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Hepatotoxicity of atenolol therapy − A report of 2 cases

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ABSTRACT

This case report highlights atenolol induced episodes of chronic and acute hepatotoxicities in 2 elderly hypertensive patients. The 1st patient manifested liver dysfunction after 8 months of 50 mg daily atenolol therapy and in the 2nd patient liver dysfunction was revealed within 3 weeks of 100 mg daily atenolol intake. There was no evidence of any other possible hereditary, traumatic, surgical, metabolic, infective, organic, or pathologic causes giving rise to these conditions. Possibilities of drug interactions were carefully ruled out and these episodes of hepatotoxicities were 'probably' drug (atenolol) induced, as depicted by CIOMS/RUCAM scale. Withdrawal of the offending drug resulted in reversal of the diseased states. Routine liver function tests may be warranted in patients on atenolol therapy.

1. Introduction

Atenolol, approved for use in the United States in 1981, is a cardio selective beta-adrenergic receptor blocker in that it has potent activity against beta 1 adrenergic receptors which are found in cardiac muscle, but has little or no activity against beta 2 adrenergic receptors found on bronchial and vascular smooth muscle and is widely used worldwide in the treatment of hypertension and angina. It is also used to reduce the risk of cardiovascular mortalities in patients with coronary artery diseases. The chemical works by slowing down the heart and reducing its workload. Unlike propranolol, atenolol does not pass through the blood-brain barrier thus avoiding various central nervous system side effects (http://en.wikipedia.org/wiki/Atenolol - cite_note-BBB-1). Common adverse effects of atenolol include bradycardia, hypotension, fatigue, dizziness, depression, memory loss and impotence. At high doses, it is less cardio selective and may cause bronchospasm. As with all beta-blockers, sudden withdrawal of atenolol can trigger rebound hypertension[1-4].

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2. Case reports

2.1. Case 1

A 55 year old non-smoker and absolutely non-alcoholic male patient, diagnosed with both systolic and diastolic hypertension for last 1.5 years, was on titrated dose of oral amlodipine 10 mg once daily with excellent regulation of blood pressure. He presented with a gradual onset of swelling of extremities and abdominal distension after taking amlodipine for initial 1.5 months. S-amlodipine being considered as an alternative 'switch over drug' in patients developing pedal edema with amlodipine, he was started with oral S-amlodipine 10 mg once daily. However, the swelling was not reduced, and as a result, the patient was switched on to oral atenolol 50 mg once daily, after which the swelling subsided completely within the next 2 weeks. His routine examination results, renal function, liver function, and cardiac status were essentially normal at that time. Since then, he was continuing atenolol with well control of hypertension. However, after 8 months of continuing atenolol, he presented with a 7 days history of gradually progressing nausea, vomiting, malaise, anorexia, fatigue, upper abdominal discomfort and jaundice.

On physical examination, his vital signs were within

normal limits. The skin was yellowish with scleral icterus, but without ecchymoses or petechiae. Cardiovascular and pulmonary findings were unremarkable. The abdomen was soft, but diffusely tender, particularly in right hypochondrium. There was no palpable organomegaly, rebound tenderness, guarding, or rigidity. Initial laboratory work-up findings are enumerated in Table 1.

2.2. Case 2

A 52 year old non-smoker and absolutely non-alcoholic female with a prior medical history of hypothyroidism and type 2 diabetes mellitus presented to the emergency department with 1 week history of crampy, mid-epigastric abdominal pain, non-bloody diarrhea and gradually developing jaundice. She had fever, nausea and vomiting, anorexia and profound fatigue for last 1 week. She did not have any pruritus, arthralgias, black tarry stools or dark urine. Drug history revealed, 3 weeks prior to this presentation, she was diagnosed with moderate systolic plus diastolic hypertension for which she was advised oral atenolol 100 mg tab once daily. Apart from that, she was taking 100 μg oral levothyroxine for last 10 years, 1g oral metformin for last 7 years and 500 mg oral calcium once daily for last 5 years.

On examination, she was afebrile and had stable vital signs. There was mild mid epigastric tenderness and no palpable organomegaly. Icterus was marked. Her initial laboratory investigation reports are elaborated in Table 1.

Serological screening for viral hepatitis (hepatitis A, B, C, E and G virus, cytomegalovirus, herpes simplex, and Epstein-Barr virus) were negative and HBV-DNA and HCV-RNA were not detected in either patient. Search for autoimmune liver disorders (anti nuclear antibodies, anti smooth muscle antibodies, and anti mitochondrial antibodies) were also negative. Results of iron, copper, ceruloplasmin metabolism and α1-antitrypsin concentrations were normal. Imaging studies (ultrasonography of whole abdomen and computed tomography of whole abdomen) in both these patients revealed normal hepatic echo texture, normal gall bladder and biliary structures with absence of any focal lesions or other diffused conditions in the liver. Upper GI endoscopy, 12 lead electrocardiography and echocardiography were also well within normal limits.

The 1st patient was non diabetic, non hyperlipidemic with no other significant medical or surgical disorders. However, the 2nd patient had co-existing hypothyroidism and type 2 diabetes mellitus.

There was no history of any herbal or any 'over the counter' drug intake in either patient. The 1st patient was previously on S-amlodipine 1.5 years back, before initiating atenolol. He was not taking any other drugs since then. But the 2nd patient was on 4 concomitant medications:

1. 100 mg atenolol once daily for last 3 weeks,
2. 100 μg oral levothyroxine once daily for last 10 years,
3. 1 g oral metformin once daily for last 7 years,
4. 500 mg oral calcium once daily for last 5 years.

The 2nd patient was treated with oral metformin, levothyroxine and calcium supplements for considerable periods of time and her liver function test was well within normal limits, as demonstrated by the periodic monitoring

Table 1
Relevant investigation results during the episodes of hepatotoxicities in 2 patients.

Serial Nos.	Parameters detected		Detected values in patient 1	Detected values in patient 2	Normal range
1		Hemoglobin	14.7 g/dL	13.9 g/dL	13.3-16.2 g/dL
2		Total WBC count	10 500/μL	9 700/μL	4 000-11 000/μL
3		ESR	25 mm after 1st h	23 mm after 1st h	0-15 mm/h
4		Platelet count	220×10^9/L	280×10^9/L	$165-415\times10^9$/L
5		Fasting blood glucose	101 mg/dL	90 mg/dL	75-110 mg/dL
6		2 hours postprandial blood glucose	126 mg/dL	115 mg/dL	70-120 mg/dL
7		Serum urea	12.3 mg/dL	10.9 mg/dL	7-20 mg/dL
8		Serum creatinine	0.8 ng/mL	0.9 ng/mL	0.6-1.2 ng/mL
9		Serum sodium	136 meq/L	141 meq/L	136-146 meq/L
10		Serum potassium	4.1 meq/L	4.5 meq/L	3.5-5.0 meq/L
11		Serum amylase	55 U/L	61 U/L	20-96 U/L
12		Serum lipase	26 U/L	31 U/L	3-43 U/L
13		Serum lactate dehydrogenase	189 U/L	201 U/L	115-221 U/L
14	Liver function tests	Total bilirubin	5.4 mg/dL	4.8 mg/dL	0.3-1.3 mg/dL
		Direct bilirubin	4.3 mg/dL	3.8 mg/dL	0.1-0.4 mg/dL
		Indirect bilirubin	1.1 mg/dL	1.0 mg/dL	0.2-0.9 mg/dL
		Serum glutamic oxaloacetic transaminase (SGOT)	555 U/L	453 U/L	12-38 U/L
		Serum glutamic pyruvic transaminase (SGPT)	460 U/L	358 U/L	7-41 U/L
		Alkaline phosphatase	176 U/L	157 U/L	33-96 U/L
		Albumin	4.8 g/dL	4.1 g/dL	4.0-5.0 g/dL
		Globulin	3.2 g/dL	3.5 g/dL	2.3-3.5 g/dL
		Prothrombin time	19.9 s	17.7 s	12.7-15.4 s

Table 2
Relevant blood investigation results after hepatotoxicities were resolved in 2 patients (responses to de challenge).

Serial Nos.	Parameters detected		Detected values in Patient 1	Detected values in Patient 2	Normal range
1		Hemoglobin	14.5 g/dL	13.8 g/dL	13.3-16.2 g/dL
2		Total WBC count	9 500/ μ L	9 200/ μ L	4 000-11 000/ μ L
3		ESR	15 mm after 1st h	13 mm after 1st h	0-15 mm/h
4		Platelet count	225×10^9/L	278×10^9/L	$165-415\times10^9$/L
5	Liver function tests	Total bilirubin	1.8 mg/dL	1.2 mg/dL	0.3-1.3 mg/dL
		Direct bilirubin	1.0 mg/dL	0.8 mg/dL	0.1-0.4 mg/dL
		Indirect bilirubin	0.8 mg/dL	0.4 mg/dL	0.2-0.9 mg/dL
		Serum glutamic oxaloacetic transaminase (SGOT)	67 U/L	61 U/L	12-38 U/L
		Serum glutamic pyruvic transaminase (SGPT)	56 U/L	62 U/L	7-41 U/L
		Alkaline phosphatase	107 U/L	97 U/L	33-96 U/L
		Albumin	4.9 g/dL	4.0 g/dL	4.0-5.0 g/dL
		Globulin	3.2 g/dL	3.4 g/dL	2.3-3.5 g/dL
		Prothrombin time	14.8 s	13.9 s	12.7-15.4 s

since the inception of above therapy, hence it is unlikely that these medications induced acute hepatocellular damage after more than 5 years of continuous use.

The above 2 clinical cases, as supported by relevant blood biochemical reports and other investigations highly suggested those to be cases of hepatocellular jaundices, related to atenolol therapy. So, in both the patients, suspected atenolol was discontinued immediately. No other therapeutic modifications were done. Both the patients were improved symptomatically within the next 2 weeks. Within 4 weeks liver function tests were found to be nearly normal in both the patients (Table 2).

The discontinuation of atenolol was resulted in complete symptomatic resolution along with normalization of elevated hepatic transaminases. None of the patients were re-challenged with atenolol. Both the patients are now being treated with oral telmisartan 20 mg daily for hypertension with excellent regulation of their blood pressure.

3. Discussion

Physical signs and symptoms evidenced by a remarkably high value of hepatocellular enzymes indicated hepatotoxicities in these 2 patients. Atenolol has been linked to rare cases of drug-induced liver injury. Hence, it is pertinent to evaluate other potential etiologies of hepatotoxicities in these patients. Drug interactions are very complex, but should always be kept in mind when confronted with adverse effects like hepatotoxicity.

In the 1st patient there was no possibility of drug interaction with the amlodipine metabolites and atenolol as the onset of hepatocellular damage i.e. sign and symptoms appeared after long duration of amlodipine withdrawn. Further, fixed dose combination of atenolol and amlodipine is widely accepted for their protective regulation of blood pressure to decrease the incidence of cardiovascular morbidity and mortality.

In the 2nd patient, either drug interaction among the 4 concomitantly used drugs might have caused hepatocellular damage or a particular drug might be responsible for it. However, there have been no known interactions with any of the concomitant drugs taken by patient 2 in the literature, except few cases of metformin induced hepatotoxicities[5-8]. Rather this widely prescribed polypharmacy strategy often resulted into safe and sustainable therapeutic outcome of these co morbid conditions.

Atenolol has been associated with a minimally increased rate of serum amino transferase elevations and have very rarely been associated with clinically apparent liver injury[9]. Isolated case reports of idiosyncratic hepatotoxicity due to atenolol have been published, but there have been no reported case series[10]. In this report, features of hepatotoxicity were evident after 8 months in patient 1 (chronic) and within 3 weeks in patient 2 (acute) of oral atenolol therapy and symptoms of hepatotoxicities were resolved on discontinuation of the drug and different investigation reports verified reversal of the processes in both the cases. In order to evaluate the relationship between the liver manifestation and atenolol treatment, the Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) scale has been used[11]. The CIOMS/RUCAM scale indicated a 'probable' relationship between atenolol therapy and hepatotoxicities. Extensive literature survey has suggested a favorable impact of atenolol on hepatic function. However 3 reports of acute hepatitis have been documented with atenolol. There are also some reports of hepatotoxicities with other beta blockers like labetolol, betaxolol, esmolol, etc[12-15].

A 73-year-old man with hypertension developed pruritus and right upper quadrant abdominal pain associated with elevated serum liver function tests within 9 months after switching from methyldopa to atenolol. Liver biopsy revealed canalicular and centrolobular cholestasis. No other etiology was found. The patient's signs and symptoms of hepatitis resolved within 1-4 weeks after stopping atenolol. Re-challenge was not done[16].

In another case, a 78-yr-old man developed hepatic dysfunction within few days of starting atenolol. Blood tests revealed abnormal liver function with markedly raised liver enzymes and moderately raised bilirubin and alkaline phosphatase, suggesting hepatocellular damage and some cholestasis. Atenolol was stopped on admission and subsequently there was an improvement in liver function and was almost normal after 2 weeks. Due to this improvement and absence of other causes, it was suspected that liver dysfunction was atenolol-induced[17].

Also, in another case report, a 57-year-old liver transplanted woman with the known history atenolol therapy for hypertension for 3 years prior to liver transplantation was reintroduced atenolol at a dose of 100 mg/day because of recurrence of hypertension. After 1 month, she presented with acute hepatitis which was evidenced by portal and centrilobular inflammatory lesions. An initial diagnosis considered in this patient was acute rejection. This diagnosis had to be reconsidered because of the unfavorable outcome, despite specific treatment of rejection. Moreover, the patient had been treated with atenolol for 3 years before liver transplantation; in the absence of any other etiology, the possibility that she had atenolol-induced cirrhosis may therefore be considered and favorable outcome was achieved only upon atenolol withdrawl[18].

The exact insight of mechanism of how atenolol related hepatotoxicity is debatable as then agent has a little or no hepatic metabolism, but their prevalence must be correlated as hepatotoxicity is a serious medical condition and can result in grave prognosis. One published case reports hypothesized an immune-mediated mechanism of hepatotoxicity based on the inflammatory infiltrates observed in the liver biopsy specimens[19,20].

When prescribing atenolol, a commitment to baseline screening and monitoring liver functions may be required to mitigate the likelihood of developing hepatic abnormalities and their associated deleterious consequences. Physicians must have a high degree of suspicion and should remain cautious and warn patients to report any symptoms of hepatotoxicity after taking this drug. There should be provisions for early withdrawing the offending drug and supportive therapy to lower the intensity of this unexpected potential life threatening drug induced complication.

Conflict of interest

We declare that we have no conflict of interest.

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