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Hepatotoxicity from Alpha-Methyldopa During Pregnancy: Two Case Reports

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Abstract

The drug-induced hepatotoxicity by α-methyldopa described by Elkington in 1969 causes asymptomatic hypertransaminasemia in 5% of the cases and liver injury in fewer than 1%.

Case 1: A 29-year-old woman in her third pregnancy (at 22 weeks), with a history of arterial hypertension under treatment with enalapril, which medication was switched to α-methyldopa on gestation week 8. She then began to experience coluria, generalized pruritus, and asthenia. Four days before consultation, she presented with jaundice.

Her prothrombin concentration was 72%, ALT 515 UI, and AST 618 UI. A viral or autoimmune origin was ruled out, and the α-methyldopa was withdrawn 5 days after manifesting jaundice. At 48 h after hospitalization, a reduction of prothrombin concentration to 35% occurred; two days later, the patient developed fulminant hepatic failure involving hepatic encephalopathy and was referred for a liver transplant, which intervention was subsequently performed with success.

Case 2: A 37-year-old woman in her third pregnancy (at 18 weeks), with a history of arterial hypertension treated with losartan and one spontaneous abortion. She presented with jaundice and hypertransaminasemia (> 10 ULN) and had been treated with α-methyldopa from gestation week 8 on. The prothrombin concentration was 48% and serologic profiles for hepatotropic viruses indicated nonreactivity. Immunology: positive ANA 1:320.

The α-methyldopa was withdrawn 48 h after the manifestation of jaundice. Thereafter the patient showed an improvement in hepatocellular function with an increase in prothrombin and a normalization of the transaminasemia after 4 weeks.

In conclusion, we present here two cases of severe acute hepatitis from α-methyldopa during pregnancy, one with a progression to hepatic failure that required liver transplantation. The drug-induced liver injury by α-methyldopa described by Elkington [1] in 1969 causes asymptomatic hypertransaminasemia in 5% of the cases and liver injury in fewer than 1% [2].

The drug-induced liver injury (DILI) attributed to α-methyldopa may cause a great variety of hepatic disorders such as asymptomatic hypertransaminasemia, acute hepatitis, chronic hepatitis, cirrhosis, features of autoimmune hepatitis, cholestasis, steatohepatitis and granulomatous hepatitis [3-6]. Of the cases treated with this drug, 10%-30% present anomalies in liver-function tests without evidence of DILI; and these changes often disappear in spite of the continuation of the treatment [7]. Less than 0.1% of those cases develop acute hepatitis, but then generally within three months after the beginning of α-methyldopa treatment, though up to 50% of the acute cases become manifest within 2-4 weeks. The clinical manifestation of the acute presentation resembles that of viral hepatitis. Liver biopsy reveals a focal or a confluent hepatocellular necrosis with acidophilic bodies and inflammatory infiltration in the portal triad, though bridging and massive hepatic necrosis can be produced. Eosinophilic inflammatory infiltrate and peripheral eosinophilia are not frequently observed, however. Most of the patients recover after suspension of the drug, but the mortality among the patients with jaundice can reach 10% or even higher. Although the pathogenesis is not completely understood, idiosyncratic immunologic mechanisms and an inhibition of the cellular pathways of drug metabolism have been thought to be involved [8].

Objective

To report two cases of toxicity from α-methyldopa during pregnancy.

Patients and Method

Case 1

A 29-year-old woman in her third pregnancy (22 weeks) was referred to the hospital with a diagnosis of acute hepatitis. She had a history of arterial hypertension diagnosed a year ago and was treated at that time with enalapril, which medication was subsequently replaced by α-methyldopa at 500 mg/day on gestation week 8. She had also been under treatment with cabergoline for pituitary adenoma since 2010 and had been taking a folic-acid and vitamin supplement since the confirmation of pregnancy. She had no history of surgery, addictions, or allergies and no family background of relevance. At 12 days before consultation she manifested coluria, generalized pruritus, and asthenia followed by a later abdominal pain in the right hypochondrium and epigastrium, with nausea and vomiting. She consulted at an institution where a medical

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Table 1: Summarizes the laboratory findings.

Case 1*								
	Hb (g/dl)	Platelets (×10^9/L)	P (%)	TB (mg/dl)	ALT (UI/L)	AST (UI/L)	AP (UI/L)	Albumin (g/dl)
Admission	11.6	290	73	21.0	515	618	273	3.1
Day 2	11.5	310	35	24.2	1058	1073	379	2.9
Day 5	11.5	367	31	34.7	1023	996	405	2.7
Day 7								

*Hb: Hemoglobin, P: Prothrombin Concentration, TB: Total Bilirubin, AP: Alkaline Phosphatase

Table 2: Summarizes the laboratory findings.

Case 2*								
	Hb (g/dl)	Platelets (×10^9/L)	P (%)	TB (mg/dl)	ALT (UI/L)	AST (UI/L)	AP (UI/L)	Albumin (g/dl)
Admission	11.9	210	48	8.1	942	856	241	3.3
Day 2	11.9	215	50	7.8	805	752	368	3.2
Day 5	11.8	196	82	5.1	421	389	296	3.4
Day 14	12.0	174	94	1.2	110	86	216	3.5
Day 21	11.9	175	96	0.9	23	19	138	3.6

*Hb: Hemoglobin, P: Prothrombin Concentration, TB: Total Bilirubin, AP: Alkaline Phosphatase

examination and laboratory tests were performed. Because at 5 days after that consultation she presented with jaundice, fever (39°C), and a pruritic erythematous cutaneous rash; she decided to return to the medical center. She was diagnosed there with acute hepatitis, was hospitalized, and finally was referred to our hospital.

Upon examination she was vigilant and oriented with no altered sleep and no asterixis. She presented with a generalized jaundice, normal fetal monitoring, and an abdominal pain in right upper quadrant.

Table 1 summarizes the laboratory findings.

Serology: nonreactive with HBsAg, antiHBc IgM, antiHCV, antiHEV, antiHAV IgM, and HSV IgM. Immunology: negative ANA, AMA, and ASMA. Abdominal ultrasound normal liver and spleen; no ascites Normal fetal monitoring before and during hospitalization

α-methyldopa was withdrawn 5 days after the presentation of jaundice at the time of hospitalization. At 48 h after hospitalization, a reduction in prothrombin concentration occurred (35%). Two days later, the patient developed a hepatic encephalopathy of Grade 2 and was referred to a liver-transplantation center. Liver transplantation was performed 26 h later with success. The native liver showed submassive hepatocyte necrosis. The pregnancy was continued under medical supervision after the liver transplant, terminating in a successful premature childbirth.

Case 2

A 37-year-old woman in her third pregnancy (18 weeks), with a history of arterial hypertension treated with losartan and one spontaneous abortion. She presented with jaundice and hypertransaminasemia (> 10 ULN). She was treated with α-methyldopa from gestation week 8 on. She had no history of surgery, addictions, or allergies and no family background of relevance. An examination revealed jaundice as the only finding. The fetal monitoring and abdominal ultrasound were both normal.

Table 2 summarizes the laboratory findings.

Serology: nonreactive with HBsAg, antiHBc IgM, antiHCV, antiHEV, antiHAV IgM, and HSV IgM. Immunology: positive ANA at 1:320 and negative ASMA; the ANA, however, became negative at six months.

The α-methyldopa was withdrawn at 48 h after the occurrence of jaundice and was replaced by labetalol. The patient showed an improvement in hepatocellular function characterized by an increase prothrombin concentration and a normalization of transaminasemia after 4 weeks.

Discussion

α-methyldopa is frequently used for the treatment of arterial hypertension during pregnancy because the drug produces less of a direct effect on the vascular system in the fetus than other antihypertensive drugs. The pathogenesis of the associated hepatotoxicity could be related to an abnormal transformation of the drug by cytochrome P450 and/or an autoimmune reaction to that metabolite [8].

Acute hepatitis caused by α-methyldopa during pregnancy is rare. We present here two patients with severe acute hepatitis from the drug-one developing into a fulminating hepatic failure requiring liver transplantation. The diagnosis was based on a combination of observations including temporal associations e.g., from the initial intake of the drug until onset of symptomology-and with respect to latency, the rate of improvement after cessation of the drug (in one of the cases), and the definitive exclusion of non-drug-related causes.

In case 1, the patient had pruritic erythematous cutaneous rash and fever, which symptoms further support our diagnosis since 25% of such patients can present fever, rash, lymphadenopathy, and/or arthralgia. In case 2, the clinical situation was probably reversed by early withdrawal of α-methyldopa. In both cases hepatocellular dysfunction was found, and in the first one developed into fulminant hepatic failure. Both those cases prove that although α-methyldopa can be safe during pregnancy, serious adverse events are possible.

In the literature that we reviewed, we found nine cases of hepatotoxicity from α-methyldopa during pregnancy (PubMed 1976-2014, key words: pregnancy, α- methyldopa, hepatotoxicity) [2,8-16]. Six of those cases involved acute hepatitis, two of them severe acute hepatitis, and one fulminant hepatic failure followed by death. The time of drug exposure was between two and nine weeks. The onset in most of the cases was characterized by asthenia, nausea, vomiting, jaundice, and coluria. In addition to those symptoms, three patients had experienced pruritus and two had presented with fever. In all those cases the presence of hepatotropic viruses was excluded and in only one serology for non hepatotropic viruses was not performed. Immunology (ANA, ASMA, AMA, LKM-1) was evaluated in six of the cases, and in two moderate-to-high titers of ANA were found. An ANA of 1:320 was found in our own case 2, though that ANA proved to be negative six months later. About half of the cases of DILI attributed to α-methyldopa exhibit a phenotype of autoimmunity similar to that seen with autoimmune hepatitis 6. In one case an increase in maternal serum α-fetoprotein was reported without an increase in amniotic fluid [10].

With respect to abdominal ultrasound, none of the nine cases in the literature reported relevant data, except one in which mild hepatosplenomegaly had been found [12]. In our cases, we also found no relevant data through abdominal ultrasound.

As to the treatment, in all the cases, the drug was suspended upon confirmation of the diagnosis; and in one case, 20 mg/day of prednisone was prescribed [10]. In eight of the nine cases the outcome was satisfactory, with a normalization of liver function between the second and tenth week after drug withdrawal. The case described by Picaud [2] turned out to be one of fulminant hepatic failure; and after challenge with the drug the patient died, though in most of the cases the symptomatology was reversed after drug withdrawal [4,9]. The challenge with the drug can be fatal and thus must be avoided.

In the cases we reported, we need to emphasize that, in the patient that had the poor development, the α-methyldopa withdrawal was delayed for much more than 48 h (for some 5 days) from the onset of jaundice.

In conclusion, we present here two cases of severe acute hepatitis resulting from the use of α-methyldopa during pregnancy, one with a development of hepatic failure that required liver transplantation. We want to accentuate the urgency of a periodic monitoring of liver function in pregnant patients treated with α-methyldopa, through consideration of the drug's potential hepatotoxicity, and the immediate withdrawal of that medication when such a pathologic

development occurs. Patients with α-methyldopa–induced liver injury must not be challenged with this medication because the recurrence of liver injury can be severe and even fatal.

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