Fluctuations in Blood Lipid Levels During Furosemide Therapy

A Randomized, Double-blind, Placebo-Controlled Crossover Study

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Background: Acute decreases in intravascular volume are associated with increases in lipid levels. Furosemide causes acute changes in intravascular volume during prolonged therapy but is thought to have little effect on lipid levels.

Methods: To determine if there are daily acute rises in lipid and lipoprotein levels associated with changes in intravascular volume during long-term furosemide ingestion therapy, we performed a randomized, double-blind, placebo-controlled crossover study in 10 patients.

Results: In the 8 hours after furosemide ingestion there were increases in levels of plasma cholesterol (10.1%; P = .001), high-density lipoprotein cholesterol (9.0%; P = .006), and apolipoprotein B (9.8%; P = .003). The increases in levels of triglycerides (11.5%; P = .17) and apolipoprotein A-1 (13.3%; P = .051) were of similar magnitude but more variable and did not achieve statistical significance. There was no substantial change in the total cholesterol–high-density lipoprotein cholesterol ratio (0.6%; 95% CI, −0.74% to 8.6%; P = .88).

Conclusion: This study indicates that there are acute increases in lipid levels after furosemide ingestion during prolonged therapy, which could affect the interpretation of lipid levels and cardiovascular risk in patients.

Arch Intern Med. 1998;158:1461-1463

The treatment of heart failure, in general, involves the use of potent diuretics, such as furosemide, which has resulted in furosemide being one of the most commonly prescribed drugs. In a preliminary study, ingestion of furosemide by healthy volunteers was associated with an 8% to 14% increase in lipid and lipoprotein levels 3 hours after ingestion. The increases in lipid and lipoprotein levels correlated with decreases in intravascular volume. Reduction in intravascular volume due to dehydration or diuresis also causes increases in serum lipid and lipoprotein levels. There are reductions in intravascular volume with each furosemide dose during long-term therapy but furosemide is not thought to cause substantial increases in lipid levels during long-term therapy. We conducted this study to determine whether there would be an acute increase in plasma lipid and lipoprotein levels following ingestion of furosemide in patients with stable chronic congestive heart failure or hypertension being treated with furosemide on a long-term basis.

Results: Six women (average [± SD] age, 66 ± 12 years) and 4 men (average [± SD] age, 56 ± 6 years) completed the study. Eight of the patients received 40 mg/d of furosemide while 2 had 60 mg/d. In 7 patients, the need for furosemide therapy was indicated by congestive heart failure and in 3, hypertension.

Figure 1 shows the average effect of furosemide use on serum lipid and lipoprotein levels and estimated changes in intravascular volume over time. Increases in lipid and lipoprotein levels occurred by 1 hour and persisted throughout the 8 hours of blood sampling (Figure 1). The average change in serum albumin and total protein concentrations and weight associated with furosemide use (relative to placebo use) is shown in the Table. There was no effect of furosemide therapy on the total cholesterol–high-density lipoprotein cholesterol ratio (Table), indicating a similar effect of hemoconcentration on the different lipid particles. There was no crossover effect, indicating the validity of pooling the results of patients randomized to receive initial furosemide and initial placebo therapy (data not shown).

Figure 2 shows the correlation between change in intravascular volume and change in lipid and lipoprotein levels over the sampling period. Most of the changes in lipid and lipoprotein levels were significantly correlated to changes in intravascular volume with the exception of changes in levels of triglycerides and apolipoprotein A-1.
PATIENTS AND METHODS

This study was a randomized, double-blind, placebo-controlled crossover design.

Twelve patients with stable class 2 (New York Heart Association) congestive heart failure or hypertension being treated with a daily furosemide dose (40-80 mg in the morning) for more than a month were studied. Patients with stable medical disorders were allowed to enter the study unless they had renal impairment (serum creatinine concentration >120 µmol/L [>1.3 mg/dL]). Patients prescribed diabetic pharmacotherapy, additional furosemide doses within 8 hours of the morning dose, and nonsteroidal anti-inflammatory drugs were excluded. Aspirin use less than or equal to 500 mg/d was allowed.

PROTOCOL

The study protocol was approved by the Faculty of Medicine Ethics Committee, University of Calgary, Alberta, and all subjects gave written consent to participate.

The patients were studied on 2 separate days, 1 week apart. Prior to each study day, the patients fasted from 6 PM. The patients were randomized to receive their usual morning dose of furosemide disguised in a capsule(s) or a similar placebo capsule(s) in a double-blind study design. Blood samples were obtained through an indwelling intravenous catheter prior to capsule ingestion and hourly for 8 hours. The patients remained fasting but were allowed water ad libitum up to 750 mL.

Levels of total cholesterol, triglycerides, high-density lipoprotein cholesterol, apolipoprotein B, and apolipoprotein A-1 were determined in each blood sample, along with complete blood cell count, total protein, and albumin. Creatinine concentration and electrolyte levels were measured in the first blood samples both study days.

The following week the crossover aspect of the study was performed exactly as in the first study, including ingestion of the same volume of water and doses of drugs other than furosemide. Two patients were excluded prior to data analysis; one had a baseline creatinine value above the exclusion criteria and the other venous access could not be obtained for blood sampling.

The blood was collected and analyzed using a protocol designed to reduce laboratory and collection-induced variability. Changes in blood volume were calculated based on changes in hematocrit and red blood cell count using the formula of Strauss et al.10

STATISTICAL ANALYSIS

After first normalizing relative to baseline values, the data were analyzed using the Laird-Ware model11 for repeated measures data, which was applied to accommodate the serial measurements made during each period of the crossover. The association between changes in blood volume and changes in lipid and lipoprotein levels were determined by Pearson product moment correlation from data pooled over both periods.

COMMENT

This study demonstrates that there are daily increases in lipid and lipoprotein levels during furosemide therapy. The increases are approximately 10% and similar in magnitude to the decreases in lipid levels that occur during dietary therapy and about one half of that expected from a single pharmacological agent at starting doses.12 A true 10% increase in cholesterol level is associated with approximately a 20% increase in cardiovascular risk.12 Because many patients receive medications prior to having blood drawn for laboratory samples, furosemide therapy could cause erroneous conclusions regarding cardiovascular risk and response to lipid-lowering therapy.

Several factors suggest that part of the mechanism by which furosemide use increases lipid and lipoprotein levels is through changes in intravascular volume. There were significant correlation coefficients between the change in many of the lipid levels and intravascular volume, and there was a similar time course for the change in intravascular volume and lipid levels. In addition, there are significant correlation coefficients between changes in lipid levels and intravascular volume in studies examining the effect of prolonged fasting, dialysis in patients with renal failure, and furosemide use in healthy volunteers.4,6 However, the changes in lipid and lipoprotein levels (9%-13.3%) were greater than the changes in intravascular volume, albumin, or total protein concentrations (5.9%-7.3%), and overall the correlation co-
function. Increases in lipid concentrations directly as- 
by reduced intravascular volume were also responsible for 
hormones (eg, epinephrine or hydrocortisone) stimulated 

Figure 2. Pearson product moment correlation coefficients of the changes in specific lipid and lipoprotein levels with changes in intravascular volume following furosemide and placebo therapy in 10 patients with congestive heart failure. In patients treated with 
long-term hemodialysis, there are substantial reductions 
in lipid and lipoprotein levels associated with changes in body weight during the interdialysis period. Lipid and lipoprotein levels may therefore be misinterpreted in volume- 
overloaded patients as well as volume-depleted patients. 

It is important that clinicians be aware of the effect of 
furosemide therapy on lipid levels to avoid erroneous as-
semsival cardiovascular risk and effectiveness of therapy. 
To avoid misinterpretation of lipid levels due to furose-
mide therapy, blood for lipid levels can be drawn prior to 
furosemide use or where appropriate, the total cholesterol– 
high-density lipoprotein cholesterol ratio could be used. Decreased intravascular volume associated with 
prolonged fasting and dialysis also has a similar effect on lipid 
levels. Efforts should be made to ensure blood for lipid lev-
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