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Case Report

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IV MEROPENEM CAUSED MARKED ELEVATION OF ALT & ALP IN CRITICALY ILL PATIENT: A CASE REPORT

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ABSTRACT

A 37 year old Malay man admitted in GICU for intra-abdominal sepsis secondary to perforated appendix and had undergone multiple laparotomy. He had no known past-medical history and his father was died of colon cancer. In the GICU, he was treated with high dose of IV Meropenem for two weeks. There were sudden increased from baseline in patient alanine transaminase (ALT) and alkaline phosphatase (ALP) five days after the initiation of therapy. Naranjo causality assessment was 5, indicated probable adverse drug reaction. IV Meropenem was then stopped after two weeks from the initiation of therapy and it was noted that serum level of ALT and ALP were gradually decreased.

KEYWORDS: Meropenem, Liver enzymes, Alanine transaminase and Alkaline phosphatase.

1. INTRODUCTION

Drug therapy is a frequent cause of hepatic injury. In the United States, more than 50% of acute liver failure cases are secondary to drug induced liver injury.[1,2] In general more than 900 drugs, toxins and herbs have been reported to cause hepatotoxicity and drugs account for 20-40% of all instances of fulminant hepatic failure.[3] Hepatocyte damage may occur as a result of a direct toxic effect of the drug or its metabolites in a predictable and dose related phenomenon.[1] Liver injury may be categorized as hepatocellular injury, cholestatic injury,

or mixed. With hepatocellular damage, liver enzyme level elevation usually occurs before bilirubin and alkaline phosphatase levels increase.[4]

2. CASE PRESENTATION

A 37 year old Malay man admitted in General Intensive Care Unit (GICU) of Penang General Hospital for intraabdominal sepsis secondary to perforated appendix. He was referred from Mutiara Hospital, one of the private hospitals available in Penang. He had undergone four times laparotomy and subsequently developed septic shock before being transferred to GICU for ICU care. He had no known history of medical problems and was not on any medication indicated for chronic illnesses. Patient was also on prolonged ventilation, had twice failed extubation and was on tracheostomy. Other medical problems encountered while patient was in GICU were difficult sugar control, on prolonged total parenteral nutrition, opened abdomen and unresolved severe nosocomial sepsis with *Acinetobacter spp* as the causative microorganism.

He was treated with IV Meropenem after two weeks in GICU when other antibiotics which included IV Amikacin, IV Vancomycin, IV Cefoperazone/ Sulbactam and antifungal, IV Amphotericin B failed to resolved the infection. He was put on high dose of IV Meropenem which was 2g every 8 hours, regimen that usually recommended for meningitis.[5,6] Two days prior to initiation of IV Meropenem, liver function tests showed abnormal findings with a serum alanine aminotransferase (ALT) of 79 U/L (normal < 55 U/L), serum aspartate aminotransferase (AST) of 63 U/L (normal 5 – 34 U/L), serum alkaline phosphatase (ALP) of 352 U/L (normal 40 – 150 U/L), total bilirubin 149 µmol/L (normal 3 – 21 µmol/L) and serum albumin 23 g/L (normal 35 – 50 g/L). Coagulation profile (PT, INR and ApTT) was normal. Five days after the initiation of therapy with IV Meropenem, there was a sudden increased in the serum ALP and ALT. ALP was 361 U/L and ALT 203 U/L. From there on, ALP and ALT were both gradually increased until IV Meropenem was stopped on day 14, two weeks after the first dose. ALP and ALT was 598 U/L and 245 U/L respectively one day prior to discontinuation of meropenem. Total bilirubin level was not affected and remained constant. The liver function tests showed serum level of ALP and ALT began to improve and gradually decreased four days after IV meropenem was ceased. While in CICU, patient also developed jaundice, on and off temperature spiking and restlessness.

3. DISCUSSION

Drug-induced liver disease occurs as several different clinical presentations and covers a wide spectrum: from asymptomatic liver test abnormalities to symptomatic idiosyncratic reactions, allergic hepatitis, toxic hepatitis, chronic active toxic hepatitis, toxic cirrhosis, liver vascular disorders.[7,8] The mechanisms of drug-induced liver diseases are diverse, representing many phases of biotransformation, and are susceptible to genetic polymorphism and some drugs the mechanism remain unknown.[7,8] Monitoring for drug-induced liver disease must be tailored to the drug and the patient's potential risk factors.[7] Since there are no specific diagnostic tests for drug-induced liver disease or a means to single out an implicated drug, the diagnosis of drug hepatotoxicity remains difficult.[7,9]

It was well reported that meropenem can cause abnormalities or increase in liver enzymes.[10,13] In an article by John F. Mohr III, it was reported that the incident of increased ALT and AST are 3.7% and 2.9% respectively in patient receiving meropenem.[12] In a pharmacokinetics study by Annete Bedikian *et al.*, 1993 it was concluded that the most common associated adverse drug reactions to meropenem were diarrhea and increased liver enzymes. They found out that among the 12 patients included in their study, three patients had increases in aspartate aminotransferase and alanine aminotransferase, and two patients had increases in alkaline phosphatase. Dose of meropenem used in this study was only 1g every 8 hours.[11], 50% less than the dose used in this case report. While meropenem was thought to be the most likely cause of the sudden elevation in ALT and ALP, some other drugs were also considered may contributed in this event. IV Amphotericin and IV Cefoperazone/ Sulbactam are two drugs that also reported to cause elevation in ALT and ALP[5]. Further investigation found out that IV Amphotericin B was discontinued two days after the commencing of meropenem therapy, Amphotericin B was administered for 14 days in this patient and all the while ALP and ALT were remained constant albeit higher than the upper normal limit. IV Cefoperazone/Sulbactam was also stopped after almost two weeks (13 days) of therapy on the day meropenem was planned to be administered and again, ALP and ALT although above the normal range still remained constant (ALT: 71–88 U/L, ALP: 208–352 U/L). However, according to one prospective study drug-induced liver injury in the US, an important finding was that more than one agent was implicated in causing liver injury in ≈ 20% of cases.[8] Based on these findings, both drugs cannot be completely excluded as the culpable agents. In a randomized, controlled clinical trial on meropenem versus imipenem/cilastatin for the treatment of bacterial infections in Chinese patients, adverse drug reactions were observed in 7 patients of the meropenem group which consist of skin rash in 2

patients, transient elevation of alanine aminotransferase (ALT) level in one, elevation of ALT and aspartate aminotransferase (AST) in 2 and elevation of ALT, AST and urea in one patient.[13] It was noted that the meropenem dose used in this clinical trial was 500mg every 12 hours or (1 g every 12 hours if necessary)[13], much lower than the dose used in this case. Most studies or clinical trials of meropenem were using dose in the range of 0.5g – 1g every 8 hours. In one pharmacokinetics and pharmacodynamics study of meropenem, results showed that if doubling of the dose from 0.5 g to 1.0 g it will caused in a two-fold increase and doubling from 1.0 g to 2.0 g resulted in a 2.4-fold increase in *C*max.[14] Some pattern of hepatic damage are dose-related, metabolite-related or idiosyncratic.[11] However, some article reported that the incidence or the nature of meropenem adverse effects do not have relationship with the dose administered.[6] Three cases of cystic fibrosis adult patients had been reported to received a high-dose and prolonged infusion of carbapenems (case 1-meropenem, 3g every 8 hours, case 2 & 3-doripenem) and were found out that they tolerated these regimens well, had no detrimental changes in baseline laboratory values and achieved peak concentrations consistent with lower doses when administered as standard 0.5 h infusions.[15] Since there is limited data on the correlation between meropenem adverse drug reactions and dosage administered or plasma concentration in the form of randomized, double-blind controlled study, the high dose used in this patient should not be ruled out as one of the factors that may be precipitated the liver enzymes abnormalities.

The best and most important technique for assessing and monitoring drug-induced liver disease is the patient's history. In this case, the existing abnormalities of liver enzymes (ALT, ALP, AST and LDH) beyond the normal range most likely induced by IV Amphotericin B or IV Cefaperazone/Sulbactam as discussed earlier. It may also caused by the administration of total parenteral nutrition for periods greater than 1 week that also reported be able to induce cholestatic changes and nonspecific enzyme elevations in some patients.[7] Two days after meropenem was stopped, liver functions test was repeated and it was found out that the level of both ALT and ALP decreased. On the fifth day after the discontinuation of therapy, further reduction in ALT and ALP were noticed. These findings were on par with one of the criterions in drug-induced liver disease diagnosis which is the disappearance of liver abnormalities after withdrawal of the treatment. It is very suggestive when clinical features disappear within a few days and when aminotransferases decrease by more than 50% in a week. Usually, complete recovery is obtained within a few weeks.[9] Apart from that, there are certain patterns of enzyme elevation that have been identified and can be helpful in

helping to determine the type of hepatic lesion.[7] Hepatocellular injuries are marked by elevations in transaminase that are at least two times normal. If the alkaline phosphatase (ALP) is also elevated, a hepatocellular lesion is still suspected when the elevation of ALT is notably higher than the elevation of ALP. If the magnitude of elevation is nearly equal between ALT and alkaline phosphatase, the lesion is likely cholestatic.[7] In this case, the injury was most probably cholestatic since the elevation of ALT and ALP were almost equal. Other method to determine the type of liver injury is by using the classification according to the International Consensus Meeting criteria, which use ALT and alkaline phosphatase (ALP) activity, expressed as a multiple of the upper limit of normality, to determine the ratio (R) of ALT/ALP. The pattern of liver damage is hepatocellular when R >5, cholestatic when R < 2, and mixed when R > 2 but < 5.[16] In this case, R was < 5 signified cholestatic type of injury. In summary, liver injury was considered if there was an increase over 2 N (upper limit of normal range) in alanine aminotransferase (ALT) or conjugated bilirubin or a combined increase in aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin, provided one of them was above 2 N.[16] Based on these criteria, this patient definitely had obvious liver injury.

Other criterion is the time interval between the beginning of the suspected treatment and the onset of liver injury; this varies widely. It is considered suggestive when the interval is between 1 week and 3 months.[7, 9] It was first noted that the sudden increased in ALT and ALP in this patient was on the 6th day after the beginning of meropenem. Liver biopsy is not necessary in most cases but it may also contribute to the diagnosis.[7, 9] It is indicated 1 to eliminate other causes of liver injury; 2 to show lesions suggestive of drug-induced liver injury; 3 to define lesions for drugs with so far unknown hepatotoxicity.[8] Unfortunately, there was no liver biopsy done in this patient, thus the exact type of liver injury and whether it was definite caused by meropenem was remain unknown.

4. CONCLUSION

Alteration in liver function test is a rare but increasingly recognized disorder involving the progressive destruction of intrahepatic bile ducts and acute liver damage. A high index of suspicion is necessary to diagnose hepatic injury and other types of drug-induced liver injury. Although many drugs, including meropenem and other antibiotics, are generally well tolerated, clinicians should consider the monitoring of liver enzymes in patients taking multiple drug therapy.

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6. CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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Nil.

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