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Original Article

OXIDATIVE STRESS-BASED HEPATOTOXICITY OF DULOXETINE IN WISTAR RATS

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ABSTRACT

Objective: Duloxetine, a selective serotonin and noradrenaline reuptake inhibitor used in major depressive disorders, urinary incontinence and diabetic peripheral neuropathic pain. It is reported to be associated with several types of liver injuries, including hepatocellular, cholestatic and mixed hepatocellular-cholestatic patterns. The objective of this study was to assess the effect of duloxetine or its metabolites on oxidative stress-induced liver damages.

Methods: In this study, animals were divided into five groups. In the first group, the only vehicle was given orally for 21 d. The second group has been considered as hepatotoxic control group where Erythromycin was given orally for 14 d and remaining three groups have been considered as test groups where duloxetine, fluvoxamine and duloxetine along with fluvoxamine were administered orally for 21 d. Liver GSH, oxidised lipid malonaldehyde (MDA), superoxide dismutase (SOD), catalase (CAT), protein carbonyl (PC) and plasma alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP) levels were measured to determine the level of hepatotoxicity. Scanning electron microscopy (SEM) study of liver tissues was also performed to examine the liver injuries.

Results: GSH and SOD levels were found to be decreased in duloxetine-treated groups with respect to the hepatotoxic control group, whereas increased level of MDA, CAT and PC signify the damages of liver cells. Increased level of plasma ALT, AST and ALP at the same time indicated liver tissue damage. Opposite effects were observed in the case of duloxetine and fluvoxamine-treated groups. SEM of liver tissues revealed that the tissue injury occurred in Duloxetin treated groups, whereas the restoration of normal tissue architecture took place due to the administration of duloxetine and fluvoxamine-treated groups.

Conclusion: Our results collectively indicated that hydroxylated and epoxide metabolites of duloxetine might have hepatotoxic potential due to oxidative stress produced by the release of free radicals or reactive oxygen species.

Keywords: Duloxetine, CYP1A2 enzyme, Hepatotoxicity, Oxidative stress

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INTRODUCTION

Duloxetine (DLX, fig. 1A) [N-methyl-γ-(1-naphthyloxy)-2-thiophene-propylamine] is a selective serotonin and noradrenaline reuptake inhibitor, approved by the USFDA for the treatment of major depressive disorders. In addition, it is also used in stress-induced urinary incontinence and diabetic peripheral neuropathic pain [1]. DLX is highly bind to plasma proteins (>90%) and mainly metabolised by various cytochrome (CYP) enzymes, such as CYP1A2 and CYP2D6 in humans. Although, the naphthyl ring underwent epoxidation and subsequently formed adduct with glutathione (GSH), but thiophene moiety showed inert after bioactivation [1]. The bioactivation of naphthyl ring mediated through CYP1A2 enzyme corresponds to 4-hydroxy DLX, 6-hydroxy-5-methoxy DLX and 4, 6-dihydroxy DLX [4]. Sometimes, naphthyl ring could generate reactive metabolites, i.e. epoxides which may cause hepatotoxicity [2]. The role of the CYP2D6 enzyme during bioactivation of DLX was not prominent in the case of both rats and humans.

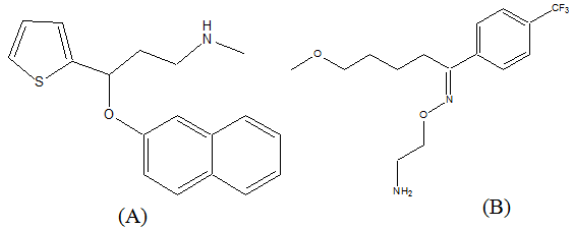

Fig. 1: Structures of (A) DLX and (B) FLX

Recently, it has been reported that DLX was reported to be associated with several cases of hepatocellular, cholestatic and mixed hepatocellular-cholestatic patterns of liver injuries [3]. Hepatobiliary diseases were estimated to occur in about 8 per 100,000 cases, while elevation of enzyme level increased thrice the value of normal range as observed in 0.9 to 1.7% of DLX treated subjects [4, 5]. Idiosyncratic liver damages were estimated to occur about 1-2 per 100,000 cases of exposure in DLX [4]. In a pooled analysis of 17615 subjects, the incidence of serum ALT level was increased three times than normal value [6]. Hanje *et al.* (2006) reported and explained the cause of fulminant hepatic failure and death during DLX therapy [7]. Taking into all these considerations related to DLX inducing hepatotoxicity, the question arose whether DLX or its metabolites has any role in hepatotoxicity or not? It has been reported that DLX is metabolised by both CYP1A2 and CYP2D6. Therefore, the objective of this study was to evaluate the effect of Duloxetine or its metabolites on oxidative stress-induced hepatotoxicity. In order to further ascertain the oxidative stress-induced hepatotoxicity, docking studies were also performed accordingly.

MATERIALS AND METHODS

Materials

Duloxetine (DLX; Batch Number: DL0040713) and Fluvoxamine (FLX; fig. 1B, Batch Number: LT-OFLM/014/12-13) were received from Indian companies namely Hetero Drugs Limited, Hyderabad, and Mehta API Pvt Ltd, Mumbai, respectively. Disodium ethylenediamine tetraacetic acid (EDTA), disodium hydrogen phosphate, potassium dihydrogen phosphate, sodium citrate and