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Meropenem - A Potential Cause of Cholestasis in Neonates

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Abstract: ***Drug induced liver injury (DILI) is an important cause of acute and chronic liver diseases in young children. Antibiotics are known to cause drug induced liver injury, predisposing neonates to the risk of liver diseases. Meropenem is a broad-spectrum antibiotic of the carbapenem beta-lactamase group with a good spectrum of activity against gram-negative and gram-positive organisms. It is commonly used for complicated infections in neonates in intensive care units. Although a safe antibiotic, it however is known to cause mild elevation in liver enzymes, usually after 14 days of its use. We report a case of full-term neonate with sepsis developing self-limiting cholestasis with elevated liver enzymes on Day12 of meropenem therapy. This report is to create awareness about the uncommon adverse effect, cholestatic jaundice with elevation of liver enzymes, following the use of meropenem. It is important because of the widespread use of meropenem in neonates due to its safety profile and increasing resistance to commonly used antibiotics.***

Keywords: Antibiotic adverse effect, Drug induced liver injury, Hepatotoxicity, Meropenem, Neonatal cholestasis

1. Introduction

Neonatal cholestasis is an important cause of chronic liver disease in young children. It results due to impaired formation or excretion of bile. The various causes of neonatal cholestasis are biliary atresia, idiopathic neonatal hepatitis, metabolic disorders and genetic diseases, and drugs. Drug induced liver injury is an important cause of liver disease in neonates. Parenteral nutrition and antibiotics are well known causes of drug induced liver enzymes.1

Meropenem is a carbapenem antibiotic with a broad spectrum of activity against gram negative and many gram-positive organisms. It is commonly used for complicated infections in neonates and children in intensive care units. It has a good penetration in most body fluids including cerebrospinal fluids, making it a favourable choice for the treatment of meningitis. It binds less to plasma proteins. Meropenem is a second line agent especially against extended beta lactamase producing E. coli and Klebsiella pneumoniae. It is used for complicated skin and skin structure infections, complicated intra-abdominal infections and bacterial meningitis. The mild transient increase in aminotransferase levels are reported with the use of meropenem and may rarely result in cholestatic liver injury. Multiple mechanisms of antibiotic-induced liver injury have been implicated, including apoptosis activated by TNF-alpha, inhibition of

Mitochondrial function and neoantigen formation.2

There is limited literature available on meropenem causing cholestatic liver injury in neonates. We report a case of a full termneonate with Klebsiella pneumoniae sepsis developing neonatal cholestasis due to meropenem. Through this case report we want to emphasize the important problem of drug induced liver injury in neonates due to meropenem.

2. Case Summary

A full-term male neonate born to a primigravida mother by vaginal delivery was admitted to the neonatal intensive care unit for Klebsiella pneumoniae sepsis. The child was born to non-consanguineous parents and was first by birth order. The antenatal and perinatal periods were unremarkable. The child had a head circumference of 36 cm and a length of 51 cm and his weight was 2.6 kg. The child received intravenous meropenem at a dose of 20 mg/kg every 8 hours as per the culture sensitivity report for a period of 14 days.

On day 12 of meropenem administration, the child developed jaundice and was evaluated for the same. On abdominal examination, hepatomegaly with a liver span of 6.8 cm was present. Other systemic examinations were normal. The child was passing yellow-coloured stools. On investigation, he had a hemoglobin level of 16 gm/dl, total leukocyte count of 15, 000 cells/µL, platelet count of 212, 000/µL and his C-reactive protein was 0.2mg/dl (normal range-<0.6 mg/dL). His liver function tests showed a total bilirubin of 16 mg/dl, conjugated bilirubin of 8.61 mg/dl, aspartate transaminase of 124 U/L (normal range-32-162U/L), alanine transaminase of 100 U/L (normal range-5-33 U/L), alkaline phosphatase of 226 U/L (normal range-90-237 U/L) and gamma-glutamyl transpeptidase of 268 U/L (normal range-23-219 U/L). The renal function test, serum electrolytes and thyroid profile was normal. His blood culture was sterile and his chest x ray was normal. His abdominal ultrasound was suggestive of an enlarged liver with altered echo-texture. The gallbladder and intrahepatic biliary tracts were visualised and normal. The liver biopsy was not done due to logistic reasons.

The possible diagnosis of cholestasis was excluded by detailed investigations. Drug-induced liver injury was therefore suspected secondary to meropenem. The child showed improvement clinically following discontinuation of meropenem as evidenced by laboratory investigations. The child was discharged on day 21 of admission. An informed consent was received from the family prior to documentation of this case report. On regular follow ups post discharge, the child showed a normal pattern of his liver function tests.

Table 1: Day wise Liver Function Test during hospital stay

	Day 0	Day 12	Day 14	Day 16	Day 20
Total Bilirubin	2.16	16	13.9	14.7	8
Conjugated Bilirubin	0.49	8.61	5.8	6.3	4.1
AST	66	124	329	434	316
ALT	38	100	144	173	152
GGT	28	268	302	396	211

Table 2: Liver function test on follow up visits

	Day 28	Day 45	Day 60	Day 80
Total Bilirubin	10	8.03	2	0.96
Conjugated Bilirubin	5.18	4.12	0.44	0.2
AST	224	196	103	42
ALT	104	90	60	38
GGT	196	110	68	72

3. Discussion

Meropenem is a beta-lactam carbapenem group antibiotic which binds to the penicillin-binding proteins and interferes with bacterial cell wall synthesis. It has a broad spectrum of activity against many gram-negative and gram-positive organisms. It is administered intravenously with the recommended dosage of 20 mg/kg/dose every 12 hours or 8 hours. It has renal excretion and is a generally well-tolerated antibiotic. The most common adverse effects are GI symptoms like diarrhoea, nausea, and vomiting.3 Meropenem is reported to cause mild, asymptomatic, transient serum aminotransferase elevation when it is used daily for more than 14 days and rarely requires dose adjustments or discontinuation.4 Though there are few case reports of meropenem induced cholestasis in adults, limited literature is available on meropenem induced cholestatic liver injury in neonates and hence we are reporting this case.

Drug induced liver injury is a serious cause of liver diseases in neonates. In the absence of pathognomonic clinical features and mild derangement of liver function tests, it is a diagnosis of exclusion.5 Its diagnosis is confirmed usually after clinical improvement following discontinuation of the drug. Antibiotics are the common drugs used in neonates and pose a potential risk for liver injury. Among antibiotics, amoxicillin-clavulanate is the most common drug that causes liver injury, however meropenem induced cholestasis and liver injury in neonates are rarely reported. A systematic review of literature shows one case series of a neonate developing neonatal cholestasis on Day 11 of meropenem and one on day 32 after meropenem use.6

The neonate in our case developed cholestasis with elevated liver enzymes on day 12 of meropenem therapy. The child showed clinical and biochemical improvement within a few days after meropenem discontinuation. After ruling out other potential common causes, we considered a diagnosis of drug induced liver injury caused by meropenem. Early recognition of drug-induced jaundice with liver injury is important and should be a part of differential diagnosis while managing neonates with abnormal liver function tests and jaundice. Clinicians should be aware of such adverse effects of meropenem since it is a widely used antibiotic in the hospital setting, especially in intensive care units.

4. Conclusion

Meropenem remains a useful antibiotic for serious infections in neonates known to cause mild elevation of liver enzymes with a good safety profile. It is important to keep in mind the possible adverse effects of meropenem in neonates who develop cholestatic liver injury. Therefore, we report this case to highlight the possibility of cholestatic liver injury after the use of meropenem in neonates.

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References

[1] Bhatia V, Bavdekar A, Matthai J, Waikar Y, Sibal A. Management of neonatal cholestasis: consensus statement of the Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics. Indian Pediatr.2014 Mar; 51 (3): 203-10. doi: 10.1007/s13312-014-0375-2. PMID: 24736908.

[2] 2. Faa G, Ekstrom J, Castagnola M, Gibo Y, Ottonello G, Fanos V. A developmental approach to drug-induced liver injury in newborns and children. Curr Med Chem.2012; 19 (27): 4581-94. doi: 10.2174/092986712803306385. PMID: 22876896.

[3] Cheung S, Bulovic J, Pillai A, Manoj T, Neeraj K. A case of meropenem-induced liver injury and jaundice. J Community Hosp Intern Med Perspect.2021 Jan 26; 11 (1): 143-144. doi: 10.1080/20009666.2020.1845929. PMID: 33552438; PMCID: PMC7850334.

[4] Tattersall T, Wright H, Redmond A. Meropenem-induced liver injury and beta-lactam cross-reactivity. BMJ Case Rep.2018 Nov 28; 11 (1): e227124. doi: 10.1136/bcr-2018-227124. PMID: 30567128; PMCID: PMC6301467.

[5] Fontana RJ, Seeff LB, Andrade RJ, Björnsson E, Day CP, Serrano J, Hoofnagle JH. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. Hepatology.2010 Aug; 52 (2): 730-42. doi: 10.1002/hep.23696. PMID: 20564754; PMCID: PMC3616501.

[6] Solarin, Adaobi&Olugbade, Olufunke. (2016). Meropenem Associated Prolonged Cholestasis in the Newborn: A Report of Two Cases. International Journal of Medical and Pharmaceutical Case Reports.7.1-5.10.9734/IJMPCR/2016/24618.

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