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NEBIVOLOL-INDUCED HEPATOXICITY: A CASE REPORT

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ABSTRACT

Nebivolol is a third-generation beta-blocker known for its high selectivity for beta-1 adrenergic receptors and its unique ability to induce vasodilation via nitric oxide (NO) release. Nebivolol, despite its favourable safety profile, can lead to significant liver injury. We describe the case of a 73-year-old hypertensive patient who developed significant liver enzyme elevations following the addition of nebivolol to her treatment regimen. Comprehensive workup ruled out other causes, leading to a diagnosis of drug-induced hepatotoxicity. Discontinuation of nebivolol resulted in normalization of liver enzymes. This case underscores the importance of monitoring liver function during beta-blocker therapy, particularly with nebivolol.

KEYWORDS

Nebivolol, hepatotoxicity

LEARNING POINTS

- Nebivolol, despite its favourable safety profile, can lead to significant liver injury.
- Clinicians should remain vigilant and consider routine liver function monitoring in patients prescribed nebivolol, particularly if they present with nonspecific symptoms or abnormal liver enzyme tests.
- Early recognition and prompt discontinuation of the offending agent are crucial in preventing severe outcomes.

INTRODUCTION

Nebivolol is a third-generation beta-blocker known for its high selectivity for beta-1 adrenergic receptors and its unique ability to induce vasodilation via nitric oxide (NO) release. Unlike other beta-blockers, nebivolol not only decreases heart rate and myocardial contractility through beta-1 receptor blockade but also promotes vasodilation by stimulating endothelial NO synthase, leading to the release of NO[1]. This dual mechanism helps reduce blood pressure by decreasing both cardiac output and peripheral vascular resistance, making it an effective treatment option for hypertension and heart failure[2]. Nebivolol is generally well-tolerated, with a safety profile that favors its use over older beta-blockers, particularly due to fewer side effects associated with the central nervous system (CNS). However, there are rare cases of drug-induced liver injury (DILI) reported in association with its use. The exact mechanism of nebivolol-induced hepatotoxicity is not fully understood but may be linked to its hepatic metabolism involving cytochrome P450 enzymes, particularly CYP2D6[2]. The metabolism and

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excretion processes could result in the formation of reactive metabolites or direct liver cell toxicity, potentially causing both hepatocellular and cholestatic liver injury patterns[3].
Given these risks, it is essential to monitor liver function tests during the early months of nebivolol therapy, especially in patients with existing liver conditions or those on other potentially hepatotoxic drugs. This case adds to the limited evidence of nebivolol-induced hepatotoxicity, highlighting the importance of vigilance in clinical practice to prevent severe hepatic complications.

CASE DESCRIPTION

A 73-year-old woman, diagnosed with hypertension in October 2023, was initially prescribed lisinopril 10 mg once daily. After 1 month, her blood pressure remained uncontrolled, prompting an increase in the lisinopril dose to 20 mg once daily. Despite this adjustment, her blood pressure continued to be elevated after 2 months of treatment. As a result, nebivolol 30 mg once daily was added to her regimen alongside lisinopril 20 mg once daily. This combination successfully reduced her blood pressure, and the patient was maintained on this treatment plan. Three months after the introduction of nebivolol, routine blood tests revealed a significant increase in her liver enzymes: aspartate aminotransferase (AST) at 65 U/l (normal <40 U/l), alanine aminotransferase (ALT) at 134 U/l (normal <40 U/l), alkaline phosphatase (ALP) at 491 U/l (normal <125 U/l), and γ-glutamyl transpeptidase (GGT) at 761 U/l (normal <40 U/l). These results indicated both cholestatic and hepatocellular patterns of liver injury.
Given these findings, a comprehensive hepatic workup was conducted. Abdominal ultrasound and compited tomography (CT) scan did not reveal any significant abnormalities that could explain the elevated liver enzymes. Serologic testing for Epstein-Barr virus (EBV), cytomegalovirus (CMV), and hepatitis A, B, C, and E was negative. Additionally, tests for antinuclear antibody (ANA), double-stranded deoxyribonucleic DNA (dsDNA), liver kidney microsome (LKM), anti-smooth muscle antibody (SMA), and anti-mitochondrial antibody (AMA) were all negative, effectively ruling out autoimmune hepatitis. The patient reported no alcohol use and had no history of liver disease.
Given the absence of other causes, drug-induced hepatotoxicity was suspected. Nebivolol was discontinued, and 4 weeks later, repeat liver function tests showed a return to baseline enzyme levels *(Table 1)*. This confirmed nebivolol as the likely cause of the hepatotoxicity. Consequently, nebivolol was replaced with atenolol 50 mg once daily.

DISCUSSION

Nebivolol is a selective beta-1 adrenergic blocker commonly used for the treatment of hypertension and heart failure. This drug also acts on the vascular endothelium by stimulating NO synthase, which induces NO-mediated vasodilation[1]. It operates primarily by reducing cardiac output and peripheral resistance. Nebivolol's reported adverse effects typically involve the CNS. Headache is the most commonly reported adverse effect (6 to 9%)[1], other less common side effects include: acute pulmonary edema, acute kidney injury (AKI), angioedema, hypersensitivity reaction, DILI, thrombocytopenia and others.
In this case, a 73-year-old female developed significant liver enzyme elevations with both hepatocellular and cholestatic patterns of injury after 3 months of nebivolol therapy, which normalized after discontinuation of the drug. This confirms the diagnosis of drug induced liver hepatotoxicity. It is important to note that drug-induced liver injury is a diagnosis of exclusion, as demonstrated in our case. The patient's lack of alcohol consumption, absence of a prior history of liver disease, the negative viral serologies for EBV, CMV, hepatitis A, B, C and E, the negative antibodies: ANA, dsDNA, LKM, SMA and AMA and the normal imaging studies further confirms the likelihood that nebivolol was responsible for the liver injury. The prompt normalization of liver enzymes following discontinuation of nebivolol and the absence of hepatotoxicity upon switching to atenolol indicate that the liver injury was indeed drug-related. The management of DILI is based upon proper diagnosis, recognition of the offending agent, and its withdrawal[4]. The mechanism by which nebivolol induces hepatotoxicity

	Baseline	3 months post nebivolol	4 weeks post nebivolol discontinuation
Bilirubin total (mg/dl)	0.50	0.57	0.53
Bilirubin direct (mg/dl)	0.20	0.23	0.22
ALP (IU/L)	70	491	77
AST (IU/L)	31	65	33
ALT (IU/L)	45	134	49
GGT (IU/L)	51	761	55

Abbreviations: ALP, alkaline phosphatase; AST, sspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase.

Table 1. Liver function tests before and after discontinuation of nebivolol.

is not well understood. Nebivolol undergoes extensive metabolism by the liver, it is a substrate of CYP2D6 and its excretion is largely biliary[5]. Similar to other beta-blockers, it may involve an idiosyncratic reaction, potentially mediated by immune mechanisms or direct hepatocyte toxicity. Mild-to-moderate elevations in serum aminotransferase levels occur in less than 2% of patients on beta-blockers and are usually transient and asymptomatic[5]. Moreover, the use of nebivolol in the elderly population, as in our patient, could be a contributing factor to the heightened risk of hepatotoxicity. The aging-related changes including increased oxidative stress, increased inflammatory response, accelerated cellular senescence, and progressive organ dysfunction significantly affect cellular responses to injury[6]. Aging is associated with decreased hepatic blood flow and altered drug metabolism, which could potentiate the hepatotoxic effects of medications like nebivolol.

The Naranjo adverse drug reaction (ADR) probability scale is a tool used to assess the likelihood that an adverse drug reaction is attributable to a specific drug. It comprises 10 questions, each assigned specific point values. The total score aids in classifying the ADR as definite, probable, possible, or doubtful[7]. In this case, the Naranjo score was calculated to evaluate the probability of nebivolol causing hepatotoxicity, yielding a total score of 8, indicating that it is "probable" that nebivolol will cause an ADR.

To our knowledge, this is one of the few reported cases of nebivolol-induced hepatotoxicity. Previous reports have primarily focused on the hepatic effects of other beta-blockers like metoprolol, with few detailing the specific impact of nebivolol. Although the exact incidence and risk factors remain poorly defined, the typical liver injury associated with beta-blockers has a latency to onset of 2 to 12 weeks[8].

CONCLUSION

This case shows that nebivolol, despite its favourable safety profile, can lead to significant liver injury. Clinicians should remain vigilant and consider routine liver function monitoring in patients prescribed nebivolol, particularly if they present with nonspecific symptoms or abnormal liver enzyme tests. Early recognition and prompt discontinuation of the offending agent are crucial in preventing severe outcomes. The diagnosis of DILI is typically made by establishing a temporal relationship between drug exposure and development of signs and symptoms of liver disease. Further studies are warranted to better understand the mechanisms and risk factors associated with nebivolol-induced hepatotoxicity, with a particular focus on genetic factors and age-related susceptibility. Nebivolol-induced hepatotoxicity may not be universally predictable but warrants vigilance, especially in long-term therapy settings.

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