

Case Report

Possible cholestatic hepatitis with clindamycin therapy: A case report

Wettasinghe I.^{1*}, Samarasinghe S.M.², Puthra S.¹, Sugathapala A.G.H.¹

¹Colombo South Teaching Hospital, Kalubowila, Sri Lanka.

²Faculty of Medicine, University of Moratuwa, Sri Lanka.

Abstract

Introduction: Clindamycin is a lincosamide antibiotic that is effective against streptococci, staphylococci, and anaerobic bacteria. Though it predominantly undergoes hepatic metabolism, no dose adjustments are recommended for patients with hepatic dysfunction. Hepatotoxicity is a rare side effect and even though transient elevation of liver enzymes has been reported, there are very few cases of acute idiosyncratic liver injury. **Case Presentation:** A 49-year-old male from Sri Lanka, with no known comorbidities, was treated with oral clindamycin for left lower limb cellulitis. He was investigated for a low platelet count and was diagnosed to have chronic liver cell disease (CLCD) on day two of admission following an ultrasound scan of the liver. On day four of treatment, the patient developed deep icterus and asterixis. The serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels rose from normal levels to 681 U/L and 1100 U/L respectively. Total bilirubin had risen to 158.5 micromole/L with a high direct fraction of 116.1 micromole/L and alkaline phosphatase (ALP) was 108 U/L. Drug induced liver injury (DILI) was suspected immediately and clindamycin treatment was withheld. The patient's symptoms improved over the next few days and the AST, ALT levels dropped immediately and returned to normal within three weeks. Serum anti-nuclear antibody and anti-mitochondrial antibody were negative. IgM antibodies for hepatitis A, C, E, and Epstein-Barr virus were negative and the test for hepatitis B surface antigen was negative. The serum ferritin and transferrin saturation were normal and there were no Kayser-Fleischer rings in the eyes. The urine toxicology screen was negative. **Conclusion:** This case highlights a rare but important complication of clindamycin treatment. Clinicians should be vigilant when starting clindamycin in a patient diagnosed or suspected to have CLCD and such patients should be monitored for DILI. Early recognition of DILI is essential and immediate discontinuation of drug is the most important intervention which alone can lead to resolution of the injury.

Keywords: Clindamycin, Cholestasis, Hepatitis

Introduction

Clindamycin is a lincosamide antibiotic that is used for the treatment of anaerobic, streptococcal, and staphylococcal including community-acquired methicillin-resistant *Staphylococcus aureus* infections [1]. It is being used as it achieves high intracellular levels in phagocytic cells, bone, and is able to reduce toxin production in toxin-elaborating strains of streptococci and staphylococci [1,2].

Clindamycin undergoes hepatic metabolism predominantly by cytochrome P450 3A4

*Corresponding author: wettasingheindika@yahoo.com

Received: 29 November 2023; Accepted: 29 December 2023

How to cite this article:

Wettasinghe, I., Samarasinghe, S.M., Puthra, S. and Sugathapala, A.G.H. Possible cholestatic hepatitis with clindamycin therapy: A case report, Journal of Health Sciences and Innovative Research, 2023;4(2):31-35

(CYP3A4) to active and inactive metabolites. It is excreted in urine and, to a lesser extent, in the bile as metabolites [1]. No dose adjustments are recommended for patients with hepatic dysfunction receiving clindamycin even though the half-life of the drug is prolonged [1].

The common side effects of clindamycin are gastrointestinal including diarrhoea, vomiting, anorexia, flatulence, and pseudomembranous colitis caused by overgrowth of *Clostridium difficile* [1]. Though transient elevation of liver enzymes has been reported, there are few cases of acute idiosyncratic liver injury [1,3]. Here we present a patient who developed acute cholestatic hepatitis after receiving oral clindamycin for left lower limb cellulitis.

Case Report

A 49-year-old male from Sri Lanka presented with fever for two days and left lower limb swelling and pain. There were no respiratory or urinary symptoms. He had no known comorbidities as he was previously unscreened, and he had an allergy to co-amoxiclav and cefuroxime which was administered in a previous admission for a respiratory tract infection. He had been a heavy alcohol consumer but had abstained for over three months. There was no history of substance or drug abuse and no family history of liver disease. On examination he was febrile, anicteric. The pulse rate was 78 beats per minute, blood pressure was 120/70 mmHg. On auscultation, lungs were clear, and abdomen was soft. A clinical diagnosis of left lower limb cellulitis was made. The patient's full blood count showed leukocytosis 16.5×10^9 cells/mm³ with neutrophil predominance of 85.8% (Table 1). The random blood sugar was 348 mg/dL and c-reactive protein was 78 mg/L. The liver enzymes and serum bilirubin levels were normal (Table 1). The patient was started on oral clindamycin 300 mg, six hourly on day one of admission.

The patient's fever settled, and inflammatory markers improved. He was further investigated for the low platelet count and the ultrasound scan abdomen on day two revealed chronic liver cell disease (CLCD) with splenomegaly and mild ascites. The patient developed deep icterus on day four. The Glasgow Coma Score was 15/15 with reversal of sleep cycle, a shortened attention span and constructional apraxia. The aspartate aminotransferase (AST) and alanine aminotransferase (ALT) had risen to 681 units/L and 1100 units/L respectively. Total bilirubin had risen to 158.5 micromole/L with a high direct fraction of 116.1 micromole/L and alkaline phosphatase (ALP) was 108 U/L (Table 1). There was no evidence of common bile duct dilatation in the repeat ultrasound scan.

The other causes for liver injury were considered. The three common causes for ALT to rise above 1000 units/L are ischemic hepatitis, viral hepatitis, and toxins/drug overdose [4-5]. Our patient had a stable blood pressure with a mean arterial pressure above 90 mmHg throughout. Common causes of viral hepatitis and autoimmune aetiology were excluded. Serum anti-nuclear antibody and anti-mitochondrial antibody were negative. IgM antibodies for hepatitis A, C, E, and Epstein-Barr virus were negative and the test for hepatitis B surface antigen was negative. The serum ferritin and transferrin saturation were normal and there were no Kayser-Fleischer rings in the eyes. The urine toxicology screen was negative and there was no history or evidence to suggest paracetamol/drug overdose. Blood culture and urine cultures were negative. Drug induced liver damage was suspected immediately with the onset of symptoms (on day four of admission) and clindamycin treatment was stopped.

The patient's symptoms improved over the next few days and the AST, ALT levels dropped immediately and returned to normal within three weeks.

Table 1: Biochemical parameters during hospital stay

Test	21/02/2023	26/02/2023	01/03/2023	09/03/2023
Full Blood Count				
WBC ($\times 10^9$)	16.59	13.09		
Neutrophils ($\times 10^9$)	14.38	9.76		
Neutrophils %	86.6	74.5		
Haemoglobin (g/dl)	10.9	10.3		
Platelets ($\times 10^9$)	122	100		
Renal Function Tests				
Sodium (mmol/L)	140	129.9		
Potassium (mmol/L)	4.8	3.1		
Urea (mmol/L)	2.1	4.2		
Creatinine ($\mu\text{mol/L}$)	78	91		
Liver Enzymes and Liver Function Tests				
AST (U/L)	56	681	149	46
ALT (U/L)	46.1	1100	539	42
ALP (U/L)		108		
Total Bilirubin ($\mu\text{mol/L}$)	8.6	158	266	20
Direct Bilirubin ($\mu\text{mol/L}$)		116.1	172	14
Prothrombin Time		12.6		12.2
INR		1.2		1.2
Inflammatory Markers				
CRP	78	59	32	8

WBC: White Blood Cells, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, INR: International Normalization Ratio, APTT: Activated partial thromboplastin time, CRP: C Reactive Protein, RBS: Random Blood Sugar

Ethical consideration***Ethical approval and consent to participate***

Our institution does not require ethical approval for reporting individual cases or case series. Informed written consent was obtained from the patient.

Patient's consent for publication

Written informed consent was obtained from the patient for publication of this case report.

Discussion

Drug induced liver injury (DILI) is categorized into intrinsic and idiosyncratic, based on the pathophysiological mechanisms [6]. Intrinsic DILI by hepatotoxins such as acetaminophen are

typically dose dependent and have reproducible animal models [7]. However, most of DILI seen in clinical practice are termed "idiosyncratic" (i.e., a mixture of characteristics unique to that individual) as they are not clearly related to the dose, route, or duration of drug administration [6].

As per Ostapowicz G, Fontana RJ et al,[8] idiosyncratic DILI is a leading cause of acute liver failure (ALF) in the United States of America and is underdiagnosed due to the need to exclude other causes of liver injury and demonstrate improvement following drug discontinuation. As idiosyncratic DILI presents with variable laboratory, clinical, and histopathological features, it is difficult to diagnose and study [6]. Therefore,

until an objective and reliable confirmatory test is developed, idiosyncratic DILI will remain a “clinical diagnosis of exclusion” that requires a high index of suspicion [9].

Patients should be investigated for viral hepatitis (A, B, E), ischemic hepatitis, overdose of paracetamol, and other hepatotoxic drugs, toxins, and autoimmune hepatitis. Liver biopsy does not provide a definitive diagnosis of DILI and is primarily used to exclude other causes or support an alternative diagnosis [10]. However, a biopsy is recommended if autoimmune hepatitis is high on the differential and if immunosuppressive medications are to be given [11].

In retrospect, a diagnosis of clindamycin induced liver injury was made as: the adverse events were detected four days after commencing the drug regimen, both clinical and laboratory markers improved after stopping the drug; the alternative causes for liver injury were ruled out. The total Naranjo Score was six which is in the probable range [12] and the RUCAM score (Roussel Uclaf Causality Assessment Method) was five which is in the probable range (without re-exposure) [13].

Regarding treatment, some guidelines advocate that when jaundice, coagulopathy, or encephalopathy develops, N-Acetyl-Cysteine (NAC) therapy should be considered, and a low threshold maintained for consultation or transfer to a liver transplant center [14]. Corticosteroids will not improve overall survival in drug-induced, indeterminate, or autoimmune ALF and were associated with lower survival in patients with the highest model for end-stage liver disease (MELD) scores [15]. In our patient, intravenous NAC was considered but there was a delay due to drug unavailability and by the time it was available, the AST and ALT levels had dropped, and the patient improved. It was decided to observe the patient without administering the drug.

Conclusion

This highlights a rare but important complication of clindamycin treatment. Clinicians should be vigilant when starting clindamycin in a patient diagnosed or suspected to have CLCD. Cholestatic hepatitis should be anticipated in such patients and those treated as outpatients should be advised to keep a look out for development of jaundice. Patients treated inward should have their liver enzymes monitored regularly in order to detect cholestatic hepatitis early. Prompt recognition of DILI is essential and immediate discontinuation of drug is the most important intervention which alone can lead to resolution of the injury.

Acknowledgement

We would like to thank the hospital staff of Colombo South Teaching Hospital for their support.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Authors Contribution

The authors were involved in the management of the patient. IW wrote and revised the manuscript. SMS, SP and AGHS revised the main manuscript. SS reviewed the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Johnson M. Clindamycin: an overview. In Hooper D (Ed.), *Uptodate*, 2017. <https://www.uptodate.com/contents/clindamycin-in-an-overview#H22>
2. Schlievert PM, Kelly JA. Clindamycin-induced suppression of toxic-shock syndrome-

- associated exotoxin production. *J Infect Dis.* 1984;149(3):471. doi: 10.1093/infdis/149.3.471.
3. Bawany MZ, Bhutto B, Youssef WI, Nawras A, Sodeman T. Acute liver failure: an uncommon complication of commonly used medication. *Am J Ther.* 2013;20(5):566-8. doi: 10.1097/MJT.0b013e3182192d5a.
 4. Xu HM, Chen Y, Xu J, Zhou Q. Drug-induced liver injury in hospitalized patients with notably elevated alanine aminotransferase. *World J Gastroenterol.* 2012;18(41):5972-8. doi: 10.3748/wjg.v18.i41.5972.
 5. Hickman PE, Potter JM. Mortality associated with ischaemic hepatitis. *Australian and New Zealand journal of medicine.* 1990;20(1):32-4. doi:10.1111/J.1445-5994.1990.TB00366.X
 6. Fontana RJ. Pathogenesis of idiosyncratic drug-induced liver injury and clinical perspectives. *Gastroenterology.* 2014;146(4):914-28. doi: 10.1053/j.gastro.2013.12.032. Epub 2013 Dec 31.
 7. Roth RA, Ganey PE. Intrinsic versus idiosyncratic drug-induced hepatotoxicity--two villains or one? *J Pharmacol Exp Ther.* 2010;332(3):692-7. doi: 10.1124/jpet.109.162651. Epub 2009 Dec 17.
 8. Ostapowicz G, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SH, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med.* 2002;137(12):947-54. doi: 10.7326/0003-4819-137-12-200212170-00007.
 9. Fontana RJ. Approaches to the study of drug-induced liver injury. *Clin Pharmacol Ther.* 2010;88(3):416-9. doi: 10.1038/clpt.2010.100. Epub 2010 Jul 21.
 10. Leise MD, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. *Mayo Clin Proc.* 2014;89(1):95-106. doi: 10.1016/j.mayocp.2013.09.016.
 11. Czaja AJ. Corticosteroids or not in severe acute or fulminant autoimmune hepatitis: therapeutic brinksmanship and the point beyond salvation. *Liver Transpl.* 2007;13(7):953-5. doi: 10.1002/lt.21088.
 12. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981 Aug;30(2):239-45. doi: 10.1038/clpt.1981.154.
 13. Danan G, Teschke R. RUCAM in Drug and Herb Induced Liver Injury: The Update. *Int J Mol Sci.* 2015;17(1):14. doi: 10.3390/ijms17010014.
 14. Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ; Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol.* 2014;109(7):950-66; quiz 967. doi: 10.1038/ajg.2014.131. Epub 2014 Jun 17.
 15. Karkhanis J, Verna EC, Chang MS, Stravitz RT, Schilsky M, Lee WM, et al. Steroid use in acute liver failure. *Hepatology.* 2014;59(2):612-21. doi: 10.1002/hep.26678. Epub 2013 Dec 24.