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Prevalence of abnormal liver-associated enzymes in cocaine experienced adults versus healthy volunteers during Phase 1 clinical trials

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Abstract

The frequency and nature of elevation of liver-associated enzymes (LAE) are important safety endpoints in Phase 1 clinical trials of new anti-cocaine agents, yet very little information is available on the prevalence of abnormal LAE in cocaine experienced adults. The aim of this retrospective study was to investigate the alterations of liver-associated enzymes (LAE) aspartate- (AST) and alanine transaminase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), and bilirubin in healthy "normal" (HN) and cocaine experienced (actively using cocaine preadmission (CE)) adults participating in long term inpatient clinical trials. We examined LAE values collected from 3 inpatient Phase 1 trials of anti-cocaine agents. Analysis of variance (ANOVA) was applied to determine the significance of various factors on LAE alterations. Gender, baseline BMI, treatment did not demonstrate significant group differences in LAE levels.

CE study volunteers were found to have significantly higher AST and ALT values than HN volunteers ($P<0.05$) during their respective inpatient stays. 94.1% of the 17 subjects with abnormal LAE were CE, and 37.5% of these CE received placebo.

In conclusion, despite normal baseline values, most subjects demonstrated an increase in the ALT level even on placebo. For CE subjects, differences (△ALT and △AST) between baseline and the maximum observed values were significantly higher than that observed for HN subjects. The potential to obscure important signals for hepatotoxicity during Phase 1 research may be higher in the CE study population.

Keywords: Liver-associated enzymes; Cocaine; Phase 1; Inpatient trials

1. Introduction

Adverse drug reactions are a major concern in the development of modern medicines, and drug-induced hepatotoxicity, manifested as a rise in liver-associated enzymes (LAE), is the most frequent reason for discontinuation

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Table 1
Effect of drug abuse status on ΔBM and BM

Drug abuse status	ΔBM (lb) mean (SD)	BM discharge (lb) mean (SD)
Cocaine users $N=65$	4.08 (6.33)	179.74 (25.25)
Normal $N=47$	1.08 (3.19)	171.31 (16.73)
P-value	0.0001	0.001

of the development of new chemical entities (NCE) [1]. However, a significant LAE increase during Phase 1 clinical trials is not always attributed to hepatotoxicity caused by an NCE [2].

Rosenzweig et al. [3] reported that 20.4% of healthy volunteers receiving placebo showed abnormal ALT values, stressing that ALT elevations during a Phase I trial may be due to nondrug-related causes, such as experimental conditions. There are many factors that can affect LAE such as diet, exercise, and individual characteristics of subjects.

The majority of early clinical studies investigating alterations of liver-associated enzymes were performed in healthy volunteers [3–10]. Because of the growing demand for the development of effective treatments for drug addiction, there are numerous Phase 1 studies conducted with drug dependent adult subjects [11,12]. This particular population group has a high prevalence of low body weight and malnutrition [13]. In subjects with compromised nutritional status, levels and activities of P450 enzymes and xenobiotic metabolism may be impaired [14,15]. These types of alterations may cause dramatic changes in liver-associated enzyme measurements compared to healthy volunteers.

The three objectives of this study were (1) to compare changes of liver-associated enzymes during inpatient clinical trials for subjects grouped according to gender; baseline BMI (normal/overweight); drug abuse status (drug user/non-user); treatment (placebo/active drug), (2) to investigate the prevalence of LAE elevation among healthy normal (HN) and cocaine experienced (CE) adults, and (3) to determine if baseline laboratory parameters may predict LAE elevation.

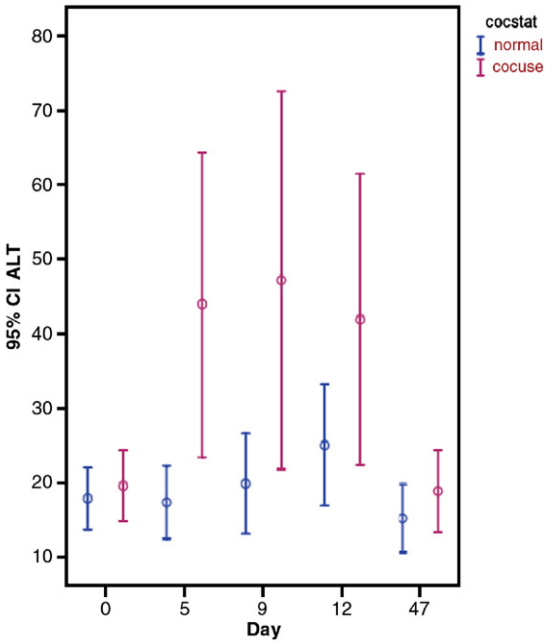

Fig. 1. Effect of drug abuse status on ALT (U l^{-1}). This figure and Figs. 1–5 represent LAE (U l^{-1}) and bilirubin (mg dl^{-1}) changes for CE and NH. Data points are determined from plasma samples taken during inpatient (study days 0, 5, 9 and 12) and outpatient (follow-up, day 47) periods.