INVITED ARTICLE: CLINICAL PEARL

A case of amoxicillin clavulanate drug induced liver injury

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Introduction

Amoxicillin clavulanate (Augmentin) is one of the most commonly used antibiotics in New Zealand (NZ).[1] There are a number of known adverse effects of this drug, affecting the cutaneous, gastrointestinal, hepatic, and haematologic systems.[2] Hepatic adverse effects, although rare (17 cases per 100,000 patients treated with amoxicillin clavulanate), include drug induced liver injury (DILI).[3,4] This case of DILI secondary to amoxicillin clavulanate after admission with choledocholithiasis highlights the importance of recognising and treating rare but severe medication adverse effects.

Case

A 26-year-old female non-smoker presented to hospital with six days of upper back, shoulder, and right upper quadrant (RUQ) abdominal pain and a two-day history of pruritis. There was no relevant past medical history, family history, drug allergies, or regular medications. No recent antibiotic use was reported. A distant medication history showed previous dispensing of multiple antibiotics, including amoxicillin, flucloxacillin, and amoxicillin clavulanate. On examination, her abdomen was soft, with mild RUQ tenderness, negative Murphy's sign, and no guarding or peritonism. Important investigative results are presented in Table 1.

Table 1: Key investigations and results

Day	Investigation	Findings and Treatment
1 Admission	Biliary USS MRCP Blood tests	Cholelithiasis + biliary sludge CBD to 8 mm GGT peaks at 353 U/L
4		Start amoxicillin clavulanate
9	ERCP	Biliary sphincterotomy + CBD balloon clearance with removal of numerous stones
11	MRCP	No extrahepatic biliary tree dilatation or intraductal stone, CBD 4 mm
12		Stop amoxicillin clavulanate
15 Discharge		
17 Readmission	Blood tests	CMV, EBV, HIV, hepatitis B, hepatitis C negative. TFTs, IgM, IgG, IgA, liver antibodies, ANCA, parietal cell antibodies within normal limits
18	MRCP	No cholelithiasis or choledocholithiasis CBD 5 mm
19	Blood tests	Bilirubin peaks at 344 µmol/L
23	Blood tests Hepatology review	PR peaks at 1.6 (reversed with vitamin K) Diagnosed with DILI secondary to amoxicillin clavulanate
25	Blood tests	ALP peaks at 268 U/L
29 Discharge		
78	Blood tests	Bilirubin normalises to 16 µmol/L

Legend: red: important admission or discharge events, blue: important blood test results

Key: ultrasound (USS), magnetic retrograde cholangiopancreatography (MRCP), common bile duct (CBD), gamma-glutamyl transferase (GGT), endoscopic retrograde cholangiopancreatography (ERCP), cytomegalovirus (CMV), Epstein Barr virus (EBV), human immunodeficiency virus (HIV), thyroid function tests (TFTs), immunoglobulin (Ig), antineutrophil cytoplasmic antibodies (ANCA), prothrombin ratio (PR), drug induced liver injury (DILI), alkaline phosphatase (ALP)

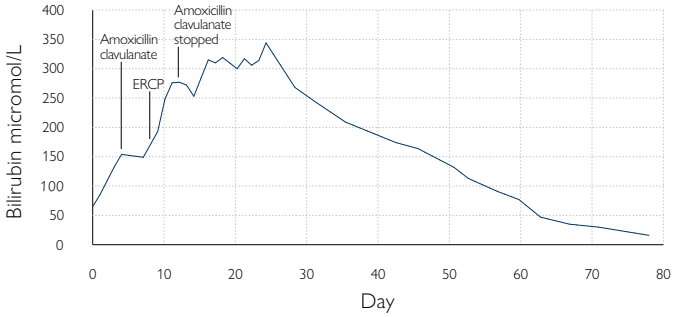
Progress

Clinically, the patient became jaundiced with worsening pruritis prior to antibiotic commencement. Biochemical and radiological investigations raised the concern of choledocholithiasis. The patient showed early signs of a developing infection; therefore, oral amoxicillin clavulanate was commenced on day four and endoscopic retrograde cholangiopancreatography (ERCP) was organised. On day nine, intravenous amoxicillin clavulanate was given and ductal stones were extracted via ERCP. Oral amoxicillin clavulanate continued post-procedure until day 12. The patient was discharged on day 15 but was readmitted on day 17 with ongoing pruritis and worsening cholestatic liver function tests (LFTs). The usual pathogenesis of choledocholithiasis would see LFT derangements improving in the days following ERCP; however, this case showed an increase in bilirubin to 344 µmol/L, peaking 16 days post-ERCP and 13 days post-cessation of the antibiotics, prompting investigations for a secondary pathology. Magnetic resonance cholangiopancreatography (MRCP) was undertaken, and did not find retained ductal stones. Viral and autoimmune hepatitis panels also returned negative results. Inpatient bile salt binders were commenced, and remaining treatment was supportive. A consulting hepatologist diagnosed the patient with amoxicillin clavulanate-induced DILI. At day 29, the patient was discharged with follow-up blood tests and ongoing bile salt binders. Continued monitoring showed normalisation of bilirubin and other LFTs on day 78 as shown in Figure 1.

Discussion

This case highlights the importance of recognising amoxicillin clavulanate as a cause of DILI. This patient presented with choledocholithiasis and obstructive jaundice which was treated with ERCP. Despite this, she developed prolonged jaundice and hepatitis. Repeat MRCP

Figure 1: Bilirubin blood test results



Key: endoscopic retrograde cholangiopancreatography (ERCP)

showed no further intraductal stones, and viral and autoimmune investigations were negative. In this case, treatment was symptomatic with bile salt binders and supportive care.

This case is a timely reminder of how a commonly prescribed antibiotic in NZ can have serious adverse effects with the potential to cause significant morbidity and mortality. In 2018, 11% of people who visited their general practitioner were prescribed amoxicillin clavulanate at least once.[1] While amoxicillin clavulanate-induced DILI is usually self-limiting with a good prognosis, there are rare reports of fulminant hepatitis resulting in death, even in the young and otherwise healthy patient.[2–5] Risk factors predisposing to acute liver failure have not been well identified.[3]

While the pathophysiology of amoxicillin clavulanate-induced DILI is unclear, it is known to be independent of the dose, duration, or route of administration.[6] The estimated risk of hepatic adverse effects is 17 per 100,000 prescriptions for amoxicillin clavulanate.[3,4] DILIs can be cholestatic, hepatocellular, or mixed. Cholestatic DILI often results in an obstructive LFT picture with an elevated bilirubin.[2,4,5] Conversely, hepatocellular DILI will result in an ALT three times normal and an ALT/ALP ratio five times normal.[2,4,7] However, patients can also demonstrate a mixed DILI with ALT three times and ALP twice that of the upper limit of normal.[2,7] Amoxicillin clavulanate-induced DILI is usually cholestatic, but can also be hepatocellular or mixed.

Current research postulates that amoxicillin clavulanate-induced DILI is an immune hypersensitivity reaction, where there is an inappropriately exaggerated immune response against an antigen.[2,4,5,6,8] Neoantigens are thought to be produced by the reactions of beta-lactam structures within the antibiotic and host proteins.[5,8] The neoantigen is presented to receptors on undifferentiated immune cells. This results in activation of the immune system, including the production of cytotoxic CD8+ T cells. Cytotoxic CD8+ T cells act in a number of ways to kill their target cell. In keeping with this, CD8+ cytotoxic T cell invasion has been observed in the portal triad of the liver, mediating damage to liver cells.[5,8]

DILI can be caused by multiple drugs, some of which include diclofenac, azathioprine, nitrofurantoin, co-trimoxazole, anti-tuberculosis treatments, antineoplastic agents, and tricyclic antidepressants.[7] Even with successful identification and withdrawal of a causative drug, approximately 4% of idiosyncratic DILI progresses to acute liver failure.[7] A prospective American DILI network (DILIN) study in 2014 included 660 patients between September 2004 to July 2011 with definite, highly likely, or probable DILI. It found that 9.4% (n=62) of patients with DILIs required a liver transplant or died within six months.[9] They found that patients with adverse outcomes were treated with the offending agent for a longer period of time (67 days) compared to those with self-limiting DILIs (31 days).[9] If DILI is not considered in the differential diagnosis, the causative agent may not be withdrawn, and the severe consequences of this could include the need for a liver transplant or even death.

Amoxicillin clavulanate is one of the most commonly prescribed antibiotics in New Zealand; however, DILI is an under-recognised and important adverse drug reaction that should not be forgotten. Early recognition is vital, as morbidity and mortality for patients can be high, especially if left untreated. Although rare, it is important for clinicians to consider DILI in the context of rising bilirubin in a patient with negative hepatobiliary imaging (MRCP) who has recently taken or is currently taking amoxicillin clavulanate.

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Acknowledgements

We would like to acknowledge our patient who kindly provided written consent for the reporting of their case.

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