The Impact of Moderate Alcohol Use on Drug Safety Parameters for Warfarin and Lovastatin

Mukamal KJ, Smith CC, Karlamangla AS, Moore AA. Moderate alcohol consumption and safety of lovastatin and warfarin among men: the Post-Coronary Artery Bypass Graft Trial. Am J Med 2006;119:434–40.

Study Overview

Objective. To determine if alcohol consumption impacts the risk of elevated mean international normalized ratios (INRs) or alanine aminotransferase (ALT) levels among men using warfarin or lovastatin.

Design. Secondary analysis of data from the Post-Coronary Artery Bypass Graft (CABG) Trial, a randomized, multicenter, double-blind, placebo-controlled trial.

Setting and participants. Participants were recruited from 5 academic medical centers in the United States and Canada. Patients were included if they were aged 21 to 74 years and had prior CABG surgery 1 to 11 years preceding study entry, a low-density lipoprotein (LDL) cholesterol level between 130 and 175 mg/dL, a plasma triglyceride level < 300 mg/dL, 2 patent saphenous vein grafts, and a left ventricular ejection fraction ≥ 30%. Patients were excluded if they had unstable angina or myocardial infarction within the preceding 6 months, heart failure, severe angina, high likelihood of revascularization or death within the next 5 years, or an absolute contraindication to warfarin or lovastatin.

Intervention. Patients were randomly allocated to 1 of 4 groups: high-dose lovastatin (40–80 mg/day), low-dose lovastatin (2.5–5 mg/day), warfarin (1–4 mg/day), or warfarin placebo. Alcohol consumption was based on participant report and was categorized as nondrinker (abstinent), light drinker (1–6 drinks/wk), moderate drinker (7–13 drinks/wk), and heavier drinker (≥ 14 drinks/wk).

Main outcome measures. The primary outcome measures were serum ALT levels and INR. ALT levels and INRs were measured every 6 weeks for the first 15 months and every 3 months thereafter for the remainder of the trial (trial duration, 5 years). ALT levels were used as a measure of lovastatin drug safety in alcohol users. ALT levels were evaluated as both the highest absolute recorded value and any ALT level ≥ 80 IU/L. INRs were used as a measure of warfarin safety in alcohol users. As with ALT levels, INRs were evaluated as both the maximal absolute value and any ratio ≥ 2.0.

Main results. 1351 patients were enrolled. 102 women and 5 men were excluded from the analysis. All women were excluded because alcohol use was very uncommon among these participants, and the 5 men were excluded due to incomplete information. Of the 1244 men evaluated (mean age, 61.5 years), most were white (94%), and alcohol users were generally younger and more likely to be smokers. Of lovastatin users, 4% (n = 45) required a dose reduction due to elevated ALT levels, and 9% (n = 106) had maximal ALT levels ≥ 80 IU/L. There was no statistically significant difference in the risk of requiring a dose reduction of lovastatin or of obtaining a maximal ALT level ≥ 80 IU/L between nondrinkers and light, moderate, or heavier drinkers. Of warfarin users, 66% (n = 313) had INR ≥ 2.0. There was no association between alcohol use and the risk of an INR ≥ 2.0. In a secondary analysis, alcohol users tended to have a lower risk of reaching an INR ≥ 2.5 (P = 0.03); however, the absolute difference was small.

Conclusion. Moderate alcohol use does not appear to interact with lovastatin or low-dose warfarin.

Commentary

It is universally agreed that heavy alcohol use adversely affects patient health. However, the health effects of moderate alcohol consumption over the past decade have been debated, as studies have consistently demonstrated that moderate alcohol use may be cardioprotective [1]. As more patients (and even providers) embrace moderate alcohol consumption as part of a "heart healthy" diet, it is prudent to consider how alcohol use might adversely interact with prescription medications. Considerable theoretical interactions between medications and alcohol have been described, but only limited data exist regarding the impact of these theoretical interactions on clinical practice [2,3].

In this study, Mukamal et al performed a secondary analysis of data from a large trial to determine if alcohol use had any impact on drug safety monitoring parameters. The investigators were unable to find an association between

alcohol use and the risk of achieving elevated ALT levels or INR. A particular strength of the study is that both ALT levels and INRs were evaluated regularly. However, the study excluded women, and therefore no conclusions can be drawn as to whether a potential alcohol-drug interaction exists in women. Although the study was large, the number of study outcomes (elevated ALT levels and INRs) was low and thus power was limited. Alcohol use was based on a single self-reported level at baseline; whether study participants changed their alcohol habits over the course of the 5-year study is unknown. Finally, the study investigated low-dose warfarin, and these findings may not be extrapolated to higher doses of warfarin.

Applications for Clinical Practice

These findings should provide reassurance to patients and providers who might be concerned about potential interactions between low-dose warfarin or lovastatin therapy and alcohol use. Nevertheless, all providers should be cautious regarding alcohol and medication interactions.

—Review by Harvey J. Murff, MD, MPH

References

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