obstruction was the primary cause (figure 4).

In our patient, vasopressor management involved the use of norepinephrine and dopamine in combination for the first

48 hours post admission. However, maintaining the heart rate was challenging. The initiation of isoproterenol led to a rapid increase in heart rate. Although blood levels of arotinolol gradually decreased, reducing isoproterenol to 0.01 µg/kg/min resulted in recurrent bradycardia, indicating that isoproterenol significantly contributed to the stabilisation of haemodynamics. Considering the mechanism of action, isolated beta-receptor stimulation may be preferable for prolonged effects of beta-blockers. Comparative studies of dobutamine and isoproterenol indicate that, although dobutamine is expected to have a positive inotropic effect, it is inferior to isoproterenol in terms of positive chronotropic effects.[18] In animal experiments, it has been reported that dobutamine did not increase the heart rate until the dose was increased to 30 µg/kg/min, whereas isoproterenol increased the heart rate at just 0.02 µg/kg/min.[19] However, dobutamine is typically selected as the first-line therapy due to the beta-2 receptor stimulation by isoproterenol, which lowers systemic vascular resistance and subsequently reduces mean arterial pressure.[20]

Drugs with alpha-receptor stimulation effects, such as norepinephrine or dopamine (alpha agonists), are also often chosen. However, there are reports of patients on beta-blockers experiencing significant vasoconstriction and severe hypertension due to excessive alpha-receptor stimulation when epinephrine is administered.[21] Therefore, it is generally preferable to select medications that primarily target beta-receptors. Despite administering dopamine at 10.7 µg/kg/min with minimal effect, isoproterenol proved beneficial for heart rate management in this case.

Concerning the timing of ERCP, a CT scan without intravenous contrast is insufficient for evaluating the cause of distal bile duct stenosis. The differential diagnosis includes gastrointestinal cancers such as pancreatic head cancer, cholangiocarcinoma, gallbladder cancer, and duodenal papilla cancer, as well as distal bile duct stenosis caused by lymph node metastases from malignant diseases or malignant lymphoma. These conditions require markedly different treatment approaches.[22] As a result, EUS was initially Performed for precise localisation and diagnosis, followed by ERCP for bile duct decompression. During this interval, if cholangitis emerged or bradycardia management proved challenging, emergency ERCP would be contemplated in consultation with the gastroenterology team. In this instance, the natural elimination of arotinolol was ongoing, and vasopressors were being tapered, allowing for elective intervention. In cases of cholestasis, if adverse events occur with bile-eliminated drugs such as arotinolol, early ERCP to expedite drug elimination is recommended.

Learning points

- There have been reports of arotinolol causing bradycardia.
- Cholestasis can lead to cardiogenic shock with bradycardia by delaying the elimination of arotinolol.
- Isoproterenol may be effective in managing bradycardia caused by beta-blockers.
- Performing endoscopic retrograde cholangiopancreatography (ERCP) significantly reduced the elimination half-life of arotinolol.
- The timing of ERCP should follow an evaluation of the obstruction mechanism using endoscopic ultrasound with stable haemodynamics.

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