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Clinical Research

Incremental Lowering of Low-Density Lipoprotein Cholesterol With Ezetimibe 20 mg vs 10 mg Daily in Patients Receiving Concomitant Statin Therapy

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ABSTRACT

Background: Ezetimibe is typically administered at a dose of 10 mg daily, with few reports of use at other doses. We compared plasma concentrations of low-density lipoprotein (LDL) cholesterol and other lipid variables in patients with dyslipidemia who were receiving ezetimibe 10 mg and then 20 mg daily.

Methods: A retrospective chart review identified 27 patients who received ezetimibe 10 mg and then 20 mg daily at different times; 15 participants were receiving stable statin therapy and 12 were not receiving concomitant statins. Plasma concentrations of lipids, creatine kinase (CK), and aspartate transaminase (AST) were determined. Plasma concentrations of ezetimibe and ezetimibe glucuronide were measured in a second group of patients.

Results: Patients taking statins and ezetimibe 20 mg had further reductions in total and LDL cholesterol of 7.1% and 10.3%, respectively (both $P < 0.05$) than did those receiving the 10-mg dose. No difference between 20-mg and 10-mg dosing was seen among patients not receiving statins. Plasma concentrations of ezetimibe and its active metabolite were about 2-fold higher ($P < 0.05$) in patients taking ezetimibe 20 mg than in those receiving 10 mg daily. All patients tolerated ezetimibe 20 mg without side effects.

Conclusions: Ezetimibe 20 mg daily reduced total and LDL cholesterol further in patients receiving statin therapy compared with 10 mg daily. Prospective studies are required to show whether the higher plasma levels of ezetimibe and its active metabolite in patients taking the

RÉSUMÉ

Introduction : L'ézétimibe est habituellement administré à raison d'une dose de 10 mg par jour, et son utilisation à d'autres doses est peu rapportée. Nous avons comparé les concentrations plasmatiques du cholestérol à lipoprotéines de basse densité (LDL) et d'autres variables lipidiques chez les patients ayant une dyslipidémie qui recevaient 10 mg d'ézétimibe par jour, puis 20 mg.

Méthodes : Une étude rétrospective des dossiers a permis de trouver 27 patients qui recevaient 10 mg d'ézétimibe par jour, puis 20 mg à différents moments; 15 participants recevaient un traitement stable par statines et 12 ne prenaient pas les statines de façon concomitante. Les concentrations plasmatiques des lipides, de la créatine kinase (CK) et de l'aspartate aminotransférase (ASAT) ont été déterminées. Les concentrations plasmatiques de l'ézétimibe et de l'ézétimibe-glycuronide ont été mesurées dans un second groupe de patients.

Résultats : Les patients prenant les statines et 20 mg d'ézétimibe ont montré des réductions supplémentaires du cholestérol total et du cholestérol LDL de 7,1 % et 10,3 %, respectivement ($P < 0,05$ pour les deux) par rapport à ceux qui recevaient la dose de 10 mg. Aucune différence entre les doses de 20 mg et de 10 mg n'a été observée chez les patients qui ne prenaient pas les statines. Les concentrations plasmatiques d'ézétimibe et de son métabolite actif ont été environ 2 fois plus élevées ($P < 0,05$) chez les patients prenant 20 mg d'ézétimibe par jour que chez ceux qui en prenaient 10 mg. Tous les

Reducing low-density lipoprotein (LDL) cholesterol decreases the risk of major cardiovascular disease (CVD) outcomes, and LDL cholesterol remains the primary target in dyslipidemia guidelines.[1-4] Ezetimibe is a cholesterol absorption inhibitor that impairs intestinal absorption of hepatically excreted biliary cholesterol and dietary cholesterol.[5,6] It is believed to reduce the overall return of cholesterol to the liver by binding the Niemann-Pick C1-Like 1 (NPC1L1) transporter that normally moves cholesterol into enterocytes from intraluminal bile acid micelles.[5,6] Decreased sterol transport from enterocytes to chylomicrons ultimately results in less cholesterol delivery to the liver. Hepatic LDL receptors become upregulated, LDL clearance from the circulation is increased, and plasma LDL cholesterol decreases.[5,6]

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20-mg dose have any detrimental effects. Increasing the ezetimibe dose to 20 mg daily might be an interesting potential approach for patients who fail to reach lipid targets on ezetimibe 10 mg daily along with maximally tolerated doses of statin.

patients ont toléré l'ézétimibe à une dose de 20 mg, et ce, sans effets secondaires.

Conclusions : L'ézétimibe à une dose de 20 mg par jour comparativement à une dose de 10 mg a davantage réduit le cholestérol LDL et le cholestérol total chez les patients recevant le traitement par statines. Des études prospectives sont nécessaires pour démontrer si des concentrations plasmatiques plus élevées d'ézétimibe et de son métabolite actif chez les patients prenant une dose de 20 mg n'ont aucun effet nuisible. L'augmentation de la dose d'ézétimibe à 20 mg par jour pourrait être une approche intéressante chez les patients qui n'ont pas atteint les cibles lipidiques par la prise d'ézétimibe à une dose de 10 mg par jour tout en prenant des doses maximalement tolérées de statines.

Ezetimibe reduces plasma total cholesterol, LDL cholesterol, and triglycerides (TGs) by ~13%, ~18%, and ~6%, respectively, and increases high-density lipoprotein (HDL) cholesterol by ~2%.[7-9] Overall, ezetimibe monotherapy is well tolerated, with a safety profile similar to that of placebo.[7-9] The only recommended and approved dose for ezetimibe is 10 mg, which was derived from early-phase dose-finding studies.[7-9]

The primary aim of this study was to evaluate whether doubling the dose of ezetimibe from 10 to 20 mg daily provides additional LDL cholesterol–lowering capability. We also measured plasma concentrations of creatine kinase (CK), aspartate transaminase (AST), ezetimibe, and the active metabolite ezetimibe glucuronide in patients receiving the 2 different doses of ezetimibe.

Methods

Study design and participants

We conducted a retrospective chart review of patients receiving ongoing care at the London Health Sciences Centre Lipid Clinic between 2008 and 2012. The study sample consisted of 27 patients with dyslipidemia who received ezetimibe 10 mg and then 20 mg, each for at least 3 months. The study was approved by the University of Western Ontario Research Ethics Board (No. 07290). Fifteen of 27 (55.6%) participants were taking a stable statin dose plus ezetimibe, whereas 12 of 27 (44.4%) participants did not receive statin therapy with either ezetimibe dose. In all cases, ezetimibe was increased to 20 mg because of failure to achieve LDL cholesterol targets despite maximally tolerated statin therapy; this included patients who could not tolerate any statin dose. All other treatments remained stable over the study period.

Biochemical tests and drug levels

Baseline data from 27 patients receiving ezetimibe treatment included the following: age, body mass index (kg/m^2), sex, family history of CVD, personal history of smoking and alcohol consumption, concomitant medications and their doses, and associated disease states such as coronary heart disease, hypertension, and diabetes. Biochemical determinations included the lipid profile, with LDL cholesterol determined using the Friedewald equation, and plasma concentrations of CK and AST.

Plasma concentrations of ezetimibe and ezetimibe glucuronide from an independent group of 13 patients taking ezetimibe 20 mg and 26 patients taking ezetimibe 10 mg daily were analyzed using liquid chromatography–tandem mass spectrometry. All chemical and deuterated standards were purchased from Toronto Research Chemicals, North York, Canada. Briefly, plasma aliquots of 100 µL were precipitated in 200 µL acetonitrile containing internal standard ezetimibe-d4 and then centrifuged. The supernatant was diluted in 0.05% formic acid (2:3, v/v). Analytes were separated with a C18 reverse-phase column using gradient elution (20%-70%) with 0.05% formic acid in water and in acetonitrile (TLX-2 high-performance liquid chromatography system; Thermo Scientific, Pittsburgh, PA). Concentrations of ezetimibe and ezetimibe glucuronide were measured using a mass spectrometer (TSQ Vantage triple-quadrupole mass spectrometer, Thermo Scientific, Pittsburgh, PA) with transitions of 408 → 271 mass-to-charge ratio (m/z) and 584 → 271, 213, 309, 408 m/z, respectively. The lower limit of quantification was 0.1 ng/mL for ezetimibe and 5 ng/mL for ezetimibe glucuronide. The interday coefficient of variation was 3% and 7%, and accuracy (bias) 6% and 8% for ezetimibe and ezetimibe glucuronide quality control samples, respectively.[10]

Statistical analyses

A paired sample *t* test was applied, which compared the mean levels using ezetimibe 20 mg and 10 mg, with and without a statin at both doses, of the standard lipid profile—namely total, LDL, and HDL cholesterol; TGs; and also AST and CK. These values were then used in a Wilcoxon score (rank sum) analysis of mean lipid profile levels for 20 mg and 10 mg ezetimibe, with and without concomitant statin therapy. SAS software, version 9.3 (SAS Institute, Cary, NC) was used for all statistical comparisons, and untransformed biochemical variables are shown in the text and tables.

Results

Participant characteristics

Patient demographics are shown in Table 1. All patients were considered to be at high risk for CVD based on current lipid guidelines.[3] Baseline lipid profiles for patients taking ezetimibe with and without statins are shown in Tables 2 and 3. Each individual on ezetimibe 20 mg or 10 mg had