THE INFLUENCE OF A LOW FAT DIET AND HOSPITALISATION ON LIVER FUNCTION TESTS IN HEALTHY JAPANESE AND CAUCASIAN MALE VOLUNTEERS RESIDENT IN A PHASE I UNIT FOR UP TO 34 DAYS

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Introduction

Hepatotoxicity is a major factor for the removal of new chemical entities (NCEs) from development. Evidence suggests that the 130 drugs withdrawn from the market for safety reasons between 1964 and 1992, adverse effects on the liver were responsible in 18% of cases. Not only does this emphasize the importance of detecting the potential hepatotoxicity of NCEs but also underscores the possibility of false negative results during early clinical studies of NCEs in healthy volunteers (Phase I trials).

Literature evidence suggests that healthy subjects on placebo in Phase I trials can have abnormalities in their liver function test (LFT) parameters, but varying and conflicting results are observed that 20.4% of healthy subjects on placebo in 13 Phase I trials for a fixed period of 14 days had elevated alanine aminotransferase (ALT) levels. Kobayashi et al. (1993) found a lower prevalence of 12.6%, but their review included a period of only 7 days. In 13 placebo-controlled multiple dose Phase I studies (mean: 13.6 days) 20% subjects had an increase in LFT parameters. Hospitalisation of healthy subjects in Phase I trials might also increase LFT parameters. Kanamaru et al. (1989) reported ALT elevation in 16 healthy volunteers who rested for 7 days. However, another study involving bed rest for a week did not report an elevation in ALT. Diet may play a role in Patillo and Ikeda (1983) demonstrated that a combination of excess calories and high sucrose intake was associated with elevation in serum transamisferases. The role of carbohydrate may be further confirmed by an 8 day three way cross over study in 12 healthy subjects that showed significant increases in ALT of 5 of 12 subjects fed a high-carbohydrate high-sucrose diet (32% sugar, 45% carbohydrates) but none of the subjects fed either a high-carbohydrate-high-fat diet (4500 kcal/day) or a balanced healthy diet (1900 kcal/day). These data indicated that excess carbohydrate rather than sucrose caloric itself was the main driver responsible for the rise in LFT parameters.

Aim

The aim of the study was to explore effects of a low fat (<20%) high carbohydrate (55%), low protein (20%) diet with hospitalisation on the levels of ALT and other liver enzymes in healthy Japanese and Caucasian subjects who were enrolled in a Phase I bridging study (who investigated the LDL lowering properties of a newly licensed medicine).

Methods

The baseline and placebo data consisted of 72 (36 Japanese and 36 Caucasian) male subjects with a body mass index (BMI) of 18.5 to 30 kg/m² with elevated low density lipoprotein cholesterol (LDL-C) levels who were otherwise healthy. Subjects were resident for 34 days in the clinical pharmacology unit and received a strict low fat diet (<20% of calories from fat) consisting of 72% carbohydrates. All 72 subjects participated in a one week in house diet run. Of these, 16 volunteers (8 Japanese and 8 Caucasian) received placebo throughout the study and were included into this post-hoc analysis.

We show that a low fat (<20%), carbohydrate rich normo-caloric diet in combination with 34 days hospitalisation lead to an increase of ALT levels in 16 of 72 subjects with 44% of subjects exceeding the UNL on Day 20. (Table 2 in Panel C)

Although there is literature evidence purporting to a potential role for placebo, length of hospitalisation and diet (particularly those that are carbohydrate rich) in increasing liver enzymes of healthy volunteers in Phase I trials, there is no information directly comparing Japanese and Caucasian subjects within the same study and there are few studies sampling for one month of continuous hospitalisation.

The results indicate that the difference observed between Japanese and Caucasian subjects was not statistically significant. However, a trend suggests that Japanese subjects are more prone to increases in liver function parameters. In particular, ALT appeared to increase sooner for Japanese subjects (after 7 days) in comparison to Caucasian subjects whose ALT levels began to rise only after 14 days.

Other studies have demonstrated a clear relationship between increases in liver enzymes and the number of days hospitalised, and that a high caloric high carbohydrate diet elicits, in particular, a larger increase in ALT (10%) and AST (10%) in Japanese subjects (43). In this study we found that a carbohydrate rich normo-caloric diet in combination with hospitalisation for one week in 72 subjects did not increase liver function parameters above the UNL and there were no noteworthy increases in ALT and AST before 7 days. This finding is in agreement with the observation made by Miknis and colleagues who showed that subjects on bed rest for a week did not report ALT elevation.

However, an extended observation period on a low fat high carbohydrate diet of up to 34 days in 16 subjects with elevated cholesterol (LDL-C) showed a time related increase of ALT after 20 days of hospitalisation. At that point, seven of 16 subjects (44%) showed increases in ALT exceeding the UNL, remaining at that level until day 34. The Japanese subjects showed the greatest change in ALT from baseline. Individual values showed remarkable steadiness in the number of values over time, with few subjects showing no change at all. Our study had limitations. First, the current study was done on healthy volunteers that have normal cholesterol (LDL-C) levels. Secondly, the study imposed a strict carbohydrate rich, low fat diet itself as a treatment; therefore one cannot assess the effect of hospitalisation or diet alone. Thirdly the sample is small and therefore the differences between Japanese and Caucasian are not statistically significant.

Discussion

Table 1: Summary of Demographic Data for Japanese and Caucasian Subjects - Placebo

Table 2: Summary of ALT Changes from Day 1 (baseline) to Day 20

References


Figure 1: ALT levels in male Japanese and Caucasian subjects, UNL ( ),..., ( ) and Japanese ( ),..., ( ) levels.

Figure 2: Effect of placebo upon ALT (A) and AST (B) levels in male Japanese (□) and Caucasian subjects (○) over a period of 34 days, UNL ( ), Caucasian (○) and Japanese (□) levels.

Figure 3: Data are presented as mean ± standard deviation. Figure 4: Data are presented as mean ± standard deviation.

Figure 5: Data are presented as mean ± standard deviation.