INTRODUCTION

Alpha-methyldopa is a commonly used class B drug in the management of hypertension in pregnancy as it is less likely to cause direct effects on fetus. Reactive hepatitis is an uncommon but severe side effect of methyldopa. Elkington described methyldopa hepatotoxicity in 1969. Acute hepatitis in pregnancy due to methyldopa is known to be rare. To the best of authors' knowledge, only three cases from United States have been reported in literature on acute hepatitis due to methyldopa in pregnancy. However, practitioners should be aware of the association of alpha-methyldopa with reactive hepatitis in pregnancy. We report a case of methyldopa induced hepatitis in a 12 weeks pregnant female and its successful management after withdrawal of the drug and a short course of corticosteroids.

CASE REPORT

A 12-week pregnant, 33 years old African American female, presented with jaundice and change in colour of urine. She was started on methyldopa 6 weeks prior to hospitalization by her primary care physician for hypertension. The initial laboratory studies revealed values of total bilirubin of 19.9 mg/dL (12.4 mg/dL conjugated), Aspartate Transaminase (AST) of 2029 Units/L, Alanine Transaminase (ALT) 1303 Units/L, Alkaline Phosphatase of (ALKP) of 134 Units/L, total proteins 6.8 g/dL, albumin 2.9 g/dL, BUN 3 mg/dL and creatinine 0.5 mg/dL. The ultrasound abdomen showed mild hepatosplenomegaly without intra- or extra-hepatic bile duct dilatation. On further work-up, acute viral hepatitis, HIV, rubella, syphilis, infectious mononucleosis, cytomegalovirus and herpes simplex infections were ruled out. Anti-nuclear antibodies, anti-smooth muscle, anti-double stranded DNA antibodies and Disseminated Intravascular Coagulation (DIC) panel were normal. A presumptive diagnosis of alpha-methyldopa induced hepatitis was made and the drug was discontinued. She was also treated with oral prednisone 20 mg orally daily. On discontinuation of the medication, the patient's liver function test showed improvement. Two weeks follow-up laboratory studies after her discharge revealed bilirubin 3.5 mg/dL, AST 25 Units/L, ALT 26 Units/L and ALKP 75 Units/L. At that point prednisone was slowly tapered and stopped in next 10 days with subsequent normalization of her liver enzymes.

DISCUSSION

Alpha-methyldopa is a pro-drug. The active metabolite, alpha-methylnorepinephrine, lowers blood pressure by stimulating central inhibitory alpha-adrenergic receptors and possibly by reduction of plasma renin levels. It is excreted as metabolites (85%) through kidneys. Some of the common side effects are well known such as peripheral edema, orthostatic hypotension, dry mouth and the central effects such as depression and anxiety. Rarely, this could also cause sexual dysfunction, gynecomastia, thrombocytopenia, hemolytic anemia, leukopenia, hyperprolactinemia, cholestasis, hepatitis and hepatocellular injury and SLE-like syndrome. Serological markers for autoimmunity are detected infrequently and less than 5% of patients have a Coombs-positive hemolytic anemia.

Though the mechanism for hepatitis is not fully understood, it is thought to be related to the abnormal transformation of alpha-methyldopa by cytochrome P450 and an immune reaction to the resultant metabolite. In <1% of patients, acute liver injury resembling viral or chronic hepatitis, or rarely, a cholestatic reaction is seen 1-20 weeks after...
Methyldopa is started. In 50% of cases, the interval is <4 weeks. The clinical presentation may start with a prodrome of fever, anorexia and malaise few days before the onset of jaundice. In 25% of cases of acute reactive hepatitis due to alpha-methyldopa rash, lymphadenopathy, arthralgia and eosinophilia may manifest. In 15% of patients with methyldopa hepatotoxicity, the clinical, biochemical and histological features are those of moderate to severe chronic hepatitis, with or without bridging necrosis and macro nodular cirrhosis. The hepatocellular damage caused by alpha-methyldopa is usually reversible on discontinuation of the medication. The use of steroid is not usually recommended but a short course of prednisone can hasten the recovery of this possible immune-related injury and may prevent development into chronic hepatitis.

To conclude, as alpha-methyldopa is commonly used to treat hypertension in pregnancy, the practitioner should be aware of the hepatotoxic effect of this agent. Since most of the methyldopa hepatitis cases are reversible on discontinuation, discontinuing methyldopa is recommended whenever possible, while investigating the cause of pregnancy hepatitis. The role of steroids can be considered on individual case basis. Serum amino-transferase levels should be periodically measured after initiating methyldopa in pregnant females.

REFERENCES