Meropenem induced mixed hepatocellular and cholestatic hepatitis: A report of two cases

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ABSTRACT

Drug-induced liver injury (DILI) is common clinic issue in clinical practice and might be induced by almost all drugs. Antibiotics (especially beta-lactams) are one of the leading cause due to their widespread use. Albeit rare, meropenem may cause DILI, even shortly after its administration. Here we report our experience of two cases with cholestatic hepatitis that occured after meropenem use. In the differential diagnosis of liver enzyme abnormalities after meropenem treatment, physicians should also prompt suspicion of an adverse drug reaction.

Introduction

Meropenem is a widely used broad spectrum carbapenem antibiotic and its most common side effects that have been reported to date are constipation (1-7%), diarrhea (4-5%), rash (2-3%), and nausea and vomiting (1-4%) (1). Occasionally, hepatitis linked to meropenem treatment has also been reported as an adverse effect. However, because it is quite rare, a correct diagnosis can only be made after exclusion potential etiological factors, as most of patients requiring meropenem treatment are multimorbid and under increased risk of adverse effects or drug reactions.

Presentation of Case 1

A 78-year-old woman with known hypertension, atrial fibrillation, chronic obstructive pulmonary disease and coronary artery disease was admitted to our outpatient clinic with recent onset cough, fatigue, dyspnea, and fever. Her medications included metoprolol 100 mg/day, dabigatran 150 mg/day, ramipril 5 mg/day, lercanidipin 10 mg/day, budenoside inhaler 400 mcg/day, formoterol 24 mcg/day. Physical examination revealed tachypnea, mild hypoxia, and widespread rhonchi. The blood test results at the time of admission were as follows; hemoglobin: 9.97g/dl (12-16), white blood cell count (WBC): 14.6x103cells/mm3 (4.8-10.8x103), neutrophil count:4.5x103cells/mm3 (1.8-7.7x103), platelets: 200x103cells/mm3 (150-450x103), creatinine: 0.67mg/dL (0.66 – 1.09), urea: 32mg/dL (17 - 43), total bilirubin: 1.34 mol/l (0.3–1.2), alanine aminotransferase (ALT): 46IU/l (10–28), aspartate aminotransferase (AST): 32IU/l(9–36), alkaline phosphatase (ALP): 25IU/l (40–120), gamma-glutamyl transferase (GGT): 44IU/l (0–38), lactate dehydrogenase (LDH): 65IU/L (0–247), serum albumin: 3.4g/l (3.5–5.2), erythrocyte sedimentation rate (ESR): 124mm/h(0–30). Chest X-ray shows left lobar infiltration. The patient was diagnosed with pneumonia and hospitalized. Meropenem 1000 mg q8h was administered. On the 11th day of the treatment, patient began to suffer from dark urine, pale stool and pruritus. Laboratory tests showed all liver and cholestatic enzymes were elevated when compared to the day of hospitalization (Table 1). Markers of viral hepatitis and autoimmune liver diseases were negative. Liver ultrasonography revealed no biliary obstruction. Abdominal magnetic resonance imaging and magnetic resonance cholangiopancreatography ruled out primary scle-

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Table 1. The treatment days and laboratory results

Meropenem day	ALP	GGT	AST	ALT	LDH	T.Bil.
0	25	44	32	46	65	1.34
11*	1554	575	288	447	341	4.16
14	1002	500	198	304	326	3.84
21	552	312	114	156	201	3.12

ALP: alkaline phosphatase (normal range:40-120 U/L); GGT:gammaglutamyl transferase (normal range:0-38 U/L); ALT:alanine aminotransferase (normal range: 10-28U/L); AST:aspartate aminotransferase (normal range: 9-36U/L); LDH:lactate dehydrogenase (normal range: 0-247U/L); T. bil/total bilirubin (normal range: 0.3-1.2mg/dL). *Meropenem is discontinued

rosing cholangitis and infiltrative diseases. This condition was thought to have been induced after initiation of meropenem. Thus, meropenem was discontinued and ursodeoxycholic acid 750 mg/day was prescribed. Although total bilirubin and liver enzymes reduced significantly during the follow-up, their levels remained above the values recorded on admission. However, further procedures including a fine needle biopsy from the liver were postponed due the available literature that the liver panel may take months to return to normal range.

Presentation of Case 2

An 81-year-old male with a history of Alzheimer's disease, diabetes mellitus and benign prostate hyperplasia (using urethral catheter) was admitted to our emergency clinic with fever, dysuria and deterioration in general condition for a few days. His current medications were repaglinide 3 mg/day, memantine 10 mg/day, trazodone 50 mg/day and quetiapine 25 mg/day. Vitals were as follows; blood pressure (BP): 85/55 mmHg, heart rate (HR): 130 beats/min, and fever 38.4°C. The blood test results at the time of admission were as follows, hemoglobin: 11.7g/dl (12-16), WBC: 19.7x103cells/mm3 (4.8-10.8x103), neutrophil count: 11.2x103cells/mm3 (1.8-7.7x103), platelets: 317x103cells/mm3 (150-450x103), fasting glucose: 153mg/dL (75 – 106), creatinine: 0.96 mg/dL (0.66 – 1.09), total bilirubin: 1.73mol/l (0.3–1.2), ALT: 73IU/l (10–28), AST: 75IU/l (9–36), ALP: 175IU/l (40–120), GGT: 45IU/l (0-38). The patient was diagnosed with sepsis due to urinary tract infection and hospitalized. Following adequate fluid support, patient's BP and HR returned to normal range (BP: 110/75mmHg, HR: 86). Meropenem 1000 mg q8h was started. On the 3th day of treatment, the patient suffered from dark urine and jaundice. Laboratory tests showed all AST, ALT, ALP, GGT, and total bilirubin levels were elevated (Table 2). After exclusion of potential etiological factors with ultrasound examination of liver and laboratory tests including viral markers for hepatitis, the patient was diagnosed with drug-induced hepatitis. Meropenem treatment was switched to piperacillin-tazobactam 4.5 g q8h. After withdrawal of meropenem, liver and cholestatic enzymes reduced significantly to almost normal range. However, the patient died on the 24th day of hospitalization due to complications of sepsis.

Discussion

Drug-induced liver injury (DILI) is presents with three injury patterns; (i) hepatocellular (cytotoxic) injury, (ii) cholestatic injury, (iii) mixed (including both injury patterns)(2). The differential diagnosis is made regarding patient's R value which is calculated by dividing the patient's ALT level by the ALP, using the upper limit of the normal range (ULN) as follows: R = (ALT ÷ ALT ULN) ÷ (ALP value ÷ ALP ULN). While an R value bigger than 5 is indicating hepatocellular injury, an R value smaller than 2 is indicating cholestatic injury. Also, an R value between 2 and 5 is indicating mixed pattern(3). Serum bilirubin levels and tests for synthesis functions may be elevated in all patterns. According to R values of our both cases, injury patterns were defined as cholestatic injury (R1:1.23, R2:0.44). In order to reveal the association of liver injury with a medication, all other causes need to be ruled out. However, even if all necessary laboratory and imaging tests were performed, existence of comorbidities, hypotension and possible unknown baseline liver disease might confound diagnosis in many cases such as we presented. In such cases, suspected medication(s) should be discontinued and liver enzymes should be monitored closely. As seen in our both cases, if the patient's liver enzymes improve during the follow-up period, this finding suggests that liver injury is mainly associated with medication.

Although most drugs may cause DILI, antibiotics (especially beta-lactams) are the leading cause due to their widespread use (4). However, meropenem associated DILI has not been shown to a common issue. In most cases, hepatic injury occurs 1 to 3 weeks after the drug administered (5). However, in our second case above, cholestatic hepatitis occurred on the 3rd day. This interesting finding suggests that DILI might also occur as an early adverse effect of meropenem. Thereby, symptoms and liver enzymes should be screened closely after such a medication initiated (6).

Conclusions

Albeit rare, meropenem may cause DILI, even shortly after its initiation. In the differential diagnosis of liver enzyme ab-

Table 2. The treatment days and laboratory results

Meropenem day	ALP	GGT	AST	ALT	T.Bil.
0	175	45	75	73	1.73
3*	662	370	183	68	25.72
6	325	189	137	58	17.44
13	215	119	67	22	2.37

ALP: alkaline phosphatase (normal range:40-120 U/L); GGT: gammaglutamyl transferase (normal range:0-38 U/L); ALT: alanine aminotransferase (normal range: 10-28U/L); AST:aspartate aminotransferase (normal range: 9-36U/L); LDH:lactate dehydrogenase (normal range: 0-247U/L); T. bil/total bilirubin (normal range: 0.3-1.2mg/dL). *Meropenem is discontinued

normalities after meropenem treatment, physicians should also prompt suspicion of an adverse drug reaction. Our experience showed both early and late improvement of elevated liver enzymes after withdrawal of meropenem, requiring no further interventions.

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Conflict of Interest

Authors are requested to disclose any conflict of interest related to their submission. This must include any financial, personal or other relationships within three years of beginning the submitted work. When there is no such relationship, the authors must type “The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.”.

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