CASE REPORT

 α -Methyldopa-induced hepatitis during the postpartum period

Soleiman Kashkooli, Brandon Baraty, Jamshid Kalantar

Nepean Hospital, Sydney,
New South Wales, Australia**Correspondence to**
Dr Soleiman Kashkooli,
solybk@yahoo.com

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SUMMARY

A 34-year-old woman, with a history of pre-eclampsia, was diagnosed with α -methyldopa-induced hepatotoxicity, after she presented with severe jaundice and hepatitis 8 weeks following delivery. Laboratory investigations and liver biopsy ruled out other causes of hepatitis. She continued to improve clinically after cessation of α -methyldopa, and was discharged 10 days after admission. This case report emphasises that it may not be possible to predict which patients may develop α -methyldopa-induced hepatitis, hence regular monitoring of liver function tests during treatment should be implemented.

BACKGROUND

α -Methyldopa is an antihypertensive agent, used regularly during pregnancy, and is a drug of choice due to its safety and tolerability profile. Although, on rare occasions, a transient, non-clinically relevant elevation of serum transaminases may be observed. A paucity of cases involving α -methyldopa-induced hepatitis during pregnancy have been described in the literature,^{1–5} and that number is even lower postpartum.⁶

We report a case of α -methyldopa-induced hepatotoxicity diagnosed 2 months postpartum in a patient with a history of pre-eclampsia, and briefly review the literature on potential mechanisms of α -methyldopa-induced hepatitis.

CASE PRESENTATION

A 34-year-old woman (gravida 4, para 3) presented with severe jaundice and hepatitis 2 months following delivery. She was diagnosed with pre-eclampsia at week 24 during her fourth pregnancy. Her previous three pregnancies were uneventful. She had no prior history of hypertension or renal disease. She was managed with α -methyldopa (500 mg 3 times a day) and hydralazine (50 mg 3 times a day). The patient required induction at 38 weeks gestation due to the severity of her pre-eclampsia, and went on to have an uncomplicated vaginal delivery.

The patient appeared to recover uneventfully and was followed up at 3 weeks postpartum by her nephrologist. At this time the hydralazine was discontinued, α -methyldopa was reduced to 250 mg three times a day, and her blood pressure was 125/85 mm Hg. Liver function tests performed 1 week prior to delivery had been within normal range. Eight weeks following delivery, during a routine postnatal visit, the patient was noted to be jaundiced, and was promptly admitted to the gastroenterology unit for further investigations, at which time the α -methyldopa was discontinued. The

patient did not report any history of intravenous drug use, medication or alcohol ingestion, and had no risk factors for viral or foodborne illnesses. There was no known family history of liver disease.

On examination the patient appeared lethargic. Her blood pressure was 115/80, temperature 36.5°C and heart rate 90 bpm. There was no indication of encephalopathy. She did not have right-upper quadrant tenderness, hepatosplenomegaly, ascites or rash. Some spider naevi were noted on the upper chest. She did not display any symptoms of fluid overload.

INVESTIGATIONS

Laboratory investigations revealed a bilirubin of 322 μ mol/L (normal 0–20), alkaline phosphatase 275 U/L (20–105), γ -glutamyl transpeptidase 123 U/L (5–35), aspartate aminotransferase 1340 U/L (5–35), alanine aminotransferase 1018 U/L (10–35) and International Normalised Ratio 1.2. Haemoglobin, platelets, white cell count, creatinine and C reactive protein were all within normal limits.

Screening for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus and herpes simplex virus was negative. Antismooth muscle antibody, antimitochondrial antibody and anti-liver kidney microsomal (LKM) were also negative. Paracetamol level in blood was not detected. Vasculitic screening revealed a mildly positive antinuclear antibody (ANA) (1/160) and elevated immunoglobulin (IgG) at 16.60 g/L (normal 0–10).

Owing to the high globulin and positive ANA, a liver biopsy was performed to exclude autoimmune liver disease. The biopsy showed extensive hepatic inflammation with mixed, predominantly lymphocytic inflammatory cell infiltrate with focal bridging necrosis. These changes, although marked, were of uncertain clinical significance. An abdominal ultrasound displayed gallbladder sludge with no evidence of gallbladder wall thickening or inflammation, and no common bile duct or biliary duct dilation.

Despite stopping α -methyldopa, the patient continued to deteriorate with rising liver enzymes and worsening coagulation profile (table 1).

TREATMENT

The patient was initiated on 10 mg/day vitamin K. Her renal function and platelet count remained normal.

Owing to the patient's clinical condition, the liver transplant unit in Sydney was notified. However, over the following days, the patient showed dramatic improvement in her liver function tests and coagulation profile, at which time vitamin K was stopped. She continued to improve clinically, and was discharged 10 days after admission.

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Table 1 Liver function test and coagulation during and before admission

	Last week of pregnancy	Admission (8 weeks postpregnancy)	5 days later	Discharge (10 days after admission)	6 weeks postdischarge
AST U/L (0–35)	18	1340	1576	605	44
ALT U/L (0–35)	6	1018	1107	725	35
ALP U/L (20–105)	196	275	287	240	143
GGT U/L (5–35)	10	122	114	168	49
Globulin (g/L)	34	37	43	39	33
Bilirubin (μ mol/L) (0–20)	3	322	379	282	20
INR (<1.1)	1	1.2	1.7	1.4	1.1

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ -glutamyl transpeptidase; INR, International Normalised Ratio.

OUTCOME AND FOLLOW-UP

The diagnosis of α -methyl dopa-induced hepatitis was made by exclusion of other causes of hepatitis. The patient's liver function tests had almost returned to normal when she was seen at follow-up 2 months later. She was normotensive at 130/85 mm Hg and her ANA, globulins and IgG levels had all returned to normal. Despite her recovery, the patient was left with residual underlying hepatic fibrosis, and will need to be monitored periodically for the development of portal hypertension.

DISCUSSION

α -Methyl dopa is a centrally acting inhibitor of the α -adrenergic receptor.⁷ It is often used in the initial management of hypertension during pregnancy, as it is well tolerated, and appears to be safer for developing fetoplacental circulations compared with other antihypertensive medications.^{7 8}

The α -methyl dopa-induced hepatitis was first reported in 1969. This condition during pregnancy is a rare, but serious complication. One case of fatal α -methyl dopa-induced toxic hepatitis occurring during pregnancy has been reported in the literature.³

An estimated 5% of non-pregnant women receiving α -methyl dopa have been reported to have mild hepatic injury. This is detected only by a transient and mild elevation of serum aminotransferases that typically disappears despite continued administration of the drug.⁹ The estimated rate of manifest hepatitis among non-pregnant women receiving α -methyl dopa is 2.5–10%.⁸ Chronic hepatitis with bridging necrosis and macronodular cirrhosis on biopsy have been seen in up to 15% of patients with α -methyl dopa-induced hepatitis.⁸

However, only a few cases of α -methyl dopa-induced hepatitis during pregnancy are well described in the literature.^{1–5} In these cases, all pregnant women developed hepatitis between 2 and 9 weeks after initiation of α -methyl dopa. Our case study remains unique because the patient developed significant hepatitis in the postpartum period, having had normal liver function tests just before delivery.

Adverse hepatocellular events secondary to drugs, may be classified as either direct hepatic injury or indirect hepatic injury which mediate an immune response.⁹ Direct hepatotoxicity by drugs such as acetaminophen,¹⁰ is usually characterised by a short latency period, and is dose related. The toxic effect is caused either by a drug itself or its metabolites. In contrast, indirect hepatotoxicity is not usually related to the dosage or duration of administration of the causative agent, and may be related to specific abnormalities of drug metabolism, or may mimic some of the features of hypersensitivity reactions. α -Methyl dopa is thought to have indirect hepatic injury effect.

It has been proposed that the pathogenesis of α -methyl dopa-induced hepatitis is secondary to an abnormal metabolism of α -methyl dopa by cytochrome P450, which may lead to the development of an immune reaction to the drug metabolites. This resembles the pattern seen in hypersensitivity reactions.⁸ Toxic metabolite build-up has also been proposed. Serological markers of autoimmunity, such as ANA, are detected infrequently with α -methyl dopa-induced hepatitis, with <5% of patients displaying a Coomb's positive haemolytic anaemia.^{11 12} Hepatitis caused by α -methyl dopa may be acute, occurring within weeks to months of treatment initiation, or chronic, arising months to years after treatment initiation. The majority of patients develop symptoms of hepatitis within 3 months of α -methyl dopa initiation.

Transaminase levels of >1000 U/L occur almost exclusively as a result of viral hepatitis, ischaemic liver injury, toxin-induced or drug-induced liver injury.

We believed that the causative aetiology of the hepatotoxicity in our patient was α -methyl dopa following exclusion of other causes of hepatitis such as infection and autoimmune hepatitis. The low titre of ANA and elevated IgG was thought to reflect the non-specific association of idiosyncratic immunologically mediated hepatic injury associated with α -methyl dopa. We did not feel that hydralazine contributed to the disorder in this instance, as it was discontinued in the early postpartum period. Although hydralazine has been documented to cause hepatitis manifesting as a hypersensitivity-type injury, with mixed hepatocellular injury, acute hepatitis, cholestatic jaundice or centrilobular necrosis with case reports noted in the literature.^{13 14}

α -Methyl dopa-induced hepatotoxicity is rare, and it is not possible to predict which patients may develop hepatitis as a result of α -methyl dopa treatment. Screening through regular monitoring of liver function tests during treatment can help manage potential α -methyl dopa-induced hepatitis. In the great majority of cases simply ceasing the medication will result in rapid improvement of symptoms.

Learning points

- ▶ α -Methyl dopa-induced hepatotoxicity is rare, and screening through regular monitoring of liver function tests during treatment can help manage potential hepatitis induced by this drug.
- ▶ α -Methyl dopa can cause severe hepatitis.
- ▶ In the great majority of cases simply discontinuing treatment with α -methyl dopa will result in rapid improvement of symptoms.

Contributors SK participated in study design and manuscript preparation. BB participated in gathering data and clinical information. JK participated in critical revision.

Competing interests None.

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