Meropenem-induced vanishing bile duct syndrome: A case report

Alexandr Zubarev1, Kavi Haji1,2, Matthew Li3, Ravindranath Tiruvoipati1,2 and John Botha1,2

Abstract
Vanishing bile duct syndrome (VBDS) refers to a group of acquired disorders associated with progressive destruction and disappearance of the intrahepatic bile ducts. We report a case of meropenem-induced VBDS in a patient who had undergone surgical repair of a ruptured abdominal aortic aneurysm. Meropenem was used to treat Serratia marcescens isolated from blood, urine, sputum, and wound swab cultures. The patient developed severe mixed liver injury with no obstruction noted in radiological imaging. Because of the patient’s increasing serum bilirubin level, VBDS was suspected and the meropenem was therefore changed to ciprofloxacin on postoperative day 18. Although the bilirubin level decreased, meropenem was restarted 3 days later because of clinical concerns regarding worsening fever and sepsis. Restarting meropenem was associated with an immediate increase in the serum bilirubin level. This further increase in bilirubin after reintroduction of meropenem strongly suggested meropenem-induced VBDS. The antibiotic therapy was changed from meropenem to ciprofloxacin and metronidazole, leading to a dramatic decrease in the bilirubin level to normal within a few weeks. In patients receiving meropenem, VBDS as a cause of deranged liver function and cholestasis should be considered after ruling out mechanical and other probable causes of liver injury.

Keywords
Meropenem, cholestasis, hyperbilirubinemia, hepatocellular injury, vanishing bile duct syndrome, bilirubin

Date received: 22 February 2020; accepted: 8 June 2020

1Department of Intensive Care Medicine, Frankston Hospital, Frankston, VIC 3199, Australia
2School of Public Health, Faculty of Medicine, Nursing and Health Sciences, Monash University, VIC 3800, Australia
3Department of Pharmacy, Frankston Hospital, Frankston, VIC 3199, Australia

Corresponding author:
Ravindranath Tiruvoipati, Department of Intensive Care Medicine, Frankston Hospital, 2 Hastings Road (PO Box 52), Frankston, Victoria 3199, Australia.
E-mail: travindranath@hotmail.com
Introduction

Vanishing bile duct syndrome (VBDS) refers to a group of acquired disorders associated with progressive destruction and disappearance of the intrahepatic bile ducts, leading to cholestasis and potentially life-threatening liver failure. VBDS has been associated with multiple causes, including congenital and genetic diseases, neoplasms, infections, and drugs. However, the pathogenesis of VBDS remains incompletely understood. We herein present a case of suspected VBDS following therapy with meropenem and a review of the literature.

Written informed consent was obtained from the patient’s caregiver for publication of this case report. Local ethics committee approval was not required for this case report because it presents anonymous data that were routinely collected and were not used for investigational research.

Case presentation

A 79-year-old man of German descent was brought to the hospital by ambulance after he had developed sudden-onset abdominal pain and collapsed at a local shop. He was found pale and hypotensive on site (blood pressure of 65/40 mmHg) and bradycardic with a heart rate of 40 to 50 beats/minute (slow atrial fibrillation). The patient was rushed to the operating room for open exploratory laparotomy, which revealed a ruptured infrarenal abdominal aortic aneurysm. Open repair of the aneurysm was successfully performed. During the procedure, the patient had significant blood loss with the cell saver returning 5.5 L of blood. He received 6 units of packed cells, 4 units of fresh-frozen plasma, 6 units of cryoprecipitate, 1 pooled bag of platelets, and 4 L of crystalloids. Postoperatively, the patient was brought to the intensive care unit (ICU) intubated and requiring a high dose of vasopressors. Repeated bedside transthoracic echocardiography revealed a normally functioning heart with no significant ventricular or valvular abnormality.

The patient had a medical history of hypertension and benign prostatic hypertrophy. His preadmission regular medications were atorvastatin, amlodipine, and dutasteride-tamsulosin. The patient had a documented allergy to penicillin in the form of a rash.

The patient remained unstable postoperatively. He developed acute kidney injury and mild abdominal hypertension requiring sedation and paralysis. He did not tolerate enteral feeding and received full total parenteral nutrition. He was extubated on postoperative day 10; however, he was reintubated a few hours later because of worsening respiratory failure. On the same day, the patient developed signs of sepsis including fever and leukocytosis, and he later became unstable and required vasopressors. Because the source of infection was unclear, meropenem and vancomycin were commenced, and Serratia marcescens was subsequently isolated in several consecutive blood cultures. The bacterium was sensitive to meropenem, ciprofloxacin, and co-trimoxazole and resistant to penicillins and cephalosporins. The same pathogen was also isolated in urine and sputum cultures. The same pathogen further grew in a wound swab culture taken 2 days later. The patient’s hemodynamic and renal function eventually improved; however, he remained ventilator-dependent and was encephalopathic. Therefore, he underwent a tracheostomy on postoperative day 14.

The patient thereafter developed hyperbilirubinemia as well as mildly deranged liver transaminase levels and biochemical markers of cholestasis. These abnormalities were attributed to bile duct obstruction despite lack of evidence of cholelithiasis or dilatation of the biliary ducts on abdominal computed tomography (Figure 1) or ultrasound imaging. The bilirubin continued to
rapidly increase to 200 μmol/L. Endoscopic retrograde cholangiopancreatography (ERCP) and subsequent transcutaneous hepatic cholangiography were performed. The imaging and ERCP (Figure 2) demonstrated widely patent right and left hepatic and common biliary ducts with smooth tapering toward the ampulla. The cystic duct was also patent. Nevertheless, a stent was inserted in the common bile duct during ERCP, and an 8.5-French external biliary drain was also inserted under fluoroscopic guidance by an interventional radiologist (Figure 3).

The patient did not improve following cholangiography and insertion of the external biliary drain, and his bilirubin level continued to rise despite the biliary drain producing up to 600 mL of bile. The patient’s direct bilirubin level reached 300 μmol/L with a conjugated bilirubin level of 169 μmol/L by postoperative day 18. Repeated abdominal computed tomography showed no evidence of an intra-abdominal collection, bleeding, or other new pathology. A subsequent cholangiogram demonstrated that the stent and bile ducts remained widely patent. On postoperative day 18, the meropenem was changed to ciprofloxacin because of suspicion of VBDS (Figure 4). This was followed by a decrease in the bilirubin level during the following few days. However, meropenem was restarted 3 days later because of clinical concern regarding worsening fever and
sepsis, and this therapy was associated with an immediate increase in the serum bilirubin level. This association of a further increase in the bilirubin level after reintroduction of meropenem (Figure 4) was strongly suggestive of meropenem-induced VBDS. The antibiotic therapy was changed to ciprofloxacin and metronidazole, leading to a dramatic decrease in the bilirubin level, which eventually normalized. Other medications that the patient received are summarized in Table 1. Changes associated with other liver enzymes are presented in Figures 5 and 6.

The biliary drain was plugged and removed with time. The patient had a prolonged ICU stay, remaining ventilator-dependent for a long period. However, he gradually improved and was decannulated and discharged from the ICU after a 3-month stay without significant organ dysfunction. The patient was treated in the general ward and ultimately discharged from the hospital.

**Discussion**

VBDS is characterized by progressive destruction and disappearance of the intrahepatic bile ducts, resulting in cholestasis and ductopenia. It involves a spectrum of hepatic injuries that are predominantly cholestatic. The injuries are attributed to necrosis, apoptosis, and mitochondrial damage to cholangiocytes. If not treated, the injuries result in further bile duct loss and may lead to secondary cirrhosis, liver failure, transplantation, or death.
The exact mechanism of VBDS is not entirely clear. However, it is associated with multiple conditions such as infection, primary liver cirrhosis, sclerosing cholangitis, graft-versus-host disease, paraneoplastic syndromes, idiopathic conditions, and administration of certain drugs. Multiple drugs have been reported to cause

Table 1. Regular medications that the patient received prior to and during the episode of hyperbilirubinemia.

| Medication     | Dose          | Treatment duration          |
|----------------|---------------|-----------------------------|
| Clindamycin    | 600 mg q8h    | POD1–3                      |
| Meropenem      | 1 g q8h       | POD10–18 POD21–23           |
| Metronidazole  | 500 mg q12h   | POD23–38                    |
| Ciprofloxacin  | 400 mg q12h   | POD23 to discharge from hospital |
| Vancomycin     | Variable*     | POD10–15                    |
| Paracetamol    | 1 g q8h       | POD1–5                      |
| Others: sedation, analgesia, TPN, etc. | Continuous infusion during admission, variable agents, no clear association with bilirubin levels |

POD, postoperative day; q12h, every 12 hours; q8h, every 8 hours; TPN, total parenteral nutrition.

*Doses of vancomycin varied from 1 g q12h to 500 mg q24h depending on the vancomycin trough levels measured in accordance with the hospital protocol.

Figure 5. Alanine transaminase and aspartate transaminase levels during admission.
Dotted lines:
1. Postoperative day 10: Meropenem was commenced
2. Postoperative day 18: Meropenem was changed to ciprofloxacin
3. Postoperative day 21: Meropenem was restarted
4. Postoperative day 23: Meropenem was discontinued
bile duct injury, which mostly affects the biliary epithelium of the interlobular ducts, thereby causing an inflammatory response directed at cholangiocytes.\(^1\) VBDS is an idiosyncratic reaction in which cholangiopathy results from immunologically mediated injury to the bile ducts in the form of an aberrant T-cell-mediated hypersensitivity reaction to the administered drug.\(^1\) This is followed by a prolonged period of cholestasis, leading to bile duct destruction and eventual bile duct loss.\(^1,2\) The onset of illness can occur from 3 to 155 days\(^6\) after commencement of the drug. Without treatment, bile duct loss becomes irreversible, leading to extensive ductopenia and biliary cirrhosis. However, withdrawing the drug with provision of supportive treatment leads to biliary epithelial regeneration with achievement of clinical recovery over weeks or months.\(^6\) The outcome often depends on the underlying cause and degree of bile duct loss. As a result, patients should be regularly followed up with liver biochemical tests.

Various drug classes that can potentially cause VBDS have been listed in the LiverTox database.\(^3\) The implicated drugs that are routinely used in the ICU include penicillins, cephalosporins, sulfonamides, macrolides, lincomycins, and antifungal agents; carbapenem was added following one case report.\(^5\) Other reported drugs include anticonvulsants, antipsychotics, lipid-lowering agents, nonsteroidal anti-inflammatory drugs, metoclopramide, omeprazole, and cardiovascular agents (hydrochlorothiazide and enalapril).\(^3\)

**Figure 6.** Gamma-glutamyl transferase and alkaline phosphatase levels during admission. Dotted lines:
1. Postoperative day 10: Meropenem was commenced
2. Postoperative day 18: Meropenem was changed to ciprofloxacin
3. Postoperative day 21: Meropenem was restarted
4. Postoperative day 23: Meropenem was discontinued
Wasuwanich et al. reviewed 37 publications of drug-induced liver injury-related VBDS and found that antibiotics, anticonvulsants, and nonsteroidal anti-inflammatory drugs were the most common drug-related culprits. Drugs that have been more frequently reported to cause VBDS on the LiverTox database include amoxicillin, amoxicillin/clavulanate, ciprofloxacin, levofloxacin, moxifloxacin, azithromycin, carbamazepine, lamotrigine, phenothiazines, allopurinol, and ibuprofen. Similarly, amoxicillin-clavulanic acid, azithromycin, and fluoroquinolones were the most common drugs associated with ductopenia in another study.6 Meropenem is an uncommon causative agent. We found only one reported case of meropenem-induced VBDS in the literature.5 Similar to our case, that patient developed mixed hepatocellular and cholestatic liver injury with jaundice and pruritus after commencing treatment with meropenem. The patient recovered completely after cessation of the drug. However, onset and recovery were significantly delayed compared with our patient.

Unlike the above-mentioned case report,5 liver biopsy was not performed on our patient. Nonetheless, VBDS was diagnosed in our patient after extrahepatic obstruction was excluded by radiological imaging, including ERCP and transcutaneous hepatic cholangiography, and based on the temporal correlation of the worsening bilirubin level with reintroduction of meropenem. Furthermore, the nature of the cholestatic injury in our patient was consistent with recently published criteria by the Drug-Induced Liver Injury Network protocol.6 The Naranjo adverse drug reaction score in our patient was also >8, which is highly suggestive of a drug reaction.8 Notably, our patient was allergic to penicillin, which caused him to develop a rash. However, the association between penicillin-induced allergic rash and meropenem-induced idiosyncratic cholestatic liver injury has yet to be explored. Considering both our patient and previously published case reports, meropenem-induced VBDS should be considered when liver injury and cholestasis develop after meropenem commencement. The level of suspicion must be further heightened when more common causes of cholestasis, such as biliary obstruction, are excluded. Early recognition of this association and cessation of the causative agent are paramount to achieving a successful outcome.

**Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

**Funding**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**ORCID iD**

Ravindranath Tiruvoipati https://orcid.org/0000-0003-3800-902X

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