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EARLY DETECTION OF NEBIVOLOL-INDUCED HEPATOTOXICITY

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ABSTRACT

Introduction: Nebivolol, a third-generation selective β1-adrenergic receptor antagonist possessing vasodilatory properties, is characterised by a favourable safety profile. However, isolated cases of drug-induced liver injury (DILI) associated with its use have been documented in the literature.

Case description: We present a case of hepatotoxicity in a 58-year-old female patient with a history of arterial hypertension, obesity and impaired glucose tolerance. Eight weeks after initiating nebivolol therapy (2.5 mg daily), a significant elevation in liver enzymes was observed: alanine aminotransferase (134.5 U/l), aspartate aminotransferase (118.1 U/l) and alkaline phosphatase (182.1 U/l), compared to previously normal baseline values. After excluding other potential causes (viral hepatitis, alcohol consumption, biliary obstruction), nebivolol was discontinued. Subsequent clinical and laboratory improvement was noted: transaminase levels decreased significantly within two weeks, and biochemical parameters had almost completely normalised after two months. The Naranjo Adverse Drug Reaction Probability Scale score was 7, indicating a probable causal relationship. Subsequent replacement of nebivolol with metoprolol did not result in recurrent hepatic dysfunction.

Conclusion: This case substantiates the potential for idiosyncratic mixed-type hepatotoxicity associated with nebivolol administration. Although rare, this report underscores the importance of clinical vigilance and the consideration of DILI in cases of unexplained liver enzyme elevations in patients receiving this agent. Monitoring of liver function during the initial months of therapy is advisable, particularly in patients with underlying comorbidities.

KEYWORDS

Nebivolol, hepatotoxicity, adverse drug reaction, beta-adrenergic antagonists

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LEARNING POINTS

- Nebivolol, despite its favourable safety profile can, rarely, cause significant mixed-type (hepatocellular-cholestatic) liver injury.
- Early recognition of drug-induced liver injury and prompt discontinuation of the offending agent are crucial for complete recovery.
- Monitoring of liver enzymes during the initial weeks of nebivolol therapy should be considered, especially in patients with metabolic risk factors.

INTRODUCTION

Nebivolol is a third-generation selective β_1-adrenergic receptor antagonist distinguished by a unique ancillary mechanism of action involving the stimulation of nitric oxide (NO) release from the vascular endothelium, thereby inducing vasodilation[1]. This dual pharmacological profile not only results in effective blood pressure (BP) reduction but is also associated with beneficial effects on peripheral haemodynamics and endothelial function, as well as antioxidant and anti-inflammatory activity[1]. A meta-analysis of clinical trials has confirmed that nebivolol is an effective antihypertensive agent, with a hypotensive effect comparable or superior to that of other major drug classes including diuretics, angiotensin II receptor blockers and other beta-blockers[2]. Importantly, nebivolol demonstrates a better tolerability profile compared to traditional beta-blockers such as atenolol and metoprolol, with a significantly lower incidence of common adverse events[2].

The metabolism of nebivolol occurs primarily in the liver via the cytochrome P450 2D6 (CYP2D6) isoenzyme, which results in significant interindividual pharmacokinetic variability depending on the genetic polymorphism of this enzyme[3]. In the available literature, nebivolol is characterised by a favourable safety profile, including with respect to hepatic adverse effects. Large-scale clinical trials, such as SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors) and systematic reviews have not identified a significant increase in the incidence of DILI associated with its use[2]. Furthermore, experimental data suggest potential hepatoprotective properties of nebivolol related to the suppression of oxidative stress, inflammation and endoplasmic reticulum (ER)-induced apoptosis[4].

However, despite its overall safety, isolated cases of hepatotoxicity associated with nebivolol administration have been documented in the global literature. The first detailed clinical case was presented by Srour et al. in 2024, describing a 73-year-old female patient who developed a significant elevation of liver enzymes with a mixed (cholestatic-hepatocellular) pattern following initiation of nebivolol therapy, with subsequent normalisation of parameters after drug discontinuation[5]. Such observations underscore that, although rare, this adverse effect is clinically significant and warrants heightened awareness.

In this report, we describe another instance of nebivolol-induced hepatotoxicity in a patient with arterial hypertension, providing a detailed analysis of the clinical and laboratory dynamics before, during and after drug withdrawal. The aim of this is to draw attention to the necessity of monitoring liver function in patients receiving nebivolol therapy, particularly during the initial phase of treatment, and to discuss the potential mechanisms underlying the development of this adverse reaction.

CASE DESCRIPTION

A 58-year-old female patient was under observation with a 15-year history of arterial hypertension. Her comorbid background included class I obesity (BMI 30 kg/m^2), impaired glucose tolerance (HbA1c 6%), mild bronchial asthma, a history of cholecystectomy (10 years prior) and a remote history of viral hepatitis A (40 years prior). At the time of initial presentation, her baseline antihypertensive regimen consisted of lisinopril (10 mg/day) and rosuvastatin (10 mg/day). Her medical history was notable for poor tolerability of previous beta-blockers (bisoprolol, carvedilol), manifested by excessive BP reduction.

On 7 October 2025, the patient attended an outpatient cardiology consultation reporting palpitations with a heart rate of up to 90 bpm. Based on the diagnoses of essential hypertension (ICD-10 code I11.9) and unspecified cardiac arrhythmia (I49.9), nebivolol was prescribed at a dose of 2.5 mg (half of a 5 mg tablet) once daily in the morning. During combination therapy with lisinopril, rosuvastatin and nebivolol, satisfactory control of BP (120/80 mmHg) and heart rate (75 bpm) was achieved.

Approximately 8 weeks later on 2 December 2025, routine laboratory evaluation during an endocrinology follow-up visit revealed significant abnormalities in liver function tests: alanine aminotransferase (ALT) 134.5 U/l, aspartate aminotransferase (AST) 118.1 U/l and alkaline phosphatase (ALP) 182.1 U/l, whereas these parameters had been within normal limits in July of the same year. Gamma-glutamyl transferase (GGT) levels may have been initially elevated due to metabolic syndrome manifested by impaired glucose tolerance and obesity[6]. These findings were indicative of a mixed (hepatocellular-cholestatic) pattern of liver injury. Upon detailed history-taking, the patient denied alcohol consumption, use of hepatotoxic over-the-counter medications or herbal products. The only new medication introduced within the preceding two months was nebivolol.

	Norm	Three months before nebivolol	One month post nebivolol	Two weeks post nebivolol discontinuation	Two months post nebivolol discontinuation
Bilirubin total (mmol/l)	Adults 5–21	9.51	9.8	-	7.5
Bilirubin direct (mmol/l)	Adults < 3.4	-	2.34	-	-
AST (IU/l)	Women < 35	32.4	118.1	39.9	22.1
ALT (IU/l)	Women < 35	24	134.5	41.1	13.2
ALP (IU/l)	Adults 30–120	-	182.1	184.8	88.6
GGT (IU/l)	Women < 38	-	-	560	125.9

Table 1. The dynamics of biochemical parameters following nebivolol withdrawal.

The official prescribing information for nebivolol recommends caution in patients with hepatic impairment, which raised suspicion of drug-induced hepatotoxicity. To substantiate this hypothesis, a literature search of the PubMed database was conducted, identifying a similar clinical case of nebivolol-induced hepatotoxicity[5].

On 4 December 2025, the patient was evaluated by a gastroenterologist; nebivolol was immediately discontinued. To exclude alternative aetiologies of liver injury, a comprehensive workup was performed: ultrasonography of the hepatobiliary system revealed no changes compared to a study performed one year earlier; serological testing for hepatitis B, hepatitis C and HIV-1/2 was negative; esophagogastroduodenoscopy was also performed. Hepatoprotective and choleretic agents were prescribed to support liver function.

The dynamics of biochemical parameters following nebivolol withdrawal are presented in *Table 1* and demonstrated a favourable trend. Two weeks after discontinuation, AST (39.9 U/l) and ALT (41.1 U/l) levels had decreased significantly, approaching reference values, although ALP (184.8 U/l) and GGT (560.0 U/l) levels remained elevated. Two months after drug withdrawal, AST (22.1 U/l), ALT (13.2 U/l) and ALP (88.6 U/l) had normalised, while GGT (125.90 U/l) showed a trend toward normalisation.

During a subsequent cardiology consultation, nebivolol was replaced with metoprolol. On metoprolol therapy, stable BP and heart rate control were maintained without evidence of hepatic dysfunction. Thus, this clinical case describes the development of mixed-type hepatotoxicity temporally associated with nebivolol administration, with complete reversibility of laboratory abnormalities following drug discontinuation, consistent with a probable causal relationship *(Table 1)*.

DISCUSSION

This case describes the development of mixed-type (hepatocellular-cholestatic) hepatotoxicity in a patient with arterial hypertension during nebivolol therapy. Normalisation of liver enzyme levels within two months following drug discontinuation, after excluding other potential causes (viral hepatitis, alcohol consumption, biliary obstruction), fulfils the criteria for DILI[7]. Such an observation adds to the extremely limited number of reports concerning this adverse reaction, emphasising that despite its favourable overall safety profile and documented hepatoprotective properties in experimental models[4], nebivolol, like any pharmacological agent, may serve as a trigger for idiosyncratic liver injury.

The clinical presentation in our case demonstrates substantial similarity to the previously reported case by Srour et al.[5]: middle-aged and elderly female patients developed concurrent elevations of transaminases and cholestatic markers (ALP, GGT) after 8–12 weeks of nebivolol therapy, followed by rapid regression upon drug withdrawal. This temporal pattern (with a latency period of 2 to 12 weeks) is typical for DILI associated with beta-adrenergic receptor antagonists[8]. It is noteworthy that our patient presented with potential risk factors that could modulate hepatotoxicity risk or influence drug metabolism: obesity, impaired glucose metabolism and a remote history of hepatitis A infection. Although a direct causal relationship between these conditions and nebivolol-induced DILI has not been established, they may have created an unfavourable metabolic and potentially pro-inflammatory milieu.

The pathogenesis of idiosyncratic hepatotoxicity associated with nebivolol remains incompletely elucidated, and individual variations in drug metabolism likely play a pivotal role. Nebivolol is a substrate of the CYP2D6 isoenzyme, whose genetic polymorphism determines patient status as an extensive, intermediate or poor metaboliser[3]. In poor metabolisers, accumulation of the parent drug or its intermediate metabolites may occur, theoretically increasing the risk of toxic reactions. Although pharmacogenetic testing was not performed in our case, variability in CYP2D6-mediated metabolism may precisely explain the rarity of this adverse effect. Interestingly, in an experimental model of lipopolysaccharide-induced sepsis, nebivolol exhibited hepatoprotective effects by suppressing oxidative stress, inflammation and ER stress-

mediated apoptosis via the Chop/Bip pathways[4]. This finding presents a paradox: a drug with demonstrated protective properties under experimental stress conditions may, in rare instances, initiate liver injury in humans. One might hypothesise that in predisposed individuals, nebivolol metabolites or immune mechanisms activated by drug administration could conversely induce ER stress and mitochondrial dysfunction in hepatocytes, triggering a cascade of cellular damage. This hypothesis warrants further investigation.

To objectively assess causality in our case, the Naranjo Adverse Drug Reaction Probability Scale was applied[9]. The total score was 7, corresponding to a probable causal relationship between nebivolol administration and the development of hepatotoxicity. Key corroborating factors included a clear temporal association, a positive de-challenge outcome and the existence of a previously published analogous case.

In the context of clinical practice, this case underscores several important considerations. First, it highlights the necessity for physician awareness regarding the potential for hepatotoxicity even among medications with an exceptionally favourable safety profile confirmed by meta-analyses[2]. Second, it suggests the utility of monitoring liver biochemical parameters (ALT, AST, ALP, GGT) at 4–8 weeks following initiation of nebivolol therapy, particularly in patients with existing risk factors (advanced age, obesity, metabolic syndrome, significant hepatic history). Third, it emphasises the importance of thorough medication history-taking and prompt discontinuation of potentially hepatotoxic agents at the earliest signs of DILI, which constitutes the cornerstone of successful management and prevention of progression to fulminant hepatic failure.

CONCLUSION

This observation serves as a reminder of the importance of pharmacovigilance and individualised therapeutic approaches, even when employing well-studied medications with established population-level safety profiles. Further research directed towards elucidating the molecular mechanisms of idiosyncratic hepatotoxicity associated with nebivolol, as well as identifying genetic and clinical risk markers, will help optimise its safe clinical use.

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