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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) form the market. Evidence suggests that of the 130 drugs withdrawn from the market for safety reasons between 1964 and 1992, adverse effects on the liver were responsible in 18% of cases[1]. Not only does this illustrate 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. Rosenzweig and co-workers[2] 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)[3] found a lower prevalence of 12.5% but their review included a period of only 7 days. In 13 placebo-controlled multiple dose Phase I studies (mean: 13.8 days) 20% of subjects had an increase in LFT parameters[4]. Hospitalisation of healthy subjects in Phase I trials might also increase LFT parameters. Kanamaru *et al*. (1989)[5] reported ALT elevation in a group of subjects who rested for 7 days. However, another study involving bed rest for a week did not report an elevation in ALT[6]. Diet may play a role: Porikos and Itallie (1983)[7] demonstrated that a combination of excess calories and high sucrose intake was associated with elevation in serum aminotransferases. The role of carbohydrates was 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-calorie diet (32% sugar, 4500 kcal/day) but none in subjects fed either a high-fat high-calorie diet (4500 kcal/day) or a balanced healthy diet (1900 kcal/day)[8]. These data indicated that excess carbohydrate rather than surplus calories[7] was the main driver responsible for the rises in LFT parameters.

Aim

The aim of paper was to explore effects a low fat (<20%) high carbohydrate (72%) diet in combination with hospitalisation on the the levels of ALT and other liver enzymes in healthy Japanese and Caucasian subjects who were enrolled in a Phase I bridging study (which 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 in. Of those, 16 volunteers (8 Japanese and 8 Caucasian) received placebo throughout the study and were included into this post-hoc analysis.

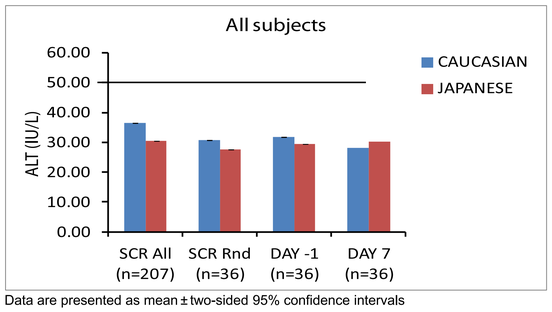
Results

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

Variable	Summary Statistics	Placebo	
		Japanese	Caucasian
n		8	8
Age (years)	Mean±SD	34.1±6.03	33.6±7.31
	med(min;max)	36.5(24;41)	32.0(25;44)
Height (cm)	Mean±SD	173.6±6.61	174.0±8.25
	med(min;max)	173.0(162;186)	175.0(162;185)
Weight (kg)	Mean±SD	70.4±12.59	79.58±11.80
	med(min;max)	66.0(59.2;97.4)	78.7(60.5;97.6)
BMI (kg/m²)	Mean±SD	23.3±3.52	26.1±2.26
	med(min;max)	22.2(19.7;28.2)	26.7(22.6;28.8)

Data are arithmetic mean ± standard deviation (SD) and median (minimum; maximum)
All subjects were male

B Figure 1: ALT levels in male Japanese and Caucasian subjects. ULN (——)



Data are presented as mean ± two-sided 95% confidence intervals

Figure 1 (Panel B) shows the ALT values for the population screened (history of high cholesterol), all subjects randomised up to Day 7, which was the end of a dietary run in. Figure 2 (Panel D) shows the effect of ALT and AST for the two ethnicities for the 16 subjects receiving placebo throughout the trial. ALT levels were well below the ULN for all subjects but show a mean change over time: ALT levels at Day -1 (admission) were not significantly different to those measured on Day 7 in both ethnicities. The findings also showed that the levels of ALT did not seem to be race dependent with very similar levels of ALT reported for both Japanese (30.14 IU/L; n=36) and Caucasian (28.17 IU/L; n=36) subjects after 7 days of hospitalisation. AST level show similar change but of a smaller magnitude. Levels of bilirubin and gamma-glutamyl-transferase (GGT) were below the ULN for all subjects; there were no increases in bilirubin in any of the subjects. Most subjects had very small increases in GGT of less than 20 IU/L.

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 13 of 16 subjects with 44% of subjects exceeding the ULN on Day 20. (Table 2 in Panel C)

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

ALT Changes	All	Caucasian	Japanese
Average Day -1 [IU/L]	29.7	34.9	24.5
Average Day 20 [IU/L]	46.8	42.3	51.2
Increase over baseline [IU/L]	17.1	7.5	26.8
Increase over baseline	58%	21%	109%
Subj. exceeding ULN Day 20	**44%**	**38%**	**50%**
Increase > 10 IU/L	56%	50%	63%
Increase > 20 IU/L	31%	13%	50%

ULN = **U**pper **L**imit of the **N**ormal reference range

D Figure 2: Effect of placebo upon ALT (a) and AST (b) levels in male Japanese (n=8) and Caucasian subjects (n=8) over a period of 34 days. ULN (—), Caucasian (◊), and Japanese (□)

Data are presented as mean ± two-sided 95% confidence intervals

Discussion

Although there is literature evidence purporting to a potential role for placebo, length of hospitalisation and diet (particularly those that are calorie and 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 hospitalisation and a high calorie high carbohydrate diet[2-5]. In particular, the importance of carbohydrate rather than calories as the primary instigator responsible for the marked rises in serum aminotransferases[8]. 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 ULN and there were no noteworthy increases in ALT and AST before 7 days. This finding is in agreement with the observation made by Mikines and co-workers who showed that subjects on bed rest for a week did not report ALT elevation[6].

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 of ALT exceeding the ULN, remaining at that level until day 34. The Japanese subjects showed the greatest change in ALT from baseline. Individual values showed remarkable steadiness in individuals over time, with few subjects showing no change at all.

Our study has limitations: First, the current study was done on 'healthy' volunteers that have abnormal cholesterol (LDL-C) levels[9]. Secondly, the study imposed a strict carbohydrate rich, low fat diet - in itself is a treatment; therefore one can not 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.

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